The role of neoadjuvant chemotherapy in the management of locally advanced cervix cancer: a systematic review

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Abstract

Cervical cancer is the second most common cancer in women. Neoadjuvant chemotherapy for patients with locally advanced cervix cancer has comparable benefits to concurrent chemoradiotherapy (CCRT), but with fewer side effects. This systematic review aims to provide a comprehensive summary of the benefits of neoadjuvant chemotherapy for the management of locally advanced cervix cancer from stage IB2 (tumor >4.0 cm) to IIIB (tumor extending to the pelvic wall and/or hydronephrosis). Our primary objective was to assess benefits in terms of survival. The data source included the USA national library of medicine, Medline search, and the National Cancer Institute PDQ Clinical Protocols. Inclusion criteria for consideration in the current systematic review included studies published between January 1997 and December 2012. In terms of histology, they had to be focused on squamous cell carcinoma, adenosquamous carcinoma, and/or adenocarcinoma. Patients should be either chemotherapy naïve or cervix cancer chemotherapy naïve, and have a performance status ≤2. The search in the above-mentioned scientific websites led to identify 49 publications, 19 of which were excluded, as they did not meet the inclusion criteria of this systematic review. Therefore only 30 studies were deemed eligible. Data was collected from 1760 patients enrolled in the current systematic review study. The mean age was 45.2 years. The mean tumor size was 4.7 cm. The most commonly used chemotherapies were cisplatin doublets. Paclitaxel was the most commonly used chemotherapeutic agent in the doublets. The mean chemotherapy cycles were 2.7. After chemotherapy, patients underwent surgery after a mean time of 2.5 weeks. The standard operation was radical hysterectomy with pelvic lymphadenectomy. Chemotherapy achieved an objective response rate of 84%. The 5-year progression-free survival and overall survival were 61.9% and 72.8% respectively. The treatment protocol was associated with a mild early toxicity profile. Leucopenia and neutropenia were the most common side effects. Late toxicity was also generally mild and mainly associated with bladder dysfunction and vaginal dehiscence. The quality of the studies was assessed using the Newcastle-Ottawa quality assessment scale. Neoadjuvant chemotherapy achieved comparable survival results to CCRT, and was associated with less toxicity.

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Introduction

cancer is the second most common cancer in women and affects 530,000 new patients annually (9% of new cases of cancer diagnosed in women).[1] According to the staging system developed by the *Féderation Internationale de Gynécologie et d'Obstétrique* (FIGO), a locally advanced cervix cancer can range from stage IB2 (bulky tumor >4.0 cm) to stage IIIB (spread of the tumor in the pelvic wall and/or hydronephrosis).[2] Concurrent chemoradiotherapy (CCRT) is considered the standard treatment for locally advanced cervix cancer. A systematic review and meta-analysis of data showed survival benefits, better local and distant control of CCRT when compared with radiotherapy alone.[3-5] However, CCRT is associated with considerable early toxicity in particular with gastrointestinal and hematological side effects. Many studies also showed significant long-term side effect rates. The study of Tan and Zahra and Green *et al.* showed grade 3 and 4 late toxicity with a range of 18.3% to 22%, and reported urinary and/or intestinal complications.[5,6]

Rationale for the neoadjuvant chemotherapy

Several studies showed that the neoadjuvant chemotherapy is effective in reducing the tumor size, expediting the elimination of micrometastasis, improving operability and surgical downstaging. Furthermore, the combination of chemotherapy followed by surgery is associated with fewer side effects than concurrent chemotherapy and radiotherapy.[7,8]

Study objectives

This systematic review aimed to provide a comprehensive summary of the benefits of neoadjuvant chemotherapy in the management of locally advanced cervix cancer. The primary endpoint was the survival benefit, including overall survival (OS) and progression-free survival (PFS). The secondary end points were treatment response, and toxicity profiles.

Materials and Methods

Study design, search method

The data source included the USA national library of medicine (http://www.ncbi.nlm.nih.gov/pubmed), Medline search (http://clinicaltrials.gov/ct2/search/advanced), and the National Cancer Institute PDQ Clinical Protocols (http://www.cancer.gov/clinicaltrials/search). The literature search was conducted in English.

