Published randomized controlled trials of surveillance in cancer patients - a systematic review

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Abstract

With solid tumor cancer survivorship increasing, the number of patients requiring post-treatment surveillance also continues to increase. This highlights the need for evidence-based cancer surveillance guidelines. Ideally, these guidelines would be based on combined high-quality data from randomized controlled trials (RCTs). We present a systematic review of published cancer surveillance RCTs in which we sought to determine the feasibility of data pooling for guideline development.

We carried out a systematic search of medical databases for RCTs in which adult patients with solid tumors that had undergone surgical resection with curative intent and had no metastatic disease at presentation, were randomized to different surveillance regimens that assessed effectiveness on overall survival (OS). We extracted study characteristics and primary and secondary outcomes, and assessed risk of bias and validity of evidence with standardized checklist tools.

Our search yielded 32,216 articles for review and 18 distinct RCTs were included in the systematic review. The 18 trials resulted in 23 comparisons of surveillance regimens. There was a high-level of variation between RCTs, including the study populations evaluated, interventions assessed and follow-up periods for the primary outcome. Most studies evaluated colorectal cancer patients (11/18, [61%]). The risk of bias and validity of evidence were variable and inconsistent across studies.

This review demonstrated that there is tremendous heterogeneity among RCTs that evaluate effectiveness of different post-operative surveillance regimens in cancer patients, rendering the consolidation of data to inform high-quality cancer surveillance guidelines unfeasible. Future RCTs in the field should focus on consistent methodology and primary outcome definition.

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Key words: Tumor; survival; surveillance; randomized controlled trials; systematic review.

Funding: McMaster is the sponsor of this review. This study did not receive any funding.

Contributions: VG, PS, BL, IM, HB, PT, LEN, MC, PW, AB carried out the review. VG, PS and KM wrote the manuscript with support from AB, DW and MG. DW helped supervise the project. VG, PS, MG conceived the original idea. MG supervised the project.

Conflict of interest: the authors declare no potential conflict of interest.

See online Appendices for additional Tables.

Received for publication: 8 October 2020.
Revision received: 16 March 2021.
Accepted for publication: 9 April 2021.

Licensee PAGEPress, Italy
Oncology Reviews 2021; 15:522
doi:10.4081/oncol.2021.522

Introduction

Surgical intervention is the primary mode of cure for many types of solid tumors including breast, colorectal, testicular and non-small cell lung cancers.[1] Following surgery, the risk of local recurrence or metastases remains a concern. Therefore, the use of post-operative surveillance protocols, which include follow-up appointments, biochemical tests and surveillance imaging in likely areas of recurrence or metastases, have become the standard of care in the management of solid cancers.[2] However, the development of guidelines for post-operative surveillance protocols that effectively balance survival benefit with cost effectiveness have been challenged by the lack of evidence on which to base them.[2,3]

Due to advancements in imaging modalities and molecular diagnostic tests to detect relapsed disease, clinicians have an expanding repertoire of surveillance options. However, adverse effects of surveillance programs that make use of more intensive imaging modalities and/or more frequent follow-up visits are noteworthy. Patients have expressed concern over harmful levels of radiation exposure used in advanced imaging techniques, as well as the direct and indirect costs associated with more frequent follow-up visits.[2,4-7] Moreover, as direct costs to the healthcare system for more intensive surveillance programs are also notable, *The American Society of Clinical Oncology (ASCO)* recommends

not to perform additional surveillance testing or imaging in asymptomatic patients if evidence suggests these tests do not improve outcomes.[7-10]

The National Comprehensive Cancer Network (NCCN) develops and updates guidelines on best-practice surveillance for various cancers based on the best available evidence.[11,12] In recent years, organizations and guideline developers such as the NCCN and the World Health Organization (WHO) are integrating randomized controlled trial (RCT) results via systematic reviews and meta-analyses, to inform high-quality evidence-based recommendations.[13] However, a recent systematic review of North American and European cancer surveillance guidelines found that only 35% of guidelines were informed by systematic reviews and no guidelines referenced a meta-analysis in their development.[3] In order to conduct a meaningful meta-analysis that may inform guideline development, certain conditions must be met, including homogeneity with respect to study design, populations, and periods of follow-up.[13-15] If studies are highly heterogenous it may not be appropriate to conduct a meta-analysis, thereby preventing organizations from developing high-quality evidence-based guidelines.[16] In order to inform future cancer surveillance guidelines, we carried out a systematic review of studies in which cancer patients were randomized to different surveillance regimens with a primary or secondary outcome of overall survival (OS), and assessed between-study heterogeneity, study risk of bias and validity.

Methods of research

This systematic review adheres to and is reported according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was submitted for registration on the International Prospective Register of Systematic Reviews (PROSPERO) (ID:150689).

Eligibility criteria

The study population included solid cancer patients, 18 years of age or older that had previously undergone surgical resection of their tumors and no metastatic disease at presentation. All oncology subspecialties were eligible. All RCTs, including cluster RCTs, that evaluated the efficacy of a post-operative surveillance regimen were eligible for inclusion. Eligible studies assessed OS as one of their primary or secondary outcomes, as the ASCO previously determined this outcome to be the most important in cancer treatment.[17] Only published journal articles in the English language were considered, with no lower limit on the study publication year.

Information sources

A comprehensive and systematic literature search of MEDLINE (OVID Interface, 1946 to present), EMBASE (OVID interface 1974 to present), and CENTRAL databases was conducted on 21 August 2019. Additionally, reference lists of included articles were scanned for potentially eligible titles.

