QUALITY ASSESSMENT ACROSS DISCIPLINES IN HEAD AND NECK CANCER TREATMENT

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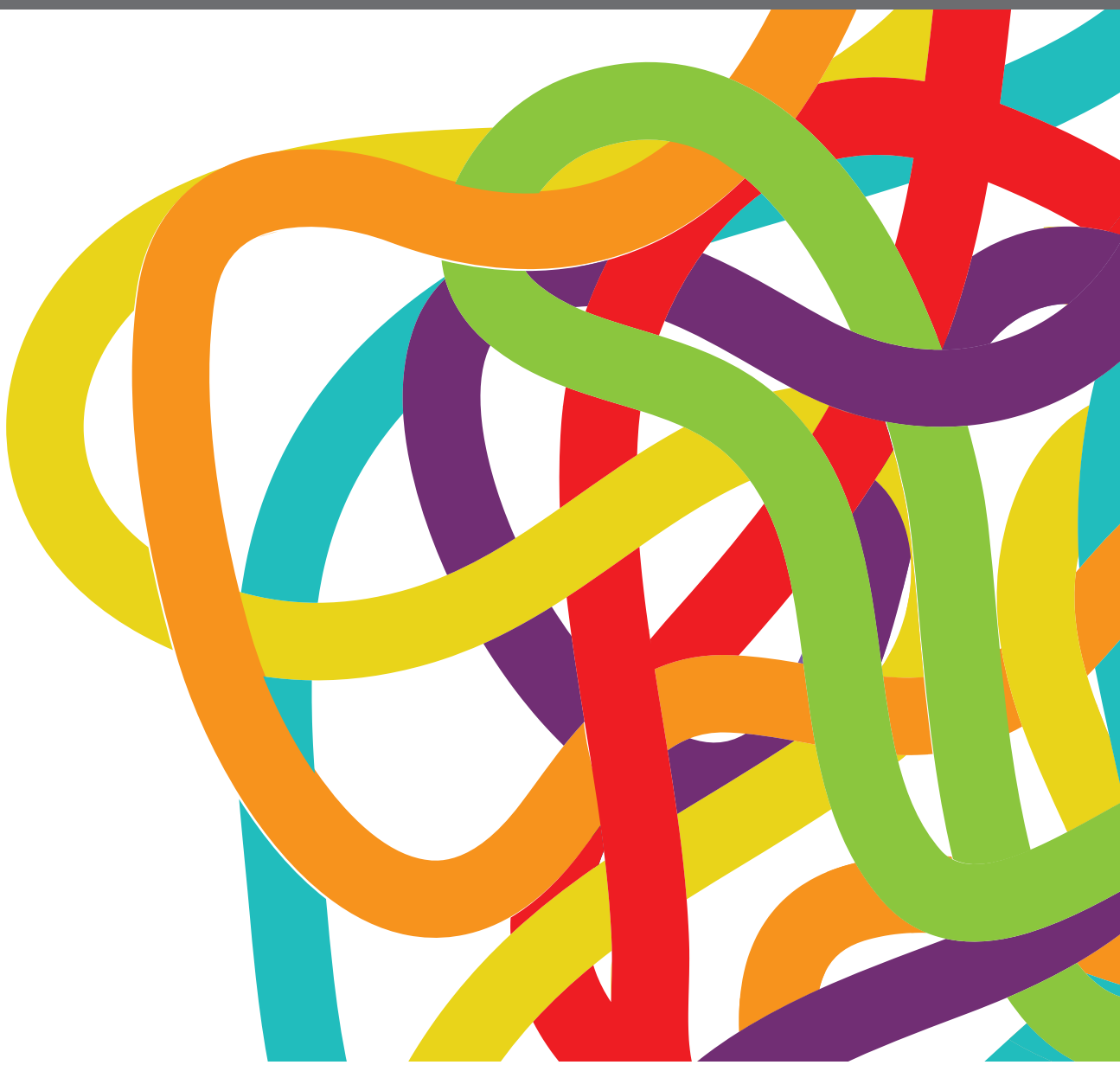

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QUALITY ASSESSMENT ACROSS DISCIPLINES IN HEAD AND NECK CANCER TREATMENT

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EDITORIAL
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Editorial: Quality Assessment Across Disciplines in Head and Neck Cancer Treatment

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Keywords: head and neck cancer, squamous cell, multidisciplinary team approach, quality assessment, quality assurance

Editorial on the Research Topic

Quality Assessment Across Disciplines in Head and Neck Cancer Treatment

INTRODUCTION

Quality assessment is indispensable in all areas of cancer care, and that is certainly true for head and neck cancer. The increased complexity of diagnosis and the multimodal and multiprofessional treatment and expanding (financial) burden to the health care system leads to concern whether new knowledge is effectively transferred to all patients. Moreover, there are major geographical differences in accessibility of radiotherapy equipment and anti-cancer drugs around the globe. Impaired quality of care results in compromised quality of life or sometimes even in impaired survival. Quality assurance must cover the entire patient care process from the diagnosis to the therapeutic decision and for that the multidisciplinary team (MDT) meetings are playing a crucial role.

TOPICS OF INTEREST

In the present Research Topic on "Quality Assessment Across Disciplines in Head and Neck Cancer Treatment" leaders in the head and neck oncology field discuss a variety of topics:

1. Quality of Care at a European Level. Based on a multidisciplinary and expert-based consensus process the main quality indicators for quality of care are considered to be the availability of a formalized multidisciplinary team, participation in clinical and translational research, timeliness of care, high quality of surgery and radiotherapy and adequate pathology reporting. These quality indicators were retrospectively tested in four European countries in patients treated in the years 2009–2011 (see Trama et al.). For head and neck cancer, the quality of care did not reach the optimal standard in most of these countries. Patients frequently were found diagnosed at an advanced stage, a high proportion showed delays in starting therapy (especially for radiotherapy) and only a limited use was made of multimodal therapy. One of the suggested options to improve these disappointing observations is referring patients to specialized centers or networks including specialized centers.
2. Quality Indicators in Belgium. In line with these observations is a nation-wide study in Belgium of 9,245 patients with squamous cell head and neck cancer diagnosed between 2009 and 2014.

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Leroy et al. reported that four quality indicators of diagnosis and staging (dedicated imaging studies, use of PET-CT, TNM reporting and interval between diagnosis and start of therapy) varied widely among hospitals in Belgium, clearly shown in room for improvement.

3. The Importance of MDT Meetings. The composition and respective roles of the different disciplines in the MDT meetings are described by Taberna et al., highlighting the role of the head and neck cancer specialized nurse, the dietitian, the speech and language pathology expert and the onco-geriatrician. They also indicate the importance of dental care and psychosocial support, and stress the importance of integrating clinical and translational research teams in the MDT meetings.
4. Diagnostic Pathology. Accurate diagnosis is key to provide a high quality clinical service for patients with head and neck cancer. Treatment should not be provided unless a histological diagnosis of cancer is made. For this to be accurate, both the laboratory and reporting service must be quality assured. Sloan and Robinson stress the importance of clinical audits as a method to improve the healthcare services, while digital pathology has the potential to bring about improvements in the safety, quality and efficiency of a cellular pathology department. Artificial intelligence systems most likely will infiltrate this arena, also in head and neck pathology. Many innovations are expected to be implemented and within that context quality assurance for molecular testing, including for biomarkers, seems indispensable.
5. Biomarkers. Economopoupou et al. provide a descriptive and detailed review of validated biomarkers in squamous cell head and neck cancer. HPV DNA/p16, PET imaging and PDL-1 are validated diagnostic and prognostic/predictive biomarkers currently used in clinical practice. The utility of several emerging biomarkers, such as e.g.; skeletal muscle mass and next generation sequencing, and their usefulness in the future are thought to depend on accuracy, reproducibility and reliability.
6. PET-CT Imaging. A more in depth quality assessment in FDG-PET-CT imaging is given by Van den Wyngaert et al., summarizing the recent technical breakthroughs in PET-CT scan design and describes the existing quality assessment frameworks with a focus on applications in head and neck cancer.
7. Best Practice in Surgical Treatment. It is already known for quite some time that high-volume hospitals provide a lower long-term mortality and this also holds for the number of patients that a physician sees (the more the better). Also center criteria like participation in clinical trials and transparency of clinical outcome are considered mandatory for high quality patient care. Simon et al. in their manuscript highlight that sticking to guidelines, avoiding delays in treatment (primary as well as adjuvant), pretreatment multidisciplinary evaluation, elective neck dissection yield of ≥18 lymph nodes and obtaining a negative surgical margin all are associated with improved survival. They describe the best practice guidelines for the surgical treatment of cancers of the sino-nasal tract, skull base, aerodigestive tract in the neck.
8. Radiotherapy Quality Assurance. Quality assurance has been taken seriously first by the radiation oncologists and is most advanced among the different disciplines involved in the treatment of patient with head and neck cancer. Because the actual radiotherapy procedures in head and neck cancer have become so complex and so precise rigorous quality assurance for all the different steps in the radiation process is essential to deliver the right dose to the right place in order to reach the best oncologic outcome with the least toxicity for the organs at risk. Again, as described for the best practice in surgery, outcome results in large volume centers are better than in low volume centers. Van Gestel et al. consider the reason for this finding likely multifactorial, including not only the quality of the radiotherapy planning and delivery, but also the quality and accuracy of other steps involved in tumor staging (e.g.; pathology, imaging) and treatment.
9. Best Practice in Systemic Therapy. Oosting and Haddad also highlight the importance of the MDT meetings within the context of quality assurance. Treatment in a multidisciplinary team is essential and improves outcome. Quality assurance in daily practice should aim at guideline implementation, specialization and multidisciplinary care and should pay attention especially to the older patients, patients with comorbidity and patients from lower socio-economic classes. With respect to the selected treatment, the preparation of the drug, the delivery to the patient (administration and dosage, giving the correct dose intensity), and handling the side effect in a timely manner are crucial in obtaining the best outcome. Several trials, both prospectively and retrospectively have indicated that suboptimal dosing of chemotherapy is leading to impaired outcome. Monitoring of outcome and benchmarking can be strong incentives to assess and improve quality of care.
10. Statistical Issues. Fortpied and Vinches elegantly explain what the tasks are of the medical statistician when performing a clinical study. They stress the importance of a good communication between the statistician and the research physician. The complexity of head and neck cancer as being a heterogeneous disease, the integration of new therapies in both the primary disease setting and the recurrent/metastatic disease setting, the change in head and neck cancer population and the comorbidities add to the already existing challenges when performing clinical trials.
11. Follow-Up of Head and Neck Cancer Survivors. How intensive should this be. The impact on overall survival has been equivocal. However, no randomized trial exploring this question has been done. Based on literature data, Szturz et al. formulated arguments in favor of and against intensive follow-up and propose a compromise in which in specific clinical situations periodic imaging can be justified.
12. Supportive Care. Bonomo et al. indicate that the quality of supportive measures are essential as "supportive care makes excellent cancer care possible". The quality of supportive care makes it possible to administer drug treatment according to planned dose intensity. Moreover, when the

primary treatment concerns surgery, prevention of infections and pain control after surgery as well as a rapid rehabilitation (early oral feeding after surgery) are important items. With respect to radiotherapy with or without systemic therapy, prevention of oral and oropharyngeal mucositis and radiodermatitis, giving nutritional support, apply swallowing exercises, giving adequate pain therapy and helping patients with psychosocial support are all important items. An early involvement of a supportive and palliative team is a central issue to allow for a better patient information and care. For patients with recurrent/metastatic disease such teams will also help to avoid administering chemotherapy in the last period of life.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REVIEW
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The Statistical Evaluation of Treatment and Outcomes in Head and Neck Squamous Cell Carcinoma Clinical Trials

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The purpose of this article is two-fold: to help statisticians confronted with the design, implementation and analysis of clinical trials and new to the field of head and neck cancer; but also to sensitize research physicians with the role, the tasks and the challenges faced by the medical statisticians. These two purposes altogether will hopefully encourage and enable fluid communication between the research physician and the medical statistician and the understanding of each other's field and concerns. In particular, the methodological challenges resulting from the heterogeneity of the head and neck cancer, the complexity of the treatments and the associated comorbidities are presented with examples borrowed from medical literature and from the practical experience of the authors in this field.

Keywords: statistical design, statistical analysis, clinical trial, head and neck cancer, treatment, comorbidities, patient population, endpoint

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INTRODUCTION

Medical research and conduct of clinical trials is inconceivable today without statistical expertise. This is officially acknowledged in Europe since 1990 when the Committee for Proprietary Medicinal Products (CPMP) (1) adopted a Note for Guidance covering the subject of Good Clinical Practice (GCP). This note stated that "access to biostatistical expertise is necessary before and throughout the entire procedure, commencing with designing of the protocol and ending with completion of the final report."

The purpose of this paper is two-fold: to help statisticians confronted with the design, implementation and analysis of clinical trials and new to the field of head and neck cancer; but also to sensitize research physicians with the role, the tasks and the challenges faced by the medical statisticians. These two purposes altogether will hopefully encourage and enable fluid communication between the research physician and the medical statistician and the understanding of each other's field and concerns.

According to the title of the paper, the first section explains what are the requirements to conduct a rigorous statistical analysis of a clinical trial: in particular the predefined analysis plan, the data, and the software. Then moving to the field of head and neck cancer, we will explain how the heterogeneity of the disease, the multimodality nature of treatments and the associated comorbidities influence the methods used to design and analyze clinical trials in this field. Key methodological and statistical concepts are explained and illustrated with examples borrowed from medical literature and from the practical experience of the authors.

WHAT MAKES A STATISTICAL ANALYSIS A GOOD STATISTICAL ANALYSIS?

Pre-defined Analysis Plan

Different statistical approaches can lead to different numerical results and hence influence the interpretation of the trial. The statistician will need to choose among the different possible statistical methods. The choice will depend on the nature of the data (e.g., continuous, binary, categorical, or time-to-event), the underlying assumptions about the statistical distribution (e.g., non-parametric, semi-parametric, or fully parametric), and the amount of data (e.g., asymptotic methods for large samples or exact methods for small samples). A demonstration of this, although based on observational data outside the medical field, is provided in the confronting article by Silberzahn et al. (2), which reports how different analytical methods can lead to different results. Lack of prespecification may affect the trial's validity by allowing the researchers to consciously or unconsciously select the analysis approach that provides the most favorable results. It is therefore important that these decisions are prespecified before seeing the trial data. This is why, and as stated in International Conference on Harmonization (ICH) E9 guideline (3), the study protocol must include the main features of the data analysis: definition of the analysis populations, timing of interim and final analyses, precise definition of the study endpoints, methods used for estimation, confidence intervals, and hypothesis testing; adjustment of significance and confidence levels; subgroup analyses. In addition, with the pre-specification of the analyses and more specifically of the hypotheses tests, the extent of multiplicity is clearly stated (multiple endpoints, multiple comparisons of treatments, repeated evaluations over time, interim analyses) and measures to control the risk of overall Type I error, i.e., of false positive findings, can be taken. Unplanned analyses are sometimes conducted. For example, when new questions based on the observed data emerge or when heterogeneity of the treatment effect across subgroups of patients needs to be assessed. When reporting and publishing the results of a clinical study, as stated in Consolidated Standards of Reporting Trials (CONSORT) guidelines (4), results from these *post-hoc* analyses have to be clearly distinguished from the results of the preplanned analyses. As the former cannot lead to firm conclusions, they are solely considered as exploratory and hypothesis generating. To ensure the completeness and the appropriateness of the written statistical analysis plan, a second statistician should ideally validate it.

The Clinical Data

Accuracy, consistency, completeness and reliability of the clinical data is obviously critical for the analysis and interpretation of the study. Data management processing involves several steps and usually a high number of actors. The design of the case report forms and the clinical database are developed by the central data manager. The reporting of each patient data is done by the investigators from source documents. The interactions between the local investigators and the central data manager allows the verification and correction of the data and the traceability of the data flow. Principles established in GCP (5) and the sponsor's standard operating procedures should constitute a safeguard against poor data management.

Computer Software Validity

Based on the statistical analysis plan, the statistician will process the data statistically. He/she will produce a descriptive analysis in the form of tables and graphical displays and an inferential analysis consisting of estimated effect sizes, their precision (such as 95% confidence interval) and significance (*p*-values). The credibility of the numerical results of the analysis depends on the quality and validity of the softwares used, either externally or internally written (3). A validated software and programming language, such as used in the Statistical Analysis System (SAS®, Cary NC, USA) should be used to produce the statistical analysis outputs. The study statistician should develop the statistical analysis programs specific to his/her study using built-in SAS procedures and in-house programmed SAS macros that automate repetitive data processes. To ensure the correctness of the results, a second, independent statistician should validate the analysis program, by independent programming, at least for the analysis of the primary and key secondary endpoints of the study.

From the Statistical Analysis to the Publication

The role of statistics is to translate information into knowledge, which is, according to the renowned statistician Stephen Senn, the challenge that faces statisticians (6). When browsing the Royal Statistical Society website (7), one can read that the medical statistician will see his/her work "influence clinical practice, help guide public health education and policies, or add to current knowledge, sometimes leading to further research studies." It is not enough to produce statistical outputs, statistical judgment must also be exercised for the interpretation and presentation of the results. The statistician will make sure that the conclusions are presented or disclosed in a manner that fairly reflects the evidence supported by the results. In this regard, we would like to caution about the use or overuse or even misuse of *p*-values: not only because the concept of the *p*-value is often misunderstood but also because it is not a substitute for medical judgement. *P*-values should not be provided alone but should be accompanied with effect sizes and their precision in order to be able to assess the clinical relevance of the results (8, 9).

All research results should be published, irrespective of the findings (both positive and negative, statistically significant, or not). As stated by Tam et al. (10), "Non publication of clinical trials breaks an implicit contract with trial participants, institutional review boards, and study sponsors and society in general." As a measure to prevent publication bias, the International Committee of Medical Journal Editors (ICJME) (11) recommends editorial decisions not to be driven by the clinical trial results but by the originality, the quality and the contribution to scientific knowledge. Furthermore, regulatory bodies, Food and Drug Administration (FDA) and European Medicines Agency (EMA), have initiated moves toward greater transparency by requesting that the aggregated results of (drug) clinical trials are disclosed in public domain to US ClinicalTrials.gov (since 2007 and then extended to non-licensed

products in 2017) (12) and/or to EMA European Clinical Trials Database—EudraCT (since 2014) (13). Keeping abreast of statistical methodology.

Again quoting the Royal Statistical Society website (7), the medical statistician is also "part of an academic group which develops statistical methodology to be applied to medical research." Up to the nineties, the methodology for the design and statistical analysis of clinical trials was well-established and statisticians could do their job with a limited number of tools. Since then, parallel developments, such as increased computer power, advances in biology science leading to the emergence of a new class of treatment called "targeted," brought new opportunities for clinical development and new methodological challenges (14). Some of these methodological challenges are discussed below in the context of head and neck cancer clinical studies.

The Medical Statistician: From the Start, in Close Interaction With the Research Physician, the Data Manager and the Clinical Operations Team

A statistical analysis can only be translated into knowledge if the study has been adequately designed to answer the key research questions of the study. The medical statistician develops an appropriate design that will ensure the trial to provide the answer to its objectives within the limits of existing statistical methodology, starting from the rationale, the objectives and the clinical background defined by the research physician. The designs consists of the statistical and methodological setup of the trial, including elements such as randomization, stratification, planning of the statistical testing of primary and secondary endpoints, adjustment of those comparisons for covariates, sample size calculation taking into account type I and type II errors. It is at this point that the statistician and the research physician need to interact closely. Discussions should identify the practical constraints of the study, particularly in terms of potential accrual and overall study duration. With these elements in hand, the statistician will propose a statistical design for the study. Several options are typically discussed before a final design is agreed upon.

In addition, as the statistician is typically concerned by bias and precision, he/she is not only involved in the pure statistical aspects of the study. But he/she will also participate in planning operational aspects that may potentially induce a bias or undesired variability affecting the interpretability of the study results. As such, the statistician carefully reviews the procedures planned for the study such as selection, diagnosis and staging of patients; treatment administration; follow-up assessments; data processing (3). He also pays attention to the potential aspects of the protocol where adherence is more difficult to achieve in order to minimize the incidence of violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol. Deviations may affect the subsequent analyses and ultimately the interpretation and conclusions of the study.

TABLE 1 | Responsibilities of the trial statistician in a study life cycle.

Study life cycle	Responsibilities of the trial statistician
Study design	• Contributes to the definition of the study objectives and to the selection of the primary and secondary endpoints • Proposes one or several statistical designs until final selection • Computes the sample size and the study duration • For randomized studies, specifies the method and parameters of the randomization procedure • Defines accurately the trial endpoints and the methods of assessment • Designs the early stopping rules and interim monitoring plan • Writes the statistical analysis plan
During the study conduct	• Monitors the assumptions underlying the statistical design • Interacts with the Independent Data Monitoring Committee, when pre-specified in the study protocol or in case of unanticipated issues • Contributes to the amendment of the study protocol in case of major changes to the statistical considerations of the trial
At each interim, final or long-term data analysis	• Assesses the quality of the clinical database for the intended analysis, in terms of completeness and consistency • Develops the analysis programs to produce the required tables, graphical displays and inferential analyses • Writes the statistical analysis report • Contributes to the presentation and publication of the study results • Submits the final study results to EMA European Clinical Trials Database (EudraCT) and to US ClinicalTrials.gov public websites

The medical statistician is thus involved from the start up to the end in a study life cycle. **Table 1** provides a synthetic list of his/her responsibilities.

THE SPECIFICITIES OF HEAD AND NECK CANCER AND STATISTICAL CONSIDERATIONS

Heterogeneity of the Disease

Head and neck cancers are a group of diseases characterized by phenotypic, etiological, biological and clinical heterogeneity. Squamous cell carcinoma is the predominant histology type (15). The complexity of the upper respiratory and gastro-intestinal apparatus creates a number of anatomical subdomains that are apprehended together. Still the prognosis is specific to each localization, correlated to a distinct TNM classification (16). Historically, the most common risk factors are tobacco and alcohol consumption, responsible for up to 75% of head and neck squamous cell carcinoma (HNSCC) (17). The etiologic association of human papillomavirus (HPV) with a distinct subset of HNSCC that occur mostly in oropharynx is increasing, affecting non-smokers in developed countries. HPV positive oropharyngeal tumors have better survival, particularly

for locoregionally advanced disease (18). The comprehensive genomic analysis performed by The Cancer Genome Atlas (19) revealed the genomic heterogeneity of this disease with clear differences between HPV negative and positive tumors. This, in the era of personalized medicine, could lead to different treatments depending on the plausible therapeutic targets.

Selection of Patient Population

A clinical research question is intrinsically defined in terms of a specific population. Eligibility criteria, assumptions about the prognosis of patients and the magnitude of the treatment effect in the intended population, stratification of patients within the clinical trial are all fundamental questions when planning a clinical trial (20). These decisive elements of the design can be obtained from expert opinion and a careful review of the medical literature.

Past and currently ongoing clinical studies define their target population based on the anatomical location of the disease, the classical TNM classification and more recently on the distinction between HPV positive and negative nature of the disease. In addition, a search of medical literature reveals an abundance of articles reporting the assessment of prognostic factors in head and neck cancer and the classification of patients according to different risk levels of progression, recurrence, or death. These analyses are useful to circumscribe the population of interest for our research question and when searching Medline for head and neck risk classification (see **Supplementary Material** for the exact Search query used), one retrieves 404 papers published in the past 10 years, 59 of them in 2018. But are all these analyses conducted adequately from a methodological point of view? Are the conclusions useful from a clinical point of view (21)? How can we separate the wheat from the chaff? The statistician will do his/her best to review these articles with a critical eye to evaluate the methodology used, and to assess how applicable and generalizable these results are. More specifically the statistician scrutinizes multiple aspects of the work, including but not limited to: characteristics of patients included in the modeling; selection and definition of the outcome of interest (locoregional failure, risk of distant metastasis, or survival); treatment received by the patients included in the analysis; set of candidate prognostic factors; data analysis method (statistical model such as Cox model or machine learning tools such as neural networks or random survival forests); model performance measures; internal and external validation procedures (22).

An example of the complexity to define the targeted patient population can be illustrated by the European Organization for Research and Treatment of Cancer (EORTC) trial 22931 (23) and the Radiation Therapy Oncology Group (RTOG) trial 9501 (24). Both trials evaluated post-operative chemoradiation vs. radiation alone in patients at high-risk of recurrence after surgery. The definition of high-risk and therefore the inclusion criteria, although sharing some common criteria, differed between the two studies. While the eligibility criteria common to both trials were the presence of extracapsular extension and/or microscopic-sized tumor involvement of the surgical margins of resection, some differed. The EORTC study included in its selection of risk factors stage III/IV disease, the presence of enlarged lymph node(s) at level IV or V in patients with oral cavity or oropharynx carcinomas, pathological demonstration of vascular embolisms, and/or perineural disease. The RTOG study included in its selection of risk factors the presence of tumor in two or more lymph nodes, as was suggested by the analysis of the RTOG database. In 2004, the publication of the two studies established, with level I evidence, that concurrent chemoradiation was more efficacious than radiation alone as adjuvant postoperative treatment, in terms of local-regional control and disease-free survival. Because of the difference in the definition of "high risk" features between the two trials, additional analyses were conducted to identify precisely which patients were more suitable for such intense treatment (25). The findings suggested that microscopically involved resection margins and extracapsular spread of tumor from neck nodes were significant prognostic factors for poor outcome. Despite the limitations inherent to a retrospective subgroup analyses, their results are now the basis for the selection of patients in clinical trials in the postoperative setting (e.g., EORTC study 1735: NCT03673735).

Another example of clinical trials based on a risk classification is given by an ongoing Canadian Cancer Trials Group study (NCT03410615), testing the effect of immunotherapy in intermediate-risk, HPV-positive, locoregionally advanced, oropharyngeal squamous cell cancer. Here the definition of intermediate-risk is based on data showing that HPV-related oropharyngeal cancer patients with limited neck disease (N0-N1) have a favorable prognosis, even without chemotherapy (26, 27).

Favorable Prognosis and Non-inferiority Designs

The majority of studies test novel treatments or combination of treatments in order to improve disease outcome and survival in patients with unfavorable prognosis, with intermediate or high risk of progression, recurrence or death. Some trials are also designed and conducted in patients with a favorable prognosis, in order to assess whether treatments reduce acute and late toxicity while preserving a similar disease outcome and survival.

Since the identification of HPV positive patients as a separate disease entity with a more favorable prognosis, a number of studies have been developed to de-intensify treatment in these patients. This is the case of RTOG 1016 study (NCT01302834) (28) and De-Escalate study (NCT01874171) (29). Both studies attempt to replace cisplatin by the epidermal growth factor receptor (EGFR) inhibitor cetuximab in patients with HPV positive oropharyngeal cancer. The objective of these studies is to maintain a similar patient survival while reducing toxicity, and as such they require a different type of design. RTOG 1016 was designed as a classical non-inferiority trial with overall survival as primary endpoint. One point of consideration for non-inferiority studies is the value of the non-inferiority margin that is considered as an acceptable loss, in disease outcome or survival in view of the gain in toxicity. It has to be put in perspective with the prognosis of patients since a loss of 10% does not mean the same when survival rate with the standard of care is at the level of 70 or 90%. This non-inferiority margin needs to be small enough to be considered as non-clinically relevant and certainly substantially lower than differences targeted in superiority trials (30). Defining the non-inferiority margin is an

essential part of a non-inferiority design just as the difference is essential to the design of a superiority or difference trial. Both have to be pre-defined based on clinical and statistical considerations and both have a strong impact on the sample size, the trial duration and its cost. The primary endpoint of RTOG 1016 was overall survival and the study was designed to reject the null hypothesis of inferiority, with a non-inferiority margin of 9%, meaning that a decrease of 9% in 5 years overall survival was considered, by the RTOG 1016 team, acceptable. By contrast, the primary endpoint of De-Escalate study was overall severe (grade 3–5) toxicity events at 24 months from the end of treatment and the study was powered to detect a reduction in the rate of severe toxicities in cetuximab arm compared to cisplatin arm. Equivalent disease control and survival between treatment arms were hypothesized but the study was not formally powered to show non-inferiority. Interestingly, overall survival and time to recurrence were planned to be compared between the two arms using the log-rank test, which is a test aiming at detecting differences, not aiming at showing non-inferiority or equivalence; now, failing to detect a difference does not mean there is no difference as "absence of evidence is not evidence of absence."

Designs for Studies in Rare Cancers and Accrual Issues in Randomized Trials

With a heterogeneous disease, distinct subtypes, in terms of tumor localization and biological characteristics, need to be investigated separately in small groups of patients. In case of a rare population, a classical design may just not be feasible and we need to reflect on the level of evidence we still wish to reach (31). One possible solution is to allow more uncertainty, that is to allow a Type I error higher than the traditional 5% two-sided that is required to reach scientific evidence for a superiority trial and/or to allow a Type II higher than the classical 10 or 20% which is equivalent to say that the study is only powered to detect large differences. In these cases, we need to be careful with the consequences of relaxing the errors/power, given that it is unlikely that another trial will be conducted to confirm the results. EORTC study 1206 (NCT01969578) aims to assess the superiority of androgen deprivation therapy (ADT) over standard chemotherapy (CT) in patients with recurrent/metastatic salivary gland cancer. It has been designed with a one-sided Type I error of 10% and with a power of 80% to detect an ambitious difference between ADT and CT in progression-free survival with a hazard ratio HR = 0.56. Because our predictions indicate that the study will likely fail to recruit the total planned number of patients in a reasonable timeframe, the design has been revised recently. An analysis of the primary endpoint from a non-inferiority perspective has been added, by pre-specifying a non-inferiority margin, in case the study fails to meet the criteria of superiority. This non-inferiority test has adequate statistical power under the hypothesis of the superiority of ADT over CT. If the objective of non-inferiority is met, this is considered valuable from a clinical point of view given the favorable safety profile of ADT compared to CT, except for sexual dysfunction, and the dismal prognosis of these patients.

EORTC study 1206 is one of the studies developed within the International Rare Cancers Initiative (IRCI) (32), a strategic collaboration between several academic organizations, including EORTC. IRCI's aim is to stimulate and facilitate the development of international clinical trials for patients with rare cancers. Some of the studies from the IRCI portfolio, focusing on rare cancers, are designed using Bayesian methodology. With this methodology, the conclusion of the study is based on the combination of the study data itself together with prior knowledge based on literature review, previous studies, meta-analyses or the elicitation of expert's opinion. Contrary to the classical (frequentist) approach, the focus of the Bayesian approach is on estimation rather than testing hypotheses, with data being used to reduce uncertainty about the size of the treatment effect. However, we remain unsure regarding the advantages of this methodology as in a small trial the choice of the prior may carry heavy weight thus influencing the final results. Moreover, in rare cancers only weak prior evidence might be available. In addition, in absence of prior information, Bayesian designs do not immediately add value over equivalent classical (frequentist) designs in terms of the statistical properties (type I error rate, type II error rate, power, sample size). However, this does not prevent that a trial designed in a frequentist setting is analyzed using Bayesian methods, and the results interpreted using the posterior distribution of the treatment effect which is obtained from the combination of prior knowledge with currently observed trial data. To our knowledge, only one prospective clinical trial in head and neck cancer is designed using a Bayesian methodology: this is two-stage phase II design of Magnetic Resonance-guided radiotherapy dose adaptation in patients with HPV positive oropharyngeal cancer. This study uses Bayesian decision rules applied to loco regional control and toxicity to make the go/no-go decision for each stage (33).

Beyond the specific case of a rare disease, accrual of patients in the clinical trial may be slower than initially expected as a result of strict eligibility criteria, over-optimism of participating institutions at the start of the study; lengthy approval of the study by competent authorities and ethic committees; patients reluctant to enter the study or to be assigned a treatment at random. Slow accrual leads to longer study duration and therefore delayed availability of the study results, possibly when the main research question posed by the study is no longer relevant given the evolution of clinical research in the field. In order to speed up accrual, some actions are envisaged such as broadening the eligibility criteria of the study; opening the study to additional treating institutions, countries, or other research organizations. In some other cases, the ultimate decision is to close the study definitely before having reached the targeted sample size. It is then necessary to evaluate to which extent the available data can be used to assess the objectives of the trial. Sometimes the available study data allows to conduct the initially planned analyses with a decreased but still acceptable statistical power, say 70% instead of the initially stated 80%. When data are scarcer, only a mere descriptive analysis of the study data is feasible. In other cases, it is possible to rescue the study through a substantial revision of the statistical analysis plan. To ensure the

validity of such a revision, it should be done before any of the data is revealed.

Treatment Allocation

These considerations about the heterogeneity of the disease are at the basis of the selection of the study population but also of the stratification of patients within the randomized clinical trial. This stratification is to be taken into account not only in the process of randomization, in order to produce comparable treatment arms in terms of factors that affect the course of the disease, but also at the data analysis levels. Due to the association between these factors and the outcome variable, adjustment for such factors generally improves the efficiency of the analysis.

Randomization tends to produce treatment arms in which the distributions of prognostic factors, known and unknown, are similar (3). Achieving a balanced allocation overall and for important prognostic factors allows to attribute differences in outcomes to differences in efficacy of the treatments under study; this is the concept of causality. In randomized studies, the most relevant factors for stratification need to be identified, bearing in mind that too many stratification factors are detrimental to a balanced allocation. The number of stratification factors and which ones to select is discussed between the research physician and the medical statistician until a compromise is found. It is particularly important to consider institution as a stratification factor in order to account for the differences across treating sites in terms of patient selection, treatment and care, assessments, and data reporting. In EORTC study 1420 "Best-of" (NCT02984410), a randomized phase III study the main objective is to assess the patient-reported swallowing function over the first year after treatment start with either Intensity-Modulated Radiation Therapy (IMRT) or Trans Oral Surgery (TOS) among patients with early stage oropharyngeal, supraglottic, or hypopharyngeal carcinoma. In this study, the eight disease localizations were classified into two strata, lateral vs. central lesions, thought to be an appropriate classification taking into account that the primary endpoint was the swallowing function. Two other clinical stratification factors were considered, N stage and the swallowing function score at baseline. Because of the relative small size of the study, 170 patients potentially accrued in more than 30 treating institutions from 8 countries, stratifying by treating institution would have resulted in too many small strata and in this study the decision was made to group them by country.

For each study, the statistician evaluates which treatment allocation method is most appropriate. The two most common methods are the static permuted blocks method and the dynamic minimization algorithm (34). While the minimization method is often discouraged by Regulatory Authorities due to theoretical concerns, a cancer-specific review published in 2010 (35), indicated that it becomes more common over time and is used more frequently when an academic cooperative group is involved. For both methods, it is recommended to perform computer simulations to assess the performance of the chosen method and the stratification design, in terms of the balance of the stratification factors over the treatment arms.

Subgroup Analyses

It is tempting to conduct multiple subgroup analyses in large studies of patients with heterogeneous characteristics. However, as indicated in ICH E9 and often reiterated in medical and statistical literature, such analyses carry the risks of generating false positive findings due to statistical testing in multiple subgroups. It also runs the risks of false negative findings due to the small size of the subgroups. The appropriateness of the use and interpretation of subgroup analyses on the basis of the CONSORT statement requirements (4) was investigated in 188 phase III randomized controlled trials in solid tumors, published between 2011 and 2013 (36). When focusing on the 102 articles claiming a subgroup difference, for 24% of them it was unclear whether the subgroup analyses were prespecified or *post-hoc*, and subgroup analyses of 36% of these trials were *post-hoc* only. Eighty-four percentage of these trials reported more than five subgroup analyses but only 6% cautioned about multiplicity. This review shows that despite recommendations from the CONSORT statement published more than a decade ago, the reporting of subgroup analyses is generally not adequate to provide valuable information in guiding clinical decisions.

It is worth emphasizing that comparing outcomes in patients subgroups defined by some other outcomes or variables measured after treatment start, such as dose intensity, compliance to treatment or adverse events require non-standard analysis methods, as these variables are themselves affected by treatment (37, 38). In particular, standard analysis methods of comparing survival between responders with non-responders are wrong and lead to biased estimates and misleading conclusions. This bias results from the fact that responders must live long enough for a response to be observed and that patients who die early without observing a response are automatically classified as non-responders. A better approach, proposed by Anderson et al. (37), is the landmark method, where each patient's response is determined at some fixed time point after treatment start and the survival estimates are calculated from that time point. This method has for example been applied in the analysis of a study of induction treatment followed by chemoradiation in advanced stage in head and neck cancer. An 8 weeks landmark analysis was carried out to compare survival between patients with positive vs. negative biopsy of the primary site done after induction. A 4 months landmark analysis was also performed to evaluate the effect of maintenance therapy on survival. Survival was computed from the landmark (39). Similarly an analysis of the predictive value of cetuximab-induced skin toxicity in recurrent or metastatic head and neck cancer was conducted using the landmark method applied to PFS and OS counted from 90 days after the start of therapy (40).

When dealing with subgroup of patients, and especially in the era of personalized medicine, the question whether some patient characteristics or some biomarkers are predictive of treatment benefit is of interest. To determine whether a biomarker is potentially predictive, a formal and adequately powered statistical test of the treatment-by-biomarker interaction needs to be performed (41). For more detailed considerations on the statistical methodology required to establish predictive

biomarkers, readers are referred elsewhere (42). To date, in the field of head and neck cancer, no biological marker has been proven to be predictive (43).

Complexity of the Treatments—Multimodality

Treatment for head and neck cancer is complex and is based on different levels of evidence as stated in the National Comprehensive Cancer Network guidelines (44). Treatment options depend on the stage of the disease: early, locally advanced or recurrent/metastatic. Surgery, radiotherapy, chemotherapy and targeted therapy are all front line options, alone or in combination, depending on the tumor characteristics and stage of the disease. New categories of treatment have been evaluated in head and neck cancer, check point inhibitors have been approved in the metastatic settings with improved survival in first [pembrolizumab (45)] and second line [nivolumab (46)]. With new treatments available, new combinations are being tested. Still multimodality remains key.

Selection of Activity/Efficacy Endpoints of Interest

The therapeutic effect of a new treatment or combination of treatments is assessed by means of endpoints selected according to the study objectives.

In early phase studies, the main endpoint is usually selected to capture the effect of the treatment on the tumor, that is whether the treatment is expected to induce a complete disappearance of the tumor, shrinkage of the tumor or a stabilization of the disease. Complete response (CR) or response (complete response CR or partial response PR), has long been selected as primary endpoint of early phase studies. However, other endpoints may be preferred, such as disease control (complete response CR or partial response PR or stable disease SD) to evaluate treatments with a mechanism of action different from chemotherapy, such as targeted or immunotherapy, or where the response to treatment is difficult to assess. Progression free survival (PFS) rate or another time to event endpoint (TTE) evaluated at a fixed point in time after randomization or start of treatment may also be used so the timing of the final analysis is fixed and not dependent on a pre-specified number of events to be observed. When designing a study to evaluate treatments that induce disease stabilization rather than disease reduction, it is recommended that the study includes an internal control arm to make sure the effect of treatment is not confounded with the natural course of the disease. This is especially important if historical information on the control treatment is lacking or limited due to differences in patient population (e.g., biomarker selected population), in staging system, in imaging / diagnostic tools for assessing outcome, etc. The EORTC study 1559 [NCT03088059 (47)] is an umbrella trial (48) with a platform for enrollment, screening and central profiling of patients who are subsequently allocated to one of the molecularly defined sub studies and treated with a matched experimental treatment. Different designs are used across the study, reflecting differences in study objectives and in the mechanism of action of the investigated treatment among the sub studies: in particular, a single arm design with response as primary endpoint is chosen for some sub studies, while others are designed as a randomized two-arm trial, with physician choice as control treatment and with progression-free survival assessed 4 months after randomization as primary endpoint.

Some early phase studies are designed with the objective to assess the feasibility of the treatment, in which case the main endpoints may be defined as the proportion of patients completing therapy, the rate of patients without severe toxicity, the rate of patients compliant with protocol treatment or similar endpoints. This is the case of the EORTC study 24061 (49), a randomized phase II feasibility study of cetuximab combined with 4 cycles of Docetaxel, cisplatin, and fluorouracil (TPF)followed by chemoradiation with platinum. The main objective of this study was to select the platinum compound, cisplatin or carboplatin, for the chemoradiation regimen to be evaluated in a future Phase III study. Unfortunately, the study was closed prematurely for safety reasons.

In phase III studies, overall survival (OS) remains the gold standard for the demonstration of clinical benefit, as it is an objective and accurate measure, its importance is unquestioned and it addresses both safety and efficacy. Because overall survival analysis requires a large sample size and may require long follow-up, the investigators may power the study for an alternative endpoint. Doing so, it reduces study timeframe, and improves study feasibility while still capturing a clinical benefit relevant for the patient. Alternative endpoint may be time to local or loco-regional recurrence/progression for early stage disease or to evaluate a local therapy (e.g., EORTC study 1219, NCT01880359); disease free survival in the adjuvant setting [e.g., EORTC study 1735, NCT03673735 or LUX-Head & Neck 2 (50)]; or progression-free survival in the advanced setting [e.g., LUX-Head & Neck 1 (51)]. In 2009, Michiels et al. (52) showed that progression-free survival, defined as the time from randomization to locoregional relapse, distant recurrence, or death whichever comes first, can be used as a surrogate endpoint for overall survival to assess the treatment effect of radiotherapy and chemotherapy in randomized trials of locally advanced HNSCC. The surrogacy has been established based on [1] the individual-level correlation between Event Free Survival (EFS) and OS, and [2] the correlation between treatment effects on EFS and OS following the methodology developed by Buyse et al. (53). However, we need to remember that, as pointed out by Michiels et al., EFS is a surrogate endpoint for OS only for chemotherapy or radiotherapy, but cannot be assumed for immunotherapy and for targeted agents, which have a different mode of action. We will come back later on this matter.

Definition of Endpoints

It is not enough to select the endpoint of interest but we also need to state how exactly it is defined and how it is assessed.

International standards are available for measuring response in clinical trials, the most common being the Response Evaluation Criteria in Solid Tumors (RECIST) (http://www.eortc.org/investigators-area/recist). Because of the loss of information inherent to categorizing a continuous measure of tumor shrinkage into categories (progression, stable, response), more and more often waterfall plots are used to display graphically the individual numerical change in tumor size for all patients.

Time to event endpoints need to be defined very clearly and it is very useful that their exact definition is accurately provided in the scientific publications, as there is considerable heterogeneity in the literature regarding these definitions (54). The methodology section should describe which events are of interest for the selected endpoint, which events constitute competing risks, which events are censored and which events are ignored. In a complex disease such as head and neck cancer with multimodal treatments, for each time-to-event endpoint other than overall survival, and depending on the setting, the following events need to be considered: residual disease after curative treatment, local, regional or distant progression, second primary cancer, death due reasons other than progression. To date there is no consensus on how these and other events such as elective neck dissection and salvage surgery (with residual disease detected or not, depending on the timing of these procedures) are taken into account in the definition of endpoints. It is the purpose of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project (55) to reach, by consensus among experts, a standardization of the definitions of commonly used time-to-event endpoints in cancer clinical trials. In addition, events such as treatment stop or switch before the event of interest being reported are not handled the same way by all methodologists, as some recommend ignoring the treatment switch while others recommend censoring these cases (56). The latter approach is highly problematic since it ignores the issue of informative censoring and is not recommended by the EMA (57) while it is proposed in FDA guidelines (58, 59).

In EORTC study 1219 (NCT01880359), a blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic cell radiosensitizer nimorazole, the primary efficacy endpoint is time to locoregional recurrence. This is counted from the day of randomization to the day of first record of appearance of local or regional progression, assessed via clinical, imaging or pathological exam. Distant recurrence/progression and second cancers diagnosed before locoregional recurrence and death in absence of locoregional recurrence are not considered events of interest. But these events are considered as competing risk events in the analysis of the primary endpoint, because they may alter or even preclude the onset of locoregional progression. Therefore, during the design phase, the statistician together with the research physician needs to make assumptions, not only regarding the risk of locoregional progressions but also the risk of distant recurrence/progression, second cancers and death in absence of locoregional recurrence. It is also recommended to monitor these assumptions regularly as they have the potential to directly impact the sample size of the trial, the timelines for the analyses and possibly the statistical power. When a marked departure from the original statistical design assumptions, such as the ones described above, is observed, the consequences need to be evaluated as well as the need for a modification of the study design. In order to maintain trial integrity, an Independent Data Monitoring Committee (IDMC) is consulted and the study design is revised, based on the IDMC recommendations, by a statistician not directly involved in the conduct of the study.

Schedule of disease assessments plays a critical role in the evaluation of endpoints. The assessments should ideally match standard practice but for the purpose of the clinical trial they should be planned adequately to capture the effect of treatment. In a multi-arm study, there should also be symmetry between treatment arms in order not to introduce a bias in the comparison of the treatments. With time-to-event endpoint other than overall survival, such as progression-free survival, the exact time of progression is unknown and progressions that occur in between visits are commonly assigned to the visit at which progression was detected. This leads to an over-estimation of the time to progression and a loss of statistical power (56). The analysis may become problematic and biases may arise when clinic visits are missed or delayed. In some cases, it is a challenge to reach a common schedule of assessment across arms because of the intrinsic difference between treatments: surgery vs. radiotherapy as in EORTC study 1420 "Best-of" (NCT02984410), chemotherapy vs. targeted agent as in EORTC study 1206, induction chemotherapy vs. no induction. When the schedules cannot be made symmetrical across arms, the time assessment biases inherent to the trial may be taken into account by the statistical analysis, by assigning the progressions or recurrences to a specific point in time (e.g., the next planned visit). This technique was used in a study comparing three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer (60). Patients were randomized between induction cisplatin/fluorouracil followed by radiotherapy, concomitant cisplatin and radiotherapy, or radiotherapy alone. The primary endpoint was a composite endpoint of laryngectomy-free survival. In this study, to account for differences between treatment arms in the timing of protocol-specified disease assessments, patients with recurrence or censored before 6 months after random assignment were counted as having treatment failure or censored at 6 months, for efficacy endpoints other than overall survival.

Definition of Analysis Populations

If all subjects enrolled into a clinical trial satisfied all entry criteria, completed treatment, followed all trial procedures perfectly with no losses to follow-up, and provided complete data records, then the set of subjects to be included in the analysis would be self-evident. But, in practice, it is doubtful if it can ever be fully achieved specially in the setting of a life-threatening disease, when dealing with complex treatments, administered concomitantly or sequentially.

The intention-to-treat principle requires that the primary analysis should include all enrolled subjects. In many clinical trials, this principle provides a conservative strategy and estimates of treatment effects that are more likely to mirror those observed in subsequent practice (3). However, in specific cases, such as early phase trials, the primary analysis is conducted in the per-protocol population, that is, in the subset of patients who are more compliant with the protocol in order to maximize the opportunity for a new treatment to show activity. For trials with a non-inferiority objective, it is recommended to conduct the main analysis on the per-protocol population in addition to the intention-to-treat population as the latter one may be biased

toward demonstrating non-inferiority. It is to be noted that the per protocol analysis may lead to biased results when adherence to the study protocol is related to treatment and outcome.

A textbook example of such bias is given by study TTCC 2002 (grupo español de Tratamiento de Tumores de Cabeza y Cuello), a randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy vs. chemoradiotherapy alone as treatment of unresectable head and neck cancer (61). The intention-to-treat analysis including all randomized patients showed no advantage of induction chemotherapy followed by chemoradiotherapy over chemoradiotherapy alone; while the analysis excluding patients from the induction arm who did not reach the chemoradiotherapy part of the study resulted in a benefit in favor of the induction arm. The latter analysis, which was the one first published (62), was obviously biased because of the selection of the "best" patients from the induction arm.

Immunotherapy: Impact on Trial Endpoints

With the advent of immunotherapies, because of the different mechanism of action, how efficacy/activity endpoints are defined and evaluated poses a number of new methodological challenges (63).

Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents were first developed and published in 2009 by Wolchok et al (immune-related response criteria:irRC) (64), as an attempt to capture new response patterns observed with immune therapy in advanced melanoma beyond those described by RECIST. These criteria, based on bidimensional measurements, were adapted in 2013 by Nishino et al. (65) to only consider unidimensional measurements. In 2017, a consensus guideline for modified RECIST for immune-based therapeutics (termed iRECIST) was published by a multidisciplinary group including academic, commercial and regulatory members for the use of modified RECIST (V1.1) in cancer immunotherapy trials (66). The guideline takes into account distinctive behaviors linked to these types of drugs, such as delayed responses and pseudoprogressions. This guideline is consensus based but is not yet validated. It defines the minimum data to be collected for future and currently in development trials, in order to facilitate the compilation of a data warehouse needed to validate iRECIST. In the meantime, it is recommended that RECIST 1.1 continues to be used as the primary criteria for response based endpoints for randomized studies planned for licensing applications. iRECIST should be considered exploratory in such trials, although earlier phase trials may consider using primarily iRECIST.