Inclusion and exclusion criteria

Inclusion criteria for trial consideration included studies published between 1st January 1997 and 31st December 2012 and studies with FIGO stages IB2 to IIIB. Histologies included squamous cell carcinoma, adenosquamous carcinoma, and/or, adenocarcinoma. Studies had to be prospective only, and either phase II, or III. Patients should be either chemotherapy naïve or cervix cancer chemotherapy naïve. The patient performance status had to be an Eastern Cooperative Oncology Group (ECOG) score less than or equal to 2.0. Exclusion criteria included patients with metastatic cervix cancer including FIGO stages IVA, and, or IVB, phase 1 trials, retrospective studies and case presentations. Trials including radiotherapy as part of the neoadjuvant treatment and studies of small-cell cancer cancers, clear-cell cancers, or other rare pathological variants were also excluded.

Outcome measures

OS was defined as the time from the beginning of treatment until death or the last follow up date of the study. PFS was defined as the time from the beginning of treatment until progression, relapse, recurrence, death, or the last follow up date. Treatment response was either complete remission (CR), partial remission (PR), stable disease (SD), or disease progression (DP). CR, PR, and SD were pooled together to generate the objective response rate (ORR).

Data collection and analysis

The study gathered information from eligible studies, such as patient and disease characteristics, chemotherapy used in neoadjuvant setting, operative details, response to treatment, survival and treatment-related side effects.

Assessment of the quality of the included studies

In the systematic review the quality of the included studies was assessed using the Newcastle-Ottawa quality assessment scale, which is based on three items: patient selection, comparability of groups and ascertainment of outcome. Studies were evaluated on the basis of a star scoring scale with higher scores for high quality studies.[9]

Statistical analysis

The statistical analysis was performed using Stat Mate version III. Data was pooled from the included trials and analyzed on the basis of means, medians, and 95% confidence intervals. Studies that did not include these items were mentioned in order to avoid selection biases. Response and survival data were analyzed by pooled analysis, and chi-square test. Pooled survival data was calculated with the Kaplan-Meier method. Survival curves were analyzed using the Log-rank (Mantel-Cox) test. For phase III trials, a comparison was made between the survival rates of neoadjuvant chemotherapy and other treatments, generating a forest plot. The statistical heterogeneity was analyzed by either X^2, or I^2 test. A P value higher than 0.10 for the X^2 test and/or a I^2 value lower than 25% were interpreted as having a low level of heterogeneity. The publication bias was assessed by visual inspection of funnel plots.

Results

Searching studies published between 01st January 1997 and 31st December 2012 in the above-mentioned scientific websites by typing some or all words of the phrase *neoadjuvant chemotherapy then surgery in locally advanced cervix cancer* enabled us to identify 49 publications. Out of the total, 19 trials were excluded, because they did not meet the inclusion criteria. Of the excluded trials, 7 had radiotherapy as part of the preoperative or postoperative treatment, 3 had patients with small-cell carcinoma, 1 was a case study, 2 were retrospective studies and 6 more studied were excluded as they included stage IVA and/or IB1 cases. Thirty studies were deemed eligible to be included in this systematic review. Data was collected from 1760 patients enrolled in the above-mentioned studies (22 studies were phase II trials and 8 were phase III trials).

Patients' characteristics

Table 1 reports patient and disease characteristics.

Treatment protocol

Neoadjuvant chemotherapy

All studies,[1-44] except the study by Lacava *et al.*[40] used chemotherapy doublets, or triplets. The most commonly used chemotherapy agents were platinum derivatives and were used in 28 out of 30 studies. Platinum derivatives were either cisplatin, carboplatin, or nedaplatin.

Table 1. Patients' characteristics.