Search

The search strategy was developed uniquely for each medical database by combining exploded medical indexing terms (MeSH® terms for MEDLINE and CENTRAL, EMTree® terms for EMBASE) and keywords using Boolean operators 'OR' and 'AND'. The search included terms to filter for RCTs as developed by the Scottish Intercollegiate Guidelines Network.[18] The full search strategy can be found in Appendix 1.

Study selection

Duplicate removal was performed in two rounds. The first round of duplicate removal was conducted manually on RefWorks by one author (BL). Following this, remaining articles were uploaded onto the DistillerSR online software (www.evidencepartners.com) to create a study database. The second round of duplicate removal utilized DistillerSR's duplicate identification feature, and two authors (BL and VG) independently audited the integrity of this feature prior to deletion. Author pairs (BL and PS/BL and HB/BL and PT/LN and AB/ML and PT/VG and PS/VG and IM/PS and PW) independently screened titles and abstracts to determine if the articles should be considered for inclusion. The following inclusion questions were used: i) Does this article describe a RCT?; ii) Do the participants of this trial have a solid tumor?; iii) Was the cancer treated with surgery with curative intent prior to inclusion in the RCT?; iv) Does the RCT assess different post-operative follow-up regimens?; v) Is there any other reason for exclusion of the study?. The full texts of included abstracts were then reviewed in duplicate (VG and IM/PS and PW) for inclusion using the aforementioned inclusion questions, in addition to the following questions: Were the participants of this trial nonmetastatic at the time of inclusion in the RCT; and vii) Is overall survival evaluated as a primary or secondary outcome?. These two inclusion questions were added at the full-text screening stage as this information was found to only be available in the full text. All discrepancies were resolved by consensus with the senior author (MG).

Data collection process and data items

Data was extracted in duplicate (VG and IM) on DistillerSR using uniquely developed Study Characteristics, Risk of Bias and Validity of Evidence, and Statistical Reporting data collection forms (Appendix 2). Additional information on RCTs was obtained from protocols or dissertations as required. Trial authors were contacted on multiple occasions for any missing data. Data extraction forms were pilot tested on two randomly selected full texts to ensure that reviewers extracted data consistently and to ensure the forms were unambiguous and free from errors.

Study characteristics

Study characteristics including year of publication, country of origin, type of cancer, RCT design, characteristics of the interventions, primary and secondary outcomes, sample size, follow-up time period, and if the study was single- or multi-center were extracted from each article.

Studies were also classified into categories in duplicate (VG and IM) based on the type of interventions assessed. If a trial was factorial in design, each comparison within the trial was categorized independently. Due to the large variation in surveillance programs, categories were predefined as per below: i) *Biological tests* - any study that evaluates more intensive *versus* less intensive or sensitive (including a reduced number or none at all) laboratory tests; ii) *Frequency* - any study that evaluates more frequent *versus* less frequent (including a reduced number or none at all) clinic visits; iii) *Imaging* - any study that evaluates more intensive *versus* less intensive (including a reduced number or none at all) imaging modalities; iv) *Practitioner type* - any study that evaluates specialist (medical oncology or surgeon)-led *versus* primary care physician or nurse practitioner-led.

Interventions within each RCT were then categorized as either the more intensive- or less intensive-group (control group). We defined more intensive surveillance as the most comprehensive treatment of the treatment groups in any given trial (*i.e.*, the treat-

ment that is: more frequent, contains more invasive surveillance component(s) or is specialist-led). Any disagreements were reconciled with the senior author (MG).

Individual study outcomes

Statistical information including event rates and related effect measures for OS were extracted from each article. Event rates were calculated from OS percentages when raw results were not reported in the RCT article. When trials presented more than one hypothesis test, we reported the most adjusted result. Each comparison in a factorial trial was evaluated independently. The most recently published article was used for OS results when updated results were published for the same trial. Results were considered statistically significant if they were indicated as such by the RCT authors.

Risk of bias and validity of data in individual studies and across studies

Author pairs (VG and IM) individually assessed the risk of bias of the included studies using the Risk of Bias and Validity of Evidence form. Part A of this form follows the Cochrane Collaboration's Risk of Bias tool.[19] Any disagreements were reconciled with the senior author (MG).

Author pairs (VG and IM) individually assessed included studies on the internal and external validity of evidence using the Risk of Bias and Validity of Evidence form. Part B of this form follows the 2010 CONSORT checklist for the reporting of randomized trials.[20] Studies were marked in each element as sufficiently and appropriately reporting details of the checklist item (Yes), not reporting the checklist item (No), insufficiently reporting details of the checklist item (Insufficient details), or as not applicable to the study (NA). Any disagreements were reconciled with the senior author (MG).

Results

Study selection

Our search of databases yielded 32,197 potentially eligible studies titles, with an additional 19 records identified through reference list screening. Following duplicate removal, 25,825 titles remained for screening. 25,772 studies were excluded following title and abstract screening due to not being RCTs, patients not having sarcoma or carcinoma, patients not treated with surgery, or the RCT not assessing different post-operative follow-up regimens. Fifty-three articles remained for full text screening. Thirty-two articles were excluded at this final stage, resulting in 21 articles reporting on 18 distinct trials included in the review.[21-41] Two RCTs published extended follow-up time frame results,[27,33] and one RCT published an additional cost-analysis of results.[24] Other reasons for exclusion included the article being a conference abstract or preliminary results from a trial that did not report OS. Study selection is presented in Figure 1.