Another issue is the delayed treatment effect leading to a separation of PFS or OS curves between treatment arms only after a lag time of several months. This phenomenon has been observed, particularly in melanoma studies (67, 68). This pattern has also been observed for OS in the phase 3 trial comparing nivolumab to standard systemic therapy in patients with recurrent HNSCC (46). Such a late separation is indicative of non-proportional hazards. This pattern may invalidate the use of classical statistical analysis methods to estimate and test treatment effects such as the Cox model, which is based on the assumption of proportional hazards. Such analyses become difficult to interpret since the treatment effect, expressed by the hazard ratio, evolves over time. Alternative analysis methods should therefore be considered and are currently being proposed (63). Models assuming a different hazard ratio for different follow-up times are one possible option. An alternative measure to quantify the treatment effect can be Restricted Mean Survival Time (RMST), which represents the area between the two survival curves up to a predefined follow-up time (69). Simulations are required to evaluate the impact of non-standard patterns on the statistical power using classical or alternative methods of analysis. A delayed treatment effect has also implications on the design of interim analyses for efficacy or futility (63). An interim look for efficacy performed too soon will unlikely result in stopping earlier for a positive outcome, while a futility interim look for futility planned too soon will likely increase the chance of erroneously terminate early the development of an active agent. Altogether this shows how critical is the assumption of proportionality of hazards for the design and analysis of clinical trials with immunotherapy agents.

Although overall survival remains the gold standard endpoint to evaluate the efficacy of treatments in oncology, a number of studies select progression/recurrence free survival as primary endpoint mainly in order to reduce the size and the duration of the studies. As indicated above, it cannot be extrapolated from the work of Michiels et al. that progression-free survival is a surrogate endpoint for overall survival to assess the treatment effect of immunotherapy agents. In addition, as the criteria for progression would be adapted following iRECIST, the issue of surrogacy might be impacted. Surrogate endpoints for immunotherapy trials are currently under investigation (70–72).

Comorbidities

Comorbidity is frequent in HNSCC patients (73, 74). The main risk factors associated to this cancer are tobacco and alcohol use, so the comorbid illnesses in these patients are largely related to these habits. The most prevalent comorbidities in this population will be cardiovascular, respiratory or neurological affections. Due to their high prevalence of comorbidities head and neck cancer patients are less often included in early phase trials because of their higher risk of complications. Clinical trials severely select patients and requirenormal organ function, whether of the heart, lungs, kidneys, liver or bone marrow at baseline. It is important to bear this in mind when generalizing trials results to the clinical practice population.

Impact on Primary Endpoints

Studies evaluating the impact of comorbidities in head and neck cancer patients show that it is an important feature of these patients, which has a detrimental impact on overall survival. Patients with head and neck cancer are concurrently at risk for other events, including second malignancies and mortality due to adverse treatment effects or comorbid diseases (75). Overall survival and progression/recurrence-free survival are composite endpoints, constituted of events of different nature, directly linked to the primary cancer (disease progression/recurrence or death due to the disease) or not (second malignancies, deaths due to treatment toxicity or comorbidities). Analyzed as composite endpoints, they are not sufficient for a complete

interpretation of the results of the trial. It is then useful to analyze the components as individual time-to-event endpoint, via cumulative incidence functions, in order to distinguish and characterize the weight of the different components on the observed outcomes.

Impact on Adherence to Treatment

Comorbidities have an influence on adherence to planned treatment (treatment missed or delayed), to protocol procedures (e.g., visits missed or delayed) and may induce loss to follow-up. The increasing complexity of treatment strategies and of trial designs with complex protocols which entail multiple procedures, adds an additional layer of difficulty for patients to adhere to treatment and protocol procedures. Oral medications and self-administered subcutaneous therapies offer the patient convenience over intravenous infusions but the responsibility of administration of these critical medications has been transferred to the patient, potentially increasing the risk of non-adherence.

A retrospective analysis of comorbidities and adherence to treatment in patients with oropharyngeal carcinoma has been reported by Hess (76), suggesting a poorer adherence to treatment in patients with HPV-negative status as compared HPV-positive, as a result of the higher comorbidities in the former patient group due to alcohol and tobacco consumption. These results add to the recognition that HPV-positive and HPV-negative oropharyngeal cancer represent distinct entities and the authors recommend to take this additional difference into account in the design of clinical trials addressing these populations.

Poor compliance does affect the analysis and interpretation of clinical trial data and represents a potential source of bias in a clinical trial. The data related to treatment exposure, the frequency and reasons for treatment interruptions or definitive withdrawals, the frequency and nature of severe protocol violations, the frequency of patients lost to follow up need to be analyzed as well as their relationship to outcome in order to identify these potential biases. Sensitivity analyses conducted in different analyses populations, i.e., intention-to-treat vs. per-protocol population, may be useful to assess the robustness of the findings.

Impact on Quality of Life and Assessment of Quality of Life in Clinical Trials

The symptoms and treatments associated with advanced head and neck cancer often have a devastating impact on quality of life. Head and neck cancer can disrupt many life essential functions. It can impact on breathing, swallowing, and speaking, and treatment can even increase the physical impairment. These consequences affect multiple spheres of daily functioning. As one consequence head and neck cancer patients have a higher risk of depression and suicide.

Quality of Life is thus an important outcome to be considered in routine treatment but also to evaluate new treatments in clinical trials, even in early stage disease. The EORTC has developed and validated tools for the assessment of quality of life in cancer patients, using high standards of methodology. These questionnaires are meant to be used primarily in clinical trials. Specifically for head and neck cancer, patients are asked to complete a list of 60 head and neck cancer-specific items comprising the recently updated EORTC head and neck module (EORTC QLQ-HN43) as well as the core questionnaire (EORTC QLQ-C30) (77, 78).

For some studies, a quality of life score has been selected as the primary endpoint. This is the case of the EORTC study 1420 "Best-of" (NCT02984410). Because the techniques that have been developed in parallel in the radiotherapy and surgical fields both have an excellent oncological control, the main focus of this prospective randomized trial is to assess which one of the two modalities provides better functional outcome and more specifically better swallowing function. This is assessed using the M. D. Anderson dysphagia inventory (MDADI), a validated and reliable self-administered questionnaire designed specifically for evaluating the impact of dysphagia on the quality of life of patients with head and neck cancer (79).

There is to date no consensus on how quality of life data in cancer clinical trials are analyzed. A variety of statistical techniques are available to handle the longitudinal nature of the data, to adjust for multiple scales and items, to deal with missing data (80). Currently the methods range from simple descriptive analyses up to complex modeling approaches. The consortium SISAQOL (Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials) has been created with the aim to develop guidelines and recommendations for the statistical analyses of quality of life data and more generally of patient-reported outcome data in cancer clinical trials (81, 82).

CONCLUSION

The medical statistician is responsible for a wide variety of tasks covering the design and the analysis of a clinical study, which requires specific competencies in terms of statistical methodology and programming skills. It is particularly important to use efficient communication, in order that the medical statistician gets some understanding of the medical field and that the research physician gets fairly acquainted with the principles of statistical methodology. Only a fluid interaction between the two fields enables that the study design addresses adequately the research question that is at the basis of the clinical trial and that the results of the analysis are interpreted appropriately.

In particular head and neck cancer is a complex field: a heterogeneous disease, with multimodality treatment and associated comorbidities. We have set out how these specificities raise a number of methodological challenges with some examples of approaches that current and future clinical researchers and medical statisticians may altogether consider useful in order to generate valuable information to guide clinical decisions and ultimately make progress in the treatment of this disease.

AUTHOR'S NOTE

There is abundant literature in the field of head and neck cancer as well as abundant literature in statistical methodology. The present article makes the bridge between the two fields hopefully encouraging and enabling fluid communication between the research physician and the medical statistician involved in clinical trials in head and neck cancer. The methodological challenges resulting from the heterogeneity of the head and neck cancer, the complexity of the treatments and the associated comorbidities are presented with examples. A formal literature search for this review was not performed. This review is based on the authors' work and expertise in designing, monitoring and analysing clinical trials as well as reading and reviewing clinical and statistical literature. The final purpose of this article is twofold: to help statisticians new to the field of head and neck cancer confronted with the design, implementation and analysis of clinical trials in oncology; but also to sensitize research physicians with the role, the tasks and the challenges faced by the medical statisticians.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Best Practice in Systemic Therapy for Head and Neck Squamous Cell Carcinoma

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Treating head and neck cancer patients with systemic therapy is challenging because of tumor related, patient related and treatment related factors. In this review, we aim to summarize the current standard of care in the curative and palliative setting, and to describe best practice with regard to structural requirements, procedures, and monitoring outcome. Treatment advice for individual head and neck cancer patients is best discussed within a multidisciplinary team. Cisplatin is the drug of choice for concomitant chemoradiotherapy in the primary and postoperative setting, and also a main component of induction chemotherapy. However, acute and late toxicity is often significant. Checkpoint inhibitors have recently been proven to be active in the metastatic setting which has resulted in a shift of paradigm. Detailed knowledge, institution of preventive measures, early recognition, and prompt treatment of adverse events during systemic therapy is of paramount importance. Documentation of patient characteristics, tumor characteristics, treatment details, and clinical and patient reported outcome is essential for monitoring the quality of care. Participation in initiatives for accreditation and registries for benchmarking institutional results are powerful incentives for implementation of best practice procedures.

Keywords: best practice, systemic treatment, chemotherapy, immunotherapy, head and neck cancer, squamous cell carcinoma

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INTRODUCTION

Patients with locally advanced or recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) constitute a challenging population for systemic treatment because of tumor related, patient related and treatment related factors. The primary tumor can cause problems with eating, dysphagia and pain, resulting in significant weight loss already before diagnosis, while weight loss of more than 5% is an independent prognostic factor for worse progression free survival (1). Patients with advanced hypopharyngeal and laryngeal carcinomas can present with airway obstruction, or develop airway obstruction early during treatment and may require a tracheostomy. Patient related factors that can complicate systemic treatment are tobacco and alcohol addiction, co-morbidity and lack of a social network. In the curative setting, high-dose cisplatin concurrent with radiotherapy is the standard of care, either as primary treatment or after surgery. Chemoradiotherapy induces high rates of acute and late or long term adverse events. On the other hand, in the recurrent/metastatic setting, the field is rapidly evolving with the emergence of immune checkpoint inhibitors. Here, we summarize standard systemic treatment regimens, and describe best practice for administering systemic treatment with regards to structural requirements, procedures and monitoring outcome.

STANDARD SYSTEMIC TREATMENT REGIMENS

Locoregionally Advanced Disease

For patients with locoregionally advanced HNSCC with non-resectable tumors or in whom functional outcome of surgery is expected to be poor, primary concomitant chemoradiotherapy (CRT) with high-dose cisplatin (100 mg/m^2) delivered every 3 weeks × 3 is the preferred treatment regimen (2–6). In **Table 1**, treatment regimens based on at least one phase III study are summarized. In oropharyngeal cancer patients accelerated fractionation radiotherapy over 6 weeks with two cycles of high-dose cisplatin resulted in similar outcome as conventional fractionation radiotherapy over 7 weeks with three cycles of high-dose cisplatin (10). Alternative concomitant systemic therapy regimens that improve overall survival compared to radiotherapy alone are carboplatin with infusional 5-fluorouracil (5FU) (13) or cetuximab (14). Based upon a lower level of evidence weekly cisplatin (40 mg/m^2) (23–25), cisplatin with 5FU (26, 27), hydroxyurea with 5FU, cisplatin with paclitaxel (26, 27), or weekly carboplatin with paclitaxel can be considered (28). Benefit of concomitant chemotherapy decreases with age, and in a meta-analysis no benefit over locoregional treatment alone could be demonstrated for patients ≥70 years of age (29). Similarly, elderly

TABLE 1 | Standard systemic treatment regimens for HNSCC*.

Setting	Regimen (reference)	Dosing schedule	Remarks
Induction chemotherapy			Benefit over CRT is unclear
	TPF (7)	Docetaxel 75 mg/m^2 + cisplatin 100 mg/m^2 on day 1 followed by continuous infusion of 5FU 1,000 mg/m^2/day for 4 days every 3 weeks for three cycles	US regimen
	TPF (8, 9)	Docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 on day 1 followed by continuous infusion of 5FU 750 mg/m^2 for 5 days, every 3 weeks for three cycles	European regimen
Primary concomitant chemoradiotherapy/bioradiotherapy			
	Cisplatin (4, 6, 10–12)	Cisplatin 100 mg/m^2 on day 1, 22, and 43 during standard fractionated RT (or on day 1 and 22 during accelerated RT)	Preferred CRT regimen Accelerated RT plus 2 cycles cisplatin was not superior to standard fractionated RT plus three cycles cisplatin
	Carboplatin/5FU (13)	Carboplatin 70 mg/m^2 on day 1–4, continuous infusion of 5FU 600 mg/m^2/day on day 1–4 in week 1, 4, and 7 during RT	Has not been compared head to head with cisplatin
	Cetuximab (14)	Cetuximab 400 mg/m^2 1 week before start of RT and weekly 250 mg/m^2 during RT	Inferior to cisplatin (for HPV related oropharyngeal cancer)
Postoperative chemoradiotherapy			
	Cisplatin (15–18)	Cisplatin 100 mg/m^2 on day 1, 22, and 43 during RT Cisplatin 50 mg flat dose weekly	Inferior LRC with weekly 30 mg/m^2 cisplatin compared to 3-weekly 100 mg/m^2 Superior LRC, OS and DFS with weekly 50 mg cisplatin compared to radiotherapy alone but has not been compared to 3-weekly 100 mg/m^2
Recurrent/metastatic palliative setting, 1st line			
	Pembrolizumab (19)	Pembrolizumab 200 mg every 3 weeks	Approved by FDA but not (yet) by EMA Superior OS compared to EXTREME in patients with CPS ≥20 and in patients with CPS ≥1
	Platinum, 5FU and pembrolizumab (19)	Cisplatin 100 mg/m^2 or carboplatin AUC 5 on day 1, plus 5FU 1,000 mg/m^2/day on day 1–4, every 3 weeks for a maximum of six cycles plus pembrolizumab 200 mg every 3 weeks until progression	Approved by FDA but not (yet) by EMA Superior OS compared to EXTREME
	EXTREME (20)	Cisplatin 100 mg/m^2 or carboplatin AUC 5 on day 1, plus 5FU 1,000 mg/m^2/day on day 1–4, every 3 weeks for a maximum of six cycles plus cetuximab 400 mg/m^2 at first dose, then 250 mg/m^2 weekly until disease progression	
Recurrent/metastatic palliative setting, 2nd line			
	Nivolumab (21)	Nivolumab 3 mg/kg (can be replaced by 240 mg flat dose) every 2 weeks	After platinum containing chemotherapy
	Pembrolizumab (22)	Pembrolizumab 200 mg every 3 weeks	After platinum containing chemotherapy Europe: restricted to patients with PD-L1 TPS ≥ 50%

**Based on at least one randomized phase III study. 5FU, 5-fluorouracil; AUC, area under the curve in mg per milliliter per minute; CPS, combined positive score for PD-L1 expression on tumor and immune cells; CRT, chemoradiotherapy; DFS, disease free survival; EMA, European Medicines Agency; FDA, US Food and Drug Administration; LRC, locoregional control; OS, overall survival; PD-L1, programmed death receptor ligand 1; RT, radiotherapy; TPF, docetaxel (Taxotere?), cisplatin (platinum), and 5FU; TPS, tumor proportion score (percentage of tumor cells with membranous PD-L1 staining).*

patients do not benefit in the same way as younger patients from the addition of cetuximab to radiotherapy (14). This is paralleled by an increase in non-cancer related deaths in elderly patients. Proper selection of fit elderly patients with geriatric assessment might identify a subgroup that derives the same benefit as younger patients, but prospective data to support this is currently lacking. Treatment of elderly head and neck cancer patients has recently been extensively reviewed (30). Hypoxia modification with nimorazole during radiotherapy has been shown to improve locoregional control compared to radiotherapy alone (31) and is used in some countries as a standard of care. Patients with locoregionally advanced human papilloma virus (HPV) associated oropharyngeal cancer have significantly better outcome than patients with non-HPV related HNSCC, and treatment de-intensification strategies are under investigation. However, two randomized studies recently demonstrated that radiotherapy with cetuximab results in inferior overall survival compared to CRT with high-dose cisplatin, which therefore remains the standard of care (11, 12).

Patients who undergo primary surgical treatment and have involved resection margins and/or extranodal extension of lymph node metastasis are at high risk of developing recurrent disease. Outcome in these patients is improved by the addition of concomitant high-dose cisplatin to postoperative radiotherapy (15, 16, 32). Results of studies with high-dose and low-dose concurrent cisplatin were recently summarized (33). Of the two randomized trials that have been reported, one study was not evaluable for efficacy due poor accrual (34). The second study compared 6–7 weekly cycles of 30 mg/m^2 with three cycles of 100 mg/m^2 cisplatin every 3 weeks (17). Locoregional control at 2 years was inferior in the low-dose arm (58.5 vs. 73.1%) and progression free survival and overall survival were numerically inferior but statistical significance was not reached for survival endpoints. It remains unclear to what extend the lower cumulative dose of the weekly regimen is responsible for inferior efficacy. Results of a third randomized phase II/III study comparing three times 100 mg/m^2 with 7 weekly cycles of 40 mg/m^2 cisplatin in the postoperative setting are awaited (35).

Induction chemotherapy followed by either radiotherapy alone, or radiotherapy with cetuximab, or CRT with weekly carboplatin, can be used as an organ preservation strategy. However, its benefit over CRT alone is not clear at this stage with conflicting phase III studies and heterogenous patient populations on these trials and the role of induction chemotherapy is therefore debated (36, 37). If induction chemotherapy is chosen, docetaxel with cisplatin and 5FU (TPF) is the preferred combination (7–9). In the United States (US) three cycles of docetaxel 75 mg/m^2 plus cisplatin 100 mg/m^2 followed by continuous infusion of 1,000 mg/m^2 5FU for 4 days every 3 weeks is used (7), while in Europe four 3-weekly cycles of docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 followed by continuous infusion of 750 mg/m^2 5FU for 5 days is used (8).

Recurrent/Metastatic Disease

For patients with metastatic HNSCC, or recurrent disease that is not amenable to curative intent treatment, the EXTREME regimen consisting of cisplatin or carboplatin with 5FU and cetuximab followed by cetuximab maintenance has been the standard first-line treatment for the last decade (20). Based upon a lower level of evidence, other chemotherapy combinations or single-agent treatment options can be considered (2). In patients who progress after platinum containing chemotherapy, treatment with an anti-programmed death 1 (PD1) antibody improves overall survival and induces durable responses in a subgroup of patients with a lower rate of grade 3–4 adverse events compared to investigator's choice systemic therapy (21, 22, 38, 39). Nivolumab was shown to improve overall survival irrespective of HPV status or programmed death ligand 1 (PD-L1) expression with better preservation of quality of life compared to the control arm (38, 40). Pembrolizumab also improved overall survival, in the entire cohort and in the subgroups of patients with PD-L1 positive tumors (22). This led to approval of pembrolizumab for patients with a PD-L1 tumor proportion score (percentage of tumor cells with membranous PD-L1 staining) $\geq$50% in 2018 by the European Medicines Agency (EMA), while the FDA granted accelerated approval irrespective of PD-L1 expression back in 2016, based on the results of the phase 1b study (41). However, treatment paradigm for the recurrent/metastatic setting will likely change again soon, since the final analysis of the KEYNOTE 048 study in the first-line recurrent/metastatic setting indicated that compared with the EXTREME regimen, pembrolizumab plus platinum and 5FU followed by pembrolizumab maintenance had superior overall survival in the PD-L1 combined positive score (CPS) $\geq$20, CPS $\geq$1, and total populations with comparable safety (19). Pembrolizumab alone had superior overall survival in the CPS $\geq$20 and $\geq$1 populations, with non-inferior overall survival in the total population, and favorable safety compared to EXTREME (19) and is already mentioned in the NCCN clinical practice guideline (2).

STRUCTURAL REQUIREMENTS

The first requirement for effective delivery of systemic therapy to HNSCC patients is identification of patients in whom systemic treatment is indicated. The best way of doing this is discussing every newly diagnosed patient, every patient with recurrent disease and every patient who requires a change in treatment plan, during a multidisciplinary team (MDT) conference. An MDT approach is associated with improved tumor staging, better adherence to quality indicators, more concomitant CRT, shorter time between surgery and adjuvant therapy, higher completion rate of adjuvant treatment, and most important: improved disease specific and overall survival (42–46). According to the Dutch guidelines, a head and neck oncology center should at minimum have in the team three head and neck surgeons (at least one otolaryngeal surgeon and one oral and maxillofacial surgeon), two reconstructive surgeons, two head and neck radiation oncologists, and at least one head and neck medical oncologist, dermatologist, head and neck radiologist, pathologist, nuclear medicine physician, oncology nurse/case manager, dietician, physiotherapist, speech-language pathologist,

dentist-maxillofacial prosthodontist, psychologist, and social worker (47). This list closely resembles the core team defined in the Canadian guidelines (48, 49). The minimum recommended volume for medical oncologists who care for head and neck cancer patients is 25 per year, although scientific evidence to support this number is lacking (48–50). In the Netherlands, the minimum required volume for immunotherapy in a hospital is 20 patients per year, but this may include different cancer types.

With regards to the healthcare facility, the optimal situation is to have the pharmacy, the infusion facility, the radiation center, the inpatient ward, specialists for treatment of immunotherapy side effects, an intensive care unit, and a 24/7 emergency department in one center. This enables quick communication between health care professionals and prompt admission to address adverse events, which helps to keep treatment breaks to a minimum.

Specific information about treatment schedules, potential side effects, instructions on when to contact the oncology nurse or medical oncologist along with contact details, is of importance for patients. This can be digital or on paper.

BEST PRACTICE PROCEDURES

After discussing a patient within the MDT, it is recommended to file a report in the patient's records which accessible for every team member and contains tumor characteristics including TNM stage, patient characteristics such as co-morbidity, medical history, tobacco and alcohol consumption, treatment intent (curative or palliative), and treatment plan (50). If the treatment advice deviates from the guidelines, it is preferable to specify the reason for it.

A longer waiting time between histopathological diagnosis and start of primary treatment is independently associated with worse overall survival in patients with HNSCC (51). The median tumor volume doubling time was shown to be 99 days in a Danish cohort, but in the half with the fastest growing tumors this was 30 days (52). Therefore, starting treatment as quickly as possible will improve patient outcome.

If systemic therapy is recommended by the MDT, the patient is referred to the medical oncologist who will carefully evaluate if systemic treatment is feasible through assessing the performance status, co-morbidity, previous medical history, organ function, and current medication. For elderly patients, geriatric screening and/or comprehensive geriatric assessment is recommended (53). Vulnerability according to the G8 was found to be independently associated with worse overall survival and persistent lower quality of life in HNSCC patients who received curative intent (chemo)radiotherapy (54).

Chemotherapy

In general, Eastern Cooperative Oncology Group (ECOG) performance status worse than 2 (where 2 is defined as ambulatory and able of all self-care but unable to carry out any work activities; up and about for >50% of waking hours) is considered a contraindication for chemotherapy. Furthermore, blood cell counts, renal function, electrolytes and liver tests need to be adequate, and have to be assessed before each cycle.

Nutritional status is of particular importance in HNSCC patients. The tumor itself can cause problems with chewing, odynophagia, and dysphagia which can result in malnutrition. In addition, tooth extractions are performed in many patients before start of radiotherapy, further limiting the ability to eat normally. Also treatment side effects, especially of concomitant CRT, can cause swallowing problems. In the acute phase this is mainly related to mucositis, while dry mouth and sticky saliva are prominent long term side effects. In order to secure nutrition during CRT, prophylactic placement of a percutaneous endoscopic gastrostomy (PEG) tube can be considered. In a randomized study prophylactic PEG tube placement resulted in less malnourished patients, longer enteral feeding and better quality of life at 6 months after treatment without increased risk of long-term dysphagia compared with a control group treated according to clinical practice (55, 56). However, not all patients need enteral feeding, and selection of patients at high risk for malnutrition based on weight loss before start of treatment, age and radiotherapy dose to the constrictor muscles, can be used to select patients for prophylactic PEG tube placement (57). Nasogastric tube feeding appears to be an effective alternative to maintain body weight and the optimal method for enteral feeding of HNSCC patients has not yet been determined (58).

It is recommended to dose chemotherapy on actual body weight or, in the case of carboplatin, on actual stable creatinine clearance. In order to check and sign that the right drug is given to the right patient at the right dose at the right moment, the pharmacist and the nurses at the infusion facility need to be informed which treatment protocol applies, what is the treatment cycle number and day, the date, the height of the patient, actual weight, body surface area and/or creatinine clearance, and whether or not a dose reduction is applied. Including this information in the prescription, and filing prescriptions in the patient records facilitates personalized treatment modifications.

Nausea is a prominent side effect of chemotherapy and cisplatin belongs to the high-emetic-risk antineoplastic agents. A combination of four drugs consisting of a neurokinin 1 receptor antagonist, a serotonin receptor antagonist, dexamethasone, and olanzapine is recommended for cisplatin (59). Carboplatin belongs to the moderate-emetic-risk category requiring a three-drug antiemetic regimen, and docetaxel, 5FU and cetuximab have a low-emetic-risk, however combinations and multiday regimens should be treated per day for the drug with the highest emetic risk, and for 2 days after the last dose (59).

In addition to general chemotherapy side effects, cisplatin can cause renal toxicity, hearing loss, and neuropathy, and it can provoke cardiovascular events. Therefore, audiometric testing and an electrocardiogram is recommended before start of treatment, and thereafter if clinically indicated. Before every cycle, presence of neuropathy has to be assessed and creatinine clearance should be $\geq$60 ml/min. Adequate intravenous hydration from 2 to 12 h prior until at minimum 6 h after the administration of cisplatin is essential to protect renal function, and forced diuresis with mannitol or diuretics may be required (60). Allergic reactions to platinum compounds can occur. Therefore, it is important to have medication and a

protocol for treatment of allergic reactions readily available at the infusion facility.

5FU is degraded into inactive metabolites by the enzyme dihydropyrimidine dehydrogenase (DPD). Variations in the gene encoding DPD result in reduced enzyme activity, increased 5FU exposure and severe mucositis and hematologic toxicity. Prospective genotyping and upfront 5FU dose reduction in patients who carry a variant allele predicting reduced metabolism can prevent potentially lethal toxicity also in patients who undergo chemoradiation with a relatively low 5FU dose (61, 62). In intermediate metabolizers, a dose reduction of 25–50% is recommended, while in poor metabolizers with complete DPD deficiency, it is recommended to avoid 5FU (63).

Docetaxel can induce fluid retention and hypersensitivity reactions characterized by generalized erythema and hypotension. In order to reduce the risk and severity of these side effects, patients can to be treated with dexamethasone for 3 days, starting the night before docetaxel administration (64). A study in Chinese patients with head and neck cancer receiving TPF showed that lower dexamethasone doses than the recommended six doses of 8 mg (twice daily) did not increase the risk of severe hypersensitivity reactions (65). The risk of alopecia from docetaxel can be reduced by scalp cooling (66). However, because of tumor localization close to the scalp, reduced efficacy as a result of cooling is a concern and therefore scalp cooling is not recommended in HNSCC patients. For the TPF regimen, antibiotic prophylaxis with ciproflacin 500 mg orally twice daily, from day 5 to 15 for prevention of neutropenic infections was administered in the pivotal trial (8). If patients develop neutropenic fever or neutropenic infection, addition of granulocyte colony stimulating factor (G-CSF) after the next cycles is recommended (67). In a retrospective analysis, primary prophylactic G-CSF did not reduce the incidence of febrile neutropenia in patients treated with TPF and ciprofloxacin or levofloxacin (68). Like for cisplatin, neuropathy is also a frequent side effect of docetaxel and assessment before each cycle is recommended.

Cetuximab

Cetuximab can induce severe infusion-related reactions, including anaphylactic reactions even within minutes of the start of the first infusion. In the registration study, an antihistamine was administered as premedication, followed by a test dose of 20 mg cetuximab in 10 min followed by 30 min of observation (69). Four out of 211 patients discontinued cetuximab because of a hypersentitivity reaction after the test dose or the first dose. The compendium advises premedication with an antihistamine and a steroid, as well as close monitoring and prompt treatment of allergic reactions (70). A frequent adverse event of EGFR targeting drugs is an acneiform skin rash. Prophylactic treatment with an oral antibiotic such as doxycycline or minocycline can be used to reduce the severity of the rash, although not all trials showed consistent results, however it is recommended to instruct patients about sunlight protection (71). Another frequently occurring side effect is hypomagnesemia, especially in patients who receive ≥7 cetuximab infusions and concurrent cisplatin or carboplatin (72). Intravenous supplementation may be required and it may take several weeks or months to resolve.

Immune Checkpoint Inhibitors

Nivolumab, pembrolizumab, and other immune checkpoint inhibitors can cause a wide spectrum of immune related adverse events. The most frequently affected organs are the skin, the gastrointestinal tract, the lungs, and endocrine organs including thyroid, pituitary, and adrenal glands. Less commonly the musculoskeletal tract, nervous system, kidneys, eyes, and heart and blood vessels are affected. Some of these side effects are potentially lethal. Prompt treatment usually results in complete resolution, although endocrinopathies may require lifelong hormonal substitution. The European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) developed guidelines for management of immunotherapy side effects (73, 74). For grade 3–4 toxicity, consultation of organ specialists such as a dermatologist, gastroenterologist, endocrinologist, pulmonologist etc. is required, which implies that a multidisciplinary team with expertise in treatment of immunotherapy side effects has to be available. In contrast to chemotherapy and cetuximab, immune checkpoint inhibitors may be continued at first progression provided that the patient has not deteriorated, although the incidence of pseudoprogression appears to be low in HNSCC (75).

OUTCOME

If there is suspicion of recurrent disease in patients treated with curative intent, imaging and biopsy is required for confirmation. In the palliative setting, assessment of disease progression and treatment response according to the Response Evaluation Criteria In Solid Tumors (RECIST) (76) is preferred, also for patients treated outside studies. For evaluation of immunotherapy, a consensus guideline called iRECIST has been developed to capture response patterns such as pseudoprogression that differ from response patterns to cytotoxic agents (77). Universal criteria for evaluation facilitate benchmarking of institutional results against data from other centers and comparison with the literature. For the same reason it is important to record the date of death and whenever possible, the cause of death in the patient file.

Documentation of complications, unexpected toxicity and serious toxicity of systemic treatment can improve safety of the individual patient, and prevent further damage. It also allows listing for periodical discussion of incidence and potential causes within the MDT. When these discussions are followed by implementation of strategies to lower complication risk, future patients will be better protected. In order to be able to compare incidence of severe toxicity and complications with the literature and with other centers, use of the Common Terminology Criteria for Adverse Events is recommended (78).

Next to medical outcome parameters, patient reported outcome measures (PROMs) are increasingly used to get insight in the impact of treatment on disease symptoms, functional ability, and quality of life (79, 80).

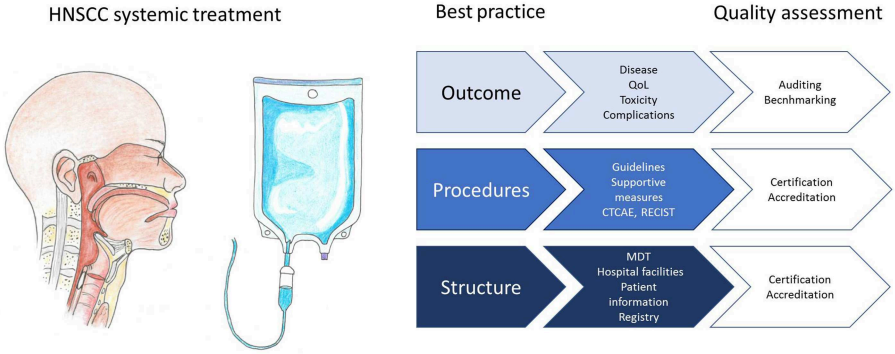

FIGURE 1 | Infographic representing best practice structural requirements, procedures, and outcome evaluation for systemic treatment of head and neck squamous cell carcinoma patients, and how quality can be assessed.

QUALITY ASSESSMENT

Several accreditation or certification programs have been launched with the aim to improve the quality of care for cancer patients. An example is ASCO's Quality Oncology Practice Initiative (QOPI)[1]. Next to a core module and a symptom/toxicity module, tumor specific modules have been developed, although not yet for head and neck cancer. To illustrate, one of the core module measures is that height, weight, and body surface area should be documented prior to curative chemotherapy. The Organization of European Cancer Institutes (OESI) has created an accreditation and designation program for Clinical Cancer Centers and Comprehensive Cancer Centers which is based on peer review[2]. Participation in such initiatives can help centers to identify and improve evidence based quality indicators (**Figure 1**). Accreditation programs are mainly focused on structural and procedural quality indicators. Monitoring with benchmarking of outcome parameters is a powerful incentive for implementing best practice procedures, but challenging to achieve, for instance because case mix variability has to be taken into account. Increasingly, national registries of real world data are set up and used for monitoring and improving quality of care (81). The Dutch Head and Neck Audit (DHNA) is a registry that was recently launched and covers a broad spectrum of structural, procedural, and outcome parameters. Participation is mandatory for head and neck cancer centers, and the first results show that even in a small country with centralized head and neck cancer care, variation exists in quality indicators (82). Results of individual centers participating in the DHNA will become publicly available in the next years to maximize transparency and to boost initiatives for implementation of best practice procedures. The registration burden of such initiatives will hopefully decrease in the near future with advanced information technology and registration at the source. Potential draw backs of public availability of institutional results include a risk that institutes will primarily accept low risk patients and that insurance companies may choose to cover costs only in the best performing centers.

In summary, best practice in systemic therapy for HNSCC involves participation in an MDT and following guidelines. It requires detailed knowledge and anticipation of side effects of systemic therapy and expertise in management of this patient population. Documentation of patient characteristics, tumor characteristics, treatment details, and clinical and patient reported outcome is essential for monitoring the quality of care. Participation in initiatives for accreditation and registries for benchmarking institutional results can empower initiatives for implementation of best practice procedures.

AUTHOR CONTRIBUTIONS

SO wrote the first draft of the manuscript. RH revised it critically for important intellectual content. Both authors approved the submitted version.

[1]https://practice.asco.org/quality-improvement/quality-programs/quality-oncology-practice-initiative (accessed on February 10, 2019).
[2]http://www.oeci.eu/Accreditation/Page.aspx?name=BACKGROUND (accessed on February 10, 2019).

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Quality of Care Indicators for Head and Neck Cancers: The Experience of the European Project RARECAREnet

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Background: Monitoring and improving quality of cancer care has become pivotal today. This is especially relevant for head and neck cancers since the disease is complex, it needs multi therapy, patients tend to be older, they tend to have comorbidities and limited social support. However, information on quality of care for head and neck cancers is scarce. In the context of the project "Information Network on Rare Cancers" we aimed to identify indicators of quality of care specific for the head and neck cancers management and to measure the quality of care for head and neck cancers in different EU Member States.

Methods: We defined indicators of quality of care for head and neck cancers based on a multidisciplinary and expert-based consensus process at a European level. To test the proposed indicators, we performed an observational population-based retrospective study in four countries (Ireland, Italy, Netherlands, and Slovenia) in the years 2009–2011.

Results: The main quality indicators identified are: availability of formalized multidisciplinary team, participation in clinical and translational research; timeliness of care, high quality of surgery and radiotherapy, and of pathological reporting. For head and neck cancers, the quality of care did not reach the optimal standards in most of the countries analyzed. A high proportion of patients was diagnosed at an advanced disease stage, showed delays in starting treatment (especially for radiotherapy), and there was only a very limited use of multi therapy.

Conclusions: According to the achieved consensus, indicators of quality of care for head and neck cancers have to cover the patient journey (i.e., diagnosis and treatment). Our results, showed suboptimal quality of care across countries and call for solutions for ensuring good quality of care for head and neck cancer patients in all EU countries. One possible option might be to refer head and neck cancer patients to specialized centers or to networks including specialized centers.

Keywords: head and neck cancers, population based studies, quality of care, quality indicators, integrated care

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INTRODUCTION

Due to the complexity of oncological care, it is essential to deliver integrated care with optimal alignment and collaboration of several disciplines (1). This is especially relevant for head and neck cancers (HNCs). HNCs involve different anatomical sites, including larynx, oral cavity, oropharynx, hypopharynx, nasopharynx, nasal cavity, and sinuses. The disease is complex, often needs multi therapy, including surgery, radiation, chemotherapy, and/or targeted therapy. Patients tend to be older, to have comorbidities and less social support (2).

In order to improve high-quality oncological care, reliable quality indicators (QIs) are indispensable. This was first highlighted in the USA by the Institute of Medicine's report, "Crossing the Quality Chasm: A New Health System for the twenty-first Century" (3). In Europe, reviews on QI of cancer care were made available by the European Partnership for Action Against Cancer (http://www.epaac.eu) and by the European CanCer Organisation Essential Requirements for Quality Cancer Care (ERQCC) (https://www.ecco-org.eu/Global/News/Latest-News/2017/02/ECCO-Essential-Requirements-for-Quality-Cancer-Care). With regards to HNCs, quality assurance (QA) has been extensively addressed for HNC radiotherapy (RT) (4, 5) and surgery (6, 7) and to a lesser extent for medical oncology (1, 8–11).

Against this background, in the framework of the Information network on rare cancers (RARECAREnet) project (www.rarecarenet.eu), we defined QIs to measure quality of oncological care for the HNC patient journey (i.e., diagnosis and treatment).

In this paper, we report on: (1) the QIs of cancer care for HNC identified by RARECAREnet; (2) the results of the study testing the proposed QIs in several EU countries.

MATERIALS AND METHODS

Quality indicators for HNC were defined through a consensus process following the steps below:

1. Identification of published QIs;
2. Discussion of the proposed QIs with an expert panel involving multidisciplinary experts in a dedicated meeting;
3. Population-based observational study in several European countries to test the proposed QIs;
4. Discussions about the results of the observational assessment with the same expert panel in a second meeting in which a final agreement on QIs was achieved with no dissent. During this second meeting, the expert panel confirmed the QIs originally proposed and added new indicators. For the latter, data were not collected because the observational assessment had ended. We refer to them as QIs agreed by consensus only (**Table 1**).

The HNC multidisciplinary expert panel included faculty members of the European Society for Medical Oncology (ESMO), authors of the ESMO clinical practice guidelines (CPG), representatives of the European Head and Neck Society (EHNS), of the European Society for Radiotherapy and Oncology (ESTRO) and representatives of the European Society of Surgical Oncology (ESSO). HNC patients were represented by the Italian association of laryngectomized patients (Associazione Italiana Laringectomizzati), which is a member of the Make Sense Campaign of the EHNS, and by the European Cancer Patient Coalition.

The observational assessment was performed in collaboration with population-based cancer registries (CRs): the national CRs of Ireland, Netherlands, and Slovenia, as well as nine Italian regional CRs. The study included only incident squamous cell carcinoma (SCC) of larynx, oral cavity, oropharynx, and hypopharynx, diagnosed in patients >15 years old. In Ireland and Netherlands all incident SCC of larynx, oral cavity, oropharynx, and hypopharynx were included in the study. In Slovenia, the study focused only on larynx however, all incident cases of larynx SCC diagnosed in Slovenia were included. In Italy, due to the lack of a national CR, nine CRs representative of the different incidence rates of HNCs considered were included. These nine CRs included all incident cases of larynx, oral cavity, oropharynx, and hypopharynx SCC diagnosed in the geographical areas covered by the selected nine CRs. **Table 2** enlists the number of cases included by country and the years of diagnosis.

We developed a data collection protocol with HNC clinical experts and CRs, we established a help desk to answer questions on the data collection and we centralized at the Istituto Nazionale Tumori (INT) data quality checks and analyses. All data obtained from CRs were fully anonymized prior to being accessed centrally at INT. The Ethics Committee of INT was notified about the RARECAREnet project including this retrospective observational study.

For HNCs, clinical stage was adapted from the ESMO CPG (13) breaking down patient populations into:

- Localized: T1-T2, N0, M0
- Advanced: T3-T4, N0, M0, or N+ with any T
- Metastatic: M+
- Unknown.

The treatment combinations for HNCs were defined as follows:

- Surgery alone; RT alone; chemotherapy alone (if each started within 3 months from diagnosis),
- Concomitant chemo-radiotherapy (CRT) (if chemotherapy and radiotherapy started on the same day, or if chemotherapy started 1 day before the radiotherapy or within max 21 days after the start of radiotherapy),
- Surgery + radiotherapy or surgery + concomitant radio-chemotherapy (concomitant if chemotherapy and radiotherapy started on the same day, or chemotherapy started 1 day before the radiotherapy or within max 21 days after the start of radiotherapy),
- Other combinations of treatments,
- No treatment.

RESULTS

Table 1 summarizes the RARECAREnet quality of care indicators for HNCs. All QIs are listed i.e., QI agreed by consensus

TABLE 1 | List of quality indicators for head and neck cancers.

Diagnostic management
1. Percentage of patients with a defined stage at diagnosis
Time to start treatment (12) **and treatment adherence to clinical guidelines** (13)
2. Time to start treatment (time between definitive pathological diagnosis and beginning of surgery or radiotherapy <1 month)
3. Time in starting post-operative radiotherapy or concomitant chemo-radiotherapy (<8 weeks from surgery)
4. Percentage of patients with early stage I and II referred for either surgery or radiotherapy
5. Percentage of patients with locally advanced stage III and IV referred for surgery plus post-operative radiotherapy or post-operative chemo-radiotherapy or concomitant chemo-radiotherapy
Quality of surgery and radiotherapy
6. Percentage of complete tumor resection (histological verification of tumor free margins after surgery)
7. Percentage of re-operation within 30 days from main surgery*
8. Percentage of grade ≥3 late toxicities (>3 months after radiotherapy)*
9. Percentage of patients receiving intensity-modulated radiation therapy vs. % receiving 3D conformal radiation therapy
10. Percentage of patients receiving the appropriate surgery for its stage (e.g., minimal invasive, reconstructive surgery)*
Quality of pathology reports after surgery
11. Percentage of pathology reports after surgery with a full set of core data items recorded. According to the Royal College of Pathologists (https://www.rcpath.org/profession/publications/cancer-datasets.html): site and laterality of the carcinoma, maximum diameter of tumor, maximum depth of invasion, histological type of carcinoma, degree of differentiation (grade), pattern of invasion, margin status, lymph node involvement.
Availability of formalized multidisciplinary decision (with member experts on head and neck cancers)*
Participation in clinical and translational research*

**Indicators agreed by consensus within the expert panel only.*

TABLE 2 | Number of patients with head and neck cancers (HNCs) included in the study by country with years of diagnosis.

Cancer	Number				
	Total	**Ireland**	**Italy***	**Netherlands**	**Slovenia**
HNCs	8,655	1,323	928	6,185	219
Hypopharynx	790	121	54	615	0
Larynx	3,168	449	398	2,102	219
Oral cavity	2,976	428	258	2,290	0
Oropharynx	1,722	325	218	1,178	0
Years of diagnosis		2009–2011	2009–2010	2009–2011	2009–2010

**Italy included nine population based cancer registries: Registro Tumori Integrato (Catania and Messina), Palermo, Ragusa, and Siracusa (Sicily-south of Italy); Modena, Parma, Reggio Emilia, and Romagna (Emilia Romagna-centre of Italy); Friuli Venezia Giulia (Friuli Venezia Giulia-north est of Italy).*

and assessed by the observational study and QIs agreed by consensus only. It was agreed that optimum management of HNC patients requires active involvement of experts from a wide variety of fields including at least: a head and neck surgeon, a radiation oncologist, a pathologist, a radiologist and a medical oncologist, high quality of surgery and radiotherapy, timely start of treatment (12), optimal supportive care management, and the ability to manage complex patients with multiple health and social care needs.

The observation study was performed on 1,323, 928 and 6,185 cases of hypopharynx, larynx, oral cavity, and oropharynx SCC in Ireland, Italy, and Netherlands, respectively. In Slovenia only larynx SCC were included in study ($N = 219$) (**Table 2**).

Tables 3–5 summarize the results of the observational assessment for the QIs included in the study by country.

Regarding staging at diagnosis (**Table 3**), in Netherlands and Slovenia, almost all patients were staged (unknown stage <5%). In Italy and Ireland, stage was unknown in about one out of six and one out of four patients, respectively. Most of hypopharynx, oropharynx, and oral cavity cancer patients were diagnosed with an advanced disease stage across all countries.

Table 4 reports the results for the timeliness in starting treatment and the adherence to CPG (Indicators 2, 3, 4, and 5). Many HNC patients started treatment with curative intent (surgery or RT) >1 month after the diagnosis. In Italy, 60% of HNC patients started the treatment within 1 month from diagnosis, in all the other countries the proportion starting the treatment on time decreased to 40%. Most of the HNC patients started adjuvant treatment <8 weeks after surgery ranging from 52% in Italy to 79% in Netherlands. The only exception was Ireland with 33% of HNC patients starting adjuvant within the recommended number of days. Adherence to CPG was high for HNC patients with localized disease stage (Indicator 4: 72–79%) but low for HNC patients with advanced disease stage (Indicator 5: 19–44%). Differences were observed in the use of surgery and radiotherapy across head and neck sites and countries. In Italy, surgery was the main treatment for all HNCs, in the other countries RT was the main treatment for larynx cancers and surgery for the other sites (data available from the corresponding author).

Table 5 describes the quality of surgery and of the pathological report after surgery (Indicators 6 and 11). CRs did not find adequate information on type of RT thus results are not reported for the indicator 9. The proportion of HNC patients with complete tumor resection after a surgery with curative intent,

TABLE 3 | Diagnostic management for head and neck cancers illustrated for larynx and other sites of the head and neck (i.e., hypopharynx, oral cavity and oropharynx), by country.

Country	Diagnostic management									
	Indicator 1. Percentage of patients with a defined stage at diagnosis									
	Larynx					Other sites				
	N	% L	% A	% M+	% Missing	*N*	% L	% A	% M+	% Missing
Ireland	449	40	35	3	22	874	17	55	4	24
Italy	398	50	30	4	16	530	24	49	8	19
Netherlands	2,102	58	37	1	4	4,083	38	55	2	4
Slovenia	219	54	41	1	4					

Indicator 1: Number (N) of cases overall and percentage (%) of patients diagnosed with localized (L), advanced (A), and metastatic (M+) disease together with % of cases with information on stage missing, by country.

ranged from 56% in Ireland to >70% in Netherland and Slovenia. The resection margin was unknown in 27% of cases in Ireland and in <15% of cases in the other countries. The pathological report after surgery included all necessary information in a minority of cases (from 1% in Slovenia to 24% in Italy). However, in most cases (80–90%), at least site and laterality of the tumor, histological type and grade were reported. The information less often described were maximum depth of invasion and the pattern of invasion (data available from the corresponding author).

DISCUSSION

We proposed QIs of cancer care for HNCs based on a multidisciplinary and expert-based consensus process at European level. The proposed QIs cover two critical steps of the patient journey (i.e., diagnosis and treatment) and are easy to collect at the hospital as well as at the population level (i.e., from CRs or administrative data sources). Previous QA for HNCs focused on surgery (6, 7) and RT (4, 5). In addition, extensive research have supported the important role of multidisciplinary team (MDT) care for HNCs (2, 14–17).

The indicators proposed for surgery include: the presence of a multidisciplinary tumor board advising on more than 90% of HNCs, the capacity to perform all necessary imaging, the existence of clinical pathways, collaboration with paramedical services, institutional guidelines' hygiene standards being monitored by an institutional board, clinical trial data managers, reports on surgical procedures as indicated by the American Academy of Otolaryngology, Head and Neck Surgery, pathology reports as indicated by the Royal College of Pathologists dataset for histopathology reporting, established reporting system for undesirable events (7).

General radiation oncology (RO)-QIs measure efficiency, waiting time, accuracy of medical records, percentage of cases discussed in a MDT setting, treatment planning based on CT, frequency of verification of treatment portal, measures of physics quality control adequacy, and patient satisfaction (18). For HNC, the National Quality Measures Clearinghouse identified two radiation oncology-related QI i.e., complete follow-up documented for patients receiving RT for glottic cancer and patients receiving post-operative head and neck RT 6 weeks after surgery or longer (4). Guidelines for the delineation of the primary tumor clinical target volumes are also available (19–21). In addition, for HNCs, it is internationally agreed that RT-QA is important, that a radiation oncologist should not practice HNC without adequate training, and that a RT-QA program should be available in RO departments treating HNC. To date, there is no strict international consensus exists on the best model of RT-QA, neither in relation to HNC nor otherwise. However, the benefits of RT-QA and peer review suggest that this has to be incorporated into routine clinical practice. Technology is evolving at a rapid rate: machine learning, artificial intelligence, deformable registration, and radiomics may bring additional refinements to the peer review process. Peer review will form an important component of adaptive treatment, but before this is implemented we will need to consider how to best add this additional burden to head and neck departments (5).