	No. (total: 1760)	%
Age		
Mean	45.2 years old	-
Median	45 years old	-
95% CI	39.3-51.5 years old	-
Tumor size		
Mean	4.7 cm	-
Median	4.4 cm	-
95% CI	3.5-5.2	-
FIGO stage		
Ib2-IIA	1230	69.8
IIb-IIIA	335	19.2
IIIB	195	11.0
Pathological type		
Squamous-cell carcinoma	1680	95.4
Adenocarcinoma	55	3.1
Adenosquamous	25	1.5
Performance status		
0	1448	82.2
1-2	244	13.8
Unknown	68	3.8

CI, confidence interval; FIGO, *Féderation Internationale de Gynécologie et d'Obstétrique.*

They were included in 25, 2, 1 studies, respectively. The mean chemotherapy cycles were 2.7 cycles, and the median was 3 cycles [95% confidence interval (CI): 2-4]. Table 2[10-16,18-40] indicates chemotherapy agents used in the 30 trials. Following chemotherapy, radiological assessment was conducted by abdominal-pelvic computed tomography in 93.3%, and magnetic resonance imaging in the remaining 6.7% of the included trials.

Chemotherapy results

All the 1760 patients were evaluated for response: 247 patients reported a CR, 880 patients reported a PR, and 352 patients reported a SD. The remaining 281 patients had a DP. The ORR of the systematic review was 84%. Trials that included platinum derivatives had an ORR of 79%. Their pooled CR and PR were 66%. While studies that did not include platinum derivatives had an ORR of 80%, with pooled CR and PR of 67%. Considering the studies of platinum derivatives, trials based on cisplatin had an ORR of 76%, with pooled CR and PR of 63%, whereas studies that did not include cisplatin achieved an ORR of 78%, with pooled CR and PR of 65%. The P value was 0.07. The response evaluation by stage was carried out in 22 out of the 30 trials. The remaining 8 studies did not define the response by stage (Figure 1).

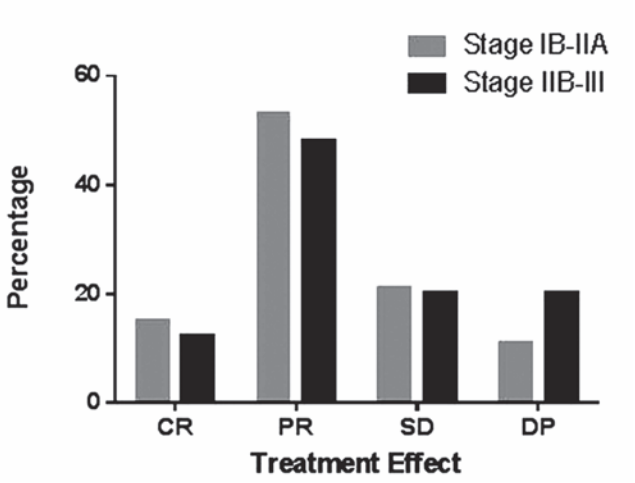

Figure 1. Treatment response by stage. CR, complete remission; PR, partial remission; SD, stable disease; DP, disease progression.

Table 2. Chemotherapy agents used in the 30 trials.