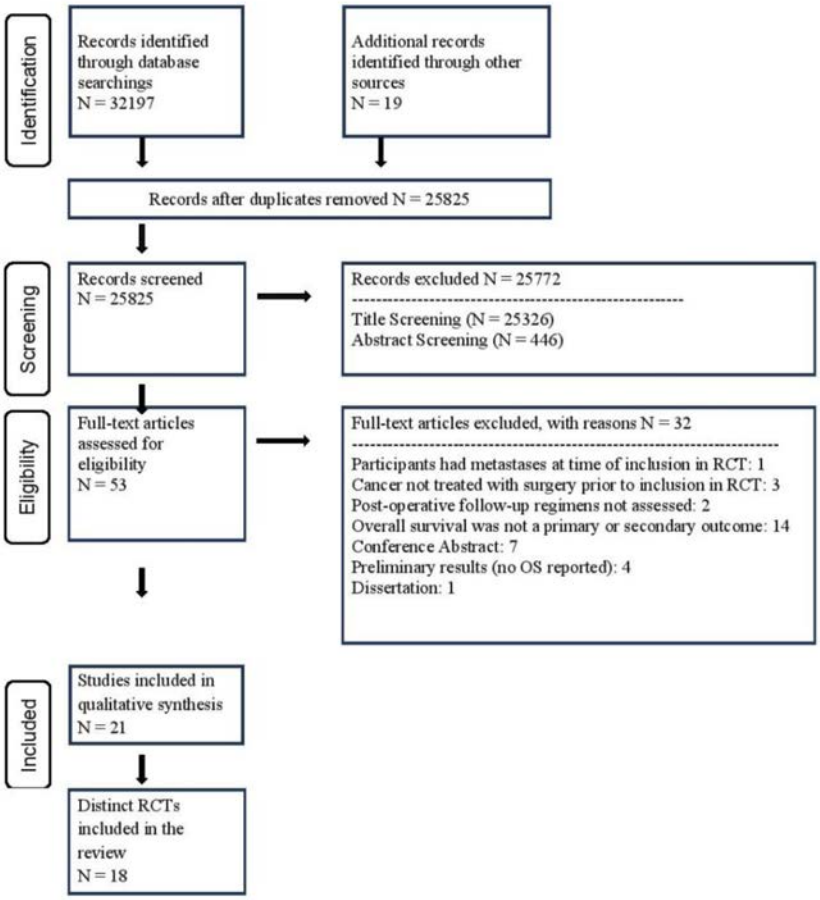

Figure 1. PRISMA flow diagram.

Study characteristics

The 18 RCTs comprised a total of 9020 participants from 11 different countries. Most trials' coordinating centers or initiating sites were based in Europe, 15/18 (83%)[21-23,25,27-31,34-39] with the remaining sites in China (1/18, [6%]),[40] India (1/18, [6%]),[32] and Australia (2/18, [11%]).[37,41] Half of the trials (50%) were single-center studies. Fourteen RCTs (78%) were published prior to 2010.[21,22,24,25,27,29,30,34,36-38,40,41] The most common type of cancer studied was colorectal cancer, (11/18 [61%]),[22,27,29-31,34,35,37-40] and one RCT included patients with only colon cancer and not rectal cancer due to slightly different follow-up programs between these cancers.[41] The remaining types of cancers studied included breast (4/17 [22%]),[21,23,25,36] lung (1/18 [6%]),[28] and bone and soft-tissue sarcomas (1/18 [6%]).[32] Fifteen RCTs were parallel group trials, (83%), with the other three of factorial design.[25,30,32] OS follow-up periods ranged from two- to five-years of follow-up. In addition to OS, common outcomes assessed included disease free survival (DFS), cost analysis and quality of life (QoL), among others. Included studies characteristics are show in Table 1.

Study outcomes

Due to the multiple comparisons made in factorial trials and one trial using different follow-up protocols for high-risk and low-risk patients,[37] a total of 23 surveillance intensity comparisons were assessed in the 18 included trials. One comparison (4%) was classified as a biological test intervention, eight (35%) were classified as frequency interventions, 12 (52%) were classified as imaging interventions, and two (9%) were classified as practitioner type interventions. Even when grouping surveillance protocols by the type of intervention, there was a high-level of variation in the intervention strategies assessed. Often, comparisons in the imaging category evaluated the presence of an imaging test *versus* not using that imaging modality at all. OS results for each comparison are presented in Table 2.

OS event rates could be extracted from all but one RCT (two comparisons).[28] Only 8/23 (35%) comparisons reported effect measures. All RCTs described the significance of intensive intervention strategies by evaluating p-values, however, four comparisons simply indicated results were not significant but did not provide point estimates.[25,28,36] Furthermore, the methods to test significance varied between RCTs.

Three comparisons (13%) reported that a more intensive surveillance program significantly improved OS outcomes. All three comparisons were classified as frequency interventions, evaluated 5-year OS and involved colorectal cancer patients.[30,38] No significant differences in more intensive *versus* less intensive protocols were reported in any other intervention category.

Risk of bias in included studies

Blinding of patients and research personnel was not possible due to the nature of the interventions; therefore, all studies had a high risk of performance bias. Many trials did not clearly report if the assessment of outcomes was blinded and if results were selectively reported. The risk of biases of included trials are presented in Figure 2.