Our QIs include the quality of both, surgery and RT and support the importance of MDT care, of timely start of treatment and of the quality of the pathology reports. A limitation of our QIs is that they do not address quality in systemic therapy. Quality assurance in the medical arena arrived most recently in comparison to other fields. At the beginning of the 90s, the European organization for research and treatment of cancer (EORTC) addressed issues related to the practice of chemotherapy delivery and the quality of data reporting. Furthermore, the EORTC quality assurance committee proposed a minimal set of quality control procedures to be implemented by all EORTC groups (10). However, QA for medical oncology in HNCs was not developed further. A major problem in HNCs medical oncology is the dose intensity in multi therapy. HNC patients with locally advanced disease stage treated with CRT experience moderate/severe side-effects limiting their tolerance to receive the intended cisplatin dose intensity (22). Chemotherapy modifications (dose reductions/delays/omissions) are common (23–40%) (23, 24). The consequence of cumulative cisplatin dose reduction is uncertain although some reports suggest a possible detrimental impact on survival (22, 23, 25). Discrepancies in treatment adherence expressed as proportion of patients who received all

TABLE 4 | Time to start treatment and treatment adherence to clinical practice guidelines by country.

	Time to start treatment and treatment adherence to clinical practice guidelines									
Country	**Indicator 2. Time to start RT or surgery**		**Indicator 3. Time in starting adjuvant therapy**		**Indicator 4% of patients with L disease stage treated with surgery or RT**			**Indicator 5% of patients with A disease stage treated with multi therapy**		
	***N* treated with surgery or RT**	**% starting surgery or RT <1 month from diagnosis**	***N* with adjuvant therapy**	**% starting adjuvant therapy <8 weeks from the surgery**	**N with L disease**	**% treated with surgery alone or RT alone**	**M%**	**N with A disease**	**% treated with multi therapy**	**M%**
Ireland	1,055	41	202	33	332	72	8	640	43	5
Italy	595	61	94	52	327	75	13	380	19	15
Netherlands	4,741	39	900	79	2,792	79	10	3,005	21	22
Slovenia	198	41	69	57	119	72	3	90	44	3

Indicator 2: Number (N) of head and neck cancer patients treated with surgery or radiotherapy (RT), percentage (%) of patients treated with surgery or RT starting surgery or RT <1 month from diagnosis. Indicator 3: Number (N) of head and neck cancer patients treated with adjuvant therapy percentage (%) of head and neck patients starting adjuvant therapy <8 weeks from the surgery. Indicator 4: Number (N) of head and neck cancer patients with localized disease (L), percentage (%) of head and neck cancer patients with localized (L) disease treated with surgery alone or RT alone and percentage (%) of missing (M) information for this indicator. Indicator 5: Number (N) of head and neck cancer patients with advanced disease (A), percentage (%) of head and neck cancer patients with advanced (A) disease treated with multi therapy** and percentage (%) of missing (M) information for this indicator. *Adjuvant therapy: post-operative radiotherapy or post-operative concomitant chemo-radiotherapy. **Multi therapy: surgery plus post-operative radiotherapy or post-operative chemo-radiotherapy or concomitant chemo-radiotherapy alone.*

planned cycles of chemotherapy could therefore be used as a QI for systemic therapy in HNC. In this regard, there is an important role for the clinician, not only to stimulate patients to adhere to the treatment schedule, but also to provide optimal supportive care in order to make it tolerable for the patient (22).

Previous studies looking at the quality of integrated care for HNC patients proposed structure and process indicators (e.g., availability of MDT, of an integrated care pathway, of a case manager, of electronic patient information system) (26, 27). Other studies proposed an extensive list of outcome, process and structure indicators that needed to be practically tested so to limit the QIs number (1). Although interesting, these studies report about one country-specific context. We tested the QIs in an observational study performed in four different European countries. The data collection, based on clinical dossiers and administrative database, was undertaken with an acceptable proportion of missing (<20–25%) in all countries and without major problems in the data collection but for 1 RT indicator. The expert panel agreed that the results of the observational study gave a good description of the quality of care for HNCs in the studies of all the countries, confirming the reliability and validity of the QI proposed in measuring quality of care.

We found that quality of care of HNC does not reach optimal standards in some of the countries analyzed. Many patients were diagnosed an advanced disease stage, which is associated with a worse prognosis (28). Another major problem was treatment delay. This happened most likely when patients were treated with RT, which could impact on their prognosis (29). Possible explanations include possible delays in referral to RO and concentration of radiotherapy facilities in a few centers with limited resources. A recent survey on radiotherapy capacities in Europe showed significant variability among countries and a lack of RT infrastructures (30). The adherence to CPG for treatment was good. However, we observed a very limited use of multi therapy for advanced-stage patients. This is relevant considering that they are associated with a higher survival (31). We observed inadequate surgery and poor quality of the pathological reports after surgery, which is a matter of concern considering that pathological reports support treatment decisions after surgery.

Our study adds evidence to previous national studies in which compliance of HNCs care to hospital or national CPG was considered a quality care marker. A Dutch study reported a compliance rate of 91% (32), one study from the USA 86% (33), going down to 57% in patients with persistent or recurrent HNCs who were referred to an expert centre (34).

Limitations of our study include the retrospective design and the potential errors in coding associated with the kind of sources of clinical data and their inherent variability in quality of reporting, although every effort was made to standardize data collection and reduce missing data. Strengths are the centralization of data quality checks and analyses along with the population-based nature of this effort, which is essential to generate real-world data.

Our results showed suboptimal standards of quality of care in some of the countries analyzed and call for solutions to increase quality care for HNC patients to ensure high quality of care

TABLE 5 | Quality of surgery and of the pathological report after surgery.

Quality of surgery and of the pathological report after surgery						
Country	**Indicator 6% of complete tumor resection**			**Indicator 11% of pathology reports with all core data**		
	***N* treated with surgery with curative intent**	**% of R0**	**M%**	***N* surgically treated**	**% of post-surgery pathological report with all core data**	**M%**
Ireland	602	56	27	NA	NA	
Italy	516	62	13	474	24	2
Netherlands	2,728	74	13	128**	16**	0
Slovenia	88	75	9	87	1	29

Indicator 6: Number (N) of head and neck patients treated with surgery with curative intent, percentage (%) of head and neck patients treated with surgery with negative resection margins (R0) and percentage (%) of missing (M) information for this indicator. Indicator 11: Number (N) of head and neck patients treated with surgery (excluding cryotherapy photodynamic therapy or electrocautery procedure, cryosurgery or laser therapy or thermo-ablation), percentage (%) of pathological report after surgery with all the information available and percentage (%) of missing (M) information for this indicator. *Surgery with curative intent: surgery alone or surgery + adjuvant treatment.*
*NA, not available. **Evaluated on a sample of 200 randomly selected case.*

across EU countries. One way of increasing quality of care for HNC patients is to refer them to specialized centers or networks involving specialized centers. Thus, the available evidence show that in the high volume context quality of care is ensured in the entire patient journey:

1) The specialized MDT, which takes considerable time, effort and financial resources works better (35); furthermore the presence of a MDT in high-volume and referral cancer centers is associated with better therapeutic decision (35);
2) The minimal level of quality of surgery is most likely to be reached considering the structural and process criteria identified by the QA programme and the number of major head and neck procedures that should be performed by a leading surgeon per year (7),
3) Experienced clinicians are available to deliver complex HNC RT treatment most accurately and to peer review RT complex plans ensuring RT-QA program (5).

Furthermore, high volume seems to be associated also with better outcomes for HNCs (36–38).

Centralization for many rare cancers including HNCs is still limited in many countries in Europe (39). Gatta et al. reported that for HNCs, 75% of patients were centralized in two top hospitals in Slovenia (2 million population, 266 treatments per hospital per year), and 12 top hospitals in the Netherlands (17 million population, 201 treatments per hospital per year). The level of centralization was lower in the other countries included in the study, resulting in a caseload of 145 treatments/year on overage in each of the 10 Bulgarian top hospitals, 106 treatments/year on average in each of the 29 top Belgian hospitals, 83 treatments/year on average in each of the top six hospitals in Finland, 77 treatments/year on average in the two top hospitals in Navarra, and 63 treatments/year on average in the top seven hospitals in Ireland (39).

It follows that the centralization of care, although hardly feasible for all HNC patients, should be an objective to be pursued. We strongly believe that this objective can only be achieved by progressively making it a national health care policy priority.

The quality ensured by the case volume could be explained by several factors: organization, facilities, processes of care, quality assurance programs, professional expertise, adherence to clinical protocols, technology. In this context, it will be important to detect which of these factors influences final outcomes among HNC patients. We are currently performing additional analyses to assess the relationship between hospital volume and the QIs proposed. We are also trying to assess whether the proposed QIs can explain the observed higher survival observed in high volume centers. In this paper, we present the QI and the process behind their definition. Furthermore, we provide data on quality of care for HNC patients across four countries. This study may be a starting point showing the variability in clinical practice as well as the need to make every effort to increase quality of care for HNC patients in all EU countries.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the IRCCS National Cancer Institute. Being a retrospective study on a rare and lethal disease, the written consent was not necessary.

AUTHOR CONTRIBUTIONS

AT: study design, supervision of data collection, results interpretation, and manuscript writing. LB and RF: study design and statistical analyses. OV: study design, data collection, results interpretation, and manuscript revision. JB: manuscript revision. TŽ, MP-Ž, and FB: data collection, results

interpretation, and manuscript revision. ND, GG, and LL: study design, results interpretation, and manuscript revision.

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REVIEW
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Diagnostic Tumor Markers in Head and Neck Squamous Cell Carcinoma (HNSCC) in the Clinical Setting

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Head and neck squamous cell carcinoma (HNSCC) represents a group of tumors arising in the oral cavity, oropharynx, and larynx. Although HNSCC is traditionally associated with tobacco and alcohol consumption, a growing proportion of head and neck tumors, mainly of the oropharynx, are associated with Human Papilloma Virus (HPV). Recurrent/metastatic disease is characterized by dismal prognosis and there is an unmet need for the development of biomarkers for detection of early disease, accurate prediction of prognosis, and appropriate selection of therapy. Based on the REMARK guidelines, a variety of diagnostic and prognostic biomarkers are being evaluated in clinical trials but their clinical significance is doubtful. Herein, we will focus on biomarkers in HNSCC used in the clinical setting and we will illustrate their clinical relevance.

Keywords: head and neck cancer, HPV, tobacco, PET/CT scan, biomarkers, PD-L1, immunoscore

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) encompasses a heterogeneous group of malignancies that arise in the oral cavity, larynx and pharynx and are mainly associated with tobacco and alcohol consumption. In addition, epidemiological, molecular pathology and cell line data indicate that a substantial proportion of oropharyngeal cancers represents a sexually transmitted disease and is causally associated with high-risk human papillomaviruses (HPV), especially type 16 (1–3). HPV-associated oropharyngeal cancers (HPV-OSCCs) represent a distinct biological and clinical entity, have a distinct mutation landscape, and are characterized by markedly improved survival (4). The majority of HNSCC patients present with locoregionally advanced (LA) disease for which multimodality therapeutic approach is employed. Despite advances in diagnostics, treatment and surveillance, the 5-year progression-free survival (PFS) of HPV negative patients with LA disease is ∼40–50% and survival rates for recurrent/metastatic (R/M) disease have not significantly changed over the past years.

Low survival rates associated with HNSCC are partly due to failure in early diagnosis. Indeed, only one third of HNSCC patients are diagnosed at an early stage (5); early diagnosis is mainly attributed to lack of appropriate screening and diagnostic biomarkers. Biomarkers are defined, according to the National Cancer Institute (NCI), as "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition" (6). Basically, biomarkers represent important tools that contribute to diagnosis, assess the likely course of the disease and predict response to treatment; thus, they are categorized as diagnostic,

prognostic or predictive, respectively. Regarding HNSCC, although many biomarkers have been suggested to significantly impact diagnosis and prognosis, few of them have been validated for use in clinical practice. Indeed, a significant proportion of biomarkers in development are not introduced into clinical practice because they lack important features, such as high specificity and sensitivity, low cost, high positive predictive value, clinical relevance, and short turnaround time (7). The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) initiative, which has been developed with the joint effort of clinicians, statisticians, epidemiologists, and journal editors, has recommended a guideline for the reporting of studies developing, validating, or updating a prediction model, whether for diagnostic, or prognostic purposes (8). Based on the REMARK criteria (9), a handful of biomarkers are validated for clinical use in HNSCC. In this review, we will focus on established diagnostic biomarkers that are in clinical use in HNSCC, and we will discuss emerging biomarkers that are in development.

VALIDATED BIOMARKERS

HPV

A growing proportion of oropharyngeal cancers is associated with HPV infection. More than 130 HPV types are known and classified as low-risk or high-risk based on their oncogenic potential; HPV16 is the most commonly found and is present in ∼90% of HPV-OSCCs (10). Two meta-analyses of case-control studies have provided epidemiological evidence of the causative role of HPV in OSCC based on strong correlation between HPV16 exposure and HNSCC in certain anatomical sites (11, 12). Indeed, a strong correlation has been described between HPV-16 detection at the time of diagnosis with tonsillar cancer (odds ratios [OR], 15.1; 95% CI, 6.8–33.7) and OSCC (OR, 4.3; 95% CI, 2.1–8.9) (11). Biologically, the integration of high-risk HPV DNA into the host genome can lead to the expression of oncogenes E6 and E7 in the host cell; however, 60% of HPV-positive OSCC can contain extrachromosomal (episomal) virus. The E6 oncogene provokes the degradation of TP53. The E7 oncogene is implicated in binding and destabilizing of the tumor suppressor retinoblastoma (pRb) (3).

HPV-OSCC differs from HPV-driven cervical cancer, in which Pap smear and HPV DNA are widely used for screening in clinical practice; in HPV-OSCC there is no identified oropharyngeal premalignant lesion and the presence of HPV DNA in the oral cavity or oropharynx is not directly linked to subsequent development of HNSCC. Although detection of HPV16 DNA by Polymerase Chain Reaction (PCR) in both salivary oral rinses and plasma has demonstrated marked sensitivity and specificity (13), it has not been incorporated into clinical practice as a screening tool.

Detection of HPV DNA in saliva samples has been shown be a predictive tool for recurrence in HPV-associated OSCC (14–16). More specifically, in a study by Rettig et al. oral rinse samples were collected from patients with HPV-OSCC at diagnosis and at several timepoints after diagnosis and evaluated for HPV DNA. HPV DNA was detected in 54% of patients at diagnosis, but only in 5% of patients post-treatment. Importantly, all patients with HPV DNA positive samples post-treatment relapsed and persistent oral HPV infection correlated with disease free survival (DFS) and overall survival (OS) (14). Two additional smaller cohort studies have reported a correlation of HPV16 DNA detection in post-treatment oral rinses with survival (15, 16). These findings support the potential utility of HPV DNA detection in post-treatment oral rinses as a clinical test for the prediction of relapse.

In addition, large case control and prospective cohort studies have reported a strong correlation between seropositivity for antibodies against HPV16 oncogenic proteins E6/E7 and risk of OSCC. More specifically, Kreimer et al. evaluated pre-diagnostic plasma samples from patients with HNSCC and controls for antibodies against oncogenic proteins of HPV (17). These patients were participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which was conducted to assess the relationship between nutrition and cancer (18); samples were collected at a median of 6 years before diagnosis. Interestingly, HPV16 E6 seropositivity was found to be present in pre-diagnostic samples for 34.8% of patients with OSCC and 0.6% of controls (OR, 274; 95% CI, 110 to 681); most importantly, the increased risk of OSCC among HPV16 E6 seropositive participants was observed more than 10 years before diagnosis. Similarly, Agalliu et al. conducted a nested case-control study among 96,650 participants, who were cancer free at baseline, with available mouthwash samples in 2 prospective cohort studies: (1) the American Cancer Society Cancer Prevention Study II Nutrition Cohort and (2) the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Among those participants, authors identified 132 cases of HNSCC during 3.9 years of follow up. It was shown that HPV-16 detection in the oral cavity, which preceded cancer diagnosis for an average of 3.9 years, was associated with a 22.4-fold increased risk of incident OSCC (95% CI, 1.8–276.7) after adjusting for smoking history and alcohol consumption, but not with risks of oral cavity or larynx SCC (19).

Furthermore, plasma and saliva HPV DNA have been shown to be important tools for predicting relapse in HPV-OSCC. In a recent retrospective study conducted in 93 patients with OSCC, among who 81 were HPV-positive, tumor DNA was detected in pre-treatment saliva and plasma samples in 53 and 67% of HPV-positive patients, respectively. When combined, pre-treatment saliva and plasma tumor DNA were 76% sensitive and 100% specific. Post-treatment saliva and plasma were 70% sensitive and 91% specific for disease recurrence (15). Finally, in a recent meta-analysis including 5 studies with both pre-treatment and post-treatment samples ($n = 600$ HNSCC patients), HPV DNA demonstrated a high pooled estimated specificity in detecting disease recurrence (100%) but an inferior pooled sensitivity (54%) (20). Recent technical advances in detecting circulating DNA using droplet digital PCR might improve sensitivity (21).

Therefore, HPV E6/E7 could be used as a clinical test to monitor treatment outcomes. Several studies have attempted to evaluate changes in HPV16 E6 and/or E7 antibody levels after treatment completion in patients with HPV-OSCC (22–28). The

majority confirm the high incidence of seropositivity at diagnosis. Six out of 7 studies describe a decline in levels of HPV16 E6 antibodies post-treatment (22, 23, 25–27, 29). Among them, two showed a correlation between stable or increasing HPV16 E6 antibody levels and relapse (22, 25), one showed that patients who recurred had a lower clearance of antibody titers and three studies failed to demonstrate any significant association between post-treatment antibody levels and disease recurrence.

Compared to HNSCC unrelated to HPV, HPV-associated OSCC has emerged as a distinct disease entity with different clinical characteristics and a unique molecular profile, emphasizing the need for routine HPV testing of OSCC. Importantly, given the distinct clinical behavior and favorable prognosis of HPV-OSCC, a separate staging system has recently been developed for HPV-OSCC (30, 31). Indeed, the importance of HPV status as a diagnostic and prognostic biomarker necessitates the establishment of HPV testing and the incorporation of HPV status in therapeutic management; indeed, HPV positive and HPV negative OSCC are now being addressed separately in clinical trials. Nevertheless, there is currently no treatment de-intensification protocol recommended for HPV-OSCC and two recently published trials have shown reduced efficacy of anti-Epidermal Growth Factor (EGFR) monoclonal antibody cetuximab-based radiation compared to standard cisplatin chemoradiation (32, 33). More specifically, in the De-Escalate HPV trial, which was conducted in patients with low risk HPV-OSCC, cisplatin based chemoradiation was associated with survival benefit comared to cetuximab-radiotherapy combination, but this was a secondary endpoint and follow up was only 26 months (32). On the contrary, in the non-inferiority RTOG 1016 that did not focus on low risk HPV-OSCC, OS was a primary endpoint and it was found to be was higher in the cisplatin-radiotherapy arm after 5 years of follow up (33). Toxicity did not differ between arms in both studies. However, in the RTOG 1016 study several adverse events such as myelosuppression, anemia, nausea, vomiting, anorexia, dehydration, hyponatremia, kidney injury, and hearing impairment were significantly more frequent in the cisplatin group.

Both the College of American Pathologists and NCCN guidelines recommend HPV testing for all oropharyngeal tumors (34). In addition, The National Cancer Institute proposes the inclusion of HPV status as a risk stratification factor in current clinical trials addressing OSCC patients. However, it has been postulated that despite strong recommendations, HPV status is routinely assessed in 79% of OSCC cases in the UK and 67% of cases in the US, possibly due to costing issues and lack of predictive significance (35).

Of note, the role of HPV in HNSCC other than OSCC remains unclear. In carcinoma of the oral cavity, a report by Zafereo et al. indicated a high incidence of p16 overexpression (36.3%, especially in the tongue), but only 6% of oral cavity tumors were considered HPV-driven (36). In laryngeal cancer, the prevalence of HPV positivity is ∼28% (37), but no correlation with survival has been reported (38). Therefore, HPV testing in patients with HNSCC other than OSCC is not routinely recommended outside of a clinical trial.

Detection strategies for HPV-OSCC differ in detection targets and include HPV DNA Polymerase Chain Reaction (PCR) for E6/E7 viral oncogenes, HPV E6/E7 mRNA detection quantitative reverse transcription-PCR (qRT-PCR), DNA *in situ* Hybridization (ISH), RNA ISH and p16 immunohistochemical staining (IHC) as a surrogate marker for HPV status (39). There is still no clear consensus about which method is the gold standard for HPV detection. For example, important advantages of standard PCR techniques include wide availability, high sensitivity (detection of HPV below one viral copy per genome cell) and cost effectiveness. However, PCR techniques are complex and have low specificity because they cannot distinguish between HPV that acts as an oncogenic driver and transcriptionally silent virus and have a high risk of contamination; these disadvantages hamper their capacity to detect a clinically relevant HPV infection (40). Importantly, detection of viral E6/E7 mRNA by RT-PCR is widely accepted as the gold standard for the detection of clinically significant HPV infection due to its generally high sensitivity, tumor-specific expression of the mRNA/DNA target and feasibility on formalin-fixed, paraffin-embedded tissue block (41). Significant limitations include that it is time-consuming and that its sensitivity decreases depending on quality of samples.

DNA ISH is a molecular method with high specificity, which enables direct detection of the presence of HPV virus in topographical relationship with pathological samples, ensuring that viral DNA originates from tumor cells and not surrounding tissues. ISH has the advantage of being feasible in both formalin-fixed and paraffin-embedded tissues, but it is a less sensitive method that is insufficiently clinically validated and is not currently used in routine screening (42). However, E6/E7-mRNA ISH, which allows direct visualization of viral transcripts in routinely processed formalin-fixed paraffin-embedded tissues, has sensitivity comparable to p16 IHC and qRT-PCR (43, 44).

P16INK4A (p16) is a tumor suppressor protein that regulates the cell cycle by inhibiting phosphorylation of CDK4 and CDK6, thus preventing Rb phosphorylation. During the HPV life cycle, the oncoprotein E7 inactivates the Rb protein, which results in the upregulation of various cell cycle associated proteins, including p16 (10). P16 is commonly used as a surrogate marker for HPV positivity and p16 IHC has been established as an essential complimentary procedure for HPV detection, due to its low cost, availability and high sensitivity (4, 45); however, low specificity limits its use as a standalone test (46). In addition, proper interpretation of p16 staining requires evaluation by trained pathologists and requires incorporation of histological and clinical information. Discordance rate between p16 IHC and direct detection of HPV DNA/RNA is estimated to be as high as 25%, with p16 + but HPV-tumors representing most of discordant cases (47).

As previously mentioned, detection of E6/E7 mRNA by PCR is suggested as the most enlightening method for determining HPV status. However, p16 IHC is widely used in clinical practice given its availability, simplicity and high sensitivity for detecting all high-risk types of HPV. Nevertheless, it cannot be utilized as a standalone test because of low specificity and a false positive rate where p16 expression is driven by non-viral mechanisms. Of

note, outside the oropharynx, where the overall HPV infection rate is probably lower than 5%, p16 IHC is demonstrated to show very low or no correlation with HPV infection (48). In addition, there is substantial evidence that p16 positivity is associated with improved survival in R/M OSCC (49). Interestingly, tumors characterized as p16+/HPV-OSCCs have been correlated with poorer survival than p16+/HPV+ cancers (50). Because of its correlation with survival, p16-positivity is included in the recent World Health organization TNM classification for OPSCC.

In clinical practice, determination of HPV status usually starts with p16 IHC; subsequently, a different method of detection is used to reinforce reliability of the result. In a recent report by Fakhry et al. ASCO and CAP suggest p16 IHC as the initial test for HPV in tissue specimens. Additional HPV testing should be performed at the discretion of pathologist or treating physician (51). In a study by Weinberger et al. cases that were dually positive for p16 IHC and Real-time PCR HPV16 DNA were the biologically relevant HPV+ OSCC cases with favorable prognosis (4). A multimodality approach with p16 IHC followed by PCR or ISH on p16+ cases is proposed as the most appropriate to ensure high sensitivity and specificity. Indeed, Dutch and English groups have validated this approach reporting a sensitivity and specificity of almost 100% (52, 53).

PET Imaging

18F-fluorodeoxyglucose PET (FDG-PET) is widely used as a diagnostic tool in HNSCC both for defining stage and evaluating treatment response. It has been shown to have higher sensitivity and a high negative predictive value compared to CT or MRI especially for identification of small lymph nodes of the neck (54, 55). This leads to a modification of treatment planning in approximately one third of the patients. Furthermore, in patients with cancer of unknown primary manifested as cervical lymph node metastases, FDG PET can identify the primary site in 25–38.5% of cases (56).

18-FDG pre-treatment parameters maximal and mean standardized uptake value (SUVmax and SUV mean), are most commonly used, despite flaws in calculation, and reproducibility (57). Several studies have shown that high pre-treatment SUV on PET/CT is an adverse prognostic factor in HNSC (58–61). In a metanalysis reported by Xie et al. both low pre-treatment and post-treatment SUV of the primary tumor was associated with improved disease-free survival (DFS), OS and local control (59); this result was confirmed in a subsequent meta-analysis by Zhang et al. (60). However, due to large differences in the SUV cut-off values and heterogeneity of various studies, the clinical utility of the results of these metanalyses is questioned.

Post-treatment FDG-PET is also commonly used for HNC-response assessment after definitive radiotherapy or chemoradiotherapy. A meta-analysis of 51 studies that included 2,335 patients showed that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG PET for the detection of residual primary HNSCC were 94, 82, 75, and 95%, respectively, (55). Notably, a positive FDG PET/CT study in the post-treatment evaluation needs thorough consideration of clinical information and endoscopy findings and might require biopsy of suspicious positive sites to confirm diagnosis, as radiation-induced inflammation can also lead to FDG uptake (62). Ong et al. retrospectively evaluated the records of patients with HNSCC treated with concurrent CRT who have underwent a PET/CT 8 or more weeks after treatment. PET/CT findings were confirmed by biopsy, neck dissection or imaging follow up. In the NPV and specificity of FDG PET/CT for residual nodal disease were 97 and 89%, respectively, whereas sensitivity was 71% and PPV was 38%. Specificity and NPV of PET/CT increased in the subgroup of patients without residual enlarged neck nodes at CT (63). On the contrary, in a study reported by Waldron et al. that included 339 patients with N2/N3, both NPV and sensitivity of PET/CT were low (53 and 73% respectively) (64). Interestingly, PET/CT scan has been reported to have high NPV and sensitivity in HPV-related HNSCC (65–67).

Mehanna et al. conducted a prospective randomized phase III trial to assess the utility of PET/CT as a biomarker of residual disease and as a tool to avoid unnecessary neck dissection post radical chemoradiotherapy (CRT) in patients with advanced N2/N3 disease. In this non-inferiority study, patients were randomized to either surveillance via PET/CT, which was performed 12 weeks post CRT, and neck dissection in the case of incomplete response or equivocal findings or planned neck dissection. Overall survival was found to be similar among the two groups, but PET/CT-guided surveillance was more cost effective and resulted in fewer surgical operations (68).

Importantly, positive PET/CT findings might be more properly interpreted if time interval between treatment completion and PET/CT exceeds 12 weeks. The results of the ECLYPS study, which sought to implement PET/CT findings according to international guidelines in patients with LA HNSCC treated with radical CRT, suggested that FDG-PET/CT can successfully identify residual neck disease 12 weeks after CRT. Importantly, although its sensitivity was high in detecting residual disease in patients who relapsed up to a 9 month horizon after imaging, sensitivity was lower for disease manifesting up to 12 months after imaging (sensitivity, 59.7%) (69). In addition, even with optimal timing, SUV cutoff is not a reliable biomarker for discrimination between cancer and radiation-induced inflammation (44); however, a reduction in SUVmax of >50% has been associated with improved outcomes (70).

Tobacco

Although smoking rates continue to decrease across the United States (US), they are particularly high among cancer patients. Indeed, ∼60% of newly diagnosed cancer patients are characterized as current or former smokers, with the highest numbers in lung cancer and HNSCC (71). The odds ratios of developing HNSCC is 2.37 (1.66–3.39) for tobacco only users, but combined alcohol and smoking consumption has a more multiplicative effect, with an odds ratio of 5.73 (3.62–9.06) (72). Smoking rates at diagnosis in patients with HNSCC range from 26.4 to 56% (73, 74) and vary across subsites, with the highest rates observed in laryngeal cancer (73, 75).

Most importantly, tobacco consumption in HNSCC is associated with inferior treatment-related outcomes, including surgical outcomes, and radiation efficacy. Furthermore, smoking

at diagnosis is associated with reduced survival rates, higher risk for second primary cancers such of the lung and esophagus, increased risk of comorbidities and competing causes of death (76, 77). In a landmark study, Ang et al. conducted a retrospective analysis in patients with stage III-IV OSCC who participated in the RTOG 0129 study that compared accelerated-fractionation radiotherapy with standard-fractionation radiotherapy, each combined with cisplatin therapy. The authors sought to assess the prognostic significance of HPV status and association with survival. Using recursive partitioning analysis, they incorporated tobacco consumption into a classification model that was based on four factors: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage; a cutoff of 10 pack years of smoking was reported to be the best predictor of survival. Patients were classified as having a low, intermediate or high risk of death (78). This study demonstrated that although HPV status is a strong predictor of survival, the favorable biologic behavior of an HPV-positive tumor may be altered by tobacco exposure; tobacco-driven molecular alterations may decrease effectiveness of radiation treatment.

A year later Gillison et al. retrospectively evaluated patients with OSCC enrolled in the aforementioned RTOG 0129 trial and the RTOG 2003 for HPV status and tobacco consumption. After adjustment for p16 and other factors, it was demonstrated that risk of death increased by 1% per pack-year or 2% per year of smoking in both trials. In addition, in RTOG 9003, overall survival was significantly associated with tobacco exposure during radiation treatment (79). Similar results had been previously reported in patients with HNSCC early in 1993; Browman et al. had demonstrated that response rate and survival were decreased among patients who smoked during radiotherapy (80). In addition, Chen et al. conducted a matched control study in patients with HNSCC receiving radiotherapy and demonstrated reduced treatment-outcomes in patients who continued to smoke as opposed to matched smokers who have quit (81). Suggested mechanisms for smoking-induced effects on survival in HNSCC include inflammation and tobacco carcinogen-induced DNA damage (82).

Although smoking status has been shown to profoundly affect treatment outcomes in HPV-related OSCC, it has not been incorporated into the novel staging system specifically developed for HPV-OSCC in the American Joint Committee on Cancer Staging (AJCC) 8th edition. Historically, successful stage grouping yields similar survival rates for patients among the same T and N subgroup and significantly different survival rates across subgroups; in addition, patients must be equally distributed between groups (83). In an attempt to provide improved predictive ability that complies with the distinct outcomes expected for patients who suffer from HPV-associated as compared to HPV-negative OSCC, Dahlstrom et al. developed a proposal for a new staging grouping for HPV-related OSCC based on recursive partitioning analysis (RPA). Indeed, stratification of patients based on smoking history using the cutoff of 10 pack years proposed by Ang et al. revealed a different PFS impact based on smoking status. However, when these groups were compared within each stage group, no difference in survival was found (84). Therefore, the authors concluded that although smoking is an important prognostic factor for HPV-OSCC, there is no need to include it into the new staging system, if TNM stage accurately reflects prognosis. Nevertheless, as the new AJCC 8th edition TNM classification starts to be used in clinical practice, new data will be encompassed into cancer registries, and these may urge future reclassification of prognostic stage groupings that might include smoking as a classification factor.

Immunoscore

Although TNM is a good prognostic system that accurately reflects patient prognosis, clinical outcomes of patients distributed across TNM stages might frequently be different than expected. For instance, some patients with small tumor burden recur quickly, whereas others with metastatic disease have an unexpectedly favorable prognosis. In recent years, it has been well-established that the immune system plays a pivotal role in the control of tumor growth (85) and it has been suggested that potentially invading cancer cells are held in an equilibrium state that is controlled by the immune system (86). Subsequently, certain tumors escape and become clinically apparent.

Accumulating evidence has emphasized the need for the development of immunological biomarkers that can offer prognostic information and facilitate clinical decision-making. Tumor-infiltrating immune cells, including T and B lymphocytes, macrophages or neutrophils can have either a negative or a positive effect on tumor expansion. Evaluation of the dynamics and functional roles of different subsets of tumor infiltrating cells in the tumor suppressive microenvironment could improve our knowledge of immunology and define subgroups of patients that are more likely to respond to immunotherapy. Cytotoxic CD8+ tumor infiltrating lymphocytes (TILs) are thought to be the major effector immune cells directed against tumor cells and have been shown to have prognostic significance in many solid tumors (87–89). On the other hand, regulatory T cells (Tregs) inhibit immune response and counteract cytotoxic T cells. Inconsistent results have been reported regarding prognostic significance of Tregs, with several studies showing association with poor prognosis in a variety of malignancies including breast, lung, cervical and ovarian cancers, while others demonstrating favorable prognostic significance, e.g., in colorectal cancer (90).

HNSCC is a disease characterized by profound immunosuppression (86). Several studies have reported a significantly increased density of TILS in HPV-positive as compared to in HPV-negative OSCC, which implies a more potent anti-tumoral immune response in HPV-OSCC (91–93). This has been suggested as the mechanism for improved outcome in HPV-OSCC across studies. In addition, high levels of TILs have been associated with improved survival in HPV-OSCC (94, 95). Interestingly, patients with HPV-positive disease and low TIL levels did not show a survival advantage compared with HPV-negative counterparts (94). On the contrary, HPV-positive patients with high TILs have been shown to have superior survival (95), suggesting the use of TILs as a future biomarker for de-intensification treatment patient selection in HPV-positive

disease. High TILs have also been associated with improved survival in tobacco-related HNSCC (96, 97).

Furthermore, levels of both CD8+ and CD3+ T cells have been associated with increased overall survival after definitive chemoradiotherapy, both in HPV-positive, and HPV-negative HNSCC (98, 99). In a more recent multicenter study of patients with HNSCC after post-operative chemoradiotherapy, high CD8 TILs density measured on tumor periphery, tumor stroma, and tumor cell area was predictive for improved OS (98). Interestingly, in another study, only stroma TILs infiltration was associated with increased survival (100).

Of note, HPV-OSCC has been shown in several studies to possess a high degree of T reg infiltration (95, 101, 102). Tregs have been shown to correlate with favorable OS and locoregional control (95, 102), possibly reflecting the downregulation of inflammation which triggers the initiation of carcinogenesis (103).

A clinical application of the prognostic significance of TILs is the establishment of an Immunoscore, which emerges as a potential algorithm to define antitumor immune responses using quantitative pathology. Immunoscore is based on the quantification of CD3+ and CD8+ TILs in the tumor core and the invasive margin of resected tumors and uses this numeration of TILs to provide a score ranging from Immunoscore 0, when low numbers of both cell types are described in both regions, to Immunoscore 4, when high numbers are described in both regions. Immunoscore has been applied in colorectal cancer in large cohorts (104). In HNSCC, both CD8+ T cells infiltrate in the tumor component of the invasive margin and PD-L1 expression in the tumor were predictive of disease recurrence (105).

PD-L1

Immune checkpoints modulate signaling and either inhibit or enhance T-cell response. Cytotoxic T lymphocyte Antigen 4 (CTLA-4) and Programmed Cell Death protein 1 (PD-1) are distinct examples of co-inhibitory molecules; because PD-L1 mediates the inhibition of T cell activity, it can be theoretically assumed that high expression might result in poor survival. PD-L1 is upregulated under inflammatory conditions and is expressed in T-cell enriched tumors (106). In a laryngeal HNSCC cohort, high PD-L1 expression assessed by Automated Quantitative protein Analysis (AQUA) was found to positively correlate with disease outcome (96). In a recent report by Yang et al. PD-L1 was shown to correlate with improved PFS but not OS in patients with advanced HNSCC. Interestingly, patients with combined low expression of TILs and high expression of PD-L1 were characterized by dismal survival (107). Another retrospective analysis that assessed PD-L1 expression in a large cohort of patients, demonstrated that high PD-L1 expression was the strongest predictor of worse outcome, independent of tumor origin (108). In cancers of the oral cavity, increased PD-L1 expression has been also shown to correlate with poor survival (109).

In early immunotherapy studies, PD-L1 expression was shown to be associated with the rate of response to immune checkpoint inhibitors and was therefore established as the most commonly used predictive biomarker (110, 111). Therefore, evaluation of PD-L1 expression currently represents a reference biomarker for clinical trials. However, accurate measurement of PD-L1 protein levels in FFPE tumor samples is hampered by technical issues, such as the use of different assays and antibodies across different studies and tumor types, the variability of cut-off values, and scoring methods and the lack of standardized methods (112). In addition, intertumoral, and intratumoral heterogeneity hampers homogeneous PD-L1 evaluation.

Indeed, it is clear that PD-L1 is an imperfect albeit useful predictive biomarker. In addition, no other biomarker has shown correlation with immunotherapy response in HNSCC. In the phase III Keynote-040 study, which assessed the efficacy of pembrolizumab vs. investigator's choice (methotrexate, docetaxel, or cetuximab) in platinum resistant R/M HNSCC, a statistically significant difference in OS in favor of pembrolizumab was shown in patients with combined positive score (CPS, defined as $\geq$1 of expression in both tumor and mononuclear inflammatory cells) $\geq$1 (8.7 months vs. 7.1 months, $p = 0.0078$), and in patients with CPS $\geq$50 (11.6 vs. 7.9 months, $p = 0.0017$) (113).

Importantly, the results of the phase III Keynote 048 trial, which compared pembrolizumab alone or in combination with chemotherapy vs. EXTREME in treatment-naïve HNSCC, were recently presented (114). Pembrolizumab significantly improved OS over EXTREME in the PD-L1 CPS $\geq$ 20 (14.9 vs. 10.7 months; $p = 0.0007$) and $\geq$1 (12.3 vs. 10.3 months, $p = 0.0086$) subgroups; and was non-inferior in the total population (11.5 vs. 10.7 months $p = 0.0199$) with favorable safety. Furthermore, pembrolizumab and chemotherapy combination was superior to EXTREME in terms of OS in both the CPS $\geq$20 (14.7 vs. 11.0 months, $p = 0.0004$) and CPS $\geq$1 (13.6 vs. 10.4 months, $p < 0.0001$) populations and in the total population (13.0 vs. 10.7 months, $p = 0.0034$). Based on these results, in June 2019, FDA has approved pembrolizumab for the first line treatment of patients with recurrent/metastatic HNSCC. Pembrolizumab and chemotherapy combination has been approved for all patients, while single agent pembrolizumab has been approved for patients with PD-L1 CPS>1; therefore, assessment of PD-L1 score has become clinically relevant for treatment selection.

In addition to pembrolizumab, other PD-1/PD-L1 antibodies have been investigated in HNSCC. Nivolumab has been assessed in the landmark phase III CHECKMATE 141 trial, which compared nivolumab to 2nd line chemotherapy or cetuximab in patients with platinum refractory HNSCC (115). Patients treated with Nivolumab had a significant improvement in OS; although OS benefit was not statistically significant in the subgroup of patients with a PD-L1 expression <1%, nivolumab received FDA approval for the treatment of platinum refractory disease regardless PD-L1 status. On the other hand, the anti-PD-L1 antibody durvalumab has been evaluated in a phase II study in 111 patients with platinum pre-treated HNSCC; a high PD-L1 expression level of $\geq$ 25% was required for inclusion in the study (116). Durvalumab was associated with an ORR of 16.2%; interestingly, HPV-positive patients had a numerically higher response rate than HPV-negative patients (29.4 vs. 10.9%).

EMERGING BIOMARKERS

Skeletal Muscle Mass

In recent years, body composition research in cancer patients has accelerated due to the use of routinely performed, diagnostic CT or MRI imaging for quantification of the different body compartments. Evidence is mounting that an abnormal body composition, in specific a low skeletal muscle mass (SMM), is an adverse predictive and prognostic factor in cancer patients. The most commonly used method for SMM measurement in cancer patients is on CT imaging a single CT slide at the level of the third lumbar vertebra (L3). The cross-sectional muscle area at this level is then normalized for height by dividing it by the squared height, in order to calculate the lumbar skeletal muscle index (lumbar SMI). This method has been validated in studies using whole body MRI, in which it has been shown that skeletal muscle area on a single transversal slice at the level of L3 is strongly correlated with total skeletal muscle volume as measured using whole body MRI (117, 118).

Abdominal CT imaging is frequently routinely performed in patients with certain cancer types during diagnostic work-up and follow-up, allowing for routine evaluation of SMM in these patients without the burden or costs of additional diagnostics. However, because abdominal CT imaging is not routinely performed in head and neck cancer (HNC), this method is not clinically applicable in HNC patients. It is known that risk factors for having a low SMM, such as malnutrition, and chronic inflammation, are highly prevalent in HNC patients (119).

Recently, a novel method to assess SMM on a single transversal CT slice at the level of the third cervical vertebra (C3) was published (120). Using this method, skeletal muscle mass is assessed measuring the skeletal muscle areas of the paravertebral muscles and the sternocleidomastoid muscles at the level of the C3 vertebra. This method allows for evaluation of SMM in HNC patients on routinely performed imaging, in a similar manner as is used in patients with other types of cancer. This measurement method has been validated in studies using whole body MRI (121), appears to be also applicable on MRI of the head and neck (122) and has a high interobserver and intraobserver agreement (123, 124). Also others found measurement of skeletal muscle area at level C3 a good alternative for measurement at level L3 (125).

Low SMM has been found to be predictive for complications and toxicity and prognostic for survival in HNC patients. Low SMM was predictive for wound complications, in particular pharyngocutaneous fistula after total laryngectomy in several studies. In 235 HNSCC patients undergoing total laryngectomy patients with low SMM (measured at C3) had more pharyngocutaneous fistulas than patients with normal SMM (34.9 vs. 20.6%, $p = 0.019$) and prolonged hospital stay (median 17 vs. 14 days, $p < 0.001$). In multivariate analysis, low SMM (HR: 2.1 95% CI: 1.5–2.9), and high N-stage were significant prognosticators of decreased overall survival (126). In retrospective analysis of 60 advanced laryngeal cancer patients who underwent total laryngectomy low skeletal mass area of paravertebral muscles at level C3 was predictive for wound complications (127). In a retrospective medical chart review of 70 patients who underwent laryngectomy low SMM, as measured at the level of L3, was an independent predictor of the occurrence of (wound) complications (128).

Low SMM was found to be also predictive for chemotherapy dose-limiting toxicity (CLDT) in patients with locally advanced HNC treated with 3 weekly high dose cisplatin concurrent radiotherapy using the C3 measurement tool. Patients with low SMM experienced CDLT three times more frequently than patients with normal SMM (44.3 vs. 13.7%, $p < 0.001$) and received a higher dose of chemotherapy/kg lean body mass (estimated from SMM, $p = 0.044$). At multivariate analysis, low SMM was independently inversely associated with CDLT (OR 0.93, 95%CI: 0.88–0.98). Patients experiencing CDLT had a lower overall survival than patients who did not (mean 36.6 vs. 54.2 months, $p = 0.038$) (129). In a study of 246 HNC patients with low SMM (measured at level C3) receiving concurrent chemoradiation were more likely to require radiation treatment breaks and suffer chemotherapy toxicity. Low SMM was also associated with worse overall survival and progression-free survival in HNC patients, except for p16-positive oropharyngeal cancer patients (130). Also in another study of 221 HNC patients receiving concurrent chemoradiation, patients with low SMM (measured at L3) required radiotherapy interruption more frequently (131).

In a retrospective study of 441 HNC patients low SMM (measured at L3) was associated with significantly poorer survival compared to non-sarcopenic patients, with the strongest association seen among overweight/obese patients (132). This negative impact on overall survival was confirmed in another study of 260 HNC patients in which SMM was measured at L3 (133). Another recent study showed that pre-treatment and post-treatment diminished SMM measured at L3 had about 3-fold increased risk of overall recurrence or death (134). Low SMM measured at L3 was also a prognostic factor affecting overall survival in advanced oropharyngeal cancer patients, independent of HPV status (135).

The exact mechanisms of the relation between low SMM and adverse outcomes are currently unknown. It is also unknown to which extent the negative effect of sarcopenia can be overturned by improving a patient's physical condition and nutritional status before and during treatment. Treatment strategies may be personalized to the patient's specific body composition to decrease the risk of adverse outcomes.

Next Generation Sequencing (NGS)

During the past few years, next generation sequencing (NGS) offers the opportunity for molecular characterization and has therefore expaned our knowledge of genetic profiles in a variety of solid tumors. In head and neck cancer, several retrospective studies have reported the presence of mutations of genes in cohorts of largely HPV-negative HNSCC, most notably TP53, PIK3CA, CDKN2A, the TERT promoter, and NOTCH pathway gene alterations (136–139). In a landmark report, Stransky et al. analyzed whole-exome sequencing data in 74 HNSCC tumor-normal pairs and found that the majority harbored mutations associated with tobacco exposure (136). In addition to identifying

TABLE 1 | Role of biomarkers in HNSCC.

Marker	Mechanism	Prognostic role	Predictive role	Diagnostic role	Limitations	Validated
HPV	Oncogenesis-driver in OSCC	Yes	No (2 clinical trials negative, other trials still ongoing)	Yes (Cancer of unknown primary presenting with cervical LNs)	Lack of specificity, applicable only in OSCC	Yes
PET imaging	-	Yes (high pretreatment SUV)	Yes (indication of residual disease for performing LN dissection)	Yes (stage, treatment response)	Appropriate interval between treatment completion and PET unclear, not always available	Yes
Tobacco	Inflammation and tobacco carcinogen-induced DNA damage	Yes (inferior treatment outcomes)	No	No	Demographic parameter	Yes
Immunoscore	Quantification of CD3+ and CD8+ TILs in the tumor core and the invasive margin of resected tumors	Yes (high number of TILs improve survival)	No (being assessed for response to immunotherapy)	No	Not always available	Yes
PD-L1	Mediates the inhibition of T cell activity	Yes (conflicting)	Yes (response to immunotherapy)	No	Technical issues in measurement	Yes
Skeletal muscle mass	Abnormal body composition	Yes (poor survival)	Yes (wound complication, fistula after laryngectomy, chemotherapy toxicity)	No		No
Next generation sequencing	Oncogenesis drivers	Yes (TP53, NOTCH1, CDKN2A mutations)	No	No	Cost, Not always avalaible	No

HPV, Human Papilloma Virus; LN, lymphnode; OSCC, Oropharyngeal Squamous Cell Carcinoma; PD-L1, Programmed Death-Ligand-1; SUV, Standardized Uptake Value; TILs, Tumor Infiltrating Lymphocytes.

previously known HNSCC genes (TP53, CDKN2A, PTEN, PIK3CA, and HRAS), the authors also demonstrated mutations in genes that regulate squamous differentiation (e.g., NOTCH1, IRF6, and TP63) (136).

On the other hand, Seiwert et al. focused more on HPV positive HNSCC by performing massively parallel sequencing of 617 cancer-associated genes in 120 matched HNSCC tumor/normal samples of which 42.5% were HPV-positive (140). It was demonstrated that HPV-positive tumors have a significantly different mutational profile compared to their HPV-negative counterparts, with unique mutations in DDX3X, FGFR2/3 genes and aberrations in PIK3CA, KRAS, MLL2/3, and NOTCH1 (Seiwert). In a more recently published prospective study, target sequencing was performed in 92 HNSCC tumors and matched blood samples (141). The most common mutations identified were TP53 was (51%), CDKN2A (25%), CCND1 (24%), and PIK3CA (21%); TP53, CDKN2A, and CCND1 gene alterations were present more frequently in HPV-negative tumors, while HPV-positive tumors were significantly associated with immune signature-related genes. In addition, several mutations such as NOTCH1 CDKN2A and TP53 were found to be prognostic for poor survival (141). **Table 1** summarizes the role of biomarkers in HNSCC.

CONCLUSIONS

Identification of appropriate biomarkers can lead to early detection of HNSCC. It is commonly accepted that a tumor biomarker is a molecular signal or process-based change that reflects the status of an underlying malignant disease and can be detected by one or more assays or tests. However, a tumor biomarker must be characterized by accuracy, reproducibility and reliability in order to be clinically useful and guide management. In HNSCC, several biomarkers have emerged, showing promising results in diagnosis, early detection and prognosis of HNSCC. HPV DNA/p16 for the determination of HPV status, PET imaging and PDL1 are validated diagnostic and prognostic/predictive biomarkers currently used in clinical practice. In the future, other patterns of molecular markers, such as interferon-γ signature and tumor mutational burden, alone or in co-ordination with imaging markers, could be utilized for early detection and prognosis of HNSCC. Importantly, better understanding of the complex tumor-immune cell interactions will contribute to the development of exceptional prognostic markers and therapeutic avenues, with the view to improve patient outcomes.