Study	Chemotherapy regimen, doses	No. of cycles
Shoji *et al*., 2013[10]	Carboplatin (AUC6), paclitaxel (175 mg/m^2)/ docetaxel (70 mg/m^2)	2 (18 patients) 3 (5 patients)
Shen *et al*., 2012[11]	Cisplatin (20 mg/m^2 D1-4)/carboplatin (AUC5), paclitaxel (150 mg/m^2)	2
Yamaguchi *et al*., 2012[12]	Nedaplatin (80 mg/m^2), irinotecan (60 mg/m^2 D1,8)	3
Pinheiro *et al*., 2011[13]	Mitomycin C (10 mg/m^2), methotrexate (300 mg/m^2 with folonic acid), bleomycin (15 mg/m^2 D1,8)	4
Vizza *et al*., 2011[14]	Cisplatin (75 mg/m^2), paclitaxel (175 mg/m^2), ifosfamide (5 g/m^2, mesna)	3
Mossa *et al*., 2010[15]	Cisplatin (50 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 D1,8)	3
Shoji *et al*., 2010[16]	Cisplatin (70 mg/m^2), irinotecan (70 mg/m^2 D1,8)	2
Cho *et al*., 2009[18]	Cisplatin (75 mg/m^2)/carboplatin (AUC5), paclitaxel (135 mg/m^2)	2
Kokawa *et al*., 2007[19]	Mitomycin-C (10 mg/m^2), irinotecan (100 mg/m^2) D1,8,15 Out of 28 days cycles	2 (28 patients) 3 (7 patients)
Sláma *et al*., 2007[20]	Cisplatin (50 mg/m^2), ifosfamide (5 g/m^2, mesna)	3
Eddy *et al*., 2007[21]	Cisplatin, vincristine	3
Choi *et al*., 2006[22]	Cisplatin (100 mg/m^2), 5-fluorouracil (1000 mg/m^2/day D2-5)	2
Cai *et al*., 2006[23]	Cisplatin (100 mg/m^2), 5-fluorouracil (1000 mg/m^2/day D2-5)	2
Termrungruanglert *et al*., 2005[24]	Cisplatin (70 mg/m^2), gemcitabine (1000 mg/m^2 D1,8)	2
Taneja *et al*., 2005[25]	Cisplatin (50 mg/m^2), bleomycin (15 mg/m^2 D1, 2), vincristine (1 mg/m^2)	3
DeSouza *et al*., 2004[26]	Cisplatin (60 mg/m^2), methotrexate (300 mg/m^2 with folonic acid), bleomycin (30 mg/m^2 twice weekly)	3
Huang *et al*., 2003[27]	Cisplatin (50 mg/m^2), bleomycin (15 mg/m^2 D1, 2), vincristine (1 mg/m^2)	3
Napolitano *et al*., 2003[28]	Cisplatin (50 mg/m^2), bleomycin (15 mg/m^2 D1, 2), vincristine (1 mg/m^2)	3
D'Agostino *et al*., 2002[29]	Cisplatin (100 mg/m^2), epirubicin (100 mg/m^2), paclitaxel (175 mg/m^2)	3
Benedetti-Panici *et al*., 2002[30]	Cisplatin (80 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 3 days)	2
Duenas-Gonzalez *et al*., 2003[31]	Carboplatin (AUC 6), paclitaxel (175 mg/m^2)	3
Duenas-Gonzalez *et al*., 2002[32]	Cisplatin (100 mg/m^2), gemcitabine (1 mg/m^2 D1,8)	3
Costa *et al*., 2001[33]	Cisplatin (40 mg/m^2), epirubicin(30 mg/m^2), etoposide(75 mg/m^2), bleomycin (15 mg D1,2)	3
MacLeod *et al*., 2001[34]	Cisplatin (50 mg/m^2)/carboplatin (AUC5) based combination	3
Aoki *et al*., 2001[35]	Cisplatin (60 mg/m^2), vinblastine (4 mg/m^2 D1, 2), bleomycin (25 mg/m^2 3 days)	2
Hwang *et al*., 2001[36]	Cisplatin (50 mg/m^2), vinblastine (6 mg/m^2), bleomycin (25 mg/m^2 3 days)	3
Chang *et al*., 2000[37]	Cisplatin (50 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 for 3 days)	3
Zanetta *et al*., 1998[38]	Cisplatin (50 mg/m^2) (75 mg/m^2 in 10 patients), paclitaxel (175 mg/m^2), ifosfamide (5 g/m^2, mesna)	3
Sardi *et al*., 1997[39]	Cisplatin (50 mg/m^2), vincristine (1 mg/m^2), bleomycin (25 mg/m^2 D1-3)	3
Lacava *et al*., 1997[40]	Vinrolbine (30 mg/m^2 weekly)	4

Surgery

Among the 1760 patients who received the neoadjuvant chemotherapy, 1596 (90%) of them underwent surgery, which was performed after a mean time of 2.5 weeks (95% CI: 2-5 weeks) after the end of chemotherapy. The standard operation was radical hysterectomy with pelvic lymphadenectomy (type III, or IV). A total of 100 patients (5.6%) underwent also para-aortic lymphadenectomy due to positive para-aortic lymphnodes.

Survival results

Only 26 out of the 30 studies measured survival. The survival rates were not reported in 4 studies.[11,16,20,40] These 4 trials evaluated the treatment response as an objective treatment effect and did not include survival data. Additionally, 5 more trials[18,26,31,35,39] were excluded from the survival analysis, because they included postoperative radiotherapy in the treatment protocol. In the remaining 21 studies, survival was assessed at 24 months, and/or 60 months. PFS and OS were measured at 24 months in 5 studies, at 60 months in 12 studies and at both 24 and 60 months in 4 studies (2 of which also measured survival at 10 years).