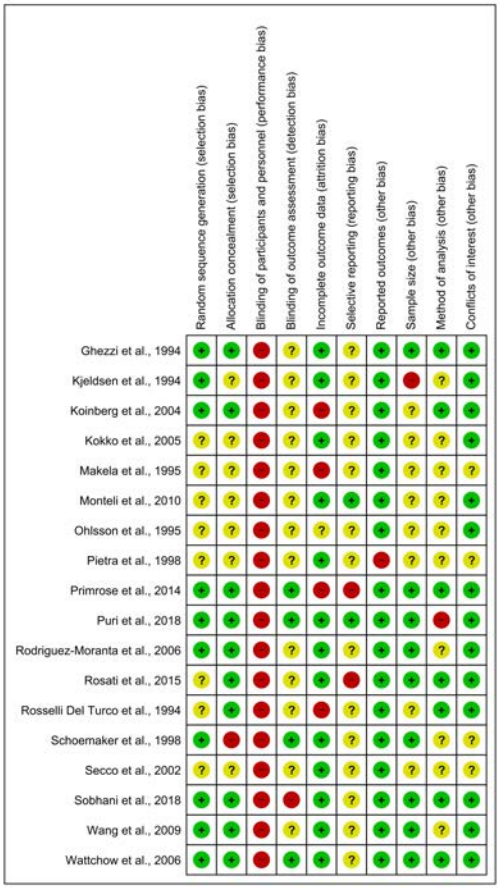

Figure 2. Risk of bias assessment of included studies. Listed in alphabetical order and assessed following the Cochrane Collaboration's Risk of Bias tool17. Unclear = ? , Low risk of bias = + , High risk of bias = −

Table 1. Study characteristics of all included studies. Ordered alphabetically. Intensive group is defined as the most comprehensive treatment of the treatment groups in any given trial (*i.e.*, the treatment that is: more frequent, contains more invasive surveillance component(s) or is specialist-led).

	Country of initiating center	Cancer type	Type of trial	Groups	Intervention strategies	Outcomes assessed	Sample size	Follow-up time frame	Single center or multi-center
Ghezzi et al., 1994[21]	Italy	Breast cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; blood test at every visit; mammography annually; chest X-ray every 6 months; bone scan and liver echography annually	OS, HR-QoL	1320	5 Years	Multi-Center
				Control	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually.				
Kjeldsen et al., 1997[22]	Denmark	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 6 months the first 3 years, then at 48, 60, 120, 150 and 180 months post-operatively	OS, DFS,	597	5 years	Single-center
				Control	Clinic visits at 60, 120 and 180 months post-operatively				
Koinberg et al., 2004[23]	Sweden	Breast cancer	Parallel Group	Intensive	Specialist Physician visits every 3 months the first 2 years, then every 6 months the following 2 years and thereafter annually; annual mammography	QoL, HAD, SaaC, OS, DFS,	264	5 Years	Multi-Center
				Control	Specialist nurse check-up visits if requested by patient; annual mammography				
Kokko et al., 2005[24,25]	Finland	Breast cancer	Factorial	Intensive	Routine Diagnostic tests of blood tests, liver enzymes; Ca 15-3 markers, and CXRs every 6 months; mammogram annually; Liver US and bone scan every 2 years	OS, DFS, cost analysis	472	5 years	Single-center
				Control	Clinically Indicated Diagnostic tests				
				Intensive	Clinic visits every 3 months for 3 years, thereafter every 6 months				
				Control	Clinic visits every 6 months				
Makela et al., 1995[26,27]	Finland	Colorectal cancer	Parallel Group	Intensive	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; video colonoscopy (or fibresigmoidoscopy) annually; liver US every 6 months; CT of the liver and primary resection site annually.	OS,	106	5 years	Single-center
				Control	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; rigid sigmoidoscopy at every visit for patients with rectal or sigmoid cancers; barium enema for all patients annually.				
Monteil et al., 2010[28]	France	Lung Cancer	Parallel Group	Intensive	CDET and Brain CT every 6 months for 2 years	DFS, OS, Cost analysis	69	2 years	Single-center
				Control	Chest, liver and adrenal gland CT, abdominal US, bone scintigraphy if there were bone symptoms every 6 months for 2 years				
Ohlsson et al., 1995[29]	Sweden	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the next 2 years, thereafter annually; CEA, proctosigmoidoscopy, fecal hemoglobin, and CXR at every	DFS, OS,	107	5 years	Multi-Center

				visit; endoscopic control of anastomosis at 9, 21 and 42 months; complete colonoscopy at 3, 15, 30 and 60 months; CT of pelvis (for required patients) at 3, 6, 12, 18, and 24 months.				
			Control	No active follow-up				
Pietra et al., 1998[30]	Italy	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the next 3 years and annually thereafter; US and CEA test at every visit; CXR and colonoscopy annually.	OS, DFS, Detection of LR	207	5 years	Single-center
				Control	Clinic visits every 6 the first year, thereafter annually after; US and CEA test at every visit; CXR, Colonoscopy and CT annually.				
Primrose et al., 2014[31]	United Kingdom	Colorectal cancer	Factorial	Intensive	CEA test every 3 months for 2 years, then every 6 months for 3 years; Chest, abdomen and pelvis CT scan every 6 months for 2 years, then annually for 3 years.	OS, Time to detection of recurrence	1202	5 years	Multi-Center
					CEA test every 3 months for 2 years, then every 6 months for 3 years; Chest, abdomen and pelvis CT scan at 12-18 months if requested at study entry by clinician.				
					Chest, abdomen and pelvis CT scan every 6 months for 2 years, then annually for 3 years.				
				Control	No scheduled follow-up; Chest, abdomen and pelvis CT scan at 12-18 months if requested at study entry by clinician.				
Puri et al., 2018[32,33]	India	Bone and soft tissue sarcoma	Factorial	Intensive	Clinic visits every 3 months	OS, DFS	495	5 years	Single-center
				Control	Clinic visits every 6 months				
				Intensive	Chest CTs				
				Control	CXRs				
Rodriguez-Moranta et al., 2006[34]	Spain	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; abdominal CT every 6 months the first 2 years then annually the following 3 years; CXR and colonoscopy annually	OS, DFS, Recurrence resect ability	259	5 years	Multi-Center
				Control	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; colonoscopy at year 1 and year 3				
Rosati et al., 2015[35]	Italy	Colorectal cancer	Parallel Group	Intensive	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually; proctoscopy at 4 and 8 months; abdomen pelvic CT at 4, 12, 24 and 48 months	OS, HR-QoL, DFS	1228	5 years	Multi-Center
				Control	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA tests at every visit; colonoscopy at 1 year and 4 years; Liver				