AUTHOR CONTRIBUTIONS

PE: writing-original draft preparation. RdB: editing and writing of the manuscript. IK: data acquisition and interpretation. AP: conceptualization, design, writing-review and editing, and supervision. All authors had read and approved the final manuscript.

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REVIEW
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Quality Assessment in Supportive Care in Head and Neck Cancer

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Quality assessment is a key issue in every clinical intervention, to be periodically performed so to measure the adherence to standard and to possibly implement strategies to improve its performance. This topic is rarely discussed for what concerns supportive care; however, it is necessary to verify the quality of the supportive measures; "supportive care makes excellent cancer care possible," as stated by the Multinational Association of Supportive Care in Cancer (MASCC). In this regard, the quality of supportive care in head and neck cancer patients is a crucial topic, both to allow administration of treatments according to planned dose intensity or surgical indications and to maintain or improve patients' quality of life. This paper aims to provide insight on state of the art supportive care and its future developments for locally advanced and recurrent/metastatic head and neck cancer, with a focus on quality assessment in relation to surgery, radiotherapy, and systemic therapy.

Keywords: supportive care, head and neck cancer, quality assessment, multimodal treatment, surgery, chemotherapy, radiotherapy

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DEFINING THE CONTEXT: WHY SUPPORTIVE CARE IS NECESSARY IN HEAD AND NECK CANCER?

The diagnosis of head and neck cancer (HNC) represents one of the most challenging scenarios in oncology, which both the affected patient and the treating physician have to deal with. To a variable extent, throughout its natural history, the progression of HNC is associated with an increasingly heavier burden of symptoms, altering the ability to eat, drink, swallow, speak, and breathe normally. Intrinsically, HNC may be the cause of severe pain (1), significant reduction of dietary intake (2), uncontrolled bleeding (3), disfigurement (4), psychological distress (5), social retirement (6), and overall marked impairment in quality of life (7). Moreover, the extent of symptoms induced by the disease may have a detrimental effect on survival. In view of the biological aggressiveness of HNC at a loco-regional level, symptom control is one of the key treatment goals pursued both in the curative and palliative setting, taking also into account that many patients consider it as their top priority even over survival (8–10).

Multimodal management of HNC is frequently associated with prohibitive toxicity. In ensuing randomized phase III trials where cisplatin-radiotherapy (RT) combination was the treatment backbone in control arms, severe toxicity rates ranged between 81.7 and 87.6% (11–13). Surgical

management of HNC is also complex, with post-operative complications yielding a 19.4% readmission rate within 30 days of reconstruction surgery in referral centers (14). For recurrent and/or metastatic (RM) disease, first-line standard of care (cetuximab combined with platinum−5-fluorouracil doublet) is associated with substantial toxicity (82% incidence of grade 3/4 adverse events) (15). More recently, the Keynote-048 clinical trial showed the efficacy of anti-PD1 (programmed death protein 1) pembrolizumab both as monotherapy and in addition to cisplatin-5-fluorouracil doublet (16); therefore, supportive care should focus also on the management of immune-related adverse events, such as endocrinopathies (e.g., hypothyroidism, hypophysitis), liver toxicity, and diarrhea.

Given these premises, supportive care is of paramount importance along the whole disease trajectory of HNC: it entails all the pharmacological interventions and domain-specific processes aimed to prevent, manage, and mitigate the multifactorial burden of symptoms that may occur as a consequence of the disease and/or its treatments (**Figure 1**). The timely implementation of intensive supportive care is crucial for oncologic success in patients with head and neck cancer. In this perspective, a virtuous circle can be envisaged (**Figure 1**): ensuring that patients receive the intended treatment intensity is of utmost importance for HNC outcome: delivering >200 mg/m^2 cisplatin dose (17), avoiding RT breaks (18), keeping a time interval <50 days between surgery and RT start (19) and achieving a prolonged treatment duration with maintenance cetuximab (20) are such known examples. In addition, addressing the acute side effects induced by multimodal treatment with adequate supportive care may be extremely relevant in order to prevent or mitigate the transition to late consequential toxicity (21). Many HNC survivors are burdened with long-lasting symptoms inflicting on their quality of life and global functioning (22), ultimately leading to potential non-cancer-related (intercurrent) mortality (23). How to assess the quality of supportive care received by the patients throughout their disease trajectory, how to control for its application and how to capture its potential impact on treatment outcome are unmet needs in head and neck oncology. The complexity of care for HNC is reflected by the notion that being treated at low-volume centers may be detrimental to survival (24, 25), underlining the importance of multidisciplinary expertise in treating the disease but also of other factors, such as the prompt availability of multidimensional supportive care.

This paper aims to provide insight on state of the art supportive care and its future developments for locally advanced and RM HNC, with a focus on quality assessment in relation to surgery, RT, and systemic therapy (**Table 1**).

FIGURE 1 | Virtuous cycle of the supportive care in head and neck cancer.

QUALITY OF SUPPORTIVE CARE IN SURGERY

Prevention of Infections and Methods for Evaluating Their Application

Surgical site infection (SSI) is a relatively frequent complication that may follow any type of surgical procedure, potentially resulting in delayed wound healing, wound breakdown, fistula formation, and compromised tissue reconstruction. Various organizations have developed guidelines detailing evidence-based criteria aimed to minimize this issue in different surgical specialties (26, 27). However, while commonly accepted antiseptic interventions represent the mainstay of surgery, head, and neck surgical procedures may need specific considerations on some of these concepts (28). A first consideration is that, in order to optimize outcomes and improve data collection, surgical patients should be assessed in a standardized manner: adequately classifying wound type (i.e., World Health Organization classification), determining risk factors for SSI, applying a predetermined protocol of antibiotic prophylaxis (AP), and assessing SSI according to accepted grading scales (29, 30).

Secondly, it should be underlined that AP is still a widely debated issue in head and neck surgery. In spite of growing evidence on its ideal duration, there is a lack of high-quality data concerning the choice of antibiotic type. Furthermore, AP is frequently administered on the basis of local indications or surgeon's personal choice, without relying on sound evidence-based criteria.

Considering available data, clean surgical procedures (e.g., thyroidectomy, parotidectomy, and submandibular gland excision) do not routinely require AP, since SSI occur in <1% of patients (31). However, the upper aerodigestive tract mucosal lining is often disrupted during head and neck surgery, resulting into a "clean-contaminated field." In this setting, a series of randomized trials clearly established the need for AP (32–34). Both randomized trials and retrospective reviews showed no additional benefits for a duration of AP longer than 24 h (35–39). In fact, prolonged courses of AP did not improve protection against SSI and had a higher incidence of antibiotic-related complications. In this field, antimicrobial stewardship programs play a pivotal role in monitoring and improvement of antimicrobial use and patient outcome (40, 41), granting the use of an appropriate antibiotic spectrum, dosage, and duration needed to prevent or treat infection, thus decreasing the use of extended spectrum agents. In fact, selection of antibiotics

TABLE 1 | Main issues in supportive care for HNC patients and proposed quality metrics.

Treatment	Supportive care issues	Quality metrics
Surgery	Prevention of SSI	Presence of evidence-based guidelines on antibiotic-prophylaxis based on prevalence of SSI and resistances to antibiotics
	Perioperative pain management	Standardized assessment of pain and its characteristics for every pt Pre, intra, and postoperative analgesic protocols
	Nutritional rehabilitation after surgery on the upper aerodigestive tract	Rate of pts with oral diet within the 5th postoperative day
Radio(chemo)therapy	Nutritional assessment before and during radio(chemo)therapy	Rate of pts receiving validated nutritional screening tools (e.g., NRS-2002, MNA, MST, MUST)
	Nutritional enteral/parenteral support	Adherence to International guidelines (e.g., ESPEN guidelines)
	Prevention of swallowing problems related to RT	Presence of a swallowing program Involvement of physiatrists/speech therapist in the MDT
	Treatment of RT-induced pain	Continuous assessment of pain during RT Protocol of treatment for background and breakthrough cancer pain
	Prevention and treatment of mucositis	Adherence to international guidelines (e.g., MASCC guidelines)
	Prevention of major infections during chemotherapy and/or RT	Rate of major infections during treatments Knowledge about pathogenic microorganisms and patterns of antibiotic resistance
	Psychological distress during treatment	Rate of pts receiving screening for distress Involvement of psycho-oncologists in the MDT (as needed)
Palliative care	Early approach with simultaneous care in the RM phase of disease	Quality of life and pt's satisfaction Rate of unplanned access to emergency services Rate of pts dying in hospice or with a home care
	Avoiding active oncological treatments in the end-of-life period	Rate of pts receiving a new treatment in the last 3 months of life Rate of pts receiving any systemic treatment in the last month of life

SSI, surgical site infections; Pt, patient; RT, radiation; MDT, multidisciplinary team; MASCC, Multinational Association of Supportive Care in Cancer; RM, recurrent and/or metastatic.

is influenced by regional policies, availability, and resistances. Ideally, each Institution should evaluate prevalence of SSI and distribution of resistances to provide evidence-based guidelines on the best AP in each setting.

Pain Control After Surgery: Guidelines and Application

Widely accepted guidelines and indications on postoperative pain (PP) control in head and neck surgery are lacking. However, it should be noted that effective management of acute PP reduces morbidity, hospitalizations, and hospital costs, while increasing patient satisfaction (42). On the other hand, narcotic medication regimens commonly used to treat PP are associated with constipation, nausea, and long-term addiction (43, 44). Consequently, the main objectives of pain management approaches are to provide an optimal PP control, while reducing the need or dose of opioids, and minimizing drug-related sequelae/side effects. In order to meet these requirements, the type of surgery should be classified according to its related pain levels (45). This allows to apply a standardized perioperative pain management protocol encompassing the pre-, intra-, and post-operative phases, aimed at maximizing efficacy while minimizing opioid use. In fact, preventive analgesia can decrease central sensitization and hyperalgesia (46), leading to a significant reduction in PP medication requirements (47). In particular, available data on otolaryngology does not show a significant increase in the risk of postoperative bleeding using NSAIDs (48), justifying their routine use before shifting to opioids. Adjunctively, local and regional intraoperative anesthesia proved to reduce analgesic consumption in the postoperative period without any increase in PP (47).

Pain should be constantly assessed using standardized scales, such as numerical rating scale or visual analog scale. Pain characteristics (background, breakthrough, and swallowing-related pain) ought to be recorded and detailed as well, in order to better tailor treatments (49).

Pre-habilitation in Surgery: the ERAS Protocol Example

The Enhanced Recovery After Surgery (ERAS) protocol represents a multimodal and multidisciplinary approach to surgical patients aimed to enhance the quality of recovery after surgery. ERAS program includes different items encompassing preoperative patient preparation, reduction of stress response to surgery, prevention of complications, and rapid return to normal functions. Cooperation of different specialists, patient collaboration, and continuous internal audit to improve the adherence to the protocol are key-points to success.

The experience in HNC is very limited, although critical issues specific to head and neck patients (cancer-related malnourishment, high comorbidity burden due to smoke and alcohol, postoperative swallowing rehabilitation, tracheostomy) may negatively impact the risk of complications and the length of hospitalization.

TABLE 2 | The most relevant domains for ERAS protocol in head and neck cancer patients.

Preadmission education, aimed at preparing both the patient and the family to the expected recovery course
Preoperative nutritional evaluation, and implementation of a nutritional plan to correct a malnourishment status (with possible placement of a nasogastric tube, or gastrostomy tube)
Reduction of preoperative fasting and administration of a carbohydrate-enriched drink to reduce catabolism and insulin resistance
Thromboembolic and antibiotic prophylaxis
Correct anesthesiologic management, which includes prevention of hypothermia and adequate perioperative fluid load (near zero balance, or goal-directed fluid therapy)
Postoperative nausea and vomit prophylaxis, and pain management
Mobilization within the first 24 h and postoperative pulmonary physical therapy
Early postoperative nutrition (within 24 h) and early oral feeding
Restricted indications to tracheotomy and timely decannulation with surgical closure, which can speed up swallowing recovery and shorten hospitalization

In 2017, an international expert group in collaboration with ERAS Society published a consensus protocol on the optimal care of patients undergoing major head and neck surgery (50); these recommendations represents the "state-of-the-art" guidelines to implement an ERAS protocol in HNC (**Table 2**).

The most relevant and controversial aspect of a rapid rehabilitation in head and neck is probably early oral feeding after surgery on the pharyngolaryngeal axis. A systematic review including four cohort studies and four randomized clinical trials demonstrated that an early and gradual reintroduction of an oral diet (between the 2nd and 5th postoperative day) after total (pharyngo)laryngectomy is not associated with an increased risk of salivary fistula (51). Conversely, it shortens the hospital stay with a possible positive impact on patients' psychological status and costs (52).

Overall, only a few papers regarding the implementation of an ERAS program in head and neck cancer have been published so far. Imai et al. compared 28 patients treated in accordance to an ERAS protocol to an historical control group and demonstrated a reduction in complication rate (17.9 vs. 36.7%; $p = 0.07$), while no difference was found according to the hospitalization time (53). Conversely, Bater et al. showed a relevant shortening in hospitalization (10 vs. 14 days; $p = 0.003$), while no difference in complication and readmission rates was evident (54). Surprisingly, McMahon et al. found no advantage for ERAS program in any outcome (55); however, they did not report any data on compliance to the protocol, which is widely recognized as one of the major factor to improve recovery outcomes (56). Overall, evidence-based data to assess the degree of benefit of an ERAS protocol in head and neck surgery is currently lacking, and large, high-quality studies are warranted. Another relevant pending question is the possible delay of adjuvant treatments due to early rehabilitation protocols. So far, the implementation of an ERAS protocol has never shown any increase of complication rate, or hospitalization length that could support this risk; however, this aspect should be considered as a relevant quality indicator in future studies.

QUALITY ASSESSMENT IN SUPPORTIVE CARE IN RADIATION WITH OR WITHOUT SYSTEMIC THERAPY

RT and chemoradiotherapy (CRT) are widely used in patients with locally advanced HNSCC, both as curative and postoperative approaches. There is a link between the compliance with the programmed therapeutic plan and outcome; this association can be preserved through the implementation of an integrated supportive care plan, declined into its nutritional, swallowing, exercise, psychological, and symptom control dimensions. Therefore, compliance to the treatment can mirror the quality of the supportive care implemented in the patient's pathway.

Nutritional Support

Weight loss during RT/CRT is associated with a significant toxicity, especially in terms of mucositis, often leading to malnutrition. In some cases, weight loss-induced body shape change leads to the necessity of re-planning of RT plan (57, 58).

Nutritional screening assessment at baseline is paramount to better frame the actual needs of each patient, in order to provide prompt interventions. After screening, periodical nutritional assessments are strongly recommended during CRT as well (59). As in every field of HNC patients' management, also for nutritional support a multidisciplinary approach is essential to tailor patients' needs and to address specific therapeutic strategies. To provide evidence-based standard of care while prescribing enteral and parenteral nutrition, adherence to international guidelines is strongly recommended (60) and adherence to guidelines should be considered a way to assess quality of the center.

Swallowing Exercises

In HNC patients, dysphagia is an important treatment-related side effect in patients treated with RT or CRT. This symptom can lead to severe life-threating complications, such as aspiration pneumonitis and malnutrition, and a feeding tube is often needed.

Several reports showed swallowing exercise may improve dysphagia and quality of life (61–65). However, since adherence to behavioral intervention may vary among patients, again a multidisciplinary approach is strongly encouraged (66). Indeed, the involvement of physiatrists and speech therapists could provide a precious help in keeping a better compliance and in avoiding both early and late complications. In this regard, quality assessment of prevention and cure of this symptom should be performed considering whether the center has implemented a swallowing program and whether a multidisciplinary group is involved.

Pain Therapy

Radiation-induced mucositis causes severe pain and poor oral intake, and often results in unplanned treatment breaks, clinic visits, and hospitalizations.

Pain during RT usually worsen in the second half of treatment period, then improve 1–2 weeks after the conclusion

of RT/CRT. Risk of treatment-related pain depends mainly on the distribution of RT dose on organs at risk (67).

Local approaches to prevent oral mucositis should be encouraged. In particular, an adequate oral hygiene and sodium bicarbonate oral rinses should be started since the beginning of treatment (68, 69). Whenever the pain of focal sites of mucositis are not controlled by treatments, the topical application of lidocaine can improve the symptom greatly, even if for a limited time period (49). To prevent painful radiodermatitis, there is strong evidence supporting the efficacy of gentle washing and moistening of the wound healing environment (70–72).

A thorough pain control program should include an early detection of the symptom and a prompt start of major analgesic therapy, generally overtaking the traditional three steps proposed by the World Health Organization (WHO). Indeed, to control odynophagia strong opioids (e.g., oral morphine sulfate) should be started precociously on an around-the-clock basis, especially before meals (73). Then, in case of background pain not manageable with dose escalation, a prolonged-release strong opioid should be started. In this regard, the use of opioids as pain treatment, tailoring the treatment according to background and breakthrough pain could be considered as metrics of the quality in head and neck cancer care.

Physicians expert in pain therapy should be involved in case of pain not manageable with pharmacological and non-pharmacological approaches.

Infections

HNC patients are known to be generally immunosuppressed (74). In this setting, the potential harm of treatment-induced further immunosuppression plays a definite role in determining a higher risk of infections. As previously mentioned, the prevention of oral and oropharyngeal mucositis and neck radiodermatitis through local approaches is crucial. Indeed, the radiation-induced solution of continuity of the natural integrity of the anatomical barrier made of anatomically intact mucosa or skin can be an entrance gate for infections. Moreover, chemotherapy-induced neutropenia may impair further the ability to fight against infections. In addition, some medical devices like central intravenous catheters could be a further significant risk factors for systemic infections.

For these reasons, an accurate follow-up with acute phase reactants (e.g., C-reactive protein; procalcitonin in case of bacterial infections) should be performed, especially in patients receiving chemotherapy. Indeed, fever may not be observed due to the anergy of head and neck cancer patients.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, whereas septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality (75). These definitions should be always kept in mind while approaching a HNC patient experiencing a systemic infection during RT/CRT. In case of acute infections in frail patients, antimicrobial drugs should be promptly started, taking into account the specific epidemiology of the geographic area.

Therefore, quality in preventing and treating infections in HNC patients can be measured by the rate of major infections during treatment and by the knowledge about the most frequent microbiological causes of infection, as well as the pattern of antibiotic resistance typical of that area.

Availability of Psychological Consultation

Between 22 and 35% of RT outpatients report clinically relevant psychological distress (76–80) and they often negatively influence treatment compliance.

Distress screening for all patients receiving RT is recommended and patients' wish for psychological support should be detected. Both patients and their caregivers should be psychologically assessed, and these evaluations should be carried on constantly during treatments (81). This is the reason why psycho-oncologists should be involved in multidisciplinary HNC boards.

One of the most commonly used distress screening questionnaires is the National Comprehensive Cancer Network (NCCN) Distress Thermometer, sometimes administered with its modifiable Problem Checklist (82). It is advisable that quality assessments of the psychological support offered to patients are regularly carried out. Possible indicators are the rate of admitted/screened patients, the adherence of the patient to the agreed schedule and his/her satisfaction that could be investigated thanks to dedicated questionnaires.

QUALITY ASSESSMENT IN SUPPORTIVE CARE DURING TREATMENT FOR RECURRENT AND/OR METASTATIC DISEASE

The Concept of Simultaneous Care to Allow for Better Patient Care

Patients with RM HNC suffer of physical, emotional, and functional symptoms, which greatly impact on their quality of life. Symptoms often affect vital functions such as eating, talking, and breathing. The facial aspect is often altered, as well as taste, hearing, and swallowing. Moreover, compared to other cancer sites, HNC patients have the highest intensity of pain (83). These aspects suggest the need of high levels of palliative and supportive care both for the patients and their family caregivers. In this regard, we need a defined framework to provide supportive and palliative care which can be directly embedded in the trajectory of care of RM HNC patients. Multimodal multidisciplinary interventions are essential for RM patients, including for instance nutritional, pain, psychological aspects, as well as targeting functional issues (84).

From this point of view, RM HNC patients are candidates for high levels of palliative and supportive care interventions from the earliest stages of diagnosis.

Indeed, a meta-analysis showed that early palliative care is able to improve patients' quality of life (85). Therefore, this precious support should not be considered only in the last months of life.

In oncology, the early onset of a palliative and supportive care in oncology patients treatment showed to favorably impact

on patients' quality of life, perception of disease, and also on end-of-life choices; more controversial is the beneficial effect on OS (86).

Recently, a study in brain cancers, a setting of care sharing challenges of physical, psychological, and functional issues with HNC patients, tried to set guidelines for supportive/palliative care (87). Similarly, there is a need to set a defined framework for the early introduction of supportive care in RM HNC patients, involving family members and caregivers as well as healthcare professionals. The compliance with this feasible framework could represent one element to evaluate how the patient is cared for.

In this regard, the assessment of the quality of supportive care during the RM phase of disease is extremely important to improve the treatment of these very frail patients. Metrics of evaluation could be represented by the number of unplanned accesses to emergency services or unplanned visits to oncology department, by the quality of life reported by the patients and caregivers and by the more controversial issue of patient's awareness about prognosis.

Another quality metric, even if difficult to be objectively measured, is the ability of the multidisciplinary team following RM HNC patients to anticipate and address emergency symptoms, such as airway obstruction and bleeding.

Discussing End of Life Choices: the Importance to Make It Early

The conventional model of shared decision-making has been shown not to fit with HNC patients suffering from pain, discomfort, and fear of imminent death (88). Often, they rely on trust and confidence with the physician, accepting treatments in the hope of "doing something" against the disease.

Therefore, anticipating the discussions about choices regarding nutrition and breathing problems, type of pain therapy, and intensity of active oncological treatment is essential to define a shared pathway of care, which could also take the patient's preferences into considerations.

The trade-off between quantity and quality of life is the crucial point in the approach to RM patients, particularly after failing a first-line treatment. An open discussion should incorporate the topics of prognosis, incremental benefit expected by a new treatment, possible complications induced by the disease and by the therapies themselves. Incorporating the results of this discussion into the patient's chart should be considered as one of the tasks of the check list of patients presenting with RM disease. Periodic re-evaluation of these choices is necessary, as patients expectations and desires may change during time.

Quality Assessment: Chemotherapy in the End of Life Period

Avoiding to perform chemotherapy in the last month (or 14 days) of life is one of the point any oncologist should consider to improve patient's quality of life and to perform an open discussion about the end of life choices (89–91). Prolonged administration of chemotherapy when clinical conditions are worsening is often a waste of time and quality of life for the patient, with an increase of toxicities, admission to emergency room and unnecessary exams and hospital visits. Continuous assessment of patients who died from cancer receiving chemotherapy in the last period of life has been considered as a key quality measure. A low-value care for patients in this setting is defined as any treatment not impacting on survival and not improving quality of life (92).

An early involvement of the supportive and palliative team is a central issue to allow better patient information and care and to avoid administering chemotherapy in the last period of life (93, 94).

CONCLUSIONS

The topic of quality assessment is rarely discussed for what concerns supportive care; however, it is necessary to verify the quality of the supportive measures because "supportive care makes excellent cancer care possible," as it is stated by the Multinational Association of Supportive Care in Cancer (MASCC). In this regard, next step to implement supportive care in HNC should be the creation of checklists specific to each setting of treatment. Compliance with them should be employed to judge the quality of support given. Moreover, there is a strong need to increase well-conducted and scientifically sound researches in this setting, so to increase the quality of evidence and strengthen the existing guidelines.

Expert consensus papers (95–98), guidelines and survivorship care plans (99, 100) provide useful indicators for clinical practice, which are center-specific; tools to measure the quality of supportive care at an individual level are critically lacking. In view of the growing elderly and frail population affected by HNC and the ceiling of toxicity reached with standard treatments, clinical investigations on this broad topic are warranted.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Head and Neck Cancer in Belgium: Quality of Diagnostic Management and Variability Across Belgian Hospitals Between 2009 and 2014

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Aims: The study assessed the quality of diagnosis and staging offered to patients with a head and neck squamous cell carcinoma (HNSCC) and the variability across Belgian hospitals.

Methods: In total, 9,245 patients diagnosed with HNSCC between 2009 and 2014, were identified in the population-based Belgian Cancer Registry (BCR). The BCR data were coupled with other databases providing information on diagnostic and therapeutic procedures reimbursed by the compulsory health insurance, vital status data, and comorbidities. The use of diagnosis and staging procedures was assessed by four quality indicators (QI) (i.e., use of dedicated head and neck imaging studies, use of PET-CT, TNM reporting and interval between diagnosis and start of treatment), for which a target was defined before the analysis. The association between the binary QIs and observed survival was assessed using Cox proportional hazard models adjusted for potential confounders.

Results: Overall, 82.5% of patients received staging by MRI and/or CT of the head and neck region before the start of treatment. In 47.6% of stage III–IV patients eligible for treatment with curative intent, a whole-body FDG-PET(/CT) was performed. The proportion of patients whose cTNM and pTNM stage was reported to the BCR was 80.5 and 78.4%, respectively. The median interval from diagnosis to first treatment with curative intent was 32 days (IQR: 19–46). For none of these QIs the pre-set targets were reached and a substantial variability between centers was observed for all quality indicators. No binary QI was significantly associated with observed survival.

Conclusions: The four quality indicators related to diagnosis and staging in HNSCC all showed substantial room for improvement. For none of them the pre-set targets were met at the national level and the variability between centers was substantial. Each Belgian hospital received an individual feedback report in order to stimulate reflection and quality improvement processes.

Keywords: head and neck cancer, squamous cell carcinoma, quality indicators, quality of care, variability in care, diagnosis, staging

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INTRODUCTION

In 2016, there were 2,694 new diagnoses of head and neck cancer in Belgium, 2,005 in males and 689 in females. The mean age at diagnosis was 64 years (1). In Belgium, head and neck cancer is the 4th most frequent tumor in males (6% of all malignancies) and the 11th most frequent in females (2%) (2). Compared to other European countries, Belgium has a very high incidence rate of head and neck cancer: Belgium ranks second for males (after France) and fourth for females (after Denmark, France and the Netherlands) (2). The 5-year relative survival rate for the Belgian 2009–2013 cohort was about 51% in males and 58% in females (2). By 2025, the annual number of patients diagnosed with head and neck cancer is expected to rise to more than 3,000 (3).

In Belgium, adult patients with head and neck cancer can be treated in any acute care hospital, leading to a wide dispersion of care. Only very recently, the first initiative has been taken to concentrate care for adults with complex and/or rare cancers: reference centers have been appointed for pancreatic and esophageal surgery (4, 5).

In recent years, the Belgian Health Care Knowledge Center (KCE) and the Belgian Cancer Registry (BCR) have collaborated intensively in quality improvement initiatives for cancer patients. These start with the development of clinical practice guidelines, followed by the development and the assessment of a set of quality indicators, the formulation of policy recommendations and last but not least individual feedback provided to all hospitals. This improvement cycle has been completed for rectal (in collaboration with PROCARE), breast, testicular, esophageal, gastric, and lung cancer (6–10). Each time clinical experts from Belgian hospitals have been heavily involved.

Given the important burden of head and neck cancer in Belgium and the complexity of its management, this cancer was selected for the following improvement cycle. Evidence-based guidelines for the diagnosis and treatment of squamous cell carcinoma of the oral cavity and the oropharynx, hypopharynx, and larynx were published by KCE in 2014–2015 (11, 12). The present study describes the quality of diagnosis and staging offered in Belgium to patients diagnosed with a squamous cell carcinoma of the head and neck (HNSCC) between 2009 and 2014. The patterns and quality of therapeutic care will be elaborated in a dedicated article.

MATERIALS AND METHODS

Data Collection

Population-based data from the nationwide Belgian Cancer Registry were used. In Belgium, cancer registration is compulsory for hospitals and for pathology laboratories (13). Completeness of incidence has been estimated to be at least 98% of all cancer cases in Belgium from 2004 onwards (14).

The BCR database comprises the following patient and tumor characteristics: age at diagnosis, gender, WHO/ECOG (Eastern Cooperative Oncology Group) performance status score [from score 0 (i.e., fully active, able to carry on all pre-disease performance without restriction) to score 4 (i.e., completely disabled; cannot carry out any self-care; totally confined to bed or chair)], clinical and pathological TNM stages (according to the 6th version of the TNM classification for incidence year 2009 and the 7th version for incidence years 2010–2014) (15, 16), and topography and histology of the tumor (ICD-O-3). The RARECAREnet definition layer 2 of topography and histology combinations was used to classify tumors into the four anatomic groups (i.e., oral cavity, oropharynx, hypopharynx, and larynx, http://www.rarecarenet.eu/). The incidence date was defined as the date of the first histopathological confirmation of the tumor.

The patients' unique social security identification number was used to link the BCR data with (a) data from the Intermutualistic Agency (IMA) providing details on diagnostic and therapeutic procedures reimbursed by the compulsory health insurance starting from 1 January of the year preceding the incidence year, until 31 December of the fifth year after the incidence year; (b) hospital discharge data, comprising (among others) the diagnosis for hospitalization, the principal and secondary diagnoses, available from 1 January of the year preceding the incidence year, until 31 December of the year following the incidence year; and (c) the vital status data of the included patients retrieved from the Crossroad Bank of Social Security (until 14 December 2017). These linkages have been approved by the Sector Committee of Social Security and of Health (Health Section) of the Belgian Privacy Commission (17, 18). At the start of this study, IMA-data were available at the BCR up to June 2016. Based on hospital discharge data, a modified version of the Charlson Comorbidity Index was calculated (19). As only patients with unique HNSCC were included in the study, the categories "Any malignancies, including leukemia, and lymphoma" and "metastatic solid tumor" were left out to calculate the index (20).

Among the 15,339 patients identified in the BCR database with head and neck cancer diagnosed in the period 2009–2014, 12,756 were diagnosed with a squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx, or larynx. IMA-data were available for 98.3% of these patients. Patients with multiple invasive tumors ($N = 3,287$) were excluded from the analyses, in order to maximally ensure that recorded diagnostic and therapeutic procedures were indeed performed for HNSCC and not for another malignancy. After additional exclusion of those patients who died around the time of diagnosis or who were lost to follow-up, a final cohort of 9,245 patients with a unique HNSCC was included.

In order to assess the concordance between the diagnostic and therapeutic procedures identified in the administrative database and the information available in the hospitals (e.g., medical files, financial data, considered as "gold standard"), a validation study and subsequent data checks were performed before the analysis of the quality indicators. It led to a further optimization of the code selections to define diagnostic and therapeutic procedures which were used for the calculation of the quality indicators (20).

Quality Indicators

A long list of potential quality indicators (QIs) was derived from published papers and quality reports, which was supplemented with QIs derived from the KCE guidelines and QIs suggested by the clinical experts. They were scored by a panel of 11

clinical experts, BCR and KCE for their relevance on a 1–5 scale. The in- and exclusion of QIs was further discussed during two consensus meetings. The 33 remaining QIs were then judged for their measurability based on the available data. To that end, the availability of administrative data for every single element of the quality indicator was evaluated. Finally, 12 measurable QIs were retained. Of these, 4 QIs assessed diagnosis and staging, 6 the processes of care and 2 QIs assessed the outcomes of care (post-treatment mortality and survival). Whenever applicable, a target was defined by expert consensus before the analysis of the QI. More information on the selection of the QIs has been published earlier (20).

The present paper focuses on the 4 QIs assessing diagnosis and staging, more precisely on the use of MRI and/or contrast-enhanced CT of the primary site and draining lymph nodes before treatment with curative intent, the use of FDG-PET(/CT) within 6 weeks before the start of treatment, the reporting of TNM staging to the BCR and the time interval between diagnostic confirmation and the start of first treatment with curative intent.

Hospital Allocation

For the benchmarking of QIs between hospitals, it was essential to identify in which hospital patients received their diagnostic and therapeutic care. In other words, each patient had to be assigned to a center, irrespective of whether the patient had received care in one or in more than one hospital.

In 63% of patients all therapeutic procedures were performed in the same hospital. For the patients who received treatment in more than one hospital, the following hierarchy was given in the assignment of the center of main treatment: center of surgery (with curative intent) if applicable, center of radiotherapy (with curative intent) if applicable, followed by the center of systemic therapy. The center of first treatment took the center of surgery with curative intent, the center of radiotherapy with curative intent and the center of systemic therapy into account. The center where the first of these treatments was performed, was selected as the center of first treatment. In other words, if induction chemotherapy was given in center A and thereafter surgery in center B, the patient was assigned to center A when benchmarking was based on the center of first treatment and was assigned to center B when benchmarking was based on the center of main treatment. The diagnostic acts were not included in the assignment algorithms as it was judged the responsibility of the therapeutic center that all essential diagnostic information was collected before the start of first treatment.

For each QI it was decided before the start of the analysis whether benchmarking between hospitals should be done based on the center of main treatment (QI 1, 2, and 4) or based on the center of first treatment (QI 3) and thus which assignment algorithm had to be applied. More details can be found in an earlier publication (20).

Statistical Analyses

Center Variability

The variability between centers is presented in scatter and funnel plots. In the latter, the estimate of an indicator is plotted on the vertical axis vs. its precision on the horizontal axis. As we were dealing with binary indicators, the estimates were plotted vs. the number of observations of the hospitals, because the precision on the proportion of a binary indicator is proportional to the unit size. The binomial distribution was used for the construction of the 95 and 99% prediction limits; the observed overall indicator result was used as the population or reference value.

As underreporting of TNM stage information (see Results section) may bias the results, those centers which had reported for <50% of their assigned patients stage information to the BCR, were represented differently (i.e., by an open triangle) in the funnel plots.

Observed Survival Analysis

Survival time was calculated from the incidence date to the date of death or until the last known date alive. The survival probability over the 0–5 year time interval was modeled with Cox proportional hazards models. Patients surviving beyond 5 years were censored at 5.05 year. Non-proportional hazards between the levels of categorical covariates were evaluated in a univariate way. Detected non-proportional hazards were resolved with a "piece-wise proportional hazards model" (i.e., proportionality assumption holds within time intervals). Then all covariates (i.e., baseline patient case mix variables: gender, age group at diagnosis, WHO performance status, combined stage, anatomic site, the Charlson Comorbidity score, and the number of previous inpatient bed days) were combined in the Cox model, including their non-proportional hazard terms. If the latter were no longer significant, they were dropped in a backwards elimination strategy. Second order interactions between the covariates were evaluated in a backwards elimination model building procedure. The model assumptions were evaluated on the basis of Schoenfeld and generalized Cox-Snell residuals (21, 22); no strong violations were observed. Clustering of patients within hospitals was taken into account by adding hospital as a random effect to the regression model. No imputation techniques were applied in case of missing observations for a covariate; they were assigned to the category "missing."

The analysis methods were agreed and finalized before the analyses were started. All analyses were performed anonymously and are reported anonymously. Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Description of the Cohort at the Time of Diagnosis

Three quarters of the 9,245 included patients were men (**Table 1**); the mean age at diagnosis was 62.3 years. Sixty percent of the 8,812 patients with available hospital discharge data had no recorded comorbidities. For those with comorbidities, the most prevalent were chronic pulmonary disease (19.4%), diabetes without chronic complications (8.0%), and peripheral vascular disease (5.6%).

Two thirds of the patients in whom clinical stages were reported were diagnosed in an advanced stage of the disease (cIII–IV, 66.7%; **Figure 1**), but this proportion varied

TABLE 1 | Patient and tumor characteristics at the time of diagnosis.

	Total (*N* = 9,245)		Oral cavity (*N* = 2,665)		Oropharynx (*N* = 2,745)		Hypopharynx (*N* = 1,137)		Larynx (*N* = 2,698)	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Gender										
Male	7,017	75.9	1,770	66.4	1,998	72.8	974	85.7	2,275	84.3
Female	2,228	24.1	895	33.6	747	27.2	163	14.3	423	14.3
Age group										
<50 years	930	10.1	339	12.7	319	11.6	84	7.4	188	7.0
50–59 years	3,058	33.1	869	32.6	1,013	36.9	437	38.4	739	27.4
60–69 years	3,047	33.0	772	29.0	916	33.4	411	36.2	948	35.1
70–79 years	1,481	16.0	410	15.4	364	13.3	146	12.8	561	20.8
≥80 years	729	7.9	275	10.3	133	4.9	59	5.2	262	9.7
Adapted charlson comorbidity index										
0*	5,359	60.8	1,548	61.8	1,598	61.6	609	55.4	1,604	61.3
1–2*	2,747	31.2	777	31.0	769	29.7	393	35.8	808	30.9
3–4*	557	6.3	145	5.8	183	7.1	69	6.3	160	6.1
>4*	149	1.7	35	1.4	43	1.7	28	2.5	43	1.6
No data available	433		160		152		38		83	

**The % for the adapted CCI were calculated excluding the missing data.*

considerably among the different anatomic sites. For all HNSCC patients who had surgery and for whom the pathological stage was reported to the BCR, pathological stage I and IVA were most common (32.8 and 35.6%, respectively). Yet, for hypopharyngeal SCC the majority of patients (68.5%) were diagnosed with a p-stage IVA.

The 9,175 HNSCC patients who could be assigned to a center of main treatment, were treated in 99 different centers.

Main Diagnostic and Staging Procedures

The most frequent imaging exams performed in the time span 3 months before until 3 months after the incidence date, were CT of the neck (92.5%) and RX of the thorax (73.3%; see **Table 2**). A MRI of the neck was performed in 30.1% of cases, ranging from 19.3% in laryngeal SCC to 37.7% in oropharyngeal SCC patients. PET(/CT) was performed in 47.9% of the total study population, with an obvious difference between the different anatomic sites (36.0% in laryngeal SCC vs. 62.3% in hypopharyngeal SCC). The most commonly performed endoscopic procedure was tracheoscopy/laryngoscopy (84.9%), which was performed in 60.0% of patients with oral cavity SCC and in 98.6% of patients with laryngeal SCC. For almost all patients (98.7%), a biopsy of the primary tumor was taken. A multidisciplinary team (MDT) meeting was recorded for 82.3% of the total study population. Additional analyses in the BCR database (results not presented) revealed that over the time span 2004–2014, the proportion of HNSCC patients discussed during a MDT meeting increased substantially. The most pronounced advances were recorded for laryngeal and oropharyngeal SCC: from 42 and 46% in 2004 to 84 and 83% in 2014, respectively.

Quality Indicator 1—Proportion of Non-metastatic HNSCC Patients Who Underwent MRI and/or Contrast-Enhanced CT of the Primary Site and Draining Lymph Nodes Before Treatment With Curative Intent

According to the guidelines, MRI is the preferred technique for primary T- and N-staging in oral cavity SCC and highly recommended in hypopharyngeal, laryngeal, and oropharyngeal SCC. However, a contrast-enhanced CT can replace MRI when (a high quality) MRI is technically impossible, likely to be distorted, or not timely available (11, 12). Overall, 25.4% of patients were staged by MRI and another 57.1% by CT, within 6 weeks before the start of treatment. The overall result (i.e., 82.5%) was below the target set at 90% (**Table 3**).

About 10 centers fell below the 99% prediction interval; only 15 centers (16%) reached the target (**Figure 2A**).

Quality Indicator 2—Proportion of HNSCC Patients Who Underwent FDG-PET(/CT) Within 6 Weeks Before Start of Treatment

A whole-body FDG-PET(/CT) is recommended for the evaluation of metastatic spread at distant sites and/or the detection of second primary tumors in patients with stage III–IV HNSCC while it is not recommended in stage I–II HNSCC (11, 12). In less than half of stage III–IV patients who underwent treatment with curative intent (47.6%), a whole-body FDG-PET(/CT) was performed, which was far below the target (≥90%, **Table 3**). On the other hand, 22.9% of stage I–II patients

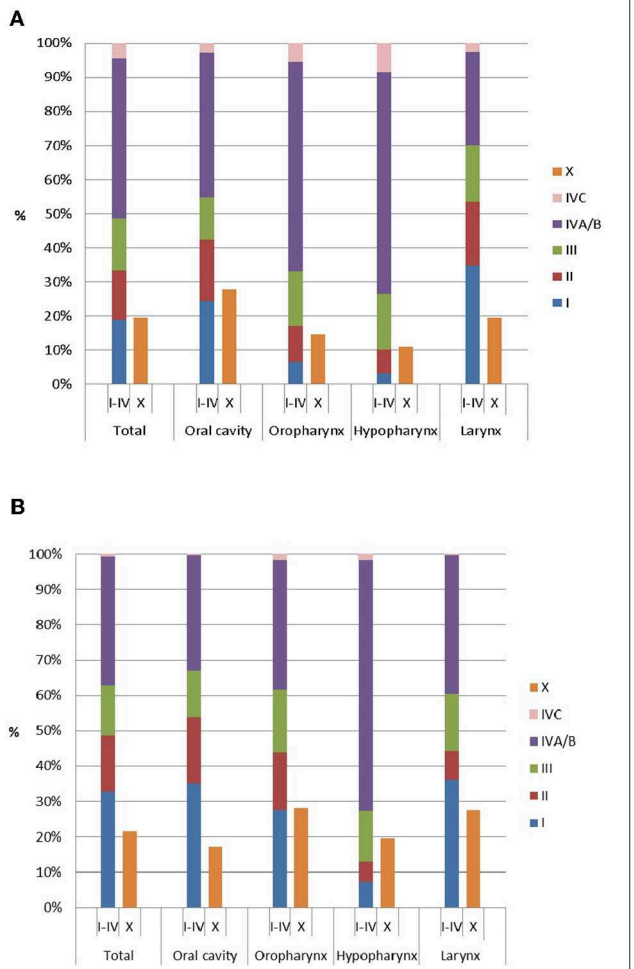

FIGURE 1 | Distribution of **(A)** clinical and **(B)** pathological stage (of surgically treated patients) by anatomic site.

who underwent any treatment had a FDG-PET(/CT), which is largely above the target (≤5%) and deemed thus unnecessary.

For FDG-PET(/CT) in stage III–IV patients, no center reached the target (**Figure 2B**), while 42 out of 86 centers performed a whole-body FDG-PET(/CT) in more than 5% of the assigned stage I–II patients (**Figure 2C**).

Quality Indicator 3—Proportion of HNSCC Patients Whose TNM Stage Information Was Reported to the Belgian Cancer Registry (BCR)

As this study is based on administrative data (hence no access to medical files), a proxy approach was used to assess the staging of the included patients: the completeness of the data transferred to the BCR was evaluated. For 80.5% of patients with HNSCC the cTNM stage was reported to the BCR, which was below the target defined by the clinical experts (95%, **Table 3**). Overall, the pTNM stage of 78.4% of patients who underwent surgery with curative intent was reported. For cTNM as well as pTNM, the proportion of patients whose staging information was reported to the BCR was much higher among those who were discussed during a MDT meeting (cTNM: 87.3 vs. 49.0%; pTNM: 81.7 vs. 64.5%).

About 15% of the centers were situated below the 99% prediction interval for clinical staging (**Figure 2D**) and about 11% for pathological staging (**Figure 2E**). Only a limited number of centers reached the target of 95%.

Quality Indicator 4—Median Time Between Incidence Date and Start of First Treatment With Curative Intent

Overall, the median interval from diagnosis to first treatment with curative intent was 32 days [Interquartile range (IQR): 19–46; **Table 3**]. When surgery was the main treatment modality this lag time was shorter (24 days, IQR: 1–40); the median delay to start of primary radiotherapy was 36 days (IQR: 26–49). Patients who received their first treatment in the same center where the diagnosis was confirmed, were treated within a shorter time frame (26 days, IQR: 10–39) than patients who were referred to another center for treatment (37 days, IQR: 26–52).

A large variability was observed between centers; the median time from incidence to treatment varied between 0 and 50 days when benchmarking was done based on the center of main treatment (**Figure 2F**).

Association Between Quality Indicators and Observed Survival

In final analyses, the association between the binary quality indicators and observed survival was assessed, taking the baseline patient case mix variables into account. As is presented in **Table 4**, none of the associations was statistically significant.

DISCUSSION

Three quarters of this national cohort of patients with HNSCC were male and nearly 60% of the study population was 60 years or older at the time of diagnosis. These observations are in line with other publications that illustrate that head and neck cancers occur predominantly in males and the older segment of the population (23, 24). Also in this study population the majority of patients was diagnosed late, which is a major concern in head and neck cancers where early detection is difficult to achieve (23, 25). One of the factors that contributes to the late diagnosis of head and neck cancers is patient delay (26, 27).

The complexity of head and neck cancers, the close proximity of functionally important anatomic structures and the fact that patients are often elderly with medical comorbidities, necessitate the coordinated professional efforts of a highly specialized multidisciplinary team to guarantee the best oncological outcome and to prevent and adequately manage any adverse effect of treatment (24, 28). Evidence from recent years illustrates that this multidisciplinary approach is beneficial for head and neck cancer patients and leads to improved survival rates (29–33). In this study group more than 80% of patients were discussed during a MDT meeting. Probably, the real frequency of MDT meetings is

TABLE 2 | Diagnostic and staging procedures performed within 3 months around the incidence date of HNSCC.

Category	Total (*N* = 9,245)		Oral cavity (*N* = 2,665)		Oropharynx (*N* = 2,745)		Hypopharynx (*N* = 1,137)		Larynx (*N* = 2,698)	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Imaging										
RX thorax	6,772	73.3	2,086	78.3	1,921	70.0	892	78.5	1,873	69.4
RX swallow mechanism /esophagus	682	7.4	45	1.7	162	5.9	171	15.0	304	11.3
RX larynx	108	1.2	12	0. 5	15	0.6	31	2.7	50	1.9
CT neck	8,548	92.5	2,289	85.9	2,644	96.3	1,111	97.7	2,504	92.8
CT skull	1,700	18.4	494	18.5	554	20.2	272	23.9	380	14.1
MRI neck	2,783	30.1	920	34.5	1,035	37.7	307	27.0	521	19.3
MRI head	589	6.4	274	10.3	188	6.9	48	4.2	79	2.9
PET(/CT)	4,425	47.9	1,093	41.0	1,653	60.2	708	62.3	971	36.0
Ultrasound neck	1,763	19.1	428	16.1	726	26.5	304	26.7	305	11.3
Ultrasound abdomen	3,178	34.4	991	37.2	1,005	36.6	426	37.5	756	28.0
Endoscopy										
Tracheoscopy/laryngoscopy	7,844	84.9	1,598	60.0	2,478	90.3	1,108	97.5	2,660	98.6
Bronchoscopy	1,874	20.3	465	17.5	582	21.2	312	27.4	515	19.1
Nasal endoscopy	745	8.1	147	5.5	275	10.0	121	10.6	202	7.5
Screening digestive tract	5,445	58.9	1,345	50.5	1,786	65.1	885	77.8	1,429	53.0
Histopathology										
Biopsy of primary tumor	9,127	98.7	2,640	99.1	2,697	98.3	1,110	97.6	2,680	99.3
Lymph node biopsy	320	3.5	68	2.6	156	5.7	46	4.1	50	1.9
Cytology	1,746	18.9	354	13.3	711	25.9	303	26.7	378	14.0
Multidisciplinary team meeting	7,608	82.3	2,071	77.7	2,358	85.9	1,009	88.7	2,170	80.4

HNSCC, head and neck squamous cell carcinoma.

TABLE 3 | Overview of 4 quality indicators for diagnosis and staging of HNSCC patients diagnosed in 2009–2014.

Number	Quality indicator	n/N	Result (%)	Target (%)
QI 1	Proportion of non-metastatic HNSCC patients who underwent MRI and/or contrast-enhanced CT of the primary site and draining lymph nodes before treatment with curative intent	6,630/8,039*	82.5	90
QI 2	Proportion of HNSCC patients who underwent FDG-PET(/CT) within 6 weeks before start of treatment Stage I–II	544/2,372**	22.9	≤5
	Stage III–IV	2,198/4,619**	47.6	≥90
QI 3	A. Proportion of HNSCC patients whose cTNM stage was reported	7,444/9,245	80.5	95
	B. Proportion of HNSCC patients who had surgery, whose pTNM stage was reported	2,758/3,518	78.4	95
QI 4	A. Median time between incidence date and start of first treatment with curative intent	(*N* = 8,040***)	32 days (IQR: 19–46)	ND

*ND, not defined; *328 patients with distant metastases and 878 patients who did not receive treatment with curative intent within six months of the incidence date were excluded from the analyses; **1801 patients with missing cTNM information were excluded from the analyses; ***327 patients with distant metastases and 878 patients who did not receive treatment with curative intent within six months of the incidence date were excluded from the analyses.*

underestimated, due to (among others) the reimbursement rules (34). For instance, from 2003 to 2010 only one MDT meeting per patient per calendar year was reimbursed by the health insurance and thus "traceable" in the administrative data (34). Yet, one should realize that these data do not reveal whether the MDT meeting was attended by sufficiently experienced medical and paramedical experts and whether it also resulted in a multidisciplinary approach throughout the whole care process (20).