Table 3[10,12-15,19,21-25,27-30,32-34,36-38] reports the detailed survival rates of the 21 trials.

In the systematic review, the mean 2-year PFS was 75%, and the median 2-year PFS was 76%. The mean 5-year PFS was 61.9%, and the median 5-year PFS was 67.5%. The mean 2-year OS was 82.1%, and the median 2-year OS was 82%. The mean 5-year OS was 72.8%, and the median 5-year OS was 70.7%. Two studies measured the 10-year OS and PFS. The mean 10-year PFS was 61%, and the mean 10-year OS was 68%. In 14 out of the 21 studies survival was identified on the basis of the different stages of the locally advanced cervix cancer. For stage IB2-IIA, the mean 2-year PFS was 79.1% and the 2-year OS was 86%. The mean 5-year PFS was 72%, and the mean 5-year OS was 83.4%. For stage IIB-III, the mean 2-year PFS was 69% and the mean 2-year OS was 75%. The mean 5-year PFS was 58.9%, and the mean 5-year OS was 62% (Table 4; Figure 2). For PFS data, the Chi square (χ^2) was 4.794, the

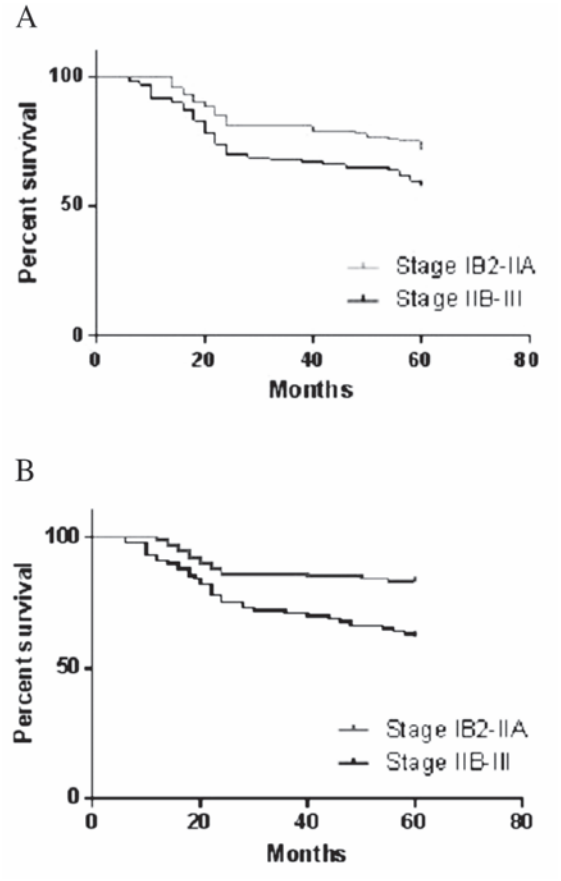

Figure 2. Survival result of the systematic review. A) Progression free survival (PFS) of the study group; B) overall survival (OS) of the study group.

Table 3. Details of the survival results of the 21 trials.