					ultrasound at 4 months and 16 months. Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA test at every visit; colonoscopy at 12 and 48 months; Chest x-ray at 12 months; Liver US at 8 and 16 months				
Rosselli Del Turco et al., 1994[36]	Italy	Breast cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years. Mammography annually; CXR and bone scan every 6 months.	OS, DFS, Metastasis-free survival	1243	5 years	Multi-Center
				Control	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually.				
Schoemaker et al., 1998[37]	Australia	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit; CXR, CT of the liver and colonoscopy annually	OS, DFS	325	5 years	Single-Center
				Control	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit				
Secco et al., 2002[38]	Italy	Colorectal cancer	Parallel Group	Intensive	High Risk patients: Clinic visits every 3 months for the first 2 years, then every 4 months the third year, thereafter every 6 months; CEA test at every visit; Abdominal and pelvis US every 6 months the first 3 years, then annually; Rigid recto sigmoidoscopy for rectal cancer patients and CXRs annually. Low Risk patients: Clinic visits every 6 months the first 2 years, thereafter yearly; CEA test and abdominal pelvic US at every visit; CXRs annually; Rigid recto sigmoidoscopy for rectal cancer patients annually for 2 years, then every 2 years.	OS, DFS, curative re-operations, cost analysis	358	5 years	Single-Center
				Control	Minimal follow-up programme performed by physicians for each risk group				
Sobhani et al., 2018[39]	France	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT and 18FDG-PET/CT every 6 months; Liver US and CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3.	% of patients with non-removable recurrence, OS, Cost	239	3 years	Multi-Center
				Control	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT every 6 months; Liver US and CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3.				
Wang et al., 2009[40]	China	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, CXR, liver imaging and colonoscopy performed at every visit.	OS, DFS	326	5 years	Single-center
				Control	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, CXR, and liver imaging performed at every visit; colonoscopy performed at 6, 30 and 60 months.				
Wattchow et al., 2006[41]	Australia	Colon cancer	Parallel Group	Intensive	Followed by Surgeon; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult	QoL, OS, DFS	203	2 years	Multi-Center

		blood tests every year; colonoscopy every 3 years
	Control	Followed by GP; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult blood tests every year; colonoscopy every 3 years

CEA, carcinoembryonic antigen; CT, computed tomography; CXR, chest radiograph (X-ray); CBC, complete blood count; CDET, coincidence detection emission tomography; DFS, disease free survival; FDG, fluorodeoxyglucose; GP, general practitioner; HAD, hospital anxiety and depression scale; HR, health related; LFT, liver function tests; LR, local recurrence; OS, overall survival; PET, positron emission tomography; QoL, quality of life; SaaC, satisfaction and accessibility scale; US, ultrasonography; wbCT, whole body computed tomography.

Validity of evidence in included studies

Most studies detailed interventions and eligibility criteria to ensure trials were replicable. However, sufficient details regarding randomization procedures were often not reported. Furthermore, although primary and secondary outcomes were often defined, details of analysis plans and presentation of results did not meet the 2010 CONSORT guidelines in many trials. Trials included in this review often failed to report absolute and relative effect sizes. Validity of evidence for included trials is presented in Table 3.

Discussion

Summary of results

The purpose of this study was to evaluate the available RCTs that assessed the effectiveness of post-operative surveillance protocols on OS in cancer patients. Following a systematic search of the literature, 18 distinct RCTs evaluated this question, contributing a total of 23 comparisons of less intensive *versus* more intensive surveillance interventions. There was a high-level of heterogeneity among included studies, with variations in populations assessed, interventions used, and follow-up time periods. Only 8/23 (35%) comparisons reported effect measures on the outcome of OS, and only three comparisons indicated more intensive surveillance programs benefited OS outcomes.

Implications

Routine follow-up after tumor resection surgery varies significantly, even within cancer types. Guidelines have been found to be inconsistent due to the high variability in research and minimal high-quality data.[3] Systematic differences between RCTs prevents meta-analyses from being performed in order to inform the development of high-quality evidence based guidelines.[14-16] No two trials evaluated identical interventions in post-operative surveillance, emphasizing that clinical equipoise exists with respect to how patients are followed after definitive treatment in each cancer subtype. Although we attempted to organize the studies using the categories of biological test, frequency, imaging and practitioner type interventions, variability persisted between interventions even within each category. Frequency interventions included RCTs that conducted clinic visits every three to every six months in intensive groups, compared to clinic visits every six months to no clinic visits at all in control groups. Evidently, an intensive intervention in one RCT could be considered a control in another RCT. Similarly, imaging modalities were prioritized differently between RCTs, with some RCTs using CXRs, CT scans and colonoscopies as the 'intensive' imaging interventions and other RCTs using the aforementioned imaging modalities as the 'control'.

Investigating surveillance strategies by cancer type did not appreciably reduce heterogeneity in surveillance interventions. Systematic differences in RCTs included the primary outcome, whereby some RCTs evaluated OS after two years and others after five years. This variation could lead to innate differences in survival outcomes.[14,16,42] Ultimately these fundamental differences in RCT design highlights the need for surveillance research evaluating OS to follow standard methods of assessment and standard definitions of a primary outcome.