Precise specification of clinical and pathological stage is an essential step in the clinical cancer pathway as it helps in planning the treatment or the renouncement of treatment (so that under- or overtreatment can be avoided), but it aids as much in predicting the patient's prognosis (35, 36). Still, the four process indicators related to diagnosis and staging which were assessed in the present study all showed substantial room for improvement. Overall 82.5% of non-metastatic patients who received treatment with curative intent were staged with MRI and/or CT of the head and neck area before the start of the first treatment, which was below the pre-set target of 90%. Yet, the results are in the order of what was observed in England and Wales (2013–2014) (37), or in Ontario (2010) (38), where 17.8

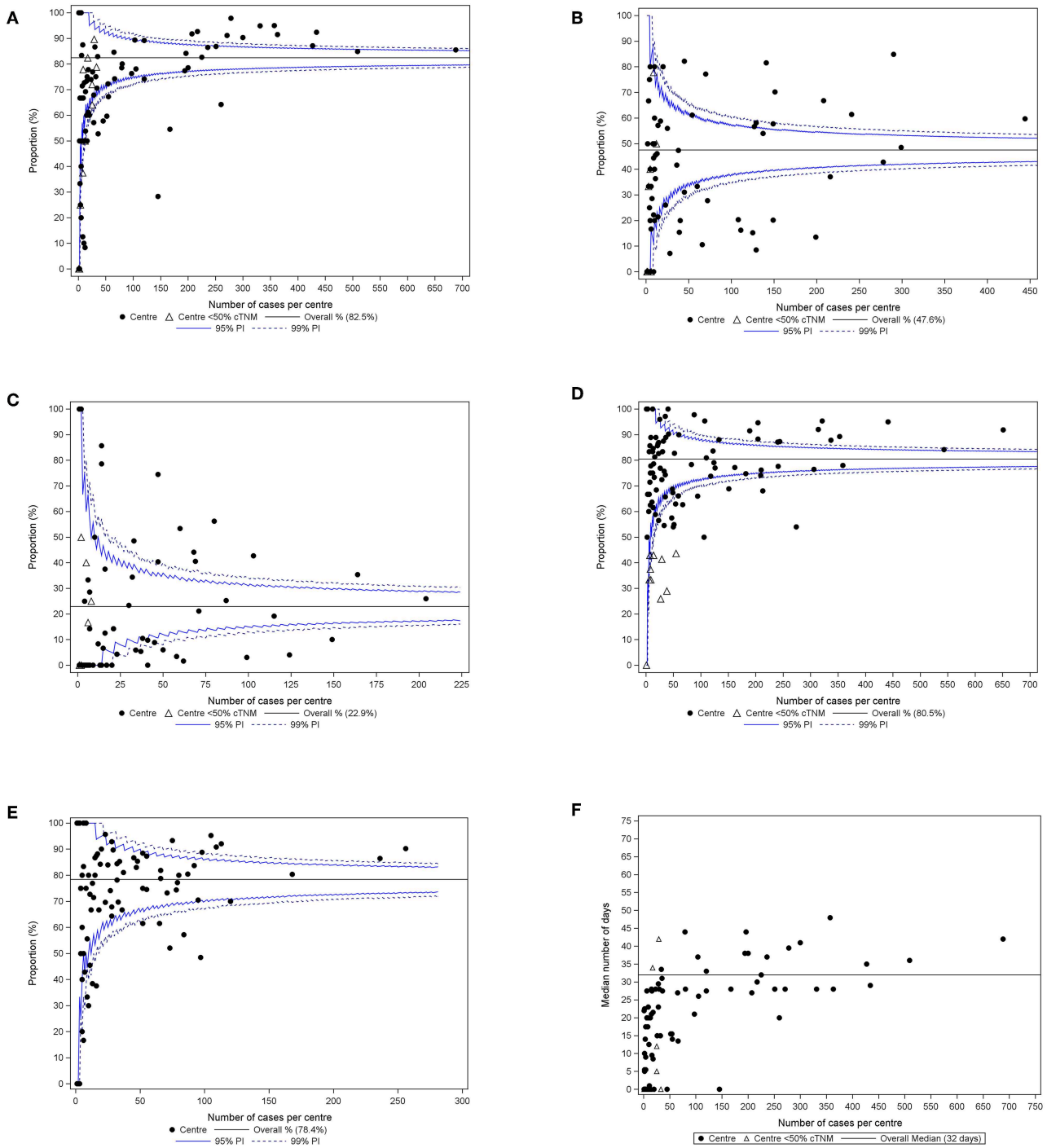

FIGURE 2 | (A) Proportion of HNSCC patients who received treatment with curative intent in whom a MRI and/or CT was obtained within 6 weeks before the start of the first treatment, by center of main treatment. Ninety-six centers reported in the funnel plot; centers which reported for <50% of their assigned patients cTNM to the BCR, are represented by an open triangle. **(B)** Proportion of clinical stage III-IV HNSCC patients who underwent treatment with curative intent in whom a whole-body FDG-PET(/CT) was obtained within 6 weeks before start of the first treatment, by center of main treatment. Eighty-seven centers reported in the funnel plot; centers which reported for <50% of their assigned patients cTNM to the BCR, are represented by an open triangle. **(C)** Proportion of clinical stage I–II HNSCC patients in whom a whole-body FDG-PET(/CT) was obtained within 6 weeks before start of the first treatment, by center of main treatment. Eighty-six centers reported in the funnel plot; one patient is not included in the analyses as he/she could not be assigned to the center of main treatment, but his/her data are included in the analyses for the overall result; centers which reported for <50% of their assigned patients cTNM to the BCR, are represented by an open triangle. **(D)** Proportion of HNSCC

(Continued)

FIGURE 2 | patients whose cTNM was reported to the BCR, by center of first treatment. One hundred and one centers reported in the funnel plot; 132 patients were not included in the analyses because they could not be assigned to a center of first treatment, but their data are included in the analyses for the overall result; centers which reported for <50% of their assigned patients cTNM to the BCR, are represented by an open triangle. **(E)** Proportion of HNSCC patients whose pTNM was reported to the BCR, by center of main treatment. Ninety-six centers reported in the funnel plot. **(F)** Time from incidence date to first treatment with curative intent, by center of main treatment. Ninety-six centers reported in the scatter plot; centers which reported for <50% of their assigned patients cTNM, are represented by an open triangle. PI, prediction interval.

TABLE 4 | Association between quality indicators and observed survival.

Quality indicator	Hazard ratio* [95% CI]
Proportion of non-metastatic HNSCC patients who underwent MRI and/or contrast-enhanced CT of the primary site and draining lymph nodes before treatment with curative intent	1.10 [0.99, 1.22]
Proportion of HNSCC patients who underwent FDG-PET[/CT] within 6 weeks before start of treatment—Stage III–IV	1.00 [0.92, 1.09]
Proportion of HNSCC patients whose cTNM stage was reported	1.12 [0.99, 1.27]
Proportion of HNSCC patients who had surgery, whose pTNM stage was reported	0.86 [0.73, 1.01]

**Hazard Ratios for all-cause death (yes vs. no) were corrected for baseline patient case mix variables: gender, age group at diagnosis, WHO performance status, combined stage, anatomic site, the Charlson Comorbidity score and the number of previous inpatient bed days.*

and 28%, respectively, of all diagnosed patients did not obtain staging information with CT, MRI, PET(/CT), or ultrasound prior to treatment. Although MRI is preferred for the staging of oral cavity SCC and highly recommended in the other anatomic sites, CT was twice as frequently performed as MRI in Belgium (57.1 vs. 25.4%, respectively). This may in part be explained by differences in availability of both technologies: the number of registered CT scans is currently at least twice the number of MRI scans. Obligatory registration of this equipment only started in 2016 (39), but one can assume that a similar ratio was also relevant for the period 2009–2014. In addition, the medical team may opt for a CT as the longer duration of a MRI examination may cause difficulty with breathing and may often be associated with movement artifacts. But also, performing a MRI of the larynx and hypopharynx requires an experienced radiologist coupled with adapted high end hard (MR and coils) and software (right sequences and software to speed-up examination) (40).

Even though a whole-body FDG-PET(/CT) is recommended in patients with clinical stage III–IV HNSCC (11, 12), it was performed in less than half of this subgroup within 6 weeks before start of the first treatment with curative intent. Several factors may explain these sub-optimal results. First of all, until 2016, staging of primary head and neck cancer was not included in the list of reimbursed indications for FDG-PET(/CT) and during the study period the overall availability of and access to FDG-PET(/CT) in Belgium was limited. In addition, there may be a slight underestimation of the real number of patients who underwent FDG-PET(/CT), as in some patients this examination may have been performed in the referring center and may have fallen outside the time frame of 6 weeks set for this quality indicator. Last, some patients may have undergone FDG-PET(/CT) in the frame of a clinical study (e.g., imaging study), which is then not included in the administrative database used for the present study as it could not be billed. Yet, no less than 22.9% of patients with early stage HNSCC, for whom this exam is not recommended, had a whole-body FDG-PET(/CT). The results illustrate that more efforts are needed in this field so that the right group of patients benefits from this diagnostic tool but equally that unnecessary exposure to irradiation and unnecessary use of costly equipment can be avoided.

In Belgium, hospitals are legally bound to report all new cancer diagnoses to the BCR, whether or not the patient is discussed during a MDT meeting (41). In parallel, the law stipulates that pathology laboratories have to transfer (among others) stage information of the pathology specimens they have received to the BCR (13). It is thus difficult to understand that clinical and pathological stage information was not reported for 19.5 and 21.6% of patients, respectively. Part of the lower than expected reporting on cTNM may be found in the underreporting of Tis and T1, especially in case of laser resections and excisional biopsies of the oral cavity. But also, in those cases where no malignancy was suspected before the surgical intervention cTNM may not have been reported to the BCR. Difficulties in accurate staging was also illustrated in other countries (37).

Timely treatment of (head and neck) cancer is essential, not only to increase the chance for cure and to increase survival rates, but also to alleviate the symptoms as soon as possible (42, 43). Half of the study population received the first treatment with curative intent within 32 days. Although the results compared favorably with those reported in other European countries (37, 44, 45), inspiration for a further improvement in this field can for instance be obtained in Denmark, where organizational reforms coupled with the implementation of a fast track program resulted in significant reductions of waiting times between diagnosis and treatment, for both surgery and radiotherapy (43). The observation that the time delay for radiotherapy was longer than for surgery, may be explained by the fact that for radiotherapy the preparatory phase needs more time. In addition, patients who will receive radiotherapy in the head and neck region, should have a thorough pre-radiotherapy dental assessment and, when indicated, treatment (46, 47). In case tooth extractions are performed, it is important to allow sufficient healing time prior to the commencement of radiotherapy. Patients who received their first treatment in the same center where the diagnosis was confirmed, started their treatment within a shorter time frame than their peers who were referred. These data should not be misinterpreted to suggest that referring patients is detrimental. The improved survival at academic and comprehensive centers

is indicative of the opposite (48). It has been suggested that treatment of head and neck cancers in high volume centers mitigates some portion of mortality risk due to prolonged time to treatment, but referral of patients should be well-organized to avoid harmful delays (48).

The funnel and scatter plots indicate that for the four QIs under study the variability between centers was substantial. For all indicators the variability between centers was more than what could be expected based on random variability. For one indicator (FDG-PET(/CT)) in advanced stage disease (**Figure 2B**), none of the centers achieved the set target. In order to improve the current situation, each Belgian hospital received an individual feedback report with its own results for the QIs, benchmarked to those of all other hospitals (which were kept blinded). The concept is that mirror-information may act as a catalyst for quality improvement in care, which ultimately may lead to a better quality of care offered to patients with head and neck cancer. In addition, it can be speculated that the centralization of care for head and neck cancer in a limited number of hospitals (at present adult patients with head and neck cancer can be treated in any acute care hospital in Belgium), will further reduce the variability between centers. At least in a Canadian study, adherence rates to guideline-recommended processes of care in the surgical management of patients with head and neck cancer were higher in high (surgeon and hospital surgical) volume centers than in low volume centers (38).

The observation that none of the binary diagnosis and staging related QIs was significantly associated with all-cause observed survival, after correction for baseline case-mix variables, is not surprising. Many other process (e.g., type of treatment, timing of treatment) and structure (e.g., hospital volume, equipment, financing) indicators may have a more pronounced impact on survival in head and neck cancer. They will be the subject of further analyses.

One of the major strengths of this study is that the quality of diagnosis and staging for 9,245 patients diagnosed with a single squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx could be assessed in a population-based database, covering more than 98% of all cancer cases in Belgium (14). Yet, the major strength of the study is at the same time also its major weakness. The interpretation of the administrative data was not always straightforward, due to among others the lack of specificity of the claims data (e.g., vague codes which may refer to a diagnostic as well as a therapeutic procedure), but also due to the careless registration in some hospitals (e.g., cTNM, pTNM, start date of radiotherapy).

In conclusion, the four process indicators related to diagnosis and staging in head and neck squamous cell carcinoma all showed substantial room for improvement. For none of them the pre-set targets were met at the national level and the variability between centers was substantial. Individual feedback reports have been sent to each Belgian hospital in order to stimulate reflection and quality improvement processes.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. The datasets for this manuscript are not publicly available because it concerns coded data at an individual level, i.e., data from the Belgian Cancer Registry (BCR) enriched with health claims data obtained via the Intermutualistic Agency (IMA/AIM). Authorization from the Belgian Data Protection Authority is necessary to access the data. Requests to access the datasets should be directed to Dr. Liesbet Van Eycken, director Begian Cancer Registry, elizabeth.vaneycken@kankerregister.org.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RL, CD, SS, VS, LV, GS, EV, IS, VG, SN, and JV contributed to the conception and design of the study and performed data interpretation. CD, VS, and GS analyzed the data. RL wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Best Practice in Surgical Treatment of Malignant Head and Neck Tumors

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Purpose of review: Defining the best practice of surgical care for patients affected by malignant head and neck tumors is of great importance. In this review we aim to describe the evolution of "best practice" guidelines in the context of quality-of-care measures and discuss current evidence on "best practice" for the surgical treatment of cancers of the sino-nasal tract, skull base, aero-digestive tract, and the neck.

Recent findings: Current evidence based on certain structure and outcome indicators, but mostly based on process indicators already helps defining the framework of "Best practice" for head and neck cancer surgery. However, many aspects of surgical treatment still require in-depth research.

Summary: While a framework of "Best practice" strategies already exists for the conduction of the surgical treatment of head and neck cancers, many questions still require additional research in particular in case of rare histologies in the head and neck region.

Keywords: head and neck cancer, paranasal sinus, skull base, quality assurance, surgery, best practice

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INTRODUCTION

Defining "best-practice" of surgical care for head and neck cancer patients is of utmost importance (1). The purpose of this article is to first summarize the evolution of such "best-practice" guidelines in the context of quality assurance (QA) programs for head and neck cancer surgery. Secondly, we will outline current evidence to be considered for "best-practice" in the field of sino-nasal/skull base, upper-aerodigestive tract, and neck surgery. Data and views provided in this review will help to define, what should be considered "best-practice" in the field of head and neck surgery in the future.

EVOLUTION OF QUALITY ASSURANCE FOR HEAD AND NECK CANCER SURGERY

History

The very first surgical quality improvement program was created in 1994 by the Veterans administration (VA) health system in North America (2). It consisted of the simple reporting of morbidity and mortality. For a longer period no further action was taken, until in 2001 the Institute of medicine (IoM) of the United States published an article with the title "Crossing the quality chasm," in which it was demanded to take action to further improve the quality of surgical care in the United States (US) (3). As a result, the American College of surgeons (ACS) and the

Veterans Administration health system created the national surgical quality improvement program (NSQIP). An additional political dimension was gained, when the ACS submitted in 2005 a three-phase improvement program to the US House of Representatives (4). This program was revised in 2007 focusing mainly on process indicators as the main indicators to act on (5). ACS-NSQIP is today the largest QA program for surgery in North America.

Surgical QA programs outside the US developed later. In 2014 the European cancer audit (EURECCA) was created by several European societies including the European Organization for Research and Treatment of Cancer (EORTC), the European Organization for Surgical Oncology (ESSO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society for Medical Oncology (ESMO) (6). Two years later EORTC together with ESSO and the Japanese Clinical Oncology Group (JCOG) founded a surgical care program called SURCARE. This program however had a more academic goal in aiming for high-quality standards in surgical clinical research (7). Another international society worth mentioning is the Society for enhanced recovery after surgery (ERAS). This society develops guidelines for perioperative patient care. Such guidelines have been published for head and neck free tissue transfer (8). ERAS protocols have been evaluated previously and demonstrated to improve quality of care, patient-reported and operative outcomes, and patient safety. They also help reduce costs (9).

Components and Confounders of a Quality Assurance Program

In 1966, Donabedian defined the components of a QA program. It consists of indicators allowing for measuring certain aspects of structure, processes, and outcomes (10). Structure herein refers to the characteristics of the healthcare system, the facilities, and hospital infrastructure. Processes are surgical procedures and perioperative treatment. Outcome refers to the results of the healthcare experience. This can be various survival endpoints (11). While structure and process indicators are typically dependent on the institution and/or physician, other variables influencing outcome of the patient are rather patient-driven, i.e., age, comorbidities, performance status, stage of disease, severity of intervention needed etc. (12). These variables need to be taken into consideration, since they serve as confounders and impact on the results of a quality program. Efforts have been made to identify such confounders with an impact on i.e., post-operative complications and various risk-calculators and even neural networks for risk-stratification have been developed (12, 13).

Critical Structure, Process, and Outcome Indicators

The number of patients a hospital is treating for a particular disease is commonly referred to as "patient volume." This is an important structure indicator. With respect to head and neck cancer patients high-volume hospitals have been demonstrated to provide a lower long-term mortality. The same holds true for the number of patients seen per physician commonly referred to as physician volume. Also the volume per physician has impact on long-term mortality if it comes to head and neck cancer patients (14).

Certain of these indicators have impact on survival only, if examined in the context of a particular tumor site. In a study on oral cavity cancer the "appropriate referral to radiation therapy" was found to be significantly associated with overall survival (OS), disease specific survival (DSS), and disease free survival (DFS) (15). However, for laryngeal cancers "pre-treatment multidisciplinary evaluation" was important for survival (16). A recent analysis based on the national cancer data base (NCDB) revealed that the delay to adjuvant therapy was associated with higher mortality (17). Adherence to guidelines from the national comprehensive cancer network (NCCN) to initiate adjuvant postoperative radiation therapy within 6 weeks was found to vary widely between institutions (18, 19). Therefore, continued performance monitoring is important to follow the implementation of clinical pathways (20). This monitoring can be assured by providing feedback to health care providers on performance indicators. This was recently demonstrated in a "post-feedback" cohort of head and neck cancer patients, where an improvement of the surgeon's performance next to a reduction of the length-of-stay of patients was observed (21).

Process and outcome indicators for surgical oral cavity cancer patients were recently reported. Besides a nodal yield upon neck dissection ($\geq$18), return to the operating room within 2 weeks, and re-admission within one month were associated with OS, DSS, and DFS (15). Also for laryngeal cancers nodal yield was impacted on survival (16). Another process indicator of importance with impact on mortality is obtaining a negative surgical margin (17).

WHAT IS "BEST PRACTICE" IN HEAD AND NECK SURGERY: SINO-NASAL AND SKULL BASE SURGERY

Under the umbrella term of "Cancer of the sinonasal tract and skull base" (CSTSB) a galaxy of rare histologies characterized by a wide variability of biological behavior is included. In recent years, this peculiarity led to an emphasis on the role of histology, apart from the site of origin and size of the lesion, in the decision-making process to select the ideal sequence of treatments ("histology-driven approach") (22). Surgery, which remains a fundamental step in the treatment pathway, currently offers a wide spectrum of procedures, ranging from minimally invasive, purely endoscopic approaches to extensive open resections needing complex reconstruction. In this view, it is essential to precisely define "best practice" in the management of CSTSB to offer an optimal treatment approach to each patient and render outcomes homogeneous across different centers.

However, in consideration of the unique profile of CSTSB (i.e., rarity and histologic heterogeneity), the absolute scarcity of clinical trials, and the lack of specific high level of evidence data, it is extremely difficult to formulate "best

practice" guidelines. One example is the American College of Radiology Appropriateness Criteria for cancers arising in the nasal cavity and paranasal sinuses, which rate the suitability of diagnostic and treatment procedures (23). A second example is represented by two documents on chordoma: a position paper on management guidelines (24) and a recent update on best practices for management of local-regional recurrent lesions (25). To get an idea of the paucity of data on CSTSB from well-conducted studies, a review of 71 clinical trials on skull base tumors published in 2017 showed that 83.1% investigated treatments for pituitary tumors, 15.5% for vestibular schwannomas, and 1.4% for sino-nasal/anterior skull base tumors. Furthermore, only 7.7% of trials included surgery (26).

Taking into consideration the main components of a quality assurance platform, as defined by Donabedian (10) (structure, process, and outcome), it is possible to identify several critical factors that play a role in determining treatment results in each of these settings.

"*Structure*" refers to the characteristics and facilities of the healthcare institution. Patient volume represents the most important factor influencing survival in this category. In fact, the expertise of the surgeon and multidisciplinary team are critical when dealing with rare and diverse tumors. However, data attesting improved survival in patients treated in high-volume centers are available only for head and neck cancer in general, with no specific information on CSTSB (14, 27). Of note, in this case, patient volume refers to the experience not only of treating physicians (i.e., surgeon, radiation oncologist, and/or medical oncologist), but also of other specialists involved in the diagnostic process and post-treatment surveillance. In fact, a dedicated and experienced head and neck radiologist is essential to adequately guide therapeutic decisions and follow-up strategies. Similarly, the experience of a dedicated head and neck surgical pathologist directly has an impact on adequate definition of the disease, and consequently, on the most appropriate treatment strategy. This has been demonstrated by several studies on tumors of the sino-nasal tract, showing that re-evaluation in high-volume institutions of biopsies revealed diagnostic errors in 10–23.8% of cases. (28–30). In this view, the International Collaboration on Cancer Reporting has devised specific guidelines aimed at improving and standardizing pathology reporting in sino-nasal cancer (31).

Finally, surgical approaches to the skull base and paranasal sinuses, especially endoscopic ones, require dedicated instruments and facilities. A multidisciplinary team should be able to prevent or manage each unexpected sequela or complication with specific tools (e.g., trans-nasal Doppler probe, hemostatic agents) and collaboration with different departments (i.e., neurosurgery, interventional radiology, intensive care unit).

Considering the "*process*" of patient management, "best practice" dictates some recommendations and quality measures that should be applied and evaluated in both the pre- and post-operative phases.

As a general rule, biopsy should be performed after adequate imaging (computed tomography, magnetic resonance, or both) to avoid complications related to unexpected hypervascular lesions or meningoencephaloceles. The procedure may be performed under local or general anesthesia; however, it is essential to obtain an adequate tissue volume, since unrepresentative biopsies may lead to misdiagnosis even when evaluated by experienced head and neck surgical pathologists. A recent paper suggests that this concept holds especially true when endoscopic and imaging findings suggest a high-grade malignancy (32).

Tumor excision with negative margins is the principal aim of oncologic surgery, and has been identified as one of the main metrics of the quality of surgery (17, 33). In CSTSB, achievement of this goal may require that the surgical team switches from an endoscopic to an external procedure, but involvement of vital structures (i.e., internal carotid artery, cavernous sinus) may sometimes lead to incomplete resection (R1-R2). However, when compared to all the other head and neck mucosal sites, the definition of "clear margins" for CSTSB is controversial and their assessment is hampered by a series of factors. In trans-nasal endoscopic surgery, resection of tumors is often performed through step-by-step disassembly of the lesion starting from the endonasal portion and moving to the periphery, so that assessment of margins is typically made on the most external layer of resection (i.e., dura, periorbita) and samples taken from the surgical bed (i.e., nasal, naopharyngeal, and/or septal mucosa). In external procedures as maxillectomies, an "en-bloc" resection is typically achieved. However, in view of the complexity of the anatomy together with the frequent presence of necrosis and mobile bony fragments, the correct orientation of the specimen with labeling of anatomic structures is of utmost importance to obtain proper evaluation of margins. However, this evaluation is typically dichotomic (yes or no), and no specific data on the millimetric definition of "free" or "close" margins do exist. A different scenario is encountered in tumors like chordoma and chondrosarcoma, where assessment of resection is not based on margin status, but according to intraoperative and post-operative radiologic evaluation. The absence of any visible tumor corresponds to "Gross Total Removal (GTR)." In spite of all these limitations and differences, several recent publications reporting the results of trans-nasal endoscopic surgery for sino-nasal cancer or clival chordoma reiterate the positive impact on prognosis of achieving negative margins or GTV, respectively (34, 35).

Furthermore, a process indicator that is relevant to all surgical procedures, including dural resection, is post-operative cerebrospinal fluid (CSF) leak. It is well-known that this complication can be influenced by several factors: location and size of the defect, communication with a cistern or ventricle, previous radiotherapy, and type of tissues used for reconstruction. Nonetheless, this variable should be regarded as an important quality metric and carefully monitored.

Finally, in view of the histopathologic variety and multidisciplinary management of CSTSB, non-surgical treatments should be precisely intertwined with surgery, with adequate indications and timing. In this regard, the

delay between the surgical procedure and adjuvant (chemo)-radiotherapy also represents a strong indicator of the quality of treatment and has been identified as a significant prognosticator in head and neck cancer.

With respect to survival "*outcomes,*" most series available in the literature are burdened by significant biases: they have frequently focused on a single treatment approach but include multiple histologies. However, treatment choice is predominantly histology-driven.

WHAT IS "BEST PRACTICE" IN HEAD AND NECK SURGERY: UPPER AERO-DIGESTIVE TRACT AND NECK

More than 80% of resectable head and neck tumors are squamous cell carcinomas situated in the oral cavity, oro- and hypopharynx and larynx (HNSCC). Best practice in surgery of HNSCC depends on the profound knowledge of surgical principles and a sufficient surgical experience. It consists of performing resections with clear pathological margins > 5 mm (R0) and obtaining good functional/esthetic outcome and quality of life, which is based on the appropriate choice of reconstruction (36).

Furthermore, best practice in head and neck surgery is associated with a multidisciplinary approach reflecting tumor board decisions and thinking in multimodal concepts combining surgery, oncology, and radiation oncology if needed. John "Drew" Ridge underscored this imperative in his presidential lecture "We show pictures, they show curves" at the AHNS annual meeting in 2010. He stated the need of an interdisciplinary education of head neck surgeons:" This is the only way that the future 'multidisciplinary team' will have not merely head and neck surgeons, but rather head and neck surgical oncologists as members; that is what I hope the guidelines come to reflect in years to come" (37). Recently Liu et al. (38) demonstrated that multidisciplinary tumor boards have a positive impact on head and neck cancer patient outcome, but further literature addressing questions of best practice in this field is lacking.

Moreover, within the "Choosing Wisely Canada" campaign, first recommendations of best practice in diagnostics in head and neck cancer have been published (39). Additionally, sentinel node biopsy in patients with oral cancer has been discussed comprehensively in the literature and surgical consensus guidelines have been published recently (40).

Retrospective data based on p16 testing show that HPV16 positive oropharyngeal cancer patients have a better survival prognosis than HPV16-negative regardless of their treatment, i.e., primary surgery or chemo-radiation (41). It is therefore not yet any adequate to discontinue any surgical treatment approaches to this disease, before clinical prospective trials have not clearly determined detrimental effects of surgery in this disease. Moreover, treatment de-escalation trials including non-surgical and surgical treatments are on the way, assessing the role of minimally invasive surgical techniques (transoral laser microsurgery: TLM, trans oral robotic surgery: TORS) to minimize functional deficits in HPV16 positive disease.

In 2009 the outcomes report from a multi-institutional retrospective trial was utilized by the United States Food and Drug Administration (FDA) to approve the use of the da Vinci Surgical System. TORS procedures have been described to manage pathologies at numerous anatomic sites from the glottis and hypopharynx to the nasopharynx and skull base (42). Today, there are no data showing superiority of surgical over non-surgical treatment in HPV-positive oropharyngeal carcinoma. TORS has gained clinical relevance also outside the oropharynx (43) owing to the competition between companies involved in the development of new transoral tools (44).

An older but well-established transoral technique to remove even larger but still accessible tumors of the upper aerodigestive tract is the transoral laser microsurgical (TLM) method, in which the tumor can be taken out in pieces, with precise visualization and control of the margin (45–50). This technique is well-established as part of routine treatments in many centers worldwide and useful in nearly all head and neck locations.

Furthermore, older techniques like open partial and total laryngectomies, laryngo-pharyngectomies, lateral pharyngectomies, and the broad spectrum of open surgery for the mandible, maxilla, and oral cavity have still a relevant place in the treatment of head and neck cancer and should belong to a curriculum, which should be part of a state-of-the-art head and neck surgical education. It is therefore not yet any adequate to discontinue any surgical treatment approaches to this disease, before clinical prospective trials have not clearly determined detrimental effects of surgery in this disease.

Modern techniques of reconstruction are strongly linked to the success of a surgical procedure. Potential defects and postoperative functional and cosmetic results should be discussed by both the patient and the surgeon. In addition, an oncological sound resection must be performed, meaning the surgeon must not compromise the completeness of the excision of the tumor, even if a larger or more challenging defect for a reconstruction may result. Besides pedicled flaps, microvascular free tissue transfer offers distinct advantages in head and neck reconstruction in particular for scalp, facial, oral cavity, osteo-cutaneous, and pharyngeal defects (51–54).

A notable technical advancement in microsurgery has been the introduction of perforator flaps (55). The great advantage of perforator flaps is a decreased donor site morbidity, better adaptation to the reconstructive challenge, and improved aesthetic outcome (56).

The treatment of the neck has been classified by Robbins (57) describing the different types of neck dissections. Neck dissection is a routine part of any head and neck surgical concept and can be neglected only in T1 N0 glottic cancer. This has been underscored by the results of a randomized controlled prospective trial comparing elective and therapeutic neck dissections in node-negative early-stage oral cancer demonstrating significantly higher rates of overall and disease-free survival in the elective neck dissection group (58).

Quality assurance in free flap reconstruction is strongly linked to failure rate and failure emergency surgery and should be benchmarked by comparing outcomes (59). Other surgical and medical complications, like unplanned tracheostomies, revision surgery for any reason, primary and secondary emergency hospital admission and factors linked to risk of in-hospital death should also be benchmarked based on national data sets for instance. An "Informatics-based Framework for Outcomes Surveillance (IFOS)" in Head and Neck Surgery has been proposed recently (60, 61).

Compared to sino-nasal and skull base surgery, literature on best practice in head and neck surgery of other locations is limited to guidelines, recommendations, and evidence related to controlled trials comparing mostly conservative therapy concepts, but not surgical techniques specifically. The problem of forced clinical implementation of new surgical techniques (i.e., TORS) without sufficient evidence from RCTs has been addressed already (62).

CONCLUSION

In the years ahead, the scientific community contributing to the evolution of management of sino-nasal and skull base cancer has the challenge and responsibility to collect a sufficient volume of high-quality data to answer open questions. This will help in the definition of "best practice" guidelines for surgery of CSTSB.

"Best practice" in head and neck surgery requires the concentration of such procedures in centers providing strict quality assurance based on certification processes. Moreover, center criteria like participation in clinical trials and transparency of clinical outcome should be mandatory for high quality patient care.

AUTHOR CONTRIBUTIONS

CS, AD, and PN: conceptualization. CS, PN, AD, and AP: formal analysis, investigation, and writing. CS: supervision.

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REVIEW
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Radiotherapy Quality Assurance for Head and Neck Squamous Cell Carcinoma

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The impact of radiotherapy (RT) quality assurance (QA) has been demonstrated by numerous studies and is particularly important for head and neck cancer (HNC) treatment due to the complexity of RT target volumes in this region and the multiple adjacent organs at risk. The RT planning process includes many critical steps including interpretation of diagnostic imaging, image fusion, target volume delineation (tumor, lymph nodes, and organs at risk), and planning. Each step has become highly complex, and precise and rigorous QA throughout the planning process is essential. The ultimate aim is to precisely deliver radiation dose to the target, maximizing the tumor dose and minimizing the dose to surrounding organs at risk, in order to improve the therapeutic index. It is imperative that RT QA programs should systematically control all aspects of the RT planning pathway and include regular end-to-end tests and external audits. However, comprehensive QA should not be limited to RT and should, where possible, also be implemented for surgery, systemic therapy, pathology, as well as other aspects involved in the interdisciplinary treatment of HNC.

Keywords: best practice, quality assurance, radiotherapy, IMRT, head and neck cancer, squamous cell carcinoma

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INTRODUCTION

Photon-based radiotherapy (RT) techniques have evolved enormously since the introduction of computerized axial tomography (CT) scanning in RT planning 30 years ago. Since then, external beam RT has evolved from two-dimensional (2D) conventional RT to 3D conformal RT, then static beam intensity-modulated RT (IMRT), and ultimately to rotational IMRT or volumetric modulated arc therapy (VMAT) (1).

IMRT is a technique that combines irradiation beams with non-uniform fluence intensity to generate steep dose gradients even in target volumes (TVs) with a concave shape (2). As a direct consequence, TVs are treated more homogeneously and with a better sparing of the nearby organs at risk (OARs), in comparison with the classical 2D or 3D RT techniques. This better sparing of the OARs is particularly relevant in areas of the body where there are relatively radioresistant TVs in close vicinity to radiosensitive OARs, such as in the head and neck area. Consequently, IMRT has become standard of care for the treatment of head and neck cancer (HNC) based on a proven superiority over 3D conformal RT in terms of prevention of xerostomia (3–7). In the last decade, another emerging technique, intensity-modulated proton therapy (IMPT), has been tested for its

potential to reduce side effects in HNC patients, beyond what IMRT using photons can achieve (8). IMPT can be more sensitive to changes in patient setup, CT scan values, and patient anatomy than IMRT because of uncertainties surrounding the precise location of the distal edge of the Bragg peak. The parallel development of high-level 3D image guidance to allow accurate on-treatment verification, including cone beam CT scan (CBCT), megavoltage CT (MV-CT), or kilovoltage CT (kV-CT), and MRI Linacs has been indispensable to allow new RT treatment techniques to reach their maximal potential (1).

The technological revolution described above has significantly increased the complexity of RT, leading to increased efforts to ensure the quality of RT planning and delivery (9). Proactive RT quality assurance (QA) programs and extended guidelines have been developed for clinical trials as well as routine practice, which should nowadays be fully implemented in every RT department. The realization that QA can have a major impact on the outcome, especially in HNC, highlights the importance of such endeavors.

In this article, we will give an overview of the recent history of RT QA, its impact on outcome in HNC patients, and the measures that can be taken to optimize RT in the management of HNC.

EARLY DATA ON THE IMPACT OF RT QA

The process of RT planning and treatment is complex and includes many steps including consultation with the patient, interpretation of diagnostic imaging, TV delineation, treatment planning, treatment delivery, and patient follow up. Each of these steps must be seamlessly integrated into the RT pathway and needs careful QA.

In 2001, the Radiological Physics Center at the MD Anderson Cancer Center (USA) compared, planned, and delivered dose in a phantom study of IMRT in HNC and found a 43% failure rate in obtaining the 5%/3 mm criteria (i.e., the measured dose at a certain point being within 5% or 3 mm of the planned dose) (10). Depending on the shape/steepness of the dose–response curves, this could potentially translate, in a patient, into significant differences in tumor control and/or toxicity. More recently, BELdART (BELgian dosimetry Audits in Radio Therapy) found one Belgian center to have a passing rate of <90% in their gamma 3%/3 mm measurements, highlighting the need for regular external audits (11).

In 2003, Khalil et al. published data on compliance to the prescribed dose-fractionation schedule and overall treatment time in five randomized controlled trials of altered fractionation RT for HNC (12). Only 30% of patients appeared to have been treated within the calculated ideal overall treatment time, a well-known factor in the local control of HNC (13, 14). Centers varied significantly in their compliance and the authors concluded that poor compliance could affect the outcome of these trials.

IMPACT OF RT QA ON OUTCOME IN HNC

The severe, often deadly RT accidents listed by Knöös et al. have received significant publicity in the past, but have become extremely rare today because of QA (15). Moreover, several studies have shown that the quality of RT can have a positive impact on outcome in patients with HNC.

TABLE 1 | The impact of QA on outcome in HNC from selected studies.

References	Organization	*N*	Main outcome and QA issue
Pajak et al. (17)	RTOG 7913 RTOG 7915	210 306	3-year OS 13% if unacceptable deviation vs. 26% if acceptable ($p = 0.01$)
Eisbruch et al. (18)	RTOG 0022	69	2/4 cases with major deviations (PTV dose) had LRR vs. 3/49 if no major deviation in PTV dose ($p = 0.04$)
Peters et al. (19)	TROG 0202	861	2-year OS 50% if major deviation ($n = 87$) vs. 70% if protocol compliant ($n = 502$) ($p < 0.001$)
Wuthrick et al. (20)	RTOG 0121	471	5-year OS 51% in low-accruing centers vs. 69.1% in high-accruing centers ($p = 0.002$)
Naghavi et al. (21)		1,390	3-year OS 57% in low-accruing centers vs. 72% in high-accruing centers ($p < 0.001$)

OS, overall survival; PTV, planning target volume; LRR, locoregional relapse; RTOG, Radiation Therapy Oncology Group; TROG, Trans Tasman Radiation Oncology Group.

Fairchild and colleagues reviewed 17 multicenter studies (1980–2012) including five studies dealing with HNC: four Radiation Therapy Oncology Group (RTOG) and one Trans Tasman Radiation Oncology Group (TROG) study (16). In four HNC trials, patients had inferior outcomes when RT was judged to be inadequate compared to when it was adequate. Three HNC trials suggested that RT that was deemed to be compliant with the study protocol significantly increased overall survival. The impact of QA on outcome in HNC from selected studies is presented in **Table 1**.

The landmark study that demonstrated the impact of QA on outcomes in HNC was the TROG 0202 study, a large international phase III trial, published by Peters and colleagues. They found that QA had a major impact on the outcome of HNC patients treated with chemo-RT (in the pre IMRT era) (19). In the study, 12% of patients with RT plans in which there were major protocol violations (3% due to poor contouring and 5% due to poor plan preparation) had a 24% lower freedom from loco-regional failure rate (54% vs. 78%; $p < 0.001$) and a 20% reduction in overall survival (50% vs. 70%; $p < 0.001$) at 2 years follow-up, compared to those with RT plans that were fully compliant from the start. The authors concluded, "It is sobering to note that the value of good RT is substantially greater than the incremental gains that have been achieved with new drugs and/or biological." Interestingly, the rate of major protocol violations per treatment center was inversely correlated with the number of patients enrolled by the center (<5 patients: 29.8%; >20 patients: 5.4%; $p < 0.001$). These data illustrate the importance of careful QA coupled with external audits for highly sophisticated RT techniques in HNC and highlight the need for centralized and experienced high patient throughput RT centers (22). Furthermore, when the investigators excluded

data from the 12% of patients with major RT protocol violations from the trial analysis they found, contrary to the initial negative results for the whole group, there was a strong tendency for improved locoregional control in favor of the experimental tirapazamine arm (79% vs. 75% at 2 years; $p = 0.067$). This indicates the enormous potential impact of RT QA on the results of multicenter trials. Previous RT trials, which were negative, might have been positive and vice versa if RT QA was insufficient. This sobering message provides a tremendous incentive for improving standardized QA measures in our future clinical trials.

The above studies were conducted in in a non-IMRT population; however, IMRT has become the standard of care for the treatment of HNC since the publication of the PARSPORT study (5). Because of its increased complexity and sophistication, an even bigger impact of RT QA can be expected with IMRT.

Boero et al. retrospectively analyzed 6,212 HNC patients on the Surveillance, Epidemiology, and End Results (SEER) population-based cancer registry and found that in the case of IMRT, the risk of all-cause mortality decreased by 21% for every additional five patients treated per provider per year, because of a decrease in HNC-specific mortality and the risk of aspiration pneumonia. No such relationship was found for conventional RT (23). Important additional evidence that patients with advanced HNC should be treated in high-volume HNC centers for optimal survival outcomes is provided by two recently published retrospective analyses using the National Cancer Database from United States. The first study included 46,567 patients diagnosed with locally advanced invasive squamous cell carcinomas of the oropharynx, larynx, and hypopharynx and undergoing definitive RT. The 5-year overall survival rate was 61.6% vs. 55.5%, respectively, for patients treated at high-volume facilities vs. lower-volume facilities ($p < 0.001$) (24). The second study, which focused on 4,469 patients with nasopharyngeal cancer, demonstrated that treatment at high-volume centers is an independent predictor of higher overall survival (HR, 0.85; 95% CI, 0.75–0.96) (25).

IMPORTANCE OF RT QA IN CLINICAL TRIALS

Learning from the negative experience of the TROG 0202 study, the EORTC organized an extended "dummy run" for their phase III EORTC 22071-26071 study designed to evaluate the addition of panitumumab to adjuvant chemo-IMRT in locally advanced, resected squamous cell HNC (19, 26) A computed tomography dataset comprising one case of NHC was sent to the participating institutions and then compared with reference contours and protocol guidelines by six central reviewers. Of the 23 datasets, 13% of the GTV (gross tumor volume = macroscopic disease), 44% of the CTV (clinical TV = zone of possible microscopic extension), and 57% of the PTV (planning TV = margin for movement and setup uncertainty) contours were evaluated unacceptable (objectives and constraints defined per protocol and taking into account all available information along with ICRU recommendations) by the expert panel. Overall, only 13% of the sites that combined TVs were considered acceptable, 43.5% had minor deviations, and 43.5% were judged to have major deviations. Of all the sites, 74, 87, and 91% met the dose constraints for the low-dose, intermediate-dose, and high-dose volumes, respectively. Almost all deviations were found in the minimal dose constraints (D98 and D95%), i.e., an underdose of a part of the TV. No statistical correlation was found between the achievement of the dose constraints and the PTV contour evaluation by the experts. For the OARs, sites met the dose constraints for an average of three OARs out of six (often at the price of PTV coverage), and for most OARs (but not for the parotid glands), a significant correlation between the quality of the contouring and the sites' ability to respect the OAR's specific dose constraints (and thus their ability to limit the toxicity) was reported. They concluded that wide variations exist despite strict guidelines, confirming the complexities involved in developing and delivering QA for IMRT-based multicenter studies for HNC. Another phase III EORTC 1219–DAHANCA 29 intergroup trial designed to evaluate the influence of nimorazole in patients with locally advanced HNC when treated with accelerated RT in combination with chemotherapy provided a RT QA program for the participating centers (27). A pre-trial benchmark case was delineated and planned and prospectively centrally reviewed. Fifty-four submissions from 19 centers were reviewed. Nine (47%) centers needed to perform the delineation step twice and three (16%) centers repeated it three times before receiving approval. The authors highlighted the importance of clearly defined protocol guidelines to avoid unacceptable errors.

While strict adherence to ICRU 83 guidelines on "Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy" can address most of the (QA) issues required to obtain adequate dose distribution during planning and delivery, work is still required to achieve consensus and QA of contouring (28). In addition to the study by Fairchild et al. mentioned above, the PARSPORT study also found large differences in contouring in 3 out of 10 submissions due to lack of adherence to the trial guidelines (26, 29). The Swiss national "dummy run" study found that more precise radiological imaging could increase homogeneity in delineation of the GTV (30). Regarding the CTVs, international consensus guidelines have been developed for the delineation of the nodal and primary CTVs that are beneficial for harmonization in routine clinical practice and essential for clinical trial RT QA (31–36). However, in 2010, Rasch et al. reported considerable heterogeneity in CTV delineation among Dutch radiation oncologists, despite the publication of guidelines on CTV delineation by Gregoire et al. (31). Furthermore, in 2017, van der Veen et al. found large discrepancies in the selection of prophylactic nodal levels and CTVs delineated among Belgian centers (14/22) (37, 38), illustrating that continued efforts are required in training and education to improve standardization.

In addition to heterogeneity in TV delineation, Nelms et al. reported major variations in the sizes and shapes of OARs contoured by different radiation oncologists from international participating centers in an oropharyngeal cancer patient (39). In the meantime, Brouwers et al. published consensus guidelines on the contouring of HNC OARs, with the aim of reducing the

heterogeneity of OAR contouring in clinical studies as well as in daily practice (40). Interestingly, this consensus was published after a delineation study of OARs by a panel of seven HNC RT experts that demonstrated significant differences in OAR contouring (coefficient of variance ranging from 12% for the parotid gland up to 56% for the glottis larynx) (41).

As a result of the heterogeneity outlined above, the EORTC HNC group and other groups including the UK RT Trials QA (RTTQA) Group have further fine-tuned the quality control of their HNC trials by adding individual patient plan reviews to the pre-trial benchmark case. Each participating center is requested to send the planning CT of each of their enrolled patients to the QA RT platform for review of the TV selection and delineation. When approved, centers are then asked to send the planned dose distribution to the QA platform. Ideally, this should be done for every single patient. For pragmatic and cost reasons, it is often prospectively performed only for the first 5 or 10 patients. The plans will, however, be collected for all patients enrolled in the trial, allowing for retrospective evaluation of all cases.

THE COST OF QA

Data on the costs associated with RT QA are scarce due to the practical difficulties associated with carrying out economic studies in this field, in terms of cost calculation and efficacy data (42).

While one might expect more/higher-level QA to result in a higher global cost, the opposite may be true. In a simulated study, Weber et al. showed that increasing QA level in a prospective HNC trial translated into better overall survival and a decreased tumor recurrence rate (43). They found a positive association between the complexity of QA procedures and the patient's outcome, resulting in a lower general cost for more complex and thus more expensive QA, due to fewer recurrences and thus fewer costs for re-treatment. It is also possible to improve patient's outcomes parallel to the care process without incurring any additional costs. Simons et al. reported the cost-effectiveness and improvement in patient outcomes seen after reducing the waiting times to start treatment (crucial for HNC patients). In their new workflow, the reduction in waiting time varied from 5 days for patients treated for oropharyngeal or hypopharyngeal cancer to 22 days for laryngeal cancer patients resulting in 0.13 to 0.66 additional quality-adjusted life years (44).

The fact that higher QA costs often have to be paid for by the RT department/hospital while the benefits (improved outcomes) are seen by society/government might deter some RT centers from stepping up to implement a higher level of QA. Therefore, efforts should be made to better reimburse these treatment-specific higher QA costs.

QA IN THE ROUTINE CLINICAL SETTING

Overall, the abovementioned studies confirm the complexity of IMRT-based multicenter studies and they stress the importance of adhering to strict QA procedures, not only in the framework of clinical trials but also in routine daily practice. When QA problems occur in studies involving motivated, well-informed RT departments guided by a detailed protocol, it is reasonable to assume that similar issues can occur in any RT department in the routine clinical setting that may or may not be identified. Therefore, consensus meetings and external audits with end-to-end testing of the whole RT process, in general, and of the QA, in particular, are of utmost importance (9, 15). Understanding the incidence, types, and reasons for variation in compliance in clinical trials contributes to the understanding of the application and limitation of RT QA in the routine clinical setting, and the training and lessons learnt from clinical trials tend to increase quality within daily practice. However, despite the move to include central individual patient contour (and dosimetry) review in recent EORTC studies, we do not yet have a technological solution to QA the most important variable in routine RT practice, i.e., TV delineation. Continuous education, practical sessions, peer review programs, automatization, and multidisciplinary contouring (e.g., with the radiologist and/or head and neck surgeon) are more important than ever to avoid geographical miss (9, 22, 45). Recent studies stress the importance of peer review. Bergamini et al. retrospectively analyzed 781 HNC patients of whom ∼70% were referred for a second opinion. Following multidisciplinary evaluation, new staging examinations were requested in 49% of patients and treatment was modified in 10% (46). A recent review by McDowell and Corry stated that even in high-volume academic HNC institutions, major plan changes are not infrequent following peer review; errare humanum est (47). Therefore, peer review should be standard practice in all centers and there is a strong argument that centers without an adequate RT QA process should not offer treatments to patients with HNC.