Study	Patients no.	Trial phase	Stage	2 year PFS%	2 year OS%	5 year PFS%	5 year OS%
Shoji *et al.*, 2013[10]	18	II	Ib2-IIb	64	78	60	68
Yamaguchi *et al.*, 2012[12]	66	II	Ib2-IIb	73.8	76	-	-
Pinheiro *et al.*, 2011[13]	27	II	Ib2-IIIb	-	-	59	67
Vizza *et al.*, 2011[14]	40	II	Ib2-IIb	87.5	90	-	-
Mossa *et al.*, 2010[15]	153	II	Ib2-IIIb	-	-	65.4	70.4
Kokawa *et al.*, 2007[19]	33	II	Ib2-IIIb	77	84	69	72
Eddy *et al.*, 2007[21]	145	II	Ib2	-	-	71	78
Choi *et al.*, 2006[22]	62	III	Ib2-IIa	77	82	71	76.4
Cai *et al.*, 2006[23]	52	III	Ib2	-	-	72.7	84.6
Termrungruanglert *et al.*, 2005[24]	25	II	Ib2	81	88.9	-	-
Taneja *et al.*, 2005[25]	22	II	Ib2-IIIb	-	-	62	69
Huang *et al.*, 2003[27]	102	II	Ib2-IIa	-	-	65	69
Napolitano *et al.*, 2003[28]	106	III	Ib2-IIb	-	-	71.7	76.4
D'Agostino *et al.*, 2002[29]	42	II	Ib2-IIa	-	-	85	90
Benedetti-Panici *et al.*, 2002[30]	152	III	Ib2-IIIb	-	-	56.5	61
Duenas-Gonzalez *et al.*, 2002[32]	23	II	Ib2-IIIb	65	69	-	-
Costa *et al.*, 2001[33]	16	II	Ib2-IIa	-	-	67	71
MacLeod *et al.*, 2001[34]	46	II	IIIb	-	-	54	60
Hwang *et al.*, 2001[36]	80	III	Ib2-IIIb	-	-	78.7	82
Chang *et al.*, 2000[37]	68	III	Ib2-IIa	74	81	68	70
Zanetta *et al.*, 1998[38]	32	II	Ib2-IIIb	76	90	-	-

PFS, progression free survival; OS, overall survival.

degree of freedom was 1, and the hazard rate (log rank) was 0.5879, 1.684. (P=0.0286) For OS data, the Chi square (χ^2) was 8.81, the degree of freedom was 1, and the hazard rate (log rank) was 0.3989, 2.507. (P=0.001) For the 6 phase III trials, a comparison was made between the group that received neoadjuvant chemotherapy and the control group that received surgery alone in 1 study, radiotherapy alone in 1, and concurrent chemoradiation in 4 trials. Figure 3 reports the forest plot which was generated.

Pattern of relapse

All the 21 studies that assessed survival reported relapse data. In this study, the 2-year relapse rate was 25%, and the 5-year relapse rate was 32.5%. During the 1st 2-years follow-up, the locoregional pattern occurred in 60% of relapsed patients, whereas a disseminated relapse occurred in 40% of them. For the 5-year follow-up period, locoregional relapse occurred in 52% of the relapsed patients, whereas a disseminated relapse occurred in 28% of them. The remaining 20% were categorized as unidentified relapse.

Toxicity profile

Early toxicity was defined as toxicity that occurred during treatment until 6-8 weeks after chemotherapy. Late toxicity was defined as toxicity that occurred >6-8 weeks after the end of the treatment protocol.

Early toxicity

All 21 studies that assessed survival reported data about early toxicity. Grade 3 and 4 toxicity was classified as hematological, and non-hematological. Among all early toxic effects, leucopenia and neutropenia were the most common and occurred in 18.3% and 33.3% of chemotherapy cycles respectively.

Table 5 reports grade 3 and 4 toxicity profiles that occurred ≥1% of cycles and the corresponding percentage.

A delay of 1-2 weeks in the chemotherapy cycles was required in 15% of cycles. No deaths due to documented chemotherapy side effects.

A common complication associated with surgery was intraoperative bleeding, which occurred in 3.5% of patients.

Late toxicity

Only 8 studies included data about late toxicity. The most common side effect due to late toxicity was bladder dysfunction and occurred in 25% of patients. All were grade 1 or 2. Vaginal dehiscence and dyspareunia were the second most common late side effect. They occurred in 7.5% of patients. They were also grade 1 or 2. Other common late side effects included grade 1 or 2 peripheral neuropathy that occurred in 7% of patients. Other less common late side effects included lower limb edema (1%), and bowel obstruction (0.6%). One severe late side effect was represented by fistulae that occurred in 2% of patients.

Quality assessment

In order to assess the quality of the 30 studies included, the questionnaire foreseen by the Newcastle-Ottawa quality assessment scale for cohort studies was used. Collectively, the studies included scored a mean of 2.2 for patient selection item, 1 for the comparability of the group item, and 1.6 for the ascertainment of the outcome item.