Relation to previous literature

Previous systematic reviews and meta-analyses of colorectal cancer demonstrated that intensive follow-up after curative resection for colorectal cancer improved five-year OS.[42-46] Limitations

Table 2. Reported statistical results for all include comparisons. Ordered by intervention categorization. Intensive group is defined as the most comprehensive treatment of the treatment groups in any given trial (*i.e.*, the treatment that is: more frequent, contains more invasive surveillance component(s) or is specialist-led).

	Investigated intervention strategies		No. of patients		No. of deaths (%)		Reported effect measure	Hypothesis test P-value
	Intensive	Control	Intensive	Control	Intensive	Control		
Biological test interventions								
Primrose et al., 2014[31]	CEA tests	No CEA tests	602	600	104 (17)	108 (18)	NR	0.74[b]
Frequency interventions								
Kjeldsen et al., 1997[22]	Clinic visits every 6 months the first 3 years, then clinic visits at 48, 60, 120, 150 and 180 months post-operatively	Clinic visits at 60, 120 and 180 months post-operatively	290	307	88 (30)	100 (33)	NR	0.48[b]
Kokko et al., 2005[24]	Clinic visits every 3 months	Clinic visits every 6 months	239	233	52 (22)	36 (15)	NR	NS
Ohlsson et al., 1995[29]	Clinic visits every 3 months the first 2 years, then every 6 months the next 2 years, thereafter annually; CEA, proctosigmoidoscopy, fecal hemoglobin, and Chest CXR at every visit; endoscopic control of anastomosis at 9, 21 and 42 months; complete colonoscopy at 3, 15, 30 and 60 months; CT of pelvis (for required patients) at 3, 6, 12, 18, and 24 months	No active follow-up	53	54	15 (28)	22 (41)	NR	0.264[b]
Pietra et al., 1998[30]	Clinic visits every 3 months the first 2 years, then every 6 months the next 3 years and annually thereafter; US and CEA test at every visit; CT, CXR and colonoscopy annually	Visits every 6 months the first year, thereafter annually; US and CEA test at every visit; CXR, and Colonoscopy annually	104	103	28 (27)	43 (42)	NR	<0.02[b]**
Primrose et al., 2014[31]	More intensive follow-up including CEA tests, CT scans and clinic visits. Combination of patients from all other 3 factors in the trial	No scheduled follow-up; Chest, abdomen and pelvis CT scan at 12-18 months if requested at study entry by clinician	901	301	164 (18)	48 (16)	NR	0.45[d]
Puri et al., 2018[32]	Clinic Visits every 3 months	Clinic Visits Every 6 Months	201	211	90 (45)	97 (46)	HR: 1.01 (90% CI: 0.82-1.2)	0.95[b]
Secco et al., 2002[38]	High Risk patients: Clinic visits every 3 months for the first 2 years, then every 4 months the third year, thereafter every 6 months; CEA test at every visit; Abdominal and pelvis US every 6 months the first 3 years, then annually; Rigid recto sigmoidoscopy for rectal cancer patients and Chest CXRs annually	Minimal follow-up of high risk patients	108	84	NR	NR	NR	<0.05[b]**
Secco et al., 2002[38]	Low Risk patients: Clinic visits every 6 months the first 2 years, thereafter yearly; CEA test and abdominal pelvic US at every visit; Chest CXRs annually; Rigid recto sigmoidoscopy for rectal cancer patients annually for 2 years, then every 2 years	Minimal follow-up of low risk patients	84	61	NR	NR	NR	<0.01[b]**

Imaging interventions								
Ghezzi et al., 1994[21]	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; blood test at every visit; mammography annually; chest X-ray every 6 months; bone scan and liver echography annually	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually	655	665	132 (20)	122 (18)	OR: 1.12 (95% CI: 0.87-1.43)	0.42[b]
Kokko et al., 2005[25]	Routine diagnostic tests which included: blood test, liver enzymes and Ca 15-3 marker tests; CXRs every 6 months, Liver US and bone scan every 2 years;	All diagnostic tests only when clinically indicated	243	229	29 (12)	34 (15)	NR	NS
Makela et al., 1995[27]	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; video colonoscopy (or fibresigmoidoscopy) annually; liver US every 6 months; CT of the liver and primary resection site annually	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; rigid sigmoidoscopy at every visit for patients with rectal or sigmoid cancers; barium enema for all patients annually	52	54	23(44)	27 (50)	NR	0.5[b]
Monteil et al., 2010[28]	CDET and Brain CT every 6 months for 2 years	Chest, liver and adrenal gland CT, abdominal US, bone scintigraphy if there were bone symptoms every 6 months for 2 years	36	33	14 (39)	10 (30)	NR	NS[c]
Primrose et al., 2014[31]	Chest CT scans	No Chest CT scans	601	601	108 (18)	104 (17)	NR	0.76[b]
Puri et al., 2018[32]	CT Scans	CXRs	196	216	92 (47)	95 (44)	HR: 0.94 (90% CI: 0.78-1.1)	0.63[b]
Rodriguez-Moranta et al., 2006[34]	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; abdominal CT every 6 months the first 2 years then annually the following 3 years; chest CXR and colonoscopy annually	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; colonoscopy at year 1 and year 3	127	132	21 (17)	27 (26)	HR: 0.87 (95% CI: 0.49-1.54)	0.62[e]
Rosati et al., 2015[35]	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually; proctoscopy at 4 and 8 months; abdomen pelvic CT at 4, 12, 24 and 48 months	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA tests at every visit; colonoscopy at 1 year and 4 years; Liver ultrasound at 4 months and 16 months. Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA test at every visit; colonoscopy at 12 and 48 months; Chest x-ray at 12 months; Liver US at 8 and 16 months	615	613	113 (18)	105 (17)	HR: 1.14 (95% CI: 0.87-1.48)	0.34[e]
Rosselli Del Turco et al., 1994[36]	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years. Mammography annually; Chest CXR and bone scan every 6 months	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually	622	621	116 (19)	121 (19)	NR	NS[c]