Routine clinical QA should go further than verification of contouring, to include QA of the dose distribution and the delivery of the correct dose of radiation within the planned time frame, as routinely studied in the context of clinical trials (15). Routine QA should also include continuous training at all steps in the RT process, rigorous image fusion, precise patient setup, verification of treatment delivery using offline or ideally online image guidance (IGRT, image-guided RT), and careful follow-up looking for late side effects, recurrences, and second primaries. In terms of IGRT, Den et al. conducted a prospective study of 28 HNC patients (1,013 kV CBCT scans) highlighting the importance of daily imaging for treatment accuracy and margin size. They found that by using daily imaging, most of the PTV margins could be reduced by as much as 50% compared to the margins applied when using non-daily imaging (mediolaterally 1.6 vs. 3.9 mm; superioinferiorly 2.5 vs. 4.1 mm; anteroposteriorly 1.9 vs. 4.9 mm, respectively). This radius reduction corresponds to a much larger reduction in the volume of healthy tissue being irradiated ($V = 4/3\pi r^3$) (48). Moreover, PTV margins should be based on the individual department's calculation of their setup margin of error; yet, in practice, many centers use PTV margins derived from the literature and implement non-daily image guidance protocols.

Maybe (one of) the abovementioned steps can explain the unexplained survival drop after 3 years in the TROG 0202 population who was made compliant or who had only minor

protocol deviations compared to the patients fully treated by protocol from the start (19). In other words, the whole process from A to Z has to be optimal to get the best results for our HNC patients. The recent technological evolution in RT paralleled with the increasing awareness of the importance of QA, as described above, means that major efforts have and are still being made to improve QA at each step of the treatment pathway, not only for trials but also in daily practice (15).

IMPORTANCE OF QA IN OTHER ASPECTS OF TREATMENT

Increasing awareness of the importance of QA and of centralization remains largely restricted to the RT aspect of HNC treatment. More and more data are converging to illustrate that the outcome of patients with HNC is better when performed in large volume centers compared to low volume centers (20, 21, 24, 25). The reason for this finding is likely multi-factorial, including not only the quality of RT planning and delivery, but also the quality and accuracy of other steps involved in tumor staging (e.g., pathology, imaging) and treatment (e.g., surgery, systemic treatment). Furthermore, proper integration of these steps into the patient care pathway is extremely important, as is the physician and hospital's capacity to react to changes and incidents occurring during the patient's journey through treatment.

CONCLUSIONS

The increasing complexity and precision of modern RT techniques, particularly for HNC, means that rigorous QA is essential in every step of the RT pathway, in order to deliver the right dose in exactly the right place to optimize tumor control and minimize toxicity. Therefore, RT QA, in routine practice as well as in clinical trials, should include a clear program to systematically control each step in the pathway as well as regular end-to-end tests and external audits. Ideally, this QA should not be limited to RT, but should also encompass every aspect of the patient pathway, in order to fully realize the benefits associated with the delivery of safe, standardized, and high-quality patient care.

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DV and TD wrote the first draft of the manuscript and VG and VB revised it critically for important intellectual content. ME edited the final manuscript. All authors approved the submitted version.

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REVIEW
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The Multidisciplinary Team (MDT) Approach and Quality of Care

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The core function of a multidisciplinary team (MDT) is to bring together a group of healthcare professionals from different fields in order to determine patients' treatment plan. Most of head and neck cancer (HNC) units are currently led by MDTs that at least include ENT and maxillofacial surgeons, radiation and medical oncologists. HNC often compromise relevant structures of the upper aerodigestive tract involving functions such as speech, swallowing and breathing, among others. The impairment of these functions can significantly impact patients' quality of life and psychosocial status, and highlights the crucial role of specialized nurses, dietitians, psycho-oncologists, social workers, and onco-geriatricians, among others. Hence, these professionals should be integrated in HNC MDTs. In addition, involving translational research teams should also be considered, as it will help reducing the existing gap between basic research and the daily clinical practice. The aim of this comprehensive review is to assess the role of the different supportive disciplines integrated in an MDT and how they help providing a better care to HNC patients during diagnosis, treatment and follow up.

Keywords: head and neck cancer, head and cancer unit, multidisciplinary team, tumor board, quality of care

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INTRODUCTION

A multidisciplinary team (MDT) in oncology is defined as the cooperation between different specialized professionals involved in cancer care with the overarching goal of improving treatment efficiency and patient care. Head and neck cancer (HNC) involves multiple and biologically distinct diseases that require different therapeutic approaches. Patient symptoms and treatment side-effects as well as physical and psychological impact will vary according to cancer location and treatment plan. Joining the efforts from different professionals is thought to improve patient management in contrast with the old idea of a global treatment offered by a single physician.

The multidisciplinary approach emerged in oncology in the mid-1980s, when the addition of chemotherapy to radiotherapy and/or surgery was proven to improve survival. In the meantime, organ-preservation strategies started to develop in HNC with the use of new available therapeutic techniques (1). The MDT initially consisted in a regulated committee that reviewed all new cancer

patients and agreed on the therapeutic plan proposed by medical and radiation oncologist and surgical specialists based on their clinical expertise and the evidence available to date.

When the MDT members became aware that this approach was actually improving patient care, additional specialities focused on supportive interventions were included in the MDTs. The addition of the latter group of professionals improved the quality of cancer care by preventing and diminishing treatment side-effects, which in turn improved patient adherence and compliance to therapies (2). The natural evolution of this approach was the development of oncological functional units: disease-site specific cancers focused on the management and provision of services for cancer patients (3). These units integrate a multidisciplinary committee and include all the departments involved in a patient's care with the aim of facilitating the intervals and interactions between the different professionals, hence reducing time to diagnosis and/or commencement of treatment.

The first functional units created in Europe were the breast cancer treatment units. It was not until 1998 at the First European Breast Cancer Conference that many medical societies focused on breast cancer treatment claimed that breast cancer care, which includes diagnosis, treatment, genetic counseling, psycho-social support, and research, should be assembled in specialized units within an institution (4). This was captured by the European Society of Breast Cancer Specialist (EUSOMA) in the 2013 publication "the requirements of a specialist breast center," a consensus on the minimum requirements for the multidisciplinary management of breast cancer in oncologic centers (5). These guidelines were well-received by many medical societies leading to the introduction of the multidisciplinary approach in many countries. To date, HNC MDTs have been successfully implemented in many countries and are now considered standard of care for the management of HNC patients (6). This comprehensive review evaluates the role of the different disciplines that should be integrated in MDTs and how they contribute to provide a better care to HNC patients during diagnosis, treatment and follow up.

THE ROLE OF THE HNC SPECIALIZED CLINICAL NURSE

Given its location, HNC often comes with a series of physical and functional complexities and as such, patients will require a comprehensive care at the bio-psycho-social level. Giving patients full support from the time of diagnosis will be crucial to complete the planned treatment. As an essential member of the MDT, the role of the specialized clinical nurse in this disease is to support patients during the whole diagnostic and treatment process, which will include not only performing nursing interventions (i.e., symptom, toxicity and/or wound management) but also operational case management such as treatment planning and coordination.

The nurse will facilitate and coordinate the activities among all the specialists of the MDT, framing their activities in care plans and integrating healthcare processes in collaboration with other professionals involved in cancer care. From a patient and family perspective, the nurse represents the anchor that will guarantee the continuity of care throughout the entire healthcare process, including the follow up.

At the time of diagnosis, the nurse will initially perform a comprehensive assessment of the patient and family (or primary caregivers). It is essential to establish a good relationship to involve both the patient and the family in the decision-making process and to educate them on how to prevent and manage treatment toxicity and how to identify new symptoms. This relationship is decisive to ensure patient adherence and compliance to treatment and will also optimize healthcare resources.

The role of the nurse specialist as part of the HNC MDT is focused on three areas of action:

Case management

The case management is described as the systematic effort to coordinate patient and family care in this complex pathology. Methodologically, the main goal is to achieve care results more efficiently, as it will allow a better control of professional resources ultimately impacting on health costs (7). The nurse applies the case management model in the context of a specific process or disease, in this case HNC patients within an hospital organization. One of the nurse aims is to work with and coordinate all the professionals that compose the MDT during the overall process of patient care. For the patient and family, the nurse represents the cornerstone from the diagnosis until the follow-up and has major supportive role until the resolution of acute toxicity. During the diagnosis and treatment planning, the nurse controls that the appointments schedule and required diagnostic assessments are carried out in a timely manner to avoid unnecessary delays in starting treatment. This is extremely important for those patients who undergo multimodal treatment, either concurrently or sequentially (i.e., definitive concurrent chemo-radiation, surgery followed by adjuvant radiation with/without chemotherapy). The nurse will not only ensure scheduling the treatments accordingly but will also help adapting it at every step based on each patient's requirements and needs.

One of the most important roles of the nurse specialist is to offer urgent assistance to patients and families through a direct connection during daytime (i.e., a mobile phone that allows the patient/family to contact the nurse). This will allow the nurse to: resolve patient questions or concerns; help managing side-effects and symptoms; and screen for potentially severe problems that require urgent attention and/or reference to the emergency room. Moreover, it allows the treating physicians to be aware of any significant event, symptom or toxicity at all times and plan visits and/or modify treatments accordingly.

The nurse must ensure that nursing care is incorporated into the design and implementation of clinical guidelines.

Operational role

The nurse ensures that patient referrals from primary care or local specialists are scheduled in a timely manner to

avoid delays, and links patients that require multimodality treatment with the physicians from the different departments (i.e., ENT surgical oncology, radiation oncology and/or medical oncology).

Once the treatment decision has been made by the HNC multidisciplinary committee, the nurse schedules an appointment with the new patient and family/caregivers. During this first visit, a comprehensive assessment of the patient is conducted, which includes medical and psychosocial status as well as support requirements. The nurse facilitates information about the treatment, including plan and logistics, explains the toxicity and resolves all doubts or concerns that may appear. This visit is instrumental to consolidate the information previously given by the specialist physician (patient information is a key part of the quality of care).

In addition to carrying out a comprehensive and individualized assessment, special attention is devoted to the detection of possible alterations that may hinder the usual treatment dynamics. This is of particular relevance in HNC patients. Specific circuits are activated to support the patients according to their needs: assessment of nutritional status, swallowing and phonation, dental evaluation, psychosocial support, rehabilitation, evaluation of toxic habits, oncogeriatrics, and palliative care. The nursing documentation for patient assessment is based on the proposal according to the Functional Health Patterns defined by Marjory Gordon (8).

Medical assistance

To provide clinical assistance is a major key role of the HNC specialized clinical nurse. The nursing care in HNC is focused on the following areas:

- Provide emotional support to patients and relatives after the impact of the diagnosis and during treatment.
- Health education to patients and family members concerning prevention, early-detection and management of symptoms and side-effects, also providing tools to enhance their autonomy.
- Collaboration in other healthcare areas (*i.e.* hospitalization, clinical trials).
- Management of feeding tubes and gastrostomies.
- Management of tracheostomies.
- Post-surgical interventions, toxicity, and treatment-induced dermatitis management (i.e., radiotherapy, anti-EGFR antibodies).

DENTAL CARE FOR HNC PATIENTS

Dental attention for HNC patients is essential and must be incorporated in each stage of the oncologic process. This process has different and independent stages where it is important to control the potential complications that can occur in the oral cavity after chemotherapy and radiotherapy (9–11). Potential toxicities and affected structures by chemotherapy, radiotherapy and/or surgery are summarized on **Table 1**.

TABLE 1 | Potential outcomes of chemotherapy, radiotherapy and surgery and the affected structures implicated.

Affected structures	Potential outcomes
Skin radiation	Dermatitis
Oral mucosa	Mucositis Infections: fungal, viral, bacterial Pain
Teeth	Caries caused by hyposalivation or direct effect of RT
Jaws/bone	Osteoradionecrosis Mastication difficulties
Salivary glands	Hyposalivation/xerostomia
Muscles and soft tissues	Fibrosis and trismus Dysphagia Speech difficulties
Temporomandibular joint	Fibrosis and trismus
Tongue and taste buds	Taste dysfunction
Alteration of smell	Anosmia, cacosmia
Others	Pain Altered quality of life

Modified from Villa and Akintoye (12).

Any dental procedure must be avoided within chemotherapy cycles due to the risk of complications. Chemotherapy-derived thrombocytopenia and neutropenia can lead to hemorrhage and infections: fungal (candidiasis), bacterial (periodontitis, abscess, necrotic gingivitis) and viral (herpes, cytomegalovirus) (13). Patients receiving chemotherapy, especially methotrexate, cyclophosphamide, cisplatin, and 5-fluorouracil, can suffer mucositis affecting the oral cavity health (14, 15). Preventive procedures to attenuate the severity of the chemotherapy-induced oral mucositis are: exhaustive oral hygiene, if possible, before the chemotherapy sessions; eating soft foods; do mouthwashes regularly when brushing the teeth (use a soft toothbrush) using saline solution (0.9%), sodium bicarbonate or methylcellulose; using floss in the inter-cycle stages of the chemotherapy to avoid bleeding and reducing the microbial load; and removal of prosthodontics (if removable) (12). Oral cryotherapy (30-min session) is a good preventive method in patients receiving 5-fluorouacil (12) and benzamine hydrochloride is a positive anti-inflammatory option. Low-level laser therapy (LLLT) or photobiomodulation has been used with good results based on the angiogenic effect, the stimulation on the production of serotonin, collagen and cortisol, and improving in conjunction the synthesis of nucleic acid (16).

Several agents can be recommended to reduce the severity of mucositis (i.e., oral Magic mouthwash®, a combination of antibiotic, antihistaminic or local anesthetic, antifungal, topical corticoid and a base that helps the other components to properly cover the affected mucosa). Dysgeusia is commonly observed in patients receiving chemotherapy, particularly cisplatin. It can decrease the appetite leading to reduced oral intake and weight loss. Zinc supplements have shown to be useful to improve the dysgeusia in a few studies (17–19).

Radiotherapy is the backbone of the multimodality treatment in HNC. Given the close location of HNC to vital anatomical structures, radiotherapy is often limited by the risk of toxicity to the surrounding organs at risk (20). The use of intensity modulated radiotherapy (IMRT), which adjusts the dose to the tumor's size, has significantly reduced but not completely eliminated the risk of late toxicity including xerostomia, cariës, trismus, and osteoradionecrosis (21). The evolution of upcoming radiation modalities such as proton-based radiotherapy with better selectivity of the tissue to be irradiated might help reducing further these toxicities (22, 23).

Preventive techniques to protect surrounding healthy tissue and reduce toxicity such as xerostomia, remain controversial. Some authors for example, prefer to use cytoprotective agents such as amifostine (WR2721), which avoid cellular oxidation in healthy cells (richer in alkaline phosphatase) preserving their correct function (24, 25).

Techniques to prevent irradiation of the salivary glands have been proposed. Auto-transplant of submandibular glands to submental space was proposed in 2001 as an effective, low-cost technique (26). Another proposed technique is the application of hydrogel in the submandibular gland, positioning it outside the irradiation area (27). Once xerostomia is established, the chances to reverse it or improve it significantly are low, and all the approaches are palliative, since none of them can regenerate the salivary glands, oral mucosa, muscular fibers, and dental tissue. A few palliative techniques have been proposed including acupuncture, low power laser, electrostimulation or the use of hyperbaric oxygen, although no randomized studies have proven their effectiveness (16, 28–30).

From a pharmacologic perspective, the administration of parasympathomimetic agents (pilocarpine, cevimeline, and bethanechol) has shown to improve the radiation-induced-xerostomia in the short-midterm but not in the long-term, and the side-effects can be a problem (31, 32). Alternative therapies such as herbs, traditional Chinese medicine and thyme honey have been also proposed in an attempt to improve patient quality of life (33, 34). In any case, continued oral hydration and the use of saliva substitutes (olive oil, betaine, or xylitol gum) are always advisable (35).

Patients undergoing oncologic treatments for HNC must take particular care of their oral health. **Table 2** summarize dental assessment and interventions to be performed in HNC patients before, during and after treatment. Any dental treatment should be preventive, if possible, because any dental treatment after the oncologic treatments will be less effective (12, 36–38). Patients must follow a strict oral health routine, using remineralization elements such as fluoride. They must follow general advice such as maintaining a balanced diet and hydric-equilibrium. Patients, and those around them, must be aware of the acute and also long-term treatment-related side-effects, the potential functional and physical limitations they might encounter and the solutions we are currently able to provide. Continued research to reduce oral cavity toxicity and to allow the regeneration of damaged structures, in some cases irreversibly, is needed.

TABLE 2 | Dental assessment and interventions to be performed in HNC patients before, during, and after treatment.

Before	During	After
Check the medical history carefully	Hydration, alkaline mouthwashes, oral mucosa protection.	Frequent control of the oral cavity and teeth (every 3 months)
Teach good oral hygiene habits	Control oral mucosa, with analgesia if needed	Good hydration. Saliva substitutes
Repair all possible teeth and remove compromised ones.	Bland diet Saliva substitutes	Parasympathomimetic Alternative therapies (low intensity laser, photobiomodulation, hyperbaric oxygen chamber, etc.)
Remove removable prosthodontics	Temporomandibular physiotherapy (this can be started before treatment)	After 6 months, consider oral rehabilitation
Explain treatment	Fluorine mouthwash without alcohol	Keep temporomandibular joint physiotherapy
Evaluate pre-treatment life quality	–	Evaluate the quality of life after the treatment
Fluorine supplementation	No dental intervention required	Fluorine mouthwash

THE ROLE OF THE SPECIALIZED DIETITIAN

Nutritional management in HNC patients is particularly complex and face unique challenges as they are at high risk of malnutrition due to tumor location and treatment toxicities (39). Despite oncologic treatments have improved both locoregional control and survival (40, 41), the acute and long-term toxicities caused by these therapies still compromise dietary intake contributing to significant nutritional deterioration (42, 43).

The heterogeneity of symptoms in HNC patients due to tumor location often overlap with local toxicity, and can all interfere with oral intake. Hence, having the support of a specialized dietitian within the MDT is crucial to ensure that the patient's nutritional status is optimized (44, 45).

The prevalence of malnutrition at diagnosis can range from 42 to 77%, and it usually worsens during treatment (46, 47). Weight loss is one of the major concerns as more than the 85% of patients will lose a substantial amount of weight from diagnoses until up to 3 months after completing treatment (44). Early nutritional assessment to optimize patient's nutritional status and to evaluate the need of a prophylactic feeding tube can contribute to minimize the impact of acute toxicity, treatment interruptions and ultimately improve survival (48).

Many studies have reported the importance of screening malnutrition among cancer patients using different validated tools (49–51). However, given the high prevalence of malnutrition in HNC patients, an early complete nutritional assessment of all patients incorporating dietetic counseling even in those well-nourished seems to be more effective (44). Dietetic counseling ameliorates malnutrition and reduces unplanned

hospital admissions during treatment (52). For those patients that are already malnourished, an early detection will help improve their nutritional status prior to treatment and will flag them to the treating physicians within the MDT to prioritize and/or adjust before the start of the oncological treatment," A few studies have shown that an improvement in the nutritional support prior to treatment reduces the incidence of infections, the time of hospitalization and the severity of toxicity and leads to improved survival (53–56).

Close nutritional monitoring during treatment is necessary to individualize and adjust the nutritional support to the emerging toxicity (47). At present, there is not enough evidence to support weekly instead of bi-weekly nutritional assessments during treatment (57) according to weight loss although weekly assessments seem to increase adherence to the nutritional interventions (58). Dietetic resources are usually limited; therefore, the coordination with other health professionals may help to improve the adherence to the nutritional support. Up to 38% of patients do not attend the follow-up appointments with the dietitian 4–8 weeks after treatment (57). Home visits, telemedicine or accommodating nutritional review right before or after the oncological evaluation may increase adherence to visits and ultimately enhance nutrition outcomes. Nutritional intervention in HNC patients is summarized in **Figures 1A,B**.

The nutritional intervention depends on multiple factors including tumor location and stage as well as type and intent of the oncological treatment (curative vs. palliative). In patients undergoing surgery, the nutritional intervention aims to meet the nutritional requirements right after the surgery trying to return to oral intake when possible. The use of gastrostomy feeding tube is still a matter of debate (59–63). Some studies have shown minimize weight loss and quick return to oral intake once the treatment is finished with the use of a nasogastric tube when clinically indicated (62, 64). However, other authors (61, 63, 65) report the use of prophylactic gastrostomy feeding tubes without increasing the risk of long-term swallowing dysfunction. Recently, a systematic review reported the advantages and disadvantages (**Figure 2**) of both percutaneous endoscopic gastrostomy and nasogastric feeding tubes (66). Patients that might require a prophylactic feeding tube prior treatment should be assessed by the dietitian at diagnosis. The indication should be individualized based on patient's baseline nutritional status, estimated time that feeding tube might be required and expected nutritional problems during treatment. Additionally, the capacity and characteristics of each hospital should be considered. The final recommendation should be agreed by both the patient and the MDT.

Sarcopenia, defined as low muscularity, has been recently shown to be a negative prognostic factor for overall survival in cancer patients (67). Specifically, in HNC, sarcopenia has been correlated with an increased rate of surgical complications in patients undergoing total laryngectomy (68) and with decreased overall survival in those treated with either radiotherapy alone (69) or with chemoradiotherapy (70). In addition to the nutritional support, the implementation of physical activity is also necessary to minimize nutritional and muscular deterioration in HNC patients. Some studies have integrated progressive resistance training programs during cancer treatment showing successful patient adherence and improvement in quality of life (71, 72).

Accumulating evidence suggests that up to 90% of HNC patients develop acute nutrition impairment due to the symptoms generated by the tumor location and treatment toxicity (i.e., dysphagia, mucositis…) (73, 74). Concurrent chemoradiotherapy is associated with higher rates of toxicity and complications when compared with surgery or radiation alone (74). Some of the treatment toxicities can be long-term and become chronic: swallowing dysfunction, xerostomia, dental problems, taste alterations, and weight loss have a significant impact on patient's quality of life (75, 76). In addition to the nutritional support, symptom-management (i.e., analgesia), psycho-oncological counseling, and speech and language rehabilitation therapy will be essential to improve their quality of life.

A few clinical guidelines for the nutritional management of HNC patients have been published (77, 78). These guidelines have significantly raised awareness on the impact of nutrition in HNC patients among oncologists and surgeons, increasing the number of early nutritional assessments and making it part of the treatment decision, particularly in patients with uncertain prognosis.

PSYCHOSOCIAL SUPPORT IN HNC PATIENTS

The diagnosis of HNC is often accompanied by difficulties in eating, chewing, drinking, breathing, and speaking as well as by changes in physical appearance. All these alterations can lead to psychosocial dysfunction. There is evidence to suggest that psychosocial interventions in these patients are effective, and as such, clinical intervention programs should be developed as part of their cancer care.

Psychosocial Needs

HNC patients experience profound functional and visible changes as a result of their disease and its treatment, having an important psychosocial impact on them and their families. The disease and treatment toxicity result in physical and psychological symptoms that patients must deal with, such as dysphagia and disfigurement. Patients have problems in the social and family setting, often related to the reduced ability to conduct many basic functions such as eating, speaking, and breathing. These problems can lead to limitations for work, and also for daily activities such as driving (79). Sometimes, it will be necessary to refer patients to a social worker to assist them with any financial burden and facilitate the access to the appropriate financial resources. Reduced libido and sexual enjoyment are common in individuals following surgery or chemoradiation. It is recommended that the treating physicians and health care professionals address this issue.

Cancer survivors with physical impairment or change in appearance or function have a high risk of

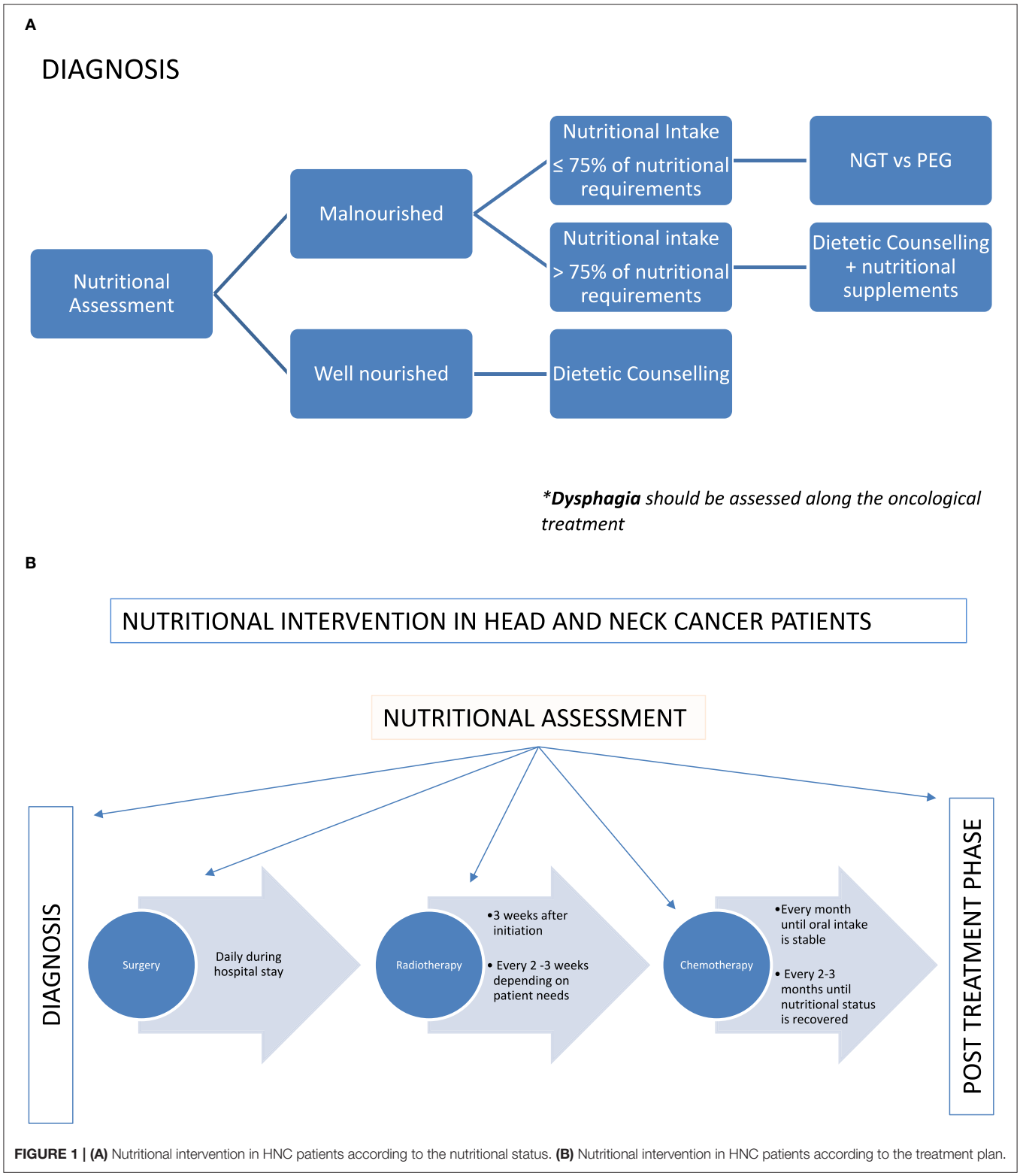

FIGURE 1 | (A) Nutritional intervention in HNC patients according to the nutritional status. **(B)** Nutritional intervention in HNC patients according to the treatment plan.

psychosocial sequelae and diminished quality of life. This is especially common among patients with HNC, and it is important to help them coping with these psychosocial aspects into their routine cancer care throughout the illness trajectory.

Psychological Distress

No one expects to be diagnosed of cancer. Patients have to assimilate and integrate the information about their condition and treatment options. HNC patients suffer from the visible nature of their disease but disfigurement and dysfunction

	Nasogastric tube	Percutaneous gastrostomy
	Advantages	*Disadvantages*
Duration of feeding	Shorter	Longer
Cost	Cheaper	10 times more expensive than NGT
Nutritional status	Lower tríceps skinfold thickness	Higher triceps skinfold thickness
Swallowing outcome	Quicker return to oral intake	Worse in long term. Longer time to oral intake
No significant differences in	✓ Complications rate ✓ Chest infection rate ✓ Overall quality of life ✓ survival	

FIGURE 2 | Nasogastric tube vs. percutaneous endoscopic gastrostomy: advantages and disadvantages [Extracted from Wang et al. (66)].

can often also result from surgery and radiotherapy (79). As a consequence of these difficulties, patients can experience depression, social anxiety, reduced self-esteem, sexual difficulties, and a generalized sense of reduced quality of life (80, 81). Ineffective coping strategies such as helplessness, hopelessness, anxious preoccupation, and fatalism are strongly associated with anxiety and depression (82). Koster and Bergsma described HNC as more emotionally traumatic than any other type of cancer (83). After treatment, HNC patients were more distressed than other groups of patients. In term of coping, they had higher levels of anxious preoccupation than other cancer patients (84). Anxiety and depression is experienced by ∼30–40% of patients following treatment of HNC (85, 86). One outcome of depression is suicide. Two head and neck cancer sites alone (tongue and pharynx) accounted for almost 20% of the total suicides among male patients with cancer (87).

Psychological Interventions

Psychological interventions include: psychoeducational counseling, psychotherapy (individual), cognitive behavioral training, supportive, and group interventions. Social support is seen as an important factor in alleviating the emotional distress and social dysfunction experienced by patients with facial disfigurement. Education or psychoeducation is composed by information about the illness and treatment, coping strategies and communication skills. Counseling or emotional support is addressed to validate and normalize the emotional reactions, getting an adequate emotional well-being. Psychotherapy can be understood as a conversation process, with the objective to change the maladaptive narrative of patients, using different psychotherapeutic techniques. One of these psychotherapeutic approaches, the cognitive-behavioral therapy and medication can be considered to reduce anxious and depressive symptoms. The most recommended psychotherapeutic approach in cancer care is the integrative psychotherapy, which focused in promoting alternative narratives, helping to cope the illness and treatment. HNC support groups provide support to patients and families by giving them the opportunity to meet others in similar situations and learn that they are not alone (88).

The classic risk factors associated to HNC such as tobacco and alcohol habits need to be addressed. Similarly, the human papilloma virus (HPV) is a new risk factor, sexually transmitted, associated with a new profile of the HNC patient, with particular emotional needs.

In conclusion, psychosocial impact of head and neck cancer on patients and their families is significant. A psychological screening intervention is an effective way to identify patients and relatives who are at risk and might be interested in receiving psychosocial support, improving physical, and psychological outcomes.

THE ROLE OF THE ONCO-GERIATRICIAN

Cancer is primarily an aging associated disease. As a result of the aging of the Western population and of a long lifetime exposure to tobacco, alcohol and other carcinogens, HNC in older patients is becoming a growing problem (89, 90). Nowadays, over a half of all newly diagnosed HNCs are in patients ≥65 years and it is estimated that in the next decade this will increase by more than 60% (89, 90). As this patient population is usually underrepresented in clinical trials, data on treatment efficacy and safety is scarce, and evidence-based guidelines are lacking (91). Due to misperceptions about reduced survival and higher risk of toxicity in older patients, oncologists are often reluctant to treat them with standard of care therapies, and patients that could potentially be cured end up receiving suboptimal treatment (92). In the overall HNC patient population, treating physicians have to decide the therapeutic strategy balancing the HNC-related risk of death against the potential survival benefit from treatment.

In the elderly, oncologists should pay particular attention to the potential increased risk of treatment toxicity, their life expectancy irrespective of their cancer and also their values and goals (93, 94).

HNC in the elderly presents with a different clinical profile when compared to younger patients: it is more frequent in women; less associated with tobacco exposure and HPV; the most common primary site is oral cavity and larynx, and they usually present without nodal involvement (95). HNC are frequently diagnosed in a locoregionally-advanced stage, and require multimodality treatment including surgery, radiotherapy and chemotherapy. The significant acute and late toxicities that come with these therapies have an impact in the quality of life of patients hence pose an extra challenge when deciding the best treatment strategy in elderly patients with HNC (96).

Aging is a process that consists on a gradual loss of physiologic reserves that lead to impaired function ranging from robust health to frailty and, finally, to disability (97). Due to the heterogeneity of the aging process, chronological age can differ significantly from biological or functional age and treatment decisions should not be based solely on this value (98). Individuals who reach old age without loss of functional capacity or severe medical conditions should be able to receive the best therapeutic strategy according to their frailty profile. The main challenge is how to identify the right patients for the right treatment. Traditional tools used by oncologists to assess functional status, such as the Eastern Cooperative Group Performance Status (ECOG-PS) or Karnosky index (KI) have shown to be inaccurate in this population (99, 100). The Gold Standard to establish the frailty profile of the elderly is the Comprehensive Geriatric Assessment (CGA). Briefly, GCA is a multidimensional battery test that screens for impairment in all patients and includes factors that might impact on patient treatment tolerance and/or increased risk of toxicity: functional status, mood, cognition, social support, nutritional status, geriatric syndromes, polypharmacy, and comorbidity (101) (**Figure 3**).

CGA helps to identify patients who are fit enough to receive standard of care treatment, those who are vulnerable and require an adapted treatment, and those unfit to receive any treatment and should be managed with best supportive care only (102, 103). In addition, CGA frequently detect geriatric impairments missed by routine oncological clinical assessment (104) which might be modifiable through subsequent geriatric-based interventions (105) (**Figure 4**). GCA has the ability to help decision-making by the initial frailty assessment but also can improve treatment adherence and tolerance by developing a tailored intervention and a supportive care plan during the follow-up. Since CGA requires an expert physician to interpret the results and therefore consumes time and resources, several screening tools like Vulnerable Elders Survey (VES-13) (106) or Geriatric-8 (G8) (107) have been developed to distinguish fit patients who are able to receive standard treatment from those who need a wider geriatric evaluation (108–110). Given the accumulating evidence supporting the role of CGA for clinical decision making, the main international societies and guidelines recommended CGA in patients aged 70 years or older before making a decision on cancer treatment (111–113). Most studies assessing the relevance of CGA have been done in cancer patients with different tumor types but the information among HNC is scarce (114). The on-going EGeSOR study is currently evaluating the impact of a multidimensional geriatric intervention based on CGA on outcome in elderly patients with HNC (NCT02025062) (115).

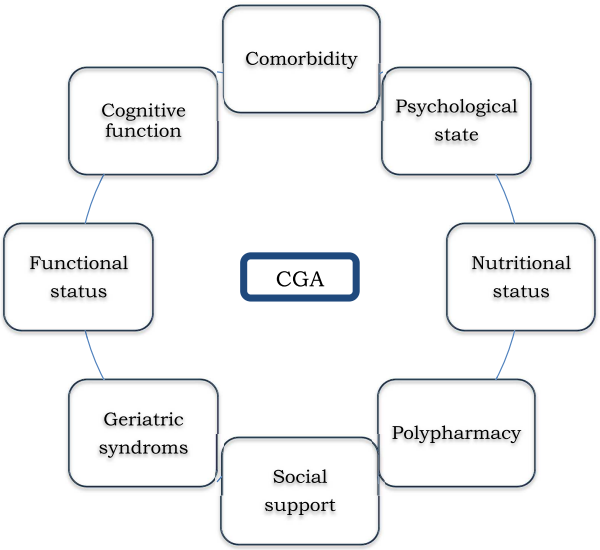

FIGURE 3 | Domains evaluated in Comprehensive Geriatric Assessment (CGA).

However, the optimal treatment should be decided considering both geriatric and oncological variables trying to find the proper balance between the tumor stage, the expected treatment benefit and toxicity and its potential impact on quality of life as well as the increased risk of toxicity and expected overall survival in the elderly. Based on this information, patients with a same geriatric profile might be considered fit enough to be treated with single-modality but not with a multi-modality treatment. That is why a CGA by an onco-geriatrician should be part of the HNC MDT (116). Recently, the ELAN-ONCOVAL (Elderly head and Neck Cancer-Oncology eValuation) study evaluating the use of a suited geriatric evaluation to stratify patients and guide therapy in patients ≤70 years old not amenable to surgery showed that, despite the initially planned treatment was changed only in 8% of the cases after a geriatric assessment, the number of patients requiring multidisciplinary interventions was significantly higher when the assessment was performed by geriatrician (71 vs. 51%) (117). The results of this study highlight the relevance of incorporating the onco-geriatrician in the decision making process for the elderly.

Multimodality treatment in HNC is associated with significant acute and long-term toxicity and represents an additional challenge in the elderly. Most of the studies evaluating therapy according to age in HNC patients did not show significant differences in survival between young and elderly patients (118). Nevertheless, older patients may experience greater

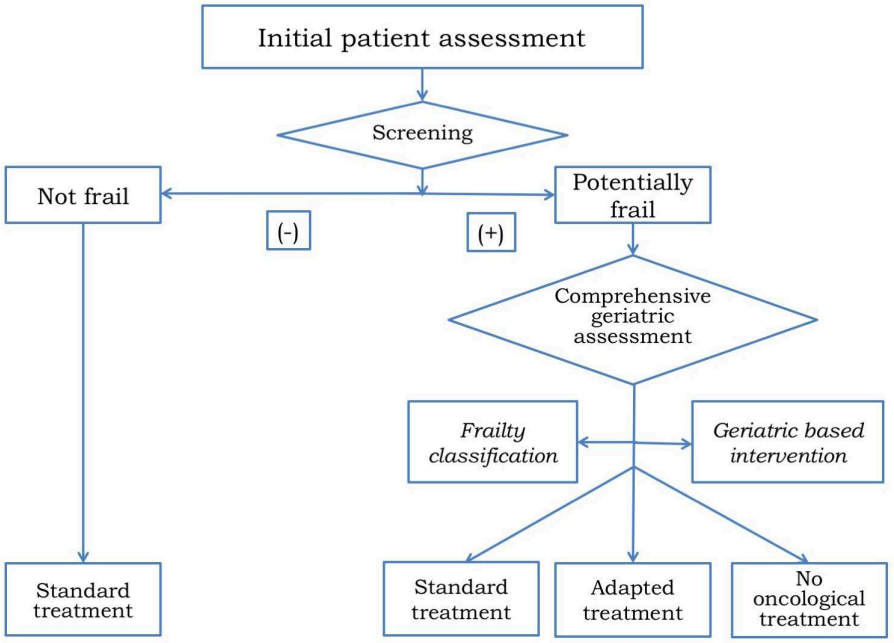

FIGURE 4 | Algorithm for treatment decision making in older patients with HNC.

treatment-related toxicity, specifically with higher intensity treatments (94). When evaluating the outcome of single modality treatments such as surgery or radiotherapy, no differences were seen between younger and older patients (119). Importantly, postsurgical complications, or toxicity rates were not influenced by chronological age. While the survival benefit from chemotherapy remained similar across age, older patients had higher rates of toxicity (nephrotoxicity, diarrhea, and thrombocytopenia) (119). The results regarding concomitant chemoradiotherapy are controversial, likely due to heterogeneous populations (120, 121). However, a study comparing elderly patients receiving radiotherapy alone vs. multimodality therapy, showed that patients from the multimodality group had similar survival rates to younger patients, while those treated with radiation alone had strikingly inferior outcome (122). The use of targeted therapies such as cetuximab is common in the elderly because they are perceived to be less toxic than platinum-based chemotherapy, but no prospective studies have compared the safety profiles in this specific patient population (91). As regards the use of immune-checkpoint inhibitors in the elderly, the trials conducted thus far do not seem to suggest that higher toxicity should be expected in this subgroup of patients (123). Based on this data, we can conclude that a subgroup of fit older patients can benefit from aggressive therapy, being comorbidity and functional age better predictors of treatment tolerance and efficacy rather than chronological age (124–126).

In summary, older patients with HNC require an "age-friendly" healthcare model based on "case management." An individualized comprehensive assessment of the elderly patients leads to a more accurate treatment decision leading to a more efficient use of the healthcare resources. A specialized geriatric assessment of elderly HNC patients is crucial to drive the optimal oncological treatment strategy and as such, it should be integrated within the MDT.

THE ROLE OF THE SPEECH AND LANGUAGE PATHOLOGY EXPERT

Patients who have undergone a total laryngectomy (TL) will inevitably have to face a wide range of sequelae that will have a considerable impact on their quality of life.

From the speech and language pathology (SLP) perspective, the most obvious and limiting handicap is the loss of the laryngeal voice and, consequently, of the person's ability to communicate orally in the same way as they did until the moment of the surgery. The voice, in addition to the basic instrument for human communication, is for everyone a hallmark of self-identity (127) and reveals aspects such as personality traits, mood or gender.

Inability to speak, or to do it with a "new voice" totally different from the one that has been "the own voice" during a person's life, involves very important changes in that person's daily life, and can significantly impact on his/her social and familiar relationships, ultimately leading to anxiety, depression, and alterations in self-esteem and self-image (128).

Vocal Rehabilitation

Vocal rehabilitation in patients treated with a TL to restore oral communication requires a process of adaptation and readjustment to this new voice that is crucial in order to improve and restore their quality of life (129). After the surgery,

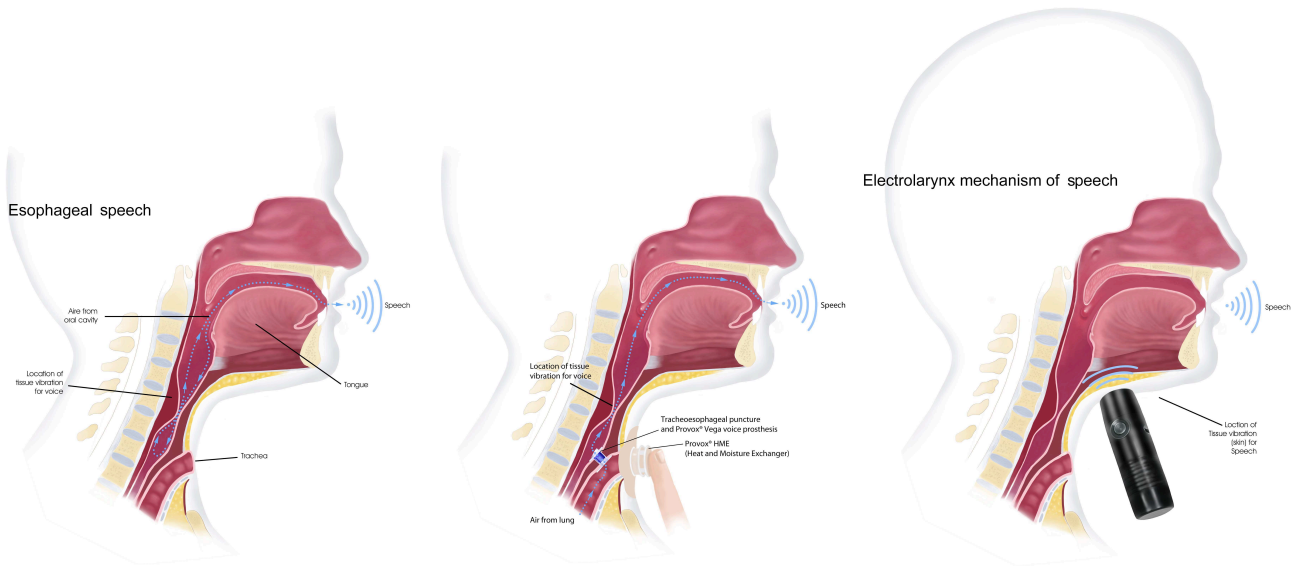

FIGURE 5 | Voice after a total laryngectomy. Vocal rehabilitation alternatives after total removal of the larynx Images courtesy of Atos medical.

patient can be taught laryngeal techniques by an SLP expert through an intensive and structured work. The alternatives of communication after the TL, are:

- Esophageal speech

TL results in a permanent separation of the airway and digestive tract. In the absence of the larynx, a patient can learn to generate a new sound—laryngeal voice- through the vibration generated by the air passing through the pharyngo-esophageal segment. This fundamental frequency will be articulated in the oral cavity, generating different phonemes or speech sounds.

In the esophageal speech, the air is injected or inhaled from the oral or nasal cavity, to the upper esophageal sphincter, and immediately returned to the oral articulatory structures. The learning process of the esophageal speech can be long and requires an intensive, guided and structured work. Hence setting realistic goals in the short term will be important to prevent demotivation. It is also necessary to systematically evaluate patient's progress during the therapy in order to identify difficulties that could make this strategy impossible, and adapt it to patient possibilities.

- Tracheoesophageal speech (voice prosthesis)

The tracheoesophaigeal speech is obtained after a surgical procedure which consists of the generation of a fistula in the posterior wall of the trachea, where a voice prosthesis is placed. A voice prosthesis (VP) is a cylindrical, silicone device that has a one-way valve mechanism that allows the passage of expiratory air flow from the trachea to the neoglottis. Airflow through the esophageal structure will generate a new fundamental tone that, as with the esophageal voice, will later be converted into speech sounds. The use of a voice prosthesis for communication requires daily maintenance and needs to be replaced approximately every 6 months, (130–132) The rate of complications can range from 15 to 72% (132), being the most frequent the leak through de voice prosthesis and the leak around the tracheoesophageal prosthesis.

The involvement of the speech pathologist to train how to manage these complications is important in order to prevent and to minimize their impact, and is also required to provide a continuous follow-up in the rehabilitation process until stabilization. A proper follow-up by an SLP expert of patients with phonatory prostheses is associated with better overall results in their rehabilitation (133).

Compared with esophageal speech, tracheoesophageal speech has demonstrated better results in some voice analysis parameters such as fundamental frequency, maximum phonation time, intensity and other aspects as speech intelligibility (134). Some studies found a correlation between the use of a VP, with a positive restoration of quality of life, self-esteem, and sexual function, with the consequent decrease in the symptoms of depression and anxiety (135).

- Electrolarynx

The electrolarynx is an external device with a sound-head cap that, when activated and in contact with the skin, generates a vibration, usually monotonal, which is transmitted to the oral cavity. To speak with an electrolarynx, the patient has to press a button and move his mouth to articulate different sounds. This system can be very useful to facilitate immediate communication during the hospitalization period, as communication through esophageal speech or VP is not possible as it requires training. When voice alternatives fail, electrolarynx is an excellent solution to allow oral communication.

Overall, the best communication system is the one that will provide the best results according to patient communicative needs and expectations. Ideally, the laryngectomized patient could develop more than one communication strategy, such as a combination of an esophageal voice and the tracheoesophageal

TABLE 3 | Areas of focus in SLP interventions.

Pre-surgery phase	
Goals	Solve all doubts that may arise to the patient and their relatives, related to what their life will be like, from the anatomical, physiological and functional point of view, after TL.
	Provide information regarding potential sequelae, such as vocal, pulmonary, eating and olfaction sequelaes. Information about their treatment and the existing devices to reduce the impact and preserve their quality of life, such as cannulas, adhesives, free hands devices for speech among others.
	Explain and show communication alternatives available.
	Promote contact with another person who has already been rehabilitated or, when appropriate, provide audiovisual materials with real examples of similar cases of patients that satisfactorily overcome their illness and rehabilitation process.
	Evaluation of vocal rehabilitation possibilities of the patient.
	Evaluate phonatory, respiratory, swallowing and olfactory patterns, to adjust an adequate prophylactic program if necessary, and determine realistic goals for rehabilitation according to the needs, expectations and commitment of the patient.
	Design a prophylactic program of pre-surgical exercises, according to time, treatment, and patient feasibility.
	Structure the therapeutic work plan after surgery, agreed between the patient and their SLP.
Post-surgery phase	
Goals	Fitting the proper system to help the patient for communication during hospitalization.
	Global evaluation to determine how is the starting point for rehabilitation, in terms of mood, communicative intention, scarring, fistulas, nasogastric tube, dysphagia, skin condition, configuration of the stoma, volume and characteristics of the secretions, voice prosthesis, weight, muscle tone…
	First adaptation of the rehabilitation devices.
	Review and start of the therapeutic work plan established in the pre-operative evaluation.
Follow-up phase	
Goals	Permanent review of concepts and doubts that the patient and or family may have.
	Prevention of difficulties associated with the use of rehabilitation devices through training in the proper use of it, and the understanding of the warning signs that the patient should inform to the professional.
	Promotion of patients' self-care regarding rehabilitation and management of the rehabilitation devices.
	Checking of the evolution of the established therapeutic goals.
	Upon discharge, providing the patient with an easily accessible SLP contact.

Intervention of the expert SLP on main sequelae groups: voice, pulmonary, eating and olfaction. TL, total laryngectomy; SLP, speech and language pathologist'.

voice, as they can easily coexist (**Figure 5**). This will allow the patient to choose the most appropriate option to speak depending on the communicative context. **Table 3** summarizes pre and post-surgical SLP recommended interventions.

In order to guide and individualize the rehabilitation therapy, many variables need to be considered: the type of surgery, adjuvant treatments, patient psycho-social status and cultural environment, motor and visual skills, communicative needs, and patient's motivation. Furthermore, speech therapy protocols should not be developed in isolation. The accumulated evidence to date and the available clinical guidelines support the idea that a multidisciplinary approach of a patient with a TL, leads to a greater and better overall therapeutic success, and facilitates the restoration of an optimal level of quality of life (129). Thus, the work of the SLP should be integrated into a well-structured MDT that guarantee a good information flow among professionals who are specialists in the different related areas (136).

In addition to the diagnostic impact, HNC patients must face the concern on how their life might change after treatment. Research and clinical experience highlight the benefits of an early involvement of an SLP expert in the treatment of TL patients who suffer voice alteration, as well as a longitudinal follow up until rehabilitation discharge.