Discussion

Nearly 50% of patients presented a locally advanced cancer cervix. The standard treatment was CCRT. Many randomized trials evaluated the benefits of CCRT including that of Morris *et al*.,[43] in which 403 patients were randomized to receive either radiotherapy or CCRT with cisplatin and 5 fluorouracil. The 5-year OR was 67% among patients in the CCRT group and 40% among patients in the radiotherapy group (P<0.001). Furthermore, the rates of both distant metastases and locoregional recurrences were significantly higher among patients treated with radiotherapy alone (P<0.001).[43]

When comparing the results of the systematic review with those of Morris *et al*.,[43] neoadjuvant chemotherapy seemed to be equivalent to CCRT in terms of survival benefit. As to early toxicity, the study of Morris *et al*.[43] showed that early side effects occurred in 64% of the group that underwent CCRT, with hematological side effects being the most common (37% of cycles). This study showed slightly lower early

Table 4. Mean survival results of the systematic review.

	2 years (%)	5 years (%)	10 years (%)
Progression free survival			
All stages	75	61.9	61
Stage IB2-IIA	79.1	72	Not identified
Stage IIB-III	69	58.9	Not identified
Overall survival			
All stages	82.1	72.8	68
Stage IB2-IIA	86	83.4	Not identified
Stage IIB-III	75	62	Not identified

Table 5. Grade 3 and 4 toxicity profiles that occurred ≥1% of cycles and their percentage.

Toxicity	%
Hematological side effects	
Leucopenia	18.3
Neutropenia	33.3
Febrile neutropenia	3
Anemia	5.5
Thrombocytopenia	2.7
Non-hematological side effects	
Nausea, vomiting	10
Liver toxicity	1.3
Diarrhea	1.2
Peripheral neuropathy	1

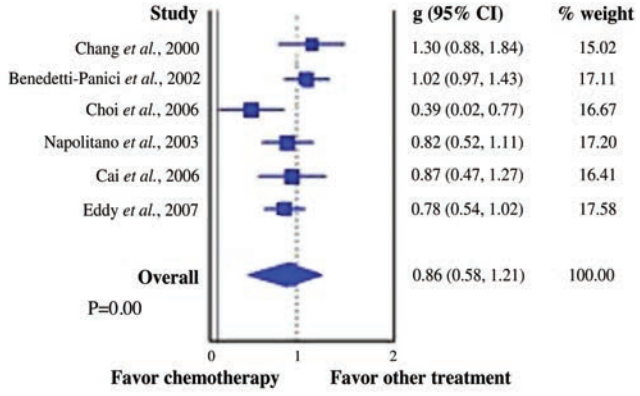

Figure 3. Comparison of the trials which favor neoadjuvant chemotherapy *vs* other treatment.

toxicity rates. On the contrary, a significant difference between this study and that of Morris *et al*.[43] was identified in terms of late toxicity. The study of Morris *et al*. that assessed late toxicity over a period of 43 months reported grade 3, and 4 late toxicity in 17.6% patients, with large bowel, and rectal side effects being the highest. Furthermore, many recent studies showed worse late sequelae associated with CCRT especially when considering long follow up periods.[5,6,43]

The primary objective of this study was to assess the benefits of neoadjuvant chemotherapy in terms of survival in locally advanced cancer cervix. Survival is the main target for this treatment having curative intent.

The studies on the role of neoadjuvant chemotherapy in the management of locally advanced cancer cervix were limited, because the standard treatment offered considerable efficacy. On the basis of the inclusion criteria, scientific websites were rigorously screened to identify eligible trials. All the included trials fulfilled all predetermined inclusion criteria items. The study of Shoji *et al.*[10] was published online in 2012, as clarified by the authors. The author preferred to exclude patients with stage IVA diseases. Although stage IVa is considered to be associated with a locally advanced disease, but including data from such extensive disease may flaw the results, and increase the heterogeneity of the trial.

The main challenge in this analysis was the heterogeneity of the included data, because the systematic review was based on a large number of trials, and most of them included a small number of patients (77% of trials included less than 60 patients). The author opted to include data from a large number of trials published over long period of time to come to a conclusion based