Schoemaker et al., 1998[37]	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit; CXR, CT of the liver and colonoscopy annually	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit	167	158	43 (26)	55 (35)	OR: 0.69 (95% CI: 0.47-1.04)	0.07[e]
Sobhani et al., 2018[39]	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT and 18FDG-PET/CT every 6 months; Liver US and Chest CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT every 6 months; Liver US and Chest CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3	120	119	13 (11)	7(6)	RR: 1.83 (95% CI: 0.76-4.42)	0.17[e]
Wang et al., 2009[40]	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, Chest CXR, liver imaging and colonoscopy performed at every visit	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, Chest CXR, and liver imaging performed at every visit; colonoscopy performed at 6, 30 and 60 months	161	158	42 (26)	50 (32)	HR: 1.41 (95% CI: 0.92-2.14)	0.25[b]
Practitioner type interventions								
Koinberg et al., 2004[23]	Specialist Physician visits every 3 months the first 2 years, then every 6 months the following 2 years and thereafter annually; annual mammography	Specialist nurse check-up visits if requested by patient; annual mammography	131	133	14 (11)	14 (11)	NR	0.6[b]
Wattchow et al., 2006[41]	Followed by Surgeon; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult blood tests every year; colonoscopy every 3 years	Followed by GP; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult blood tests every year; colonoscopy every 3 years	106	97	11 (10)	8 (8)	NR	0.69[b]

[a] Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; CXR, chest radiograph (X-ray); CBC, complete blood count; CDET, coincidence detection emission tomography; FDG, fluorodeoxyglucose; LFT, liver function tests; US, ultrasonography; wbCT, whole body computed tomography; GP, general practitioner; PET, positron emission tomography; RR, risk ratio; OR, odds ratio; HR, hazards ratio; CI, confidence interval; NR, not reported; NS, not significant (authors in respective articles stated the difference was not significant but did not present a value). [b] Calculated by log-rank test; [c] Calculated by Student's T-test; [d] Calculated by Chi squared statistic; [e] Calculated by Cox proportional hazards test. **Significant, as reported by the trial authors.

Table 3. Validity of evidence of included studies. Listed in alphabetical order and assessed following the *2010 Consolidated Standards of Reporting Trials* (CONSORT) tool.[20]

	Ghezzi et al., 1994	*Kjeldsen et al., 1997*	*Koinberg et al., 2004*	*Kokko et al., 2003*	*Makela et al., 1995*	*Monteil et al., 2010*	*Ohlsson et al., 1995*	*Pietra et al., 1998*	*Primrose et al., 2014*	*Puri et al., 2018*	*Rodriguez-Moranta et al., 2006*	*Rosati et al., 2015*	*Rosselli Del Turco et al., 1994*	*Schoemaker et al., 1998*	*Secco et al., 2002*	*Sobhani et al., 2018*	*Wang et al., 2009*	*Wattchow et al., 2006*
1a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
1b	IS	IS	IS	IS	IS	IS	IS	IS	Y	IS	Y	Y	Y	N	IS	Y	IS	IS
2a	Y	IS	Y	Y	Y	Y	Y	Y	Y	Y	Y	IS	Y	Y	Y	Y	Y	Y
2b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3a	IS	IS	Y	IS	Y	Y	N	IS	Y	Y	Y	N	IS	IS	N	IS	IS	Y
3b	NA	NA	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
4b	IS	IS	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IS	N	IS	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6a	Y	IS	IS	IS	IS	Y	Y	Y	Y	Y	Y	Y	IS	IS	IS	IS	Y	IS
6b	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	Y	NA	NA	NA	NA	NA	NA
7a	Y	N	Y	N	N	N	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y
7b	NA	NA	NA	NA	N	NA	NA	NA	Y	Y	NA	Y	NA	NA	NA	NA	Y	NA
8a	Y	Y	Y	N	N	N	N	N	Y	Y	Y	N	N	Y	N	Y	Y	Y
8b	Y	N	IS	Y	N	N	N	N	Y	Y	Y	Y	Y	IS	N	Y	N	Y
9	Y	N	Y	N	N	N	N	N	Y	Y	Y	N	IS	IS	N	Y	IS	IS
10	IS	N	N	N	N	N	N	N	Y	Y	IS	Y	IS	N	N	Y	N	Y
11a	N	IS	N	N	N	N	N	N	Y	IS	N	N	N	N	IS	Y	N	Y
11b	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
12a	Y	Y	Y	N	Y	Y	IS	Y	Y	Y	Y	Y	N	IS	IS	Y	Y	Y
12b	IS	N	N	N	N	N	N	N	Y	IS	Y	Y	N	Y	IS	Y	Y	Y
13a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IS	Y	IS	Y	Y	Y
13b	Y	N	Y	N	N	N	Y	N	Y	Y	Y	Y	IS	Y	Y	Y	Y	Y
14a	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IS	Y	Y	Y
14b	NA	NA	NA	NA	NA	NA	NA	N	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA
15	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y[B]	Y	Y	Y	Y
16	Y	IS	Y	Y	IS	Y	IS	IS	Y	Y	IS	Y	Y	IS	IS	Y	IS	Y
17a	Y	Y	IS	IS	IS	IS	IS	IS	IS	Y	Y	Y	IS	Y	Y	Y	Y	Y
17b	Y	N	N	N	N	N	N	N	N	IS	Y	Y	N	IS	IS	Y	Y	N
18	N	N	N	N	N	N	N	N	Y	N	Y	Y	IS	Y	IS	Y	Y	Y
19	N	N	N	N	Y	N	N	N	N	N	N	N	IS	Y	Y	Y	Y	Y
20	Y	Y	Y	Y	IS	Y	IS	Y	Y	Y	Y	IS	IS	N	N	Y	IS	IS
21	Y	N	Y	N	N	N	N	N	Y	N	Y	IS	IS	N	N	Y	N	Y[A]
22	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	IS	IS	Y	N	Y	Y	Y
23	N	N	N	N	N	Y	N	N	Y	Y	N	Y	N	N	N	Y	N	N
24	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N
25	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y