Providing information, support, and solving issues related to sequelae will facilitate a better quality of care and greater therapeutic success, which in turn will have a positive impact on the primary purpose of the multidisciplinary approach; restore as much as possible, the quality of life of our HNC patients.

THE CLINICAL AND TRANSLATIONAL RESEARCH IN HNC PATIENTS

Head and neck MDT and HNC units have been shown to be an effective tool to facilitate collaboration between professionals and hence improve care outcomes. This concept is accepted worldwide as the "gold standard" of cancer care (137).

Although MDTs are the central component of cancer care in many countries, there is a notable gap regarding how clinical and translational research can be integrated into these teams. Several publications involving multiple cancer types have described the importance of MDTs and oncological functional units to facilitate the smooth cooperation between cancer care professionals and improve patient cancer care. However, none of them discussed the potential benefits of incorporating the translational research teams within these units (6, 138).

We believe that clinical and translational research should be integrated within the HNC units. The prognosis of HNC patients remains guarded with a 5-year survival rate of 50% (139). The implementation of clinical trials provides an opportunity to offer more effective and less toxic treatment options in these patients. As HNC management is multidisciplinary, involving the different MDT professionals in the development of clinical trials is essential to design more accurate studies, especially in the locoregionally-advanced setting. The management of recurrent/metastatic disease is often complex and also requires multidisciplinary evaluation. Adapting the diagnostic and treatment circuits to facilitate the screening assessments required for clinical trials in this setting such as biopsies will avoid delays in the commencement of treatment and the successful patient enrolment in these studies.

Additionally, the integration of translational research teams in tumor boards and MDTs can help reducing the existing gap between current clinical practice and basic research. The input that basic researchers can receive from clinicians might be useful to guide translational projects. The reciprocal interaction and feedback from researchers and physicians will also contribute to improve prospective studies and determine the feasibility of the correlative analysis. The success of a translational project involving patient care is based on the coordination of the team. Tumor biopsies and collection of other specimens such as saliva, blood or stool are currently requested by prospective clinical and also correlative studies. Therefore, the collaboration and the timely coordination between research laboratories and clinics are crucial to conduct these studies smoothly and successfully.

Proposed recommendations to succeed in the integration of clinical and translational research within the MDT and HNC units are:

- Elect a coordinator for clinical and translational research within the unit.
- Promote periodic meetings to update projects and explain novel proposals.
- Make it open to all members of the unit so that everyone can contribute with new ideas and lead projects.
- Include educational programs to young members and trainees.
- Create working groups to distribute projects with appointed project leaders among the MDT members.

CONCLUSION

MDTs and oncologic functional units significantly improve the quality of cancer care. The integration of all the departments and professionals involved in the treatment of a specific cancer guarantees full and continued support to patients during diagnosis, treatment and follow-up periods and it is perceived positively by most patients. The different members of an MDT will provide close management of symptoms and acute/long-term side effects; adequate nutritional support, psychosocial reinforcement, and individualized follow-up. A comprehensive assessment and monitoring of HNC patients by specialized MDTs will result in better treatment adherence and tolerance, reduction in long-term side effects, improved quality of life and ultimately improved treatment outcome and survival.

AUTHOR CONTRIBUTIONS

MT and RM: review concept, review design, and interpretation. All authors: manuscript preparation and manuscript review.

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REVIEW
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Quality Assessment Across Disciplines in Head and Neck Cancer Treatment Diagnostic Pathology in HNSCC

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Quality assured pathology services are integral to provision of optimal management for patients with head and neck cancer. Pathology services vary globally and are dependent on resources in terms of both laboratory provision and availability of a highly trained and accredited workforce. Ensuring a high-quality pathology service depends largely on close working and effective communication between the clinical team providing treatment and the pathologists providing laboratory input. Laboratory services should be quality assured by achieving external accreditation, most often by conforming to International Organization for Standardization (ISO) standards such as ISO15189 sometimes with ISO17025 or alternatively ISO17020. Quality of diagnostic reporting can be assured by the ISO but clinical teams should endeavor to work with pathologists who engage in continuing professional development, external quality assurance and audit. Research also contributes to diagnostic reporting quality. A number of initiatives in the UK such as the EPSRC/MRC funded Molecular Pathology Nodes and the National Cancer Research Institute Cellular-Molecular Pathology initiative (C-M Path), for example, have linked pathologists, industry and researchers. This has resulted in centers leading in digital innovation, artificial intelligence, translational research and clinical trials supported by pathologists. For rare tumors and contemporary molecular diagnostics, biopsy material can increasingly be shared with expert specialist pathologists working in specialist centers, particularly by using digital pathology platforms with potentially global reach. High quality services for the majority of diagnostic processes required for head and neck cancer management is best provided by local pathologists where communication with the treating team is more effective than with pathologists working in remote centers. Quality assurance is an increasingly important aspect of pathology, assuring not only effective turnaround times and accuracy for the diagnostic service but also high quality consistent reporting for clinical trials where even small pathology errors can potentially produce a significant bias and in the worst case negate the value of a completed trial. Better outcomes have been associated with centers engaged in clinical trials than in non-participating centers. Provision of a quality assured pathology service should extend to both the research and diagnostic services.

Keywords: quality assurance, head and neck pathology, molecular pathology, accreditation, cancer

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INTRODUCTION

Management of patients with head and neck cancer relies on accurate pathological diagnosis. Quality assurance underpins the pathology service and must cover all stages of the diagnostic pathway from the time tissue samples leave the clinic or operating room to the receipt of the diagnostic report by the clinical team. Interpretation of pathology reports is further quality assured by clinical correlation and discussion at the multidisciplinary team meeting or tumor board. The importance of quality assurance for laboratories globally is recognized by the World Health Organization (1). The WHO Laboratory Quality Management System Handbook sets out international standards and brings together the key documents of the International Organization for Standardization (ISO) and the Clinical and Laboratory Standards Institute (CLSI). The standards set out by CLSI are fully compatible with ISO and it is therefore important for the clinical team to ensure that they work with a laboratory that is accredited by the International Organization for Standardization. Some national laws require accreditation of the whole or parts of pathology laboratory services but in many parts of the world accreditation is voluntary and some diagnostic services lack the resources to achieve accreditation. Pathology accreditation should be to minimum standard ISO15189:2012, though additional accreditation may be offered for specific areas such as Biobanking (ISO 20387:2018) if these activities are undertaken in the laboratory (**Table 1**). External Quality Assurance (EQA) also plays an important role in driving quality improvement and maintaining a high-quality laboratory test repertoire and the interpretation of those tests by cytologists, pathologists and advanced practitioner biomedical staff.

Proper documentation is essential to provision of a high quality diagnostic service. Standard Operating Procedures (SOPs) are used to document a series of detailed protocols and working procedures that can be followed by all of the laboratory staff so that a continuous quality service can be provided. SOPs must be regularly updated and held in a central repository so that only current documents are used for service provision. It is important to involve the whole clinical head and neck team in the preparation of those SOPs that relate to clinical practice and communication. The use of transoral robotic surgery (TORS), for example, has necessitated the formulation of new pathology protocols for handling the surgical specimen. The protocol can best be optimized through discussion between the surgeon and pathologist (**Figure 1**). Good laboratory services seek to continuously improve and implement innovations and should welcome regular external inspections and regulatory visits to maintain quality. Effective communication between the pathologists and clinical team is vital and there should be SOPs to cover communication. There are risks associated with multiple pathology reports and separate ancillary and molecular test reports. Laboratory information management systems (LIMS) should aim to collate this information into integrated pathology reports which ideally would automatically upload into a comprehensive electronic medical record. The multi-disciplinary team meeting (MDTM) or tumor board should include pathologists as core members to facilitate effective communication and service improvements.

QUALITY ASSURANCE IN THE LABORATORY

Almost all head and pathology is undertaken within large multi-disciplinary laboratories that have documented quality assurance procedures in place. It is not practical for very small laboratories to obtain accreditation and many have merged with larger laboratory services. A quality manager is essential to ensure that all processes and procedures are being correctly carried out in the laboratory. Accreditation in the pathology laboratory is generally to minimum standard ISO 15189: 2012. In the UK and Ireland accreditation to ISO 15189 is mandatory and regulated by the United Kingdom Accreditation Service (UKAS). Increasingly ISO 15189 accreditation is required by

TABLE 1 | International Organization for Standardization and laboratory accreditation.

ISO standard	Description
15189	Specifies requirements for quality and competence in medical laboratories. Can be used by medical laboratories in developing their quality management systems and assessing their own competence. It can also be used for confirming or recognizing the competence of medical laboratories by laboratory customers, regulating authorities, and accreditation bodies. https://www.iso.org/standard/56115.html
17020	Specifies requirements for the competence of bodies performing inspection and for the impartiality and consistency of their inspection activities. Professional bodies may seek accreditation from ISO under this standard and then use their own guidelines for laboratory accreditation. https://www.iso.org/standard/52994.html
17025	Specifies the general requirements for the competence, impartiality and consistent operation of laboratories. It is applicable to all organizations performing laboratory activities, regardless of the number of personnel. Laboratory customers, regulatory authorities, organizations and schemes using peer-assessment, accreditation bodies, and others use this standard in confirming or recognizing the competence of laboratories. https://www.iso.org/standard/66912.html
20387	Specifies general requirements for the competence, impartiality and consistent operation of biobanks including quality control requirements to ensure biological material and data collections of appropriate quality. This document is applicable to all organizations performing biobanking, including biobanking of biological material from multicellular organisms (e.g., human, animal, fungus, and plant) and microorganisms for research and development. Biobank users, regulatory authorities, organizations and schemes using peer-assessment, accreditation bodies, and others can also use this document in confirming or recognizing the competence of biobanks. For entities handling human materials procured and used for diagnostic and treatment purposes ISO 15189 and other clinical standards are intended to apply first and foremost. https://www.iso.org/standard/67888.html

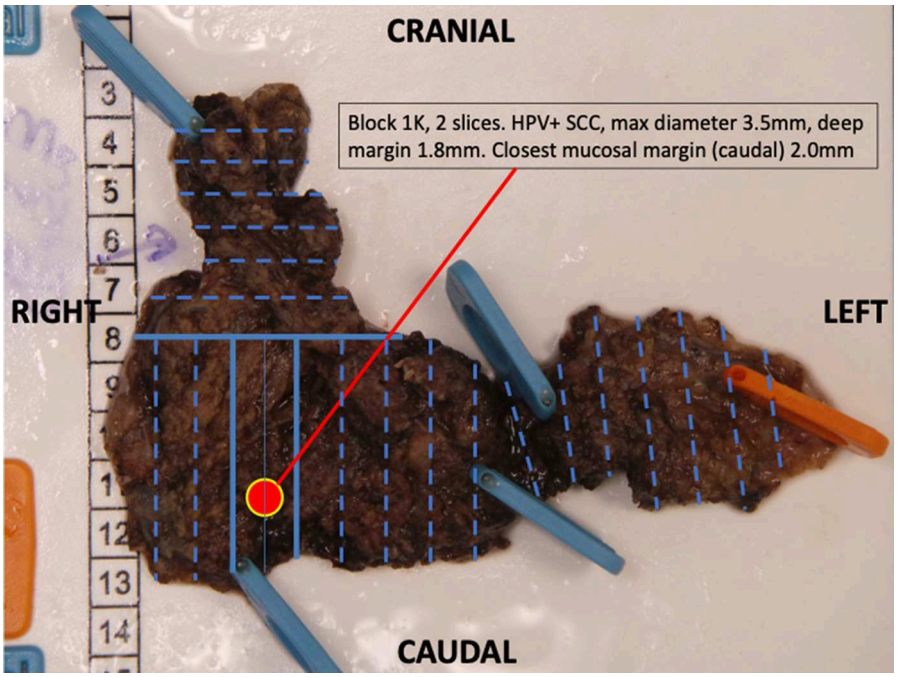

FIGURE 1 | A transoral robotic excision of base of tongue to identify an unknown primary lesion. Following the agreed protocol, the resection has been pinned mucosa side down. The entire specimen is blocked out (Blue lines) and annotated so that the primary lesion can be located to aid further management.

countries in continental Europe and the standard is being rolled out globally. Other standards may be applied for example in Finland and Switzerland accreditation to ISO 15189 and ISO 17025 is required covering both the clinical decision making and metrical aspects. In Germany, accreditation to ISO 15189 is voluntary for a pathology laboratory. A minimum requirement, however, is compliance with the Quality Assurance of Medical Laboratory Testing Guideline (Rili-BÄK) issued by the German Medical Association, and this standard is accredited under ISO 17020. There is a bias in ISO 15189 toward laboratory processes whereas the Rili-BÄK guideline covers the whole diagnostic service including both the laboratory processes and reporting standards of the pathologists (2). Accreditation organizations in the USA must submit proof that their practice standards meet the minimum requirements set out by the Clinical Laboratory Improvement Amendments (CLIA) regulations (3).

According to the ISO accreditation guidelines, all processes, procedures and examinations related to pathology diagnostics must be documented as standard operating procedures (SOPs) that are current and accessible to the laboratory staff. Initial documentation of these processes, procedures and examinations allows the laboratory head, manager and staff to perform internal evaluations that can eliminate unnecessary steps and improve efficiency and accuracy. These collected records (SOPs and their precursor "working instructions") comprise an enduring intellectual property of the lab, guaranteeing that experientially gained technical knowledge will be maintained without regard to personnel changes. Finally, they create a basis for a standardized rather than experiential induction for new employees into the work process.

Head and neck pathologists working within large multidisciplinary laboratory services participate in laboratory accreditation through creation and updating of SOPs and also by audit (see below). It should be remembered that accreditation to ISO 15189 relates to diagnostic procedures and processes within the laboratory but does not assure overall diagnostic quality. Head and neck pathologists should participate in quality assurance, audit, and educational events to ensure ongoing competency in diagnostic reporting and clinical trials if included in their practice.

Competency assessment for all staff is an essential part of quality assurance in the pathology laboratory. Responsibility for provision of a quality diagnostic service reaches out beyond the laboratory itself to a whole range of staff including those who transport and receive samples, medial secretaries who handle patient data, IT support, biomedical staff, managers, and advanced practitioners who are authorized to issue reports. It is of key importance that any person in the laboratory performing a task is competent to undertake that task. Such competencies must be documented and should form part of an activity log for laboratory staff who are on an approved training pathway programme (2).

QUALITY ASSURANCE FOR HEAD AND NECK PATHOLOGISTS

Training

In order to develop the skills and knowledge to provide a high-quality pathology service, it is important that trainees have

the opportunity to engage in a properly structured programme delivered by pathologists who are motivated to provide high quality education. Recruitment is a key factor and some programmes have not been able to attract sufficient numbers of high quality trainee applicants to maintain the workforce. In the UK for example there has been a steady decline in the numbers of academic pathologists over the last 15 years (**Figure 2**). A similar trend of declining workforce has been recognized in North America where from 2010 to 2019 over 40% fewer US medical students chose to pursue pathology residency programmes (4). The reasons for difficulty in recruitment to pathology are uncertain and several factors have been cited. Revision of medical curriculum in many medical schools has resulted in less undergraduate exposure to pathology. Pressures on the pathology service have resulted in pathologists having less time to provide teaching and the falling numbers of academic pathologists has compounded this in the UK and elsewhere. Remuneration and reward for junior doctors may also affect recruitment if trainee pathologists are disadvantaged compared to other specialities.

An important aspect of training is programme structure and competency assurance. In the United Kingdom for example, the Royal College of Pathologists sets out the curriculum and provides examinations that assure competency as the trainee progresses through the training stages. The College of American Pathologists has a similar function in the United States where residency programmes lead to Board certification. In some areas of pathology such as neuropathology and forensic pathology, sub-speciality training must be followed. However, head and neck pathology is not generally recognized as a sub-speciality for training. Pathologists who wish to practice in head and neck pathology follow the general pathology training route and gain specialist training post-qualification by engaging in specialist practice with experienced colleagues or through courses and research. Globally, training is more variable and often the pathology department itself has a greater degree of autonomy in determining curriculum, examinations and competency assurance. Training records are helpful for self-assessment of progress and are essential particularly if pathologists wish to relocate in the future. As with other disciplines, training in pathology is a mixture of academic knowledge and skill sets documented by meetings records, competency assessments and examination results with clinical practice. It is important for trainees to document their clinical activity and experience throughout the programme, including specimen numbers and types as well as complex trimming and autopsy experience. In that way, a comprehensive record of training can be built that may be used to provide evidence of satisfactory training. Workplace based assessments such as directly observed procedures and extended case based discussions should be regularly undertaken and can be assessed at an annual review of competency progression. Independent practice is very important as the trainee progresses. Audit of trainee reports by senior pathologists provides both quality assurance for the clinic and useful feedback for developing competency. Training programmes vary internationally but should set out a clear curriculum, objectives, experiential requirements and competency assessment processes, with a certificated outcome. Most substantive pathology posts are currently advertised with a requirement for one or more specialist areas and increasingly pathology departments are organized into specialist teams able to mentor newly qualified pathologists. Many pathologists who specialize in head and neck pathology practice in an additional complementary specialist area such as dermatopathology, endocrine pathology or bone, and soft tissue pathology.

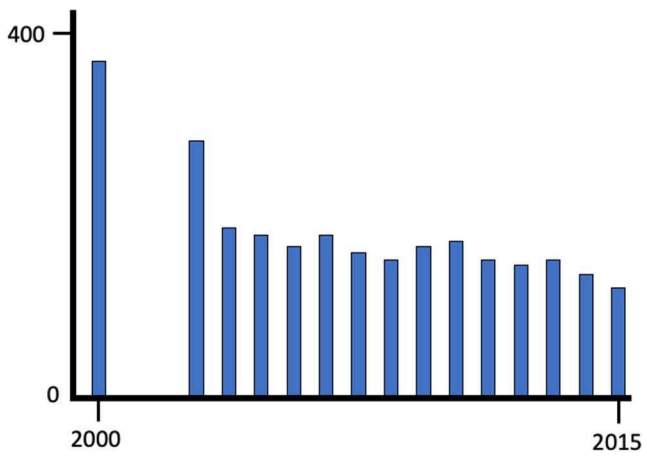

FIGURE 2 | The decline in clinical academic posts in pathology between 2000 and 2015 in the United Kingdom; data from the C-M Path website (accessed 05.05.2019). Over the same period clinical academic posts as a whole remained relative stable.

Interestingly, more than one pathway of training for head and neck pathology exists in several countries. Oral and maxillofacial pathology training pathways are open to dentally qualified individuals. Quality assurance requirements and health economic considerations have resulted in merger of small dedicated oral and maxillofacial pathology laboratories into larger centralized laboratory services. Oral and maxillofacial pathologists working in such a setting have typically expanded their range of practice and undertake head and neck work and often a second speciality. Alternatively, medically qualified trainees may follow a conventional general pathology pathway and then specialize in head and neck pathology, often in combination with another speciality. As skill mix changes are developed it is likely that many tasks currently performed by pathologists such as dissection of surgical specimens and reporting of less complex cases will be undertaken by non-medically qualified advanced practitioners working within the head and neck pathology team.

External Quality Assurance Schemes

Pathologists must be up to date with recent developments in the field including new entities, tumor classification and increasingly molecular pathology testing for diagnosis and targeted therapies. It is also important for pathologists to assure themselves that their competencies have been maintained. Participation in external

quality assurance (EQA) schemes ensures quality and forms an important part of continuing professional development (CPD, see next section). Pathology practice is increasingly specialized and there are now several specialist EQA schemes as well as general schemes in the United Kingdom. The principle is essentially the same for both types of scheme (5). Diagnostic slides are contributed to the EQA co-ordinator who makes up sets of slides and distributes them with case histories to the participating centers (**Figure 3**). Pathologists then make their individual diagnoses, or if a differential diagnosis is appropriate give their preferred diagnosis in ranked order and state how they would reach a definitive diagnosis. Participants are given a number known only to themselves and the scheme manager ensuring anonymity. There is typically circulation of a new slide set every 6 months. For head and pathology there may be subsections of oral and maxillofacial pathology, ENT pathology and common slides, with participants able to undertake selected sections or the whole set. Once the returns are made a national meeting is held (often as a satellite of a specialist society meeting) to which all participants are invited. A consensus diagnosis is reached at the meeting based largely on the returns but also through discussion. If no consensus can be reached then the case is declared educational and excluded from the marking scheme. Pathologists participating in the EQA scheme later receive their individual mark along with information about the submitters diagnosis, the consensus diagnosis, and results of any molecular testing not previously given in the history. Statistical data relating to the overall marking is also provided so the individual pathologist can measure their own performance against that of the participating group as a whole. A reflective note can be written for cases out of consensus that forms part of the CPD record. Where there is significant underperformance, for example benign disease confused with cancer, then the EQA scheme organizer may contact the pathologist through the manager. Typically, underperformance in any particular circulation is usually followed by improvement in the next round. When a pattern of persistent underperformance is found, then the scheme organizer will contact the individual and ascertain the reasons. Ultimately, in the UK, the Royal College of Pathologists may be notified and the medical director of the hospital can also be informed and local investigation may take place. Fortunately, persistent underperformance is very rare.

Head and neck pathology services are provided by oral pathologists, specialist head and neck pathologists and general pathologists. To assure quality, it is desirable for these pathologists to enroll in an interpretive external quality

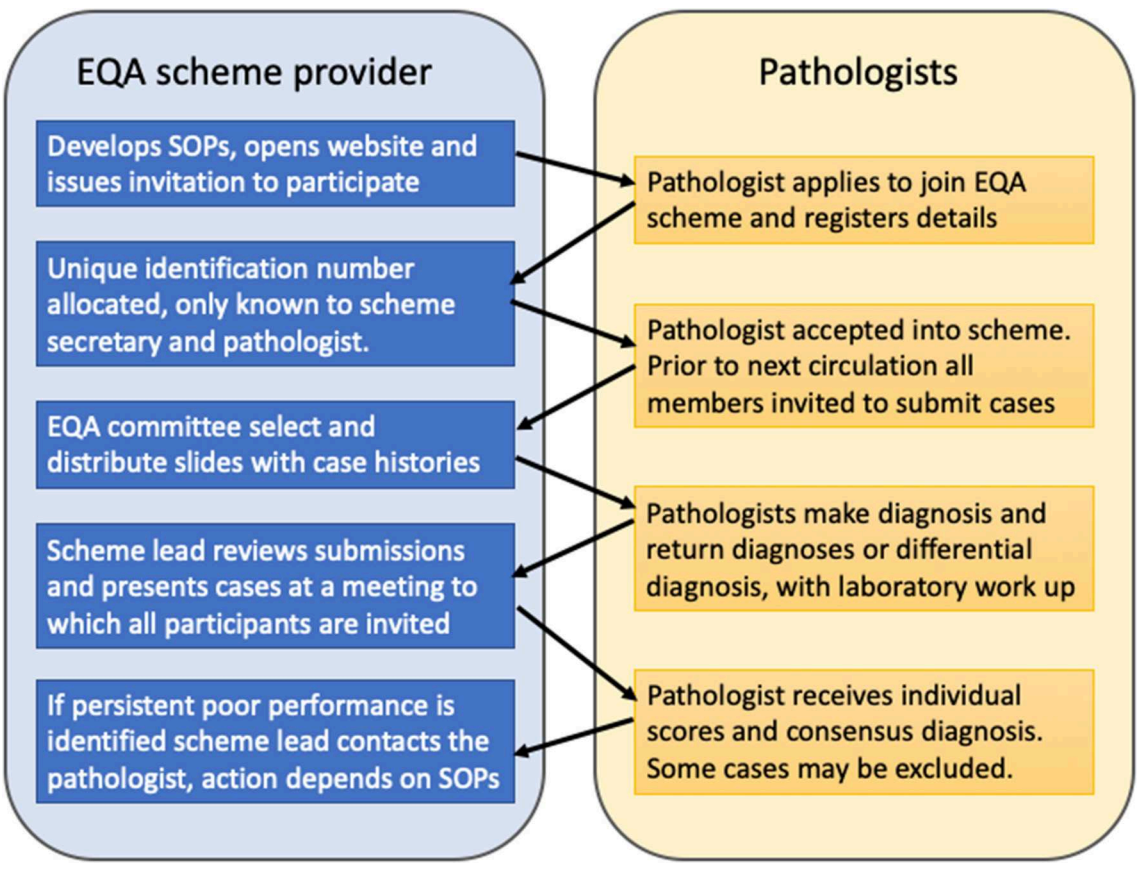

FIGURE 3 | The United Kingdom external quality assurance scheme cycle. Cases are contributed by scheme members and bi-annual slide review ensures quality, through feedback, and discussion. Cases where no consensus diagnosis can be reached are designated "educational" and excluded from the scoring scheme.

assurance scheme, such as that provided by the BSOMP (https://www.bsomp.org.uk/eqa) accredited by the Royal College of Pathologists. The scheme has many members outside the UK and participation can be done using digital pathology with archived slide sets available for reference (https://www.virtualpathology.leeds.ac.uk/eqa/specialist/headneck). Unfortunately, EQA schemes in head and neck pathology are rare outside of the UK, even though analysis of the UK scheme showed wide participation and encouraged oral and maxillofacial pathologists to broaden their practice and improved quality (5).

Continuing Professional Development

An important part of quality assurance for head and neck pathologists is their participation in relevant meetings and educational activities, including on-line modules and self-assessment packages. Such activities must be documented and considered as part of an appraisal or maintenance of competency recording. In North America, the Canadian Association of Pathologists- Association canadienne des pathologistes provides on-line modules including head and neck pathology. The Royal College of Pathologists hosts a CPD scheme open globally through affiliate membership. In Europe, the European Society of Pathology accredits meetings for continuing medical education (CME) points that include head and neck pathology. Similar schemes exist in many countries and participation is essential to maintain competency and implement new knowledge and practices into the service. From a global perspective, quality assurance can help developing pathology services in countries where resources are limited. Services are advancing rapidly and fostering international communication and training opportunities is an essential part of achieving worldwide high standards. Setting of international standards such as defining the classification and genetics of head and neck pathology (6) and producing accessible guidelines for minimum datasets (7) can form the basis for self-assessment and define areas where CPD can be useful. The work of international committees such as those of medical charities and the Royal College of Pathologists (https://www.rcpath.org/international/about-international.html) can also drive quality assurance through provision of training opportunities and CPD.

Case Consensus Meetings

Increasingly, head and neck pathology is provided by specialist pathologists who work in small teams often in centers providing head and neck oncology services. An important part of quality assurance on a day to day basis is the "double reporting" of cancer cases either in real time or at a dedicated weekly meeting around a multi-headed microscope. Through holding a regular consensus meeting, colleagues can not only look at cancer histology slides and discuss interpretation, but can also build a local database of cases. The consensus meeting also affords the opportunity to discuss implementation of new practices and monitor laboratory quality issues. A short weekly meeting is more effective than a programme of less frequent lengthy meetings, as issues can be resolved quickly. In head and neck pathology, it is often useful to discuss cases where agreement is known to be poor between pathologists, such as the presence or absence of extra-nodal extension in metastatic deposits, grading of epithelial dysplasia, interpretation of small poorly orientated biopsies, equivocal immunohistochemistry, HPV status and rare disorders. The consensus meeting is also useful for the education of trainee pathologists. A Standard Operating Procedure should cover the recording of the consensus meeting data as this forms part of the hospital record. Telepathology can be used to link pathologists working in accredited pathology services to colleagues in low resource areas to help reach a consensus diagnosis as well as facilitating external quality assurance schemes and post-graduate training (8).

Audit

Clinical audit is a process that seeks to identify where improvements can be made within healthcare services by measuring them against evidence based standards. Specific areas for quality improvement can then be targeted to ensure that patients receive the best possible care. In order to maintain safe and high quality practice in head and neck pathology, it is important to audit the service. Individuals and teams can then demonstrate that their practice and procedures meet standards. Clinical audit is the best method for generating this evidence. Audit topics may be identified by local issues or patients' concerns, hospital, and laboratory priorities, new guidelines, treatments of procedures and cost-effectiveness. A specific aim should be identified that measures a gap between ideal practice (determined from evidence, guidelines and standards) and actual practice. Appropriate standards to compare practice against must be identified and where possible published international, national, regional, or local standards should be selected. If published standards do not exist then objectives can be developed and research evidence, past audits and consensus opinion can be used to formulate a gold standard. Once the audit has been completed a report or presentation should be prepared and change can be implemented. After a suitable period of time a re-audit should take place to judge whether changes have been effective, thus completing the audit cycle (**Figure 4**). Audits can be submitted for formal evaluation by peer review at the Royal College of Pathologists in the UK who also provide open access guidance on the principles of conducting a high-quality clinical audit (www.rcpath.org).

Patient Safety Systems

Patient safety companies such as Datix (Swan court, London) and Global Research for Safety (Gesellschaft für Anlagen- und Reaktorsicherheit, Cologne) offer software packages that aim to capture clinical incidents and thus enable risk reduction by learning from errors that have occurred and thereby enhance quality assurance. Clinical errors that occur in head and neck pathology can be logged in such databases if implemented in the hospital management system. Reporting of incidents enables efficient identification of areas for improvement and training that may be required. This helps not only to create a patient safety culture and also to mitigate future risks. The advantage of participation for head and neck pathology is that incidents can be viewed in the wider clinical context, providing insights for pathologists and the clinical team. Errors that occur in the

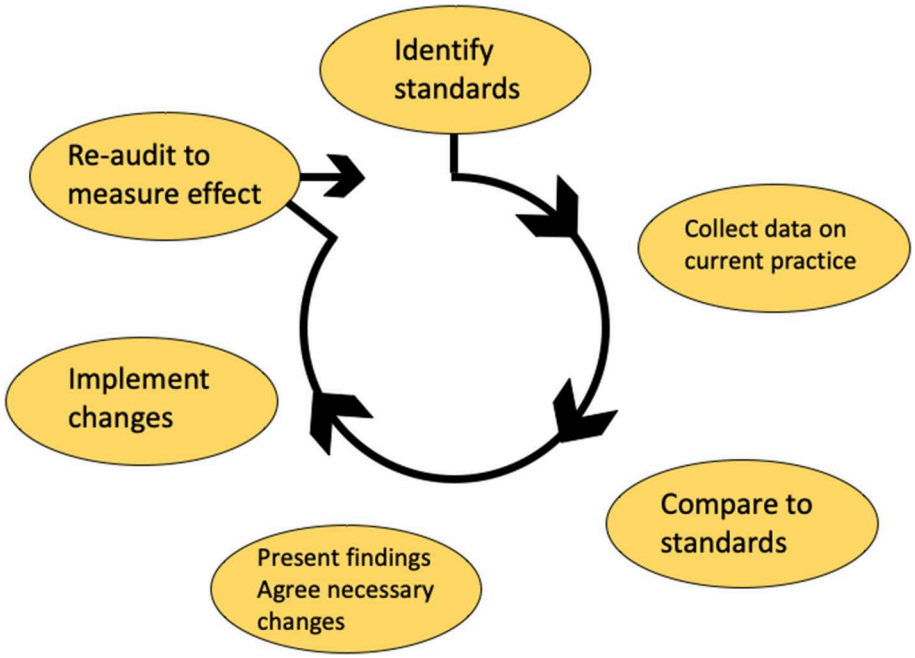

FIGURE 4 | The audit cycle used in the United Kingdom NHS service. Standards are first identified and the process to be audited is measured against the gold standard. Once changes identified by the audit are implemented, then the process should be re-audited until standards are met.

pathology laboratory may ultimately lead to a clinical incident and it is important that feedback is provided to the laboratory quality manager so that changes can be implemented with urgency if sub-optimal practice is identified. It is good practice for quality managers to maintain a "dashboard" to monitor critical incidents and "at risk" activities, for example when staff absence, reagent supply or machine failure threatens the service. Rapid communication with the head and neck clinical team is vital to ensure patient safety in case of discovery of an error and withdrawal of a laboratory reagent because of failure uncovered by quality control. Patients affected must be quickly identified and appropriate remedial action taken.

QUALITY ASSURANCE FOR DIGITAL PATHOLOGY

There is huge interest globally in digital pathology for provision of routine clinical reporting, education and quality assurance. Digital pathology can be integrated with other digital tools such as barcoding, specimen tracking and voice recognition to ensure a seamless cellular pathology workflow. Such systems also enable effective archiving and offer the possibility to link many types of clinical data. Digital pathology has the potential to bring about improvements in the safety, quality and efficiency of a cellular pathology department. Much has been written about the possibility of using artificial intelligence (AI) systems and it is likely that many innovations will be implemented into head and neck pathology in the future whilst others may not be validated for clinical use.

As with any rapidly advancing technology, it is important that validation takes place at every stage of implementation of digital pathology. Further, the regulatory framework must be complied with to ensure proper accreditation of the pathology service. Slide scanners and image analysis algorithms when intended for medical use (including diagnosis) are classed as medical devices (9, 10). The US FDA is testing a new Pre-Cert model (10) with the intention of demonstrating by premarket review and excellence appraisal that the same quality of information as a traditional approach to ensure safety and effectiveness standards are met. Pre-market review of digital health tools as medical devices includes implementing a new approach to the review of artificial intelligence tools. Formal studies of digital vs. conventional slide based assessment are required. Recently for example it has been shown that a group of pathologists could achieve 100% concordance on reporting of immunohistochemistry (11). However, it was found necessary to scan slides at x40 resolution rather than x20 to achieve confident digital reporting. This level of detail is necessary in order to develop detailed protocols and SOPs for routine practice. In head and neck pathology interpretation of *in situ* hybridization for high risk HPV DNA can be challenging and may require careful study of glass slides using high magnification at different focussing planes. It is not known whether digital pathology could be used for such an application and validation would be needed before implementation into the diagnostic service. Another example is that research has demonstrated that tumor infiltrating lymphocytes (TILs) in head and neck squamous cell carcinoma are highly prognostic and can sub-stratify HPV associated oro-pharyngeal carcinoma (12, 13). Algorithms have been developed that can measure TILs but using

such data to provide make clinical decisions must be viewed with caution until AI testing has been validated and accredited for clinical use. Equally, it is likely that testing based on AI algorithms will underpin future targeted or immunomodulatory therapies for head and neck cancer (14).

QUALITY ASSURANCE FOR CLINICAL TRIALS

Accurate pathological diagnosis is central to clinical trial entry and treatment stratification. Molecular testing often divides traditional entities into smaller subcategories requiring large multicentre, often multinational, interventional studies. Such studies require quality assured laboratory services, high diagnostic standards and validated reporting uniformity. Central pathology case review was first adopted in the 1960s following the identification of poor inter-observer variation between pathologists assessing lymphoma as a source of bias (15). Widespread central pathology case review occurs in clinical trials and is particularly valuable where rare or morphologically challenging diagnostic disorders are being considered. Currently, most central reviews occur after implementing patient management decisions for quality control prior to publication, rather than in "real time" for trial entry. One example is the central review of sentinel nodes in the SENT trial where surgical centers contributed slide sets for review by a group of trial pathologists (16). Only two discrepancies were identified; both where the local pathologist had reported individual tumor cells that were considered to be cytokeratin positive non-viable cell debris by the trial pathology group. Both patients had undergone neck dissection with no tumor found and were excluded from the analysis. The central review process led to greater understanding of interpretation of sentinel nodes in the context of metastatic oral cancer and formulation of guidelines for pathology. Central review that involves reviewing slides risks loss or breakage during transportation and it may not be possible to produce replacement slides from limited remaining tissue. Digital pathology has the potential to ameliorate many of these issues. Scanning of trial slides and image storage should be considered when planning new clinical trials where pathology is involved. Shortage of skilled trial pathologists is becoming a key issue in the conduct of clinical trials within the UK (17, 18). Digital pathology enables linking of distant pathology centers and could expand access to expert pathologists. Real time dissemination of identical images to multiple centers can allow simultaneous case review, reducing turnaround times and ensuring consensus opinion before therapeutic allocation (19). Diagnostic re-classification at the end of a study may identify suboptimal patient care and negate the significance of investigational findings. Even minor errors in diagnostic accuracy can affect the statistical significance of trial outcomes (19, 20). In head and neck pathology, real time central HPV testing has been implemented for clinical trials recruiting patients with oropharyngeal cancer (e.g., DeEscalate HPV and PATHOS), the latter also includes quality assurance of the surgical pathology (primary resection and neck dissections) to ensure patients are allocated to the correct risk group in the trial protocol (21, 22).

HEAD AND NECK GUIDELINES AND STANDARDS

International Collaboration on Cancer Reporting

In order to quality assure any head and neck service, it is important that pathological data are recorded in a consistent way. The International Collaboration on Cancer Reporting (ICCR) aimed to define a portfolio of minimum datasets available globally (7). Nine new datasets for head and neck pathology were published in September 2018. Each minimum dataset identifies elements that are mandatory and advisory. An accompanying paper has been published for many datasets and there is always useful narrative that accompanies each dataset, providing guidance on interpretation and rationale of the dataset. The ICCR datasets harmonize the previous datasets provided by Colleges and professional associations around the world and many of these organizations have endorsed the datasets. Pathology departments in hospitals treating head and neck cancer may simply check that their current recording systems are compliant with ICCR, or they may decide to incorporate the ICCR proformas into their reporting system. Minimum datasets are currently available for:

- Carcinomas of the Oral Cavity
- Carcinomas of the Hypopharynx, Larynx, and Trachea
- Carcinomas of the Nasopharynx and Oropharynx
- Carcinomas of the Major Salivary Glands
- Carcinomas of the Nasal Cavity and Paranasal Sinuses
- Ear and Temporal Bone Tumors
- Malignant Odontogenic Tumors
- Mucosal Melanomas of the Head and Neck
- Nodal Excisions and Neck Dissection Specimens for Head and Neck Tumors.

Staging and Diagnostic Entities

In order to quality assure head and neck outcomes it is important that accurate staging data are recorded. The AJCC and UICC TNM8 provide up to date guidance and is used in the ICCR datasets. For consistency, the published UICC text and any electronic versions must be updated to correct errors using the published errata [https://www.uicc.org/sites/main/files/atoms/files/UICC%20TNM%208th%20Edition%20Errata_09.05.2017.pdf]. For the first time in head and pathology, TNM8 has separate categories for clinical and pathological staging. Use of a biomarker (p16) to identify HPV associated oropharyngeal cancer is now mandatory as different staging is used for HPV positive and negative cases. The WHO Pathology and Genetics series provides a global standard for definition of diagnostic entities and the head and neck volume was last updated in 2017 (6). For quality assurance, it is important for pathologists to use this series as a reference standard. As evidence accumulates, then the series is updated. Other pathology literature such as authoritative textbooks and original scientific articles should

also be used to provide evidence for good pathology reporting practice. Guidelines for pathology in head and neck are provided by the College of American Pathologists (CAP), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and UK Multidisciplinary Guidelines for Head and Neck Cancer. With a multiplicity of guidelines in the literature, harmonization should be aimed for wherever possible and evidence cited in a reference section that reflects source data. Local guidelines always have to be agreed to match services with resources available. It is not always possible for every treatment center to follow every aspect of international guidelines. Patients should be informed and local guidelines followed by the treatment center.

QUALITY ASSURANCE FOR MOLECULAR TESTING IN HEAD AND NECK PATHOLOGY

Whole genome sequencing or whole exome sequencing is being introduced into clinical service, though at present most molecular testing utilizes validated immunohistochemistry, cytogenetic methods or panel sequencing. In the UK, whole genome sequencing is being introduced into the NHS clinical service from July 2019 though only for sarcoma, hematological malignancy and pediatric oncology initially. Whole genome sequencing can be of value in head and neck squamous cell carcinoma, where prognostic subsets can be identified that may ultimately guide therapy (23–26). In the pathology laboratory cellularity scoring is necessary to ensure that sufficient tumor DNA is present in a sample; currently for whole genome sequencing 40% tumor cells from has been set as a threshold with DNA quality control after extraction from 5 mm cube of fresh tissue. It is likely that the tumor volume and threshold of cellularity will be reduced as technology develops. The results of the UK external quality assurance scheme have shown that there is wide variation in cellularity scoring amongst pathologists. This has prompted the production of an open access on line training package for pathologists (https://www.genomicseducation.hee.nhs.uk/courses/) that covers the principles and pitfalls of cellularity scoring on sections. These relate to issues around 3-dimensional architecture and the relative size of cell nuclei, both of which tend to lead to overestimation of the ratio of the genomes, particularly in lymphocyte rich tumors.

Quality assurance for biomarkers such as PDL-1 can be provided through training packages and evaluation (https://www.agilent.com/en/product/pharmdx/pd-l1-ihc-28-8-pharmdx-interpretation-training). Quality assurance schemes for immunohistochemistry are provided by NordiQC (http://www.nordiqc.org/) and NEQAS (https://www.ukneqasiccish.org/). The College of American Pathologists accredits laboratories and advises on quality assurance for immunohistochemistry, based on defined principles (27). Clinical trial pathologists should undertake Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) training with documented refreshment of learning biannually. These set out internationally recognized basic standards and are a minimum requirement for non-accredited laboratories involved in biomarker research and application. Both GCP and GCLP are broad ranging in scope and cover issues outside the more complex laboratory accreditation schemes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Follow-Up of Head and Neck Cancer Survivors: Tipping the Balance of Intensity

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The traditional concept of post-treatment surveillance in head and neck cancer patients relies on examinations directed at early detection of disease recurrence and/or second primary tumors. They are usually provided by ear, nose and throat specialists with complementary input from radiation oncologists and medical oncologists. Emerging evidence underscores the importance of monitoring and effective management of late adverse events. One of the major drawbacks is a lack of prospective controlled data. As a result, local institutional policies differ, and practice recommendations are subject to continuing debate. Due to the economic burden and impact on emotional comfort of patients, intensity and content of follow-up visits are a particularly conflicting topic. According to the current evidence-based medicine, follow-up of head and neck cancer patients does not prolong survival but can improve quality of life. Therefore, an approach giving priority to a multidisciplinary care involving a speech and swallowing expert, dietician, dentist, and psychologist may indeed be more relevant. Moreover, on a case-by-case basis, some patients need more frequent consultations supplemented by imaging modalities. Human papillomavirus positive oropharyngeal cancer tends to develop late failures at distant sites, and asymptomatic oligometastatic disease, especially in the lungs, can be successfully salvaged by local ablation, either surgically or by radiation. The deep structures of the skull base related to the nasopharynx are inaccessible to routine clinical examination, advocating periodic imaging supplemented by nasofibroscopy as indicated. Anamnesis of heavy smoking justifies annual low-dose computed tomography screening of the thorax and intensive smoking cessation counseling. Finally, some cancer survivors feel more comfortable with regular imaging, and their voice should be taken into consideration. Future development of surveillance strategies will depend on several variables including identification of reliable predictive factors to select those who could derive the most benefit from follow-up visits, the availability of long-term follow-up data, the results of the first randomized trials, resource allocation patterns, infrastructure density, and the therapeutic landscape of locally advanced and recurrent and/or metastatic disease, which is rapidly changing with the advent of immune checkpoint inhibitors and better utilization of local approaches.

Keywords: head and neck cancer, survivorship, surveillance, recurrence, metastasis, second primary tumor, late toxicity, quality of life

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INTRODUCTION

Aiming at different aspects of post-treatment monitoring, follow-up has always been an integral part of modern oncology care. In head and neck cancer, the target group of patients consists of those who underwent curative therapy for early or locoregionally advanced disease, although this paradigm may soon be changing. Distant metastases have traditionally portended a dismal prognosis with median overall survival of <1 year. The recent advent of immunotherapy together with better integration of local ablative modalities holds the promise of an improved, yet still rare long-term disease- and treatment-free survivorship even in patients initially managed with palliative intent (1, 2). The concept of post-treatment surveillance is based on the following two premises. First, compared with self-referral, it allows early detection of an abnormality. Second, early detection, compared with late diagnosis, preferably in the asymptomatic stage, leads to improved outcomes. However, neither of these hypotheses has been supported by strong evidence, partly due to ethical reasons related to the design of the control arm which should be ideally based on very reduced or no-follow-up approaches. Until present, no randomized trial has successfully compared two different follow-up strategies or a given follow-up protocol with no surveillance. Nevertheless, most of the internationally recognized societies recommend an intensive search for a locoregional failure during the first 2–3 years corresponding with the biologic behavior of recurrent disease. As a result, appointments can be as frequent as every 1–3 months at the beginning, progressively dropping off on each consecutive year, so that patients are usually seen annually after 5 years (3). Of note, these guidelines are not uniformly accepted but rather adapted by practicing physicians sometimes to their personal beliefs such as the notion about the allegedly beneficial use of routine positron emission tomography/computed tomography scan imaging (PET/CT) in asymptomatic cancer survivors (4).

The key question to address is whether available data sufficiently endorse intensive follow-up protocols or whether we can decrease the frequency of appointments without harming our patients. In this respect, disease-oriented examinations focusing on tumor detection should be distinguished from patient-oriented appraisal of late adverse events. In this paper, the term "intensive follow-up" partly overlaps with the general impression of current follow-up protocols, but due to existing variations among different centers, it should rather be perceived as a relative concept allowing us to discuss different comparisons with "less intensive" approaches. Another intriguing issue is possible personalization of surveillance based on disease subsite, biological characteristics, and molecular biomarkers or patient risk factors. The disease group of interest here comprises primarily squamous cell carcinoma of the head and neck (SCCHN), i.e., of the oral cavity, oropharynx, larynx, and hypopharynx, and nasopharyngeal cancer, but the obtained findings can be, to a certain extent, extrapolated to some less frequent entities of the head and neck region due to a paucity of data relevant to rare diseases. The presented conclusions do not apply to primary response assessment in SCCHN by means of clinical evaluation and imaging within 3 months after radiotherapy or chemoradiotherapy, which belong to the standard of care and have been covered elsewhere (5).

REPORTING AND INTERPRETATION OF FOLLOW-UP STUDIES

When evaluating different surveillance programs, the key objective is to determine how many patients could benefit from early detection of recurrence and/or second primary tumor. Overall survival remains the best indicator of that. Secondary endpoints include proportion of detected recurrences or second primary tumors (pick-up rate), proportion of patients eligible for a curative approach and of those who finally undergo such treatment, quality of life, and early detection rate of late adverse events and comorbid conditions. As opposed to clinical trials exploring a new therapeutic modality, the hallmark of surveillance studies are the characteristics of follow-up visits which may influence the actual intervention. Therefore, a recurrence rate *per se* reported in clinical studies does not sufficiently describe the effectiveness of surveillance programs analyzing the utility of different follow-up schedules and of the respective modalities used (physical examination, endoscopy, imaging, blood tests, etc.).

A rigorous interpretation of the results starts with collecting the pick-up rate data and distinguishing between symptomatic and asymptomatic cases followed by identifying the proportion of eligible and intervened patients, the latter of which qualify for comparative survival assessments. Important is to avoid confusion with self-referral which informs us about symptomatic patients examined at off-schedule visits and corresponds thus with a no-follow-up approach. Typical symptoms necessitating further evaluation include new onset or worsening of pain, hoarseness, and a lump in the neck. Analogously to screening programs, the calculated benefit of a given follow-up protocol vs. self-referral can be overestimated by lead-time and length-time biases. In addition, two further aspects should be addressed. Cost-effectiveness calculations usually focus on the amount of costs necessary to detect one recurrence. The obvious limitation is the lack of information on the real benefit reflected by the resulting impact on overall survival. The second point is quality of life characterized by several contributing factors, not only by disease recurrence, but also by second primary tumors, late adverse events, and lifestyle behaviors (mainly smoking and alcohol intake).

Next to elaboration of the optimal timing and procedures of the follow-up routine, further efforts urge to define patient subgroups who benefit most. In this respect, life expectancy, disease stage, primary site (oral cavity, larynx, and the subdivisions of pharynx), and molecular markers such as human papillomavirus (HPV) status or p16 status as its surrogate marker belong to commonly used criteria in clinical practice. Of note, more intensified surveillance is often prescribed to patients initially presenting with advanced disease. While in these cases, recurrences are indeed more frequent than in early stage head

and neck cancer, they are less likely to be successfully salvaged (6, 7).