*Although the authors noted the limitations of their study, as the trial included different types and grades of sarcoma and was only single-centered, the generalizability of trial findings in inadequate. [a]Generalizable and appropriate interpretations, however it is noted that the study could be underpowered to detect differences in death; [b]Baseline demographic information is described in results section, however, this data is not presented in the table; only baseline clinic data is.

of the aforementioned studies include limited quantities of eligible studies and the high risk of bias in the included trials. Furthermore, many of the systematic differences observed in the compilation of our review, including variations in the primary outcome and intervention types, are prevalent within these meta-analyses thereby raising concerns about the validity of the results.[42,43,46] Although three comparisons in our review indicated that five-year OS could be improved with more intensive surveillance protocols in colorectal cancer patients, the remaining ten comparisons of colorectal cancer patients indicated that a more intensive surveillance protocol did not improve OS.

Although the risk of bias was generally low across all included studies, the validity of evidence is questionable. In the evaluation of binary outcomes such as OS, the 2010 CONSORT guidelines recommends reporting both the absolute and relative effect sizes.[20] Only eight of 23 comparisons (seven trials) reported a relative effect size and no trial reported the absolute effect size. Although our review was interested in varying surveillance protocol's effect on OS, many trials identified OS as a secondary outcome and indicated they were underpowered to detect differences in death between intervention groups. The external validity is further questioned in many trials due to the lack of generalizability of results. Half of the included trials were conducted at a single-center alone, thereby preventing generalizability to various populations. A recent systematic review reported that single-center trials estimated significantly larger treatment effects compared to multi-center trials, cautioning against forming recommendations based on single-center trials alone.[47] In the assessment of validity of included trials, it is evident that large RCTs powered to evaluate discrete intervention types for each cancer subtype should be conducted.

The publication date of many of the included trials predates advancements made in both RCT reporting and cancer management. Previous CONSORT checklists were not as comprehensive as the 2010 update.[20] Fourteen of 18 RCTs included in our review were published prior to 2010, possibly attributing to the lack of detailed information on checklist items such as randomization procedures, effect measures, and discussions of limitations in many of the articles. In fact, four trials were published prior to 1996, preceding any development of CONSORT guidelines. The wide range in publication dates may also prevent comparisons between RCTs due to changes in methods of trial design and interventions available for use. Use of certain imaging modalities may not have been a feasible intervention in older trials.[48] Furthermore, many of the included trials predate advancements in the management of cancer, including wider tumor resection and the use of combined therapies, which have been documented to improve survival.[49]

While this review focused on OS as the most important outcome in cancer treatment, additional outcomes including costs to the healthcare system and patient's quality of life should also be considered when conducting and evaluating RCTs and developing guidelines for post-operative surveillance in cancer patients. A systematic review of breast cancer surveillance programs reported that the adoption of less intensive surveillance programs that do not compromise OS can result in savings of $8,000 USD per patient per quality adjusted life year.[50] Furthermore, patient anxiety and burdens due to more frequent follow-up visits could be reduced by a less intensive surveillance program.

Limitations

Despite the large number of RCTs included in this review, this study has some limitations. All patients in the RCTs were post-operative patients who were treated for a solid tumor, excluding many cancer types that are primarily treated by chemotherapy and radiation. The variability between RCTs in respect to intervention design, populations and tumor characteristics, and follow-up periods prevents the integration of evidence and thereby the development of high-quality, evidence-based recommendations. Furthermore, this review did not have any publication date restrictions. Considering advancements in cancer management and diagnostic tests to detect malignant disease, guideline developers may only be interested in the most up-to-date RCT evidence when refining post-operative surveillance guidelines. Moreover, there is great variation in respect to how metastatic disease is treated in different cancer subtypes, possibly affecting proposed follow-up protocols. Due to the lack of detailed reporting on many 2010 CONSORT checklist items, both the internal and external validity should be questioned for all included trials. We recommend that the critical appraisal of RCTs within this review is taken into consideration when developing cancer type specific, large multi-center RCTs.

Conclusions

In this systematic review, we found tremendous heterogeneity among published cancer surveillance RCTs with respect to surveillance protocols, including definitions of 'intensive' surveillance, and RCT design. Research on patient-important outcomes should be standardized to allow for further high-quality studies and meta-analyses and ultimately the development of evidence-based clinical guidelines. Optimal surveillance protocols for each cancer type should continue to be investigated in large RCTs powered to evaluate standardized definitions of OS, while also considering other patient-important outcomes and health system costs.

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