ARGUMENTS AGAINST INTENSIVE FOLLOW-UP

There has been weak evidence of improved outcome resulting from a salvage intervention of recurrences detected at routine follow-up visits when compared with those detected at self-referral. In one retrospective study, 428 patients with SCCHN were treated between 1979 and 1983 and followed for 84–126 months. The follow-up schedule consisted of a locoregional examination and medical history performed regularly at given time points with a decreasing intensity for a total of 10 years (6x during the first year, then 4x and 3x during the second and third years, respectively, then 2x until the end of the fifth year and annually afterwards). An annual chest X-ray was mandatory. The authors found a significantly better mean survival (58 vs. 32 months, $p < 0.05$) after detection of an event (i.e., recurrence or second primary tumor) with a routine follow-up (185 events in 6,350 appointments, pick-up rate 1 in 34) vs. self-referral (20 events in 54 appointments, pick-up rate 1 in 2.7), respectively. The corresponding cure rates were 1 in 78 and 1 in 6.8 appointments, respectively. Of note, 67% of events detected at routine follow-up were symptomatic. The study, thus, excels in providing us with very detailed and rigorous reporting, but due to the small number of patients in the self-referral cohort, the results should be regarded with caution (8). In addition, quantitatively more data, albeit still retrospective, did neither confirm such survival benefit nor find a correlation between follow-up intensity and survival (7, 9–11). The relevance of intensive follow-up is further undercut by the fact that the majority of recurrences (56–85%) are symptomatic and therefore potentially amenable to a successful self-referral (7, 8, 10–16). The real-world setting brings another important factor to the forefront, i.e., compliance. According to different author groups, non-adherence to surveillance protocols varies, being more often found in patients with small primary tumors, who live far from a hospital and continue to smoke (6). Nevertheless, this does not seem to have influence on survival outcomes (7).

It can be argued that the reason why the majority of recurrences are symptomatic is the insufficient detection capacity of a physical examination supplemented by endoscopy as indicated. At first glance, this seems to be a credible statement since very small neoplastic changes remain clinically silent. In this respect, biochemical tumor markers are commonly prescribed in oncology practices with varying degree of supporting evidence. In SCCHN, this diagnostic approach lacks sufficient sensitivity (17). The only exception could be Epstein-Barr virus deoxyribonucleic acid (DNA) analysis in nasopharyngeal cancer survivors with emerging new data on HPV cell-free DNA monitoring in viral-related oropharyngeal cancer (18, 19). As none of these has been standardized for routine clinical use yet, much attention has been paid to imaging modalities. Formerly recommended annual chest x-rays capture only a minority of lung tumors in their asymptomatic growth phase. According to a recent meta-analysis, a chest X-ray misses about 25% of cancer lesions (20). Notwithstanding the diagnostic pitfall when differentiating a SCCHN lung metastasis from a lung primary, most of the cases diagnosed by plain radiography correspond to head and neck cancer dissemination (21). Computed tomography alone or in combination with PET imaging indeed improves detection of asymptomatic lesions. Surveillance imaging by means of PET/CT has very good sensitivity and negative predictive value but only moderate specificity and positive predictive value (22). On the contrary, conventional evaluation by a physical examination, chest X-ray, CT, and magnetic resonance imaging has lower sensitivity but higher specificity (23). Positron emission tomography was shown to influence treatment decision in about 1 out of 3 cases. Unfortunately, no impact on survival has been demonstrated yet, probably due to the low yield of hypermetabolic lesions (about one third at maximum), of which not all are amenable to surgery and not all of the amenable cases finally undergo a resection (22, 24, 25). Illustrative to that is a recent retrospective study of 326 patients in which a clinical and radiological follow-up involving periodic CT, magnetic resonance imaging, and PET scan identified more recurrences in the asymptomatic phase than were patient-detected cases, which were symptomatic at a scheduled appointment or revealed during an unplanned, symptom-driven consultation. However, the proportion of patients eligible to a curative treatment remained comparable as well as their survival outcomes (26).

The choice of therapeutic approach depends on clinical setting. In oligometastatic disease (1–5 metastases), quantitatively more data support surgery which remains thus the gold standard in this scenario (5-year overall survival about 30%) (2, 27). As a viable alternative to an invasive procedure, stereotactic radiotherapy yields similar outcomes, although we lack a direct comparison between the two modalities (28). In the rare cases of solitary metastases, both surgery and radiotherapy show the maximum efficacy with a 5-year survival rate of up to 56% (29). A different situation exists when locoregional recurrence develops because the respective anatomical region was already subjected to prior interventions. The ensuing consideration are survival rates in those who undergo a salvage procedure by different modalities. Surgical resection of locally and/or regionally recurrent disease, if technically possible, yields the best results with a 5-year overall survival of up to 39%, particularly in early disease and laryngeal primary (30, 31). Interestingly, such outcomes seem to be preserved even after operating on a second recurrence (32) On the other hand, definitive re-irradiation in patients with an unresectable disease, with or without chemotherapy, should be delivered with caution. The low survival rates of 10–30% at 2 years are further dampened by 40% of severe late toxicities and 10% treatment-related mortality (33). More recently, comprising nine centers from the United States, the Multi-Institution ReIrradiation (MIRI) Consortium analyzed about 500 patients with a resectable or unresectable recurrence or second primary tumor treated by radiotherapy or more commonly by chemoradiotherapy. At 2 years, overall survival reached up to 35% with severe acute toxicity not exceeding 22%. Based on a recursive partitioning analysis (RPA) of time from

first course of radiation, resectability, and organ dysfunction, 3 prognostic subgroups were defined. Of note, RPA class III patients (i.e., time from first-course radiotherapy of 2 years or less and the presence of organ dysfunction) are not ideal candidates for protracted chemoradiation regardless of resection status (34–36).

Unfortunately, the majority of patients with recurrent and/or metastatic SCCHN are eligible neither for surgery nor radiotherapy, and the remaining options are limited, questioning thus the role of intensive follow-up. Even the most potent systemic treatment combining a chemotherapy doublet with an immune checkpoint inhibitor should be regarded as a palliative measure. The expected median overall survival only slightly exceeds over 1 year, albeit with a chance of long-term survivorship for a minority of patients (perhaps 10–20%) (37). Noteworthy, early initiation of systemic therapy to improve outcome has not been based on any strong evidence, and recommended factors guiding our decision include disease kinetics, risk of treatment-related toxicities, and presenting symptoms (38).

Last but not the least, follow-up visits contribute to healthcare resource consumption. Although we lack direct comparisons between different surveillance programs, unjustified follow-up visits are not cost-effective. According to a 1998 publication, the estimated costs per detected recurrence or second primary tumor ranged from $2,587 for non-intensive to $49,242 for intensive follow-up (39). The proponents of intensive follow-up might argue that the results of such analyses should be put into the context of modern immunotherapy currently approved for palliative treatment of recurrent and/or metastatic SCCCHN. As an example, it was shown that about $300,000 may be needed to invest to gain one quality-adjusted life-year (QALY) when treating with second-line nivolumab relative to a standard-of-care chemotherapy or cetuximab (40).

ARGUMENTS IN SUPPORT OF INTENSIVE FOLLOW-UP

Besides recurrent disease, follow-up visits address the risk of second primary tumors sharing the same risk factors as most of the head and neck cancer cases, i.e., tobacco and alcohol. Second primary tumors occur at an average rate of 2–4% per year with a cumulative incidence of 5–35% predominantly in the head and neck region if the index cancer was localized in the oral cavity and oropharynx, but also at other sites as the lungs in patients with a past medical history of laryngeal or hypopharyngeal cancers and in the esophagus. Generally, they have better prognosis than recurrent tumors (41, 42). Hypopharyngeal cancer is associated with the highest probability of second primary tumors (6, 42). The risk of metachronous tumors should be a sufficient reason for smoking cessation and has an important implication for periodic CT scans in heavy smokers. According to the National Lung Screening Trial, there is level I evidence for reduced lung-cancer mortality in persons between 55 and 74 years of age who stopped smoking 15 years ago or earlier and who have a strong history of tobacco smoking of at least 30 pack-years when subjected to annual low-dose CT screening (43). Moreover, cancer survivors are advised to participate in colorectal, breast, and cervical screening programs. Less evidence is available for screening interventions to prevent other malignancies, and attentive symptom-directed investigations should be pursued in these cases.

The role of imaging methods differs according to the site of primary tumor, which impacts on screening of both locoregional and distant recurrences, and we will discuss these two clinical scenarios separately. Due to the inaccessibility of the deep structures of the skull base to routine clinical examination, periodic imaging, supplemented by nasofibroscopy if need be, is warranted in nasopharynx cancer survivors. Similarly, post-radiotherapy changes in laryngeal tissues may necessitate supplementary endoscopy or imaging in these patients (44). Frequent early endoscopic examinations are also suggested in patients who underwent endoscopic surgery, either transoral laser microsurgery (TOLS) or transoral robotic surgery (TORS), because more extensive resection is often feasible in local recurrences (author experience). In the majority of SCCHN cases, distant metastases are not the predominant type of failure except for the following two subsites, nasopharyngeal cancer and human papillomavirus positive oropharyngeal cancer. Here, additional efforts have been exerted to define appropriate surveillance.

Human papillomavirus positive oropharyngeal cancer represents a distinct entity characterized, among other things, by younger age of patients, usually a long-term survivorship, and a specific recurrence pattern. As opposed to its HPV-negative counterparts and other SCCHN cases, hematogenous dissemination is the prevailing type of failure and occurs over a longer period of time. While in HPV-negative disease, the majority of distant recurrences develop within the first 2 years, more than 10% of HPV-positive oropharyngeal cancer cases, notwithstanding an overall better distant control of around 85–90%, continue to metastasize beyond 3 years and a smaller proportion even after 6 years from diagnosis. Overall survival after distant failure is longer in HPV-positive patients, where oligometastatic disease of the lungs, i.e., one to five lesions, portends a potential for curative management in about one third of patients, primarily using surgery or radiotherapy (45–47). Importantly, most of the distant recurrences detected by surveillance imaging, such as PET/CT, are asymptomatic (48). Taken together, these findings support the notion that HPV-positive oropharynx cancer patients can also benefit from intensive follow-up involving imaging methods. Another head and neck cancer subsite known for the prevailing pattern of distant failure is the nasopharynx with analogous consequences in terms of radiological surveillance, as in the case of HPV-positive oropharyngeal cancer, in addition to the recommended periodic imaging to detect local recurrences as alluded to above (49, 50). Here, patients with pulmonary metastases alone may experience longer survival if local ablation is combined with systemic treatment (51).

As alluded to above, an essential part of post-treatment surveillance, especially in those treated with a bimodality or trimodality approach, consists of an active search for and

management of late side effects which may sometimes have equally debilitating consequences as re-appearance of malignant outgrowth (52, 53). Among the most common complications, resulting from the treatment but also from the initial disease spread, are problems with swallowing, sometimes accompanied by pain, weight loss, xerostomia, and dental issues. Further impact on the quality of life may have unrecognized or untreated hypothyroidism, depression, carotid stenosis, and problems with speech and hearing. A secondary analysis of three chemoradiotherapy trials revealed a crude rate of late toxicity of 43%, mostly in terms of pharyngeal and laryngeal toxicity. Predisposing factors were identified on multivariate analysis including older age, advanced T stage, primary site in the larynx or hypopharynx, and neck dissection after completion of chemoradiotherapy (53).

More recently, in a meta-analysis of aggregate data from 31 prospective trials exploring the standard concurrent chemoradiotherapy with three-weekly high-dose cisplatin, overall prevalence of severe late toxicity was about 20% with xerostomia, dysphagia, and subcutaneous fibrosis each not surpassing 10%. Pooled rates of grade 1–2 xerostomia after definitive and postoperative chemoradiation were 59 and 81%, respectively (54). However, it should be kept in mind that reporting of late adverse events often suffers from inconsistency and incompleteness. As an example, possibly reflecting an increase in delayed adverse events, the updated results of the Radiation Therapy Oncology Group (RTOG) 91-11 trial suggested worse long-term outcome in the standard chemoradiotherapy arm as compared to the group treated with induction chemotherapy followed by radiotherapy alone (55). Looking retrospectively at long-term side effects in 10-year survivors, another author group identified about 20% of patients, treated with conventional (2-dimensional) radiotherapy with or without chemotherapy, requiring permanent gastrostomy tube placement at a median of 5.6 years (range 0–20.3) and about the same proportion of cases developing osteoradionecrosis at a median of 7.2 years (range: 0.5–15.3) (56). Fortunately, modern radiotherapy techniques, such as Intensity-Modulated Radiation Therapy (IMRT), are expected to reduce these unfavorable late toxicity rates (57, 58).

Delayed side effects have a substantial influence on quality of life and a properly conducted follow-up should involve speech and swallowing evaluation for timely interventions. Appearing with a variable time of onset, hypothyroidism, either subclinical or as clinically overt disease, is a frequent side effect of radiotherapy, necessitating thyroid-stimulating hormone testing at least once per year (59). Head and neck cancer survivors fear recurrence and need emotional support. Contrasting with

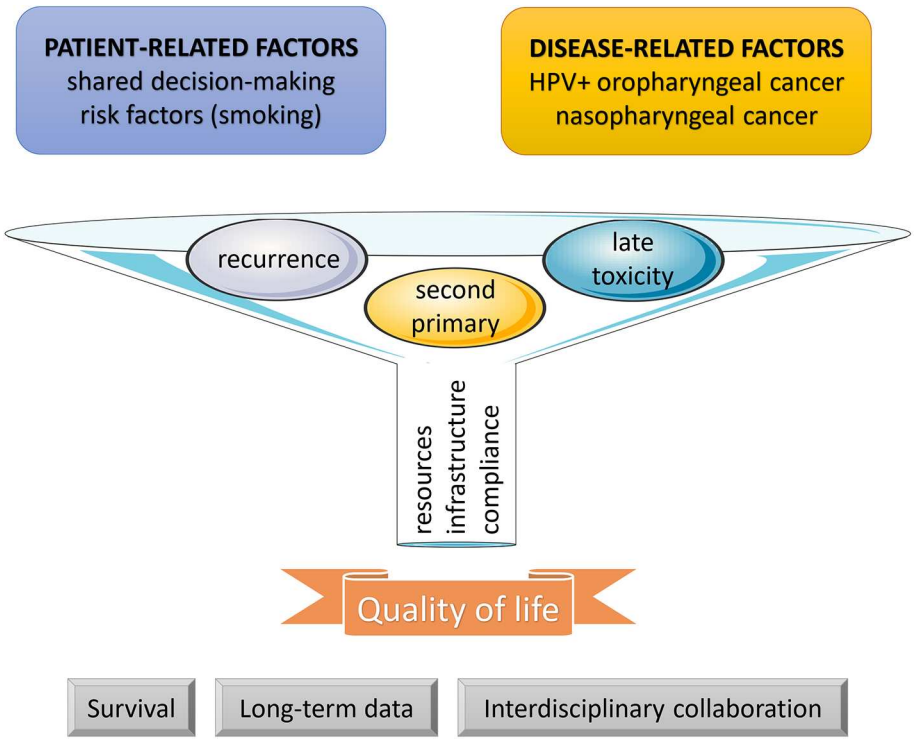

FIGURE 1 | Follow-up funnel. During the post-treatment phase, surveillance is indicated in all cancer patients. As defined by patient- and disease-related factors, a more intensive approach may be considered. In head and neck cancer survivors, the three main goals of surveillance include an early detection and management of recurrences, second primary tumors, and late adverse events. The results depend on patient compliance and available resources and infrastructure. Until present, improvement in quality of life has remained the strongest outcome, and further efforts are needed to clarify the impact on survival, to collect sufficient evidence from long-term data, and to structuralize interdisciplinary collaboration between all professional stakeholders.

underutilization of mental health services, depression is relatively common in this population with a prevalence of about 15%. Factors associated with post-(chemo)radiotherapy depressions encompass tracheostomy or gastrostomy tube and continued smoking (60). Psychological distress occurs after primary surgery at comparable rates (61, 62). Together with anxiety and fatigue, depression has one of the strongest correlations with quality of life (63). Of note, head and neck cancer survivors have the second highest mortality rate from suicide which is twice as high as compared with other oncology diagnoses and more than 3 times higher than the general US population (64, 65). In this context, the importance of social support and its periodic evaluation should be underlined.

Finally, in the era of shared medical decision making, the patient's voice should also be heard. Albeit still scarce and to a certain extent contradictory, the available retrospective data do not equivocally endorse that patients demand a less intensive follow-up protocol. On the contrary, they seem to feel more comfortable with regular imaging (66–69). However, the feeling of reassurance and satisfaction with the care they get may in some cases be counterbalanced by harmful aspects of such close surveillance including scan-associated distress, ultimately leading to a worse quality of life, excessive radiation exposure, unnecessary additional work-up, low cost-effectiveness, and even distraction from other recommended follow-up procedures (22, 70).

FINDING A COMPROMISE

In the absence of randomized prospective evidence, our decision making depends on retrospective data analyses and expert opinion. On the one hand, the economic and resource burden imposed by unnecessary follow-up visits on the health-care system is considerable, on the other hand, the multifaceted and complex character of head and neck cancer advocates frequent consultations to address the diverse issues these patients face. A possible solution could be to replace some of the routine physical examinations by a specific appraisal of nutritional, swallowing, dental, and psychosocial status. Especially good-prognosis young patients, such as those with HPV-related oropharyngeal carcinoma or nasopharyngeal carcinoma, could benefit from such approach, along with an adequate imaging surveillance. According to this conception, follow-up should not be diminished but rather reorganized and rationalized to a more cost-effective model which does not primarily limit the costs but increases efficacy by improving quality of life, offering a better rehabilitation, and enhancing return to work. In this respect, new cost-effective options such as nurse-led follow-up care may even be beneficial in terms of health-related quality of life (71). Due to the respective competences and accreditation for clinical examination, the head and neck surgical discipline has a major role in the surveillance of patients who have been treated for head and neck cancer. However, a holistic approach to patient follow-up should be pursued whenever possible. It can be offered by a dedicated team consisting not only of an ENT specialist, but also a medical and radiation oncologist, a specialized nurse, a swallowing expert, a dietician, a dentist, and a psychologist.

FUTURE OUTLOOKS

At this moment, improved quality of life depending on early detection of late toxicities and their appropriate management remains the strongest advantage of surveillance in head and neck cancer patients after treatment termination, albeit not supported by prospectively controlled evidence (**Figure 1**). Data on the outcomes of recurrence management are still scarce and do not allow us to make firm conclusions. Informative in this respect might be the currently ongoing SURVEILL'ORL (NCT03519048) and HETeCo (NCT02262221) trials aiming to randomly assign a total of almost 1500 participants between conventional surveillance and follow-up strategies intensified mainly by imaging methods after curative therapy of head and neck cancer with a primary outcome measure of overall survival (SURVEILL'ORL) and cost-effectiveness (HETeCo). Besides that, two promising techniques have recently emerged that will probably contribute to shaping oncology care in the future. The first are Electronic Patient Reported Outcomes (ePROs), allowing real-time symptom monitoring and even offering a survival benefit as demonstrated in a lung cancer study, in which after introduction ePROs, median overall survival rose from 13.5 to 22.5 months (72). A second innovative approach consists of circulating tumor cells enumeration which has been found associated with an increased risk of distant metastases, thus harboring potential for their early detection during follow-up (73). In theory, the latter technique may also open new avenues for experimental preemptive treatments.

Another crucial aspect impacting on future evolution of surveillance protocols involves the changing landscape of treatment-related morbidity. Together with advances in surgery (robot-assisted interventions) and radiotherapy (IMRT, stereotactic procedures, and proton therapy), the advent of the new class of immunotherapeutic agents (immune checkpoint inhibitors such as pembrolizumab and nivolumab) has been exerting powerful influences on the therapeutic landscape of head and neck cancer. It will not take long before we start following patients who were treated with these medicines in the past, most commonly in the context of locoregionally advanced disease. In addition, long-term survivors of recurrent and/or metastatic disease, who are not on immunotherapy any more, represent an emerging group of patients requiring a more focused care. Given the immune-related adverse events which are still difficult to predict and can even be delayed appearing after the treatment has already been terminated, an additional work-up during surveillance might be warranted. Consequently, the concept of follow-up will need to be rethought, tipping the balance of intensity once again.

AUTHOR CONTRIBUTIONS

All authors participated in the preparation of this manuscript.

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REVIEW
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Quality Assessment in FDG-PET/CT Imaging of Head-and-Neck Cancer: One Home Run Is Better Than Two Doubles

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2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) is indicated in head-and-neck cancer for the initial workup when clinically indicated (e. g., large tumors, clinically positive neck, cervical adenopathy from an unknown primary, etc.), for the assessment of treatment response 12 weeks after completion of (chemo)radiotherapy, and during follow-up when there is suspicion of relapse. The successful implementation of FDG-PET/CT in routine clinical practice requires an in-depth understanding of the recent advances in physics and engineering that have significantly improved the imaging capabilities of PET/CT scanners (e.g., digital silicon photomultipliers, point-spread function modeling, and time-of-flight, and Bayesian penalized likelihood reconstruction). Moreover, a coordinated harmonization effort from professional societies (e.g., EANM) and international bodies (e.g., IAEA) has resulted in the creation of quality assurance frameworks (e.g., QUANUM, EARL, GMP) and guidelines that collectively cover the entire spectrum from tracer production, hardware calibration, patient preparation, and scan acquisition, to image interpretation (e.g., PERCIST, Hopkins criteria). The ultimate goal is to standardize the PET/CT technique and to guarantee accurate and reproducible imaging results for every patient. This review summarizes the recent technical breakthroughs in PET/CT scan design and describes the existing quality assessment frameworks with a focus on applications in head-and-neck cancer. Strict adherence to these harmonization efforts will enable leveraging the full potential of PET/CT and translate the proven benefits of this technique into tangible improvements in outcome for patients with head-and-neck cancer in routine clinical care.

Keywords: FDG-PET/CT, quality, harmonization, quantification, head and neck cancer

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INTRODUCTION

2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) is a hybrid functional imaging technique that visualizes tumor glucose metabolism. In head-and-neck cancers, the use of FDG-PET/CT is supported by the National Comprehensive Cancer Network (NCCN) and other societies for the initial workup when clinically indicated (e.g., large tumors, clinically positive neck, cervical adenopathy from an

unknown primary, etc.). Also, the technique is recommended for the assessment of treatment response 12 weeks after completion of (chemo)radiotherapy, and during follow-up when there is suspicion of relapse (1). Subsequent technological advances in both PET and CT devices over the last decade have resulted in significant improvements in the imaging capabilities of the latest generation of integrated PET/CT scanners, resulting in improved sensitivity, higher image resolution, and important reductions in patient radiation exposure.

In routine clinical practice PET/CT images are usually reported using a strictly visual interpretation. Yet, there is increasing interest in leveraging the intrinsically quantitative nature of PET data. The use of standardized uptake values (SUV) is however prone to errors introduced by various factors. Therefore, a thorough understanding of these potential pitfalls is increasingly important to avoid erroneous interpretation and conclusions. This is also apparent in the setting of multicenter imaging trials, where patients are scanned across many sites using various scanners (2–4). In order to overcome the limitations of scanner and reconstruction specific SUV values, a coordinated effort of harmonization has been conducted to standardize the FDG-PET/CT technique. In parallel, a broader initiative to develop quality management in nuclear medicine has also contributed to improving the standard of care.

The aim of this narrative review is to highlight the various quality measures that exist today, focusing on the use of FDG-PET/CT in head-and-neck cancer. When possible the impact of these procedures will be illustrated with real-world evidence. This text is not intended to be exhaustive or a detailed recipe for high-quality FDG-PET/CT imaging, but rather a gentle introduction to the underlying critical concepts and frameworks.

METHODS

A best evidence review was performed by searching the PubMed database for English language publications indexed up to August 2019 using the keywords "positron emission tomography," "PET," "quality," "harmonization," and "FDG." The abstracts of all 94 results were screened to identify publications addressing the technical basis supporting the need for harmonization, existing frameworks to perform standardized FDG-PET/CT imaging, and clinical data illustrating the impact of the use of these guidelines on reporting outcomes. Full-text published sources were preferred over abstract-only publications, whenever possible. Selected publications were screened for secondary references.

APPROPRIATE USE CRITERIA FOR FDG-PET/CT IMAGING IN HEAD-AND-NECK CANCER

Over the last decade, clinical trials have contributed to better defining the place of FDG-PET/CT in head-and-neck cancer, in particular in identifying the impact on patient management and outcomes. In particular, the prospective, randomized, controlled PET-NECK trial demonstrated non-inferior overall survival outcomes when FDG-PET/CT surveillance was performed 12 weeks after the end of chemoradiotherapy. In the FDG-PET/CT arm of the study, neck dissection was only performed if incomplete or equivocal response was seen on FDG-PET/CT, in contrast with planned neck dissection in patients with stage N2 or N3 disease in the comparator arm (5). In addition, FDG-PET/CT was also shown to be the more cost-effective strategy and associated with fewer complications than neck dissection (6).

These findings were quickly incorporated in the imaging recommendations of various societies, including the previously mentioned NCCN alliance (1). For example, the United Kingdom national multidisciplinary guidelines on imaging in head-and-neck cancer now conclude that currently a negative, normal FDG-PET/CT 12 weeks post-treatment likely offers the best prognostic reassurance (7). Also, it endorses the use of the technique to evaluate patients with malignant cervical adenopathy from an unknown primary as up-front indication, with a detection rate of an occult primary in approximately one third of cases. According to the same guideline, FDG-PET/CT is also valuable in the assessment of suspected recurrence of head-and-neck cancer when there are extensive, confounding post-treatment changes on conventional imaging modalities. Of note, the 12 week interval between the end of radiotherapy and FDG-PET/CT imaging to allow the resolution of inflammatory changes is now firmly established (8).

Similarly, a quality initiative from the Belgian Health Care Knowledge Centre concluded in 2015 that FDG-PET/CT is not recommended for the evaluation of metastatic spread and/or the detection of second primary tumors in patients with stage I–II squamous-cell head-and-neck tumors, while it is recommended for patients with stage III–IV disease (9). Nevertheless, a 2019 follow-up study noted that the use of this imaging technique in stage I–II patients was still 23%, well above the appropriate use target. Conversely, the same study found that only 48% of stage III-IV patients were offered FDG-PET/CT imaging for their disease, constituting a dramatic underuse (10). These findings underline the challenges of implementing existing guidelines in routine practice, which hampers improvements in patient outcomes.

RECENT TECHNOLOGICAL ADVANCES IN PET/CT IMAGING

This section together with **Table 1** presents a more technical overview of the recent advances in PET/CT physics and engineering for the interested reader, but can be skipped without loss of continuity.

Traditionally hampered by a rather modest image resolution, PET imaging has seen significant technological advances over the last decade resulting from improvements in detector hardware and advances in image reconstruction algorithms. Most notably, the introduction of (digital) solid-state photodetectors, time-of-flight (TOF) image reconstruction, point-spread-function (PSF) modeling, and Bayesian penalized likelihood (BPL) based reconstructions, have contributed to higher image quality.

TABLE 1 | Impact of recent technical breakthroughs on PET/CT image quality.

Technical advance and image impact
Digital silicon photomultiplier (SiPM)
• **Increased sensitivity** results in better statistics and less noise in the image. Equivalent image quality can be achieved with less activity administered to the patient, without increasing the scan time.
• The increased sensitivity allows the use of smaller voxels without significant increase in noise related to limited statistics. This results in an **increased spatial resolution** and **signal-to-noise ratio** and thus small lesion detectability.
• **Improved timing resolution**, see Time-of-flight (TOF) below.
Time-of-flight (TOF)
• Including the position of the annihilation on the line of response (LOR) allows for better discrimination between random and true coincidence events. Random events with TOF detection will often result in placement of the event outside the imaged body, which will not contribute to the noise inside the body and reduce the noise in the image. Thus **increasing the signal-to-noise ratio**.
• The higher peak noise equivalent count rate results in a **better and more uniform convergence** of the reconstruction algorithm. This improves the quantitative accuracy and the lesion detectability, especially in obese patients.
Point-spread function modeling
• Point-spread function modeling includes the physical processes that cause image degradation, including positron range, photon non-collinearity, and detector-related effects (including crystal widths, intercrystal scattering, and intercrystal penetration). This results in **noise reduction** and **spatial resolution uniformity**.
Bayesian penalized likelihood reconstruction
• The reconstruction introduces a term which penalizes noisy solutions that increase the variation between neighboring voxels. Therefore, the algorithm can run until full convergence, which leads to a better quantitative accuracy.
• By penalizing noisy solutions the signal-to-noise ratio is decreased, which improves image contrast in particular for small lesions.

The bold words summarize the key benefits of a particular technical breakthrough.

Progress in detector design includes the introduction of (digital) solid state photodetectors like the digital silicon photomultiplier (SiPM) (11). These have contributed to a higher image quality, improved small lesion detection, and allow for a lower administered activity of FDG, reducing patient radiation exposure. The improvements in reconstruction algorithms can be briefly summarized as follows. PET relies on the detection of two coincident photons generated by positron annihilation events to determine the location of the source. This requires multiple detected photon pairs within the circular PET detector. However, time-of-flight reconstructions improve this process by also taking into account the time difference between the detection of both annihilation photons, requiring less photon pairs for equivalent information on the source position. The use of TOF image reconstruction improves the signal-to-noise ratio (in particular in obese patients), improves the detection of small lesions, and enables imaging with lower injected activities (12). In addition, point-spread-function modeling addresses the physical characteristics of the different components of the PET detector system improving the uniformity of the spatial resolution and reducing image noise (13).

Image quality can be further improved with the use of latest generation image reconstruction algorithms. For example, the Bayesian penalized likelihood method results in improved image quality in particular for small lesions. The image resolution of PET systems is usually expressed using the standardized "full width half maximum" (FWHM) methodology, meaning that two ideal point-sources will appear separate in the image when they are a distance greater than the FWHM apart. For the latest generations whole-body systems this ∼3.5–4 mm in the transaxial axis (14, 15), with a theoretical physical lower limit of clinical PET imaging systems of ∼2 mm (16).

CLINICAL IMPACT OF NEWER PET/CT DESIGNS

Taken together, the type of PET/CT scanner and the chosen method of image reconstruction nowadays more than ever determines the quality and potential artifacts of the generated images. In clinical practice this is especially important when patients are scanned using different scanners during follow-up, as the observed changes in tumor metabolic activity may be real or caused by differences in the used devices or reconstruction settings.

In the coming years, it is expected that further technological advances will change clinical practice and revolutionize the PET/CT arena. In particular, the first full-body PET/CT devices have now become commercially available, enabling unprecedented image quality with very small amounts of activity (25 MBq [0.7 mCi] or less) and scan times of ∼1 min (17). This represents reductions of 80–90% in both injected activity and scan duration compared to previously available scanners.

FROM QUALITATIVE TO QUANTITATIVE INTERPRETATION

In routine clinical practice, the mainstay of PET/CT examinations are reported by visual qualitative assessment of regional tracer distribution where both the intensity and pattern of uptake will guide the judgment on calling a lesion benign or malignant. Obviously, this type of assessment is prone to error due to both technical and reader related issues, and may be associated with considerable inter-rater variability depending on expertise. Yet, due to the physical characteristics of the

PET technique, the image data is inherently quantitative and early-on the SUV emerged as semi-quantitative measure of tracer uptake, becoming the predominant metric for quantification of FDG-PET/CT scans. Indeed, oncology PET literature data is entrenched with proposed SUV thresholds to distinguish benign from malignant disease.

However, the SUV is not without flaws as this metric is vulnerable to many sources of unwanted variability, including patient preparation and characteristics, scanner capabilities, and calibration, image reconstruction settings, and tumor volume-of-interest (VOI) delineation techniques (18). Biologic factors that result in artificially lower SUVs include lower body fat percentage, higher blood glucose level, and shorter post-injection uptake time (19). Therefore, an SUV should always be interpreted with caution if information on these factors is lacking. Recognizing these issues, it was recommended early-on that imaging should be performed on the same scanner using the same image acquisition and reconstruction protocols when serial SUV measurements are used to assess treatment response, as well as meticulous attention to accurate determination of the administered radiopharmaceutical activity (19). While this may be feasible in a single-center setup, this becomes much harder when collaborating in a group of hospitals or in the context of a multi-center clinical trial. To overcome these limitations, a number of quality assurance and control measures have been proposed together with a framework for the harmonization of FDG-PET/CT acquisition and reconstruction.

In a recent multi-center study of FDG-PET/CT surveillance 12 weeks after concurrent chemotherapy, it was demonstrated that using an SUV threshold (SUV_{70} 2.2) performed equally well as visual analysis to detect nodal relapse, but required that SUV was measured using standardized acquisitions and reconstructions. Comparing with a historical control cohort of patients imaged in non-standardized conditions, the same authors showed that SUV ratios consisting of lesion uptake and a background region (e.g., the liver) may help to reduce some of the variability introduced by using non-standardized protocols (20). This may be explained by the fact that systematic system errors causing over- or underestimation of SUVs are canceled out to some extent by using relative ratios.

QUALITY MANAGEMENT IN NUCLEAR MEDICINE

Ideally, the quality measures described below are implemented within the context of a quality management system that standardizes the process to guarantee consistency in providing high level services to patients, referring physicians, and other stakeholders in a safe environment. To this end, the International Atomic Energy Agency (IAEA) has developed the Quality Management Audits in Nuclear Medicine Practices (QUANUM) framework to guide nuclear medicine services to achieve this goal (21).

QUALITY ASSURANCE AND CONTROL OF FDG-PET/CT

Quality assurance (QA) is the collective set of pro-active measures taken to ensure the quality of the entire process involved in performing the diagnostic study. It aims to prevent any errors or issues with the examination that may affect its quality by focusing on this process. In contrast, quality control (QC) describes the set of *post-hoc* activities that are carried out after the examination has been performed to ensure its quality, with the aim of identifying and correcting any errors or issues. As discussed previously, the quantification of PET data is particularly susceptible to variations in administered activity, tracer incubation times, scanner characteristics and image reconstructions settings. Therefore, it is not surprising that many of the measures listed below will aim to reduce variability in procedures by standardizing these parameters (**Figure 1**).

Tracer Production

The routine synthesis of FDG is semi-automated and multiple commercial systems are available to produce this radiopharmaceutical for just-in-time delivery in a way that is fully compliant with Good Manufacturing Practice (GMP) (22, 23). Using this approach, FDG can nowadays be reliably synthesized meeting the quality requirements as outlined in various pharmacopeia (24). As a consequence, issues in the production of FDG as cause for errors in PET/CT scans have become virtually non-existent.

Patient Preparation

Real-world data confirms that there is considerable heterogeneity in clinical routine practice of FDG-PET/CT imaging with respect to the imaging protocol used (25). This is probably inspired by the numerous studies reporting alternate patient preparation or scanning protocols over the years (26–30). In order to reduce this variability and possible errors introduced by this practice, the European Association of Nuclear Medicine (EANM) has published a detailed guideline for FDG-PET/CT imaging in oncology, including recommended acquisition protocols (31). While a detailed discussion is beyond the scope of this paper, the EANM guideline provides useful recommendations on:

- Food and drink consumption before the study
- Physical activity prior to the study
- Management of patients with diabetes
- Management of serum glucose level before tracer administration
- Measures to reduce physiologic tracer uptake in brown adipose tissue
- Hydration status
- Administered activity
- Suggested environmental conditions during the FDG uptake phase
- Patient positioning during the scan.

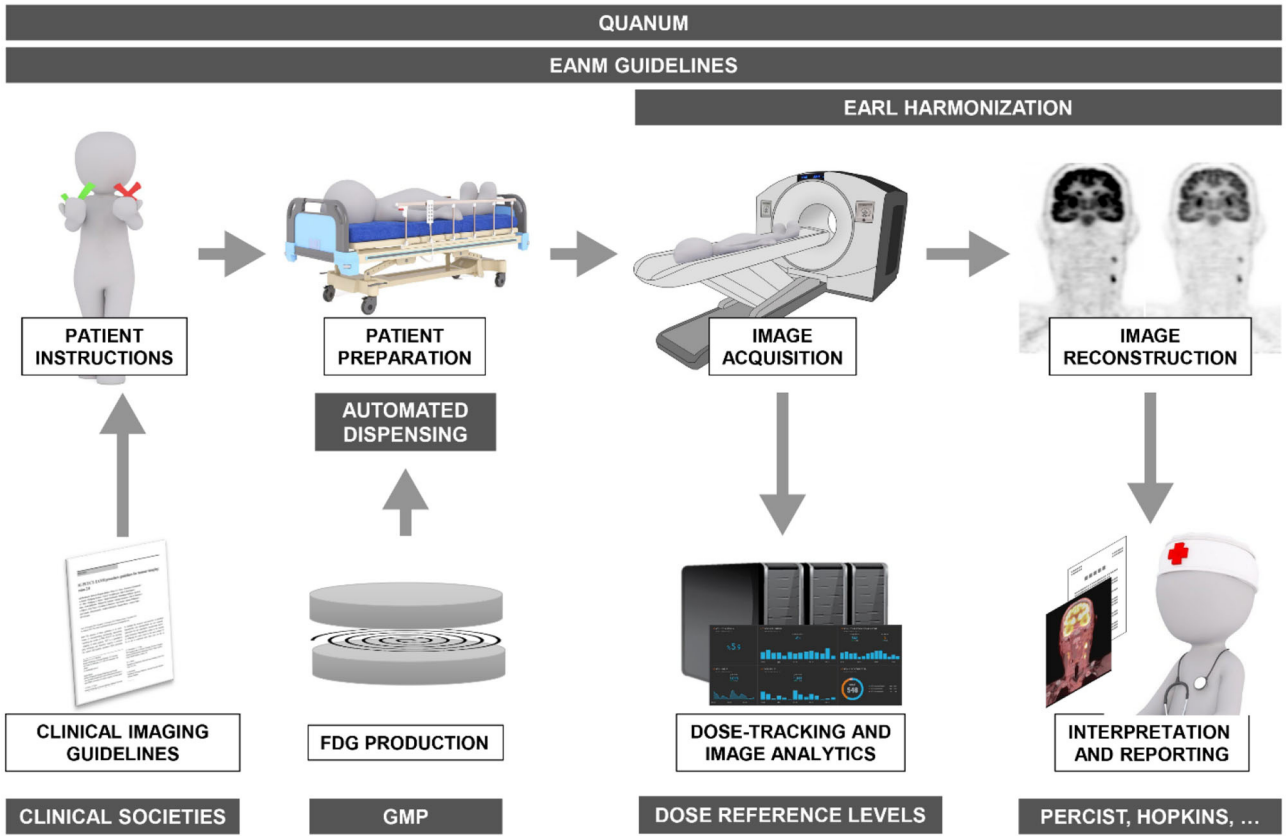

FIGURE 1 | Overview of the various quality assurance/control mechanisms (gray boxes) and frameworks in operation today covering the entire spectrum from FDG synthesis, patient instructions and preparation, to image acquisition, reconstruction, and reporting to ensure optimal diagnostic accuracy of FDG-PET/CT imaging in oncology.

Automated Dispensing and Injection

FDG is usually delivered as a multi-dose vial and subsequently dispensed and administered to the patient. This means that a manual procedure is required to remove the desired amount of activity from the vial and inject this into the patient. Not only does this repeated manual dispensing and administration expose the imaging technician to a significant amount of radiation, it also introduces the possibility of unintended over- or underdosing by errors in using the dose calibrator or unintentional residue left in the syringe or tubing.

To overcome this source of error, automated dispensing and injection systems have been developed. These systems have a built-in reservoir for storing FDG in a sterile and shielded way, contain a dose calibrator connected with the reservoir, and have a system of tubing and pumps that are able to deliver a requested amount of activity to a shielded syringe or device ready for injection into the patient. Data has shown that these systems are accurate, deliver activities for injection within a 3% margin of that requested, combined with reductions in the radiation exposure to the hands and fingers of technologists of 80–94% compared to manual dispensing and injection (32, 33).

Acquisition Protocol

The EANM guideline also gives guidance for the acquisition protocol (31), both for the PET and CT parts. Focusing on head-and-neck cancer, it is noteworthy to highlight the recommended two-step protocol to reduce artifacts in the head-and-neck region caused by the patient's arms when imaging in the arms up position: first the head-and-neck portion is imaged with the arms down, followed by a scan from apex of the lung through the mid-thigh with the arms up (34). In addition, acquisition of an additional dedicated head-and-neck image series with a higher PET resolution than that of the whole-body image set together with a contrast enhanced CT is recommended in the staging of head and neck cancer as it improves the detection of small lymph node metastases (35).

When the PET/CT study will be used for radiation planning, the patient positioning should mimic that of the radiotherapy set-up as closely as possible, including the use of a radiotherapy table top, laser alignment, immobilization devices, and measures (36). Especially for the head-and-neck region, immobilization techniques should be used to prevent movement of the head between the acquisition of the CT scan and the PET images. Indeed, while PET/CT scanners are hybrid imaging devices, the CT and PET study are not acquired at the same time, but rather

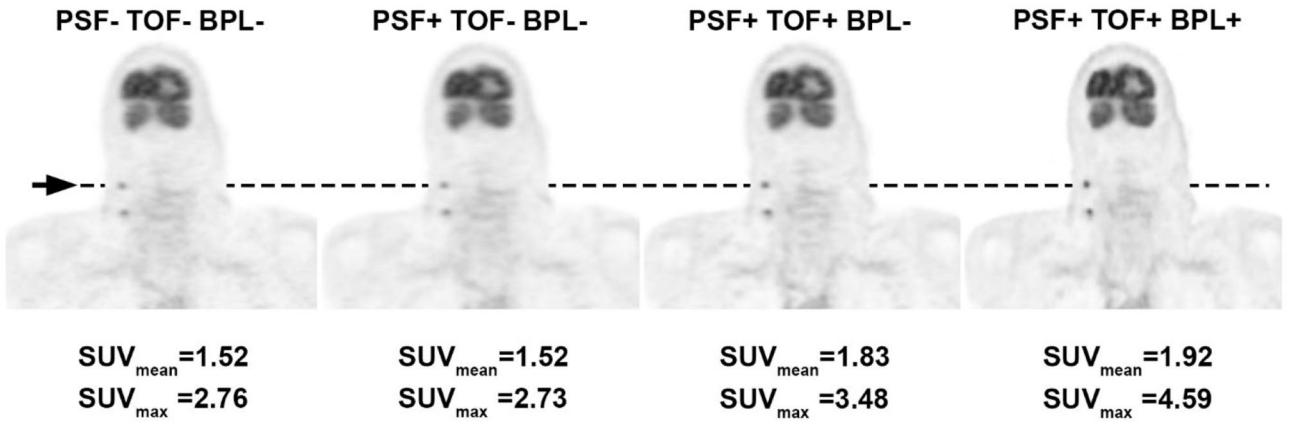

FIGURE 2 | Illustration of the upward creep in SUV values resulting from the use of recently introduced novel reconstruction techniques. The same FDG PET dataset in a patient with cervical lymph node metastases of a head-and-neck malignancy was reconstructed using a traditional iterative algorithm and subsequently with additional image improving techniques: PSF, point-spread-function modeling; TOF, time-of-flight; BPL, Bayesian penalized likelihood. SUV values are presented for the same cervical lymph node and measured in the same 1 cm^3 volume-of-interest (arrow), showing a clear increase in value, in particular for the maximum SUV of the lesion.

in a sequential fashion. Any patient movement between the two acquisitions will result in misregistration artifacts when viewing the fused images and may lead to errors in lesion localization.

Device Calibration

System calibrations typically include a daily check, periodic detector normalization, two to three dimensional radioactivity concentration calibration, as well as other parameters considered critical for quality assurance. A recent interim report from the IAEA QUANUM audits presenting results collected mostly in South America and Asia noted that the checklists covering quality control for imaging equipment showed the lowest values of conformance (68.3%), highlighting the need for continued attention in this area (37). Data from Austria obtained outside the scope of QUANUM confirm that the use of standardized QC procedures is a point for improvement in order to increase quantitative accuracy across PET/CT centers (25).

Harmonization

The most important contribution to the standardization of quantification of PET/CT across centers has without doubt been the harmonization effort set-up by the European Association of Nuclear Medicine (EANM) through their EANM Research Ltd (EARL) subsidiary. This accreditation program started in 2010 and has since been endorsed by the European Organisation for Research and Treatment of Cancer (EORTC) Imaging Group. Other efforts with similar goals have been initiated by American Society of Nuclear Medicine (38) and international consensus protocols have also been published (39).

The specific aim of EARL is to ensure the exchangeability of quantitative PET/CT metrics (like SUV) in a multicenter setting or to improve the implementation of quantitative interpretation criteria (such as SUV thresholds) in routine clinical practice (40). While a detailed description of the EARL protocol is beyond the scope of this text, it has been shown that compliance with EARL is feasible and able to resolve most causes of errors in quantitative PET measurements when combined with adherence to the FDG-PET/CT imaging guidelines (41). Designed in 2010, the EARL currently do not cover newer systems, that have been shown to produce higher maximum SUV values (**Figure 2**) resulting in discordant treatment response assessments (42). Based on these findings, an update of the EARL system has recently been proposed to include modern PET/CT equipment to mitigate these discrepancies (43).

Standardized Reporting

With the acquisition process and image reconstruction being harmonized, the next source of variability in FDG-PET/CT imaging is the interpretation of the images by the reading physician. In particular in the setting of treatment response assessment, the need for standardization of reporting was recognized early on. In 1999 the EORTC criteria were published, based essentially on changes in SUV (44). This was later superseded PERCIST, which also uses quantification as means to standardize the interpretation of response (45). New concepts introduced by PERCIST were:

- Checking variability of uptake between scans in a fixed background region (i.e., the liver) to assess whether comparisons between scans are appropriate
- Establishing a threshold of minimum uptake in a target lesion on the baseline scan required for a meaningful comparison
- The use of lean body mass adjusted standardized uptake value (SUL) to minimize the impact of body weight
- Selection of SULpeak (i.e., the highest average SUL in a sphere with predefined size contained in the lesion) rather than SUVmax (i.e., the hottest pixel in the lesion) as outcome metric.

In patients with head-and-neck squamous cell carcinoma receiving FDG-PET/CT before and ∼3 months after concurrent

chemoradiotherapy, response as assessed with PERCIST was found to be a predictor of progression-free and overall survival (46). This has prompted interest in using FDG-PET/CT earlier during treatment to identify patients who may not respond. For example, a recent study suggested that FDG-PET/CT performed 14 days after the start of neo-adjuvant chemotherapy in patients with locally advanced disease was able to identify patients with poor outcomes, based on an increase in regional lymph node maximum SUV and insufficient decrease in primary tumor uptake after 2 weeks of treatment (47). Currently, the PERCIST thresholds (decrease $\geq$30%) do not vary according to the number of treatment cycles received (i.e., mid-treatment or end-of-treatment), which may change in subsequent versions (48).

Specifically for head-and-neck cancer response assessment, Marcus et al. proposed the Hopkins 5-point interpretation criteria to assess locoregional response after chemoradiotherapy. This system compares the tracer uptake of residual lesions with that of the activity in the internal jugular vein or the liver. Only uptake higher than that of the liver is deemed to be residual malignant disease (49, 50). The clinical value of the Hopkins scoring system was validated in a prospective multicenter study, showing that the system is reliable when used for FDG-PET/CT surveillance 12 weeks after concurrent chemoradiotherapy (51). Of note, this study did highlight that the sensitivity of the Hopkins scoring system was strongly time dependent, meaning that while it detects residual disease in patients who relapse up to a 9-month horizon after imaging with high sensitivity, it is less able to do so for patients who relapse later on, possibly because residual disease is either still below the detection threshold or metabolically inactive at the 12-week imaging timepoint. Therefore, clinicians may consider a second surveillance scan at $\sim$12 months after the end of chemoradiotherapy.

Dose-Tracking and Imaging Analytics Platforms

Over the last years, a number of platforms have been introduced allowing automatic analysis of imaging studies on a hospital-wide scale using data stored in the Picture Archiving and Communication System (PACS), presenting useful metrics in a convenient dashboard-style interface. For example, using this technology patient radiation exposure from the CT part can be monitored on a population level for compliance with national dose reference levels (DRL) (52). For the PET part, conformance with the EANM imaging guideline can be checked and systematic sources of error can more easily be identified and subsequently corrected to prevent future errors. With advances in artificial intelligence it can be expected that the ability of these platforms to detect deviations from imaging protocols will increase, and where they are now primarily used to detect issues after the facts, it is not inconceivable that they may evolve to gatekeepers running in the background that are able to prevent errors before they occur.

CONCLUSIONS

FDG-PET/CT has evolved to a clinically important imaging modality in head-and-neck cancer with a significant impact on patient management and outcome. Subsequent technical advances have increased the capabilities, but also the complexity, of the latest PET/CT scanners. Combined with a desire to move to more quantitative image analysis, it has become apparent that rigorous quality assurance is required spanning the entire workflow from tracer synthesis to patient preparation, image acquisition and reconstruction, and interpretation. Thanks to a coordinated effort over the last decade of industry, academia, and professional societies the frameworks that allow harmonization of FDG-PET/CT are in existence today and should be implemented across the board in order to consolidate PET/CT as leading standardized functional imaging technique.

Referring to the subtitle of this review: recent technical advances may usher in the next homerun for PET/CT, but only if we control for the potential pitfalls by rigorous harmonization and conforming practice to applicable guidelines. If not, we risk diluting the tremendous potential of the latest generation of PET/CT scanners and loose the opportunity to put a prestigious run on the scoreboard for this great technique.

AUTHOR CONTRIBUTIONS

TV performed the literature search and wrote the manuscript. SD contributed to the physics parts of the text. LC reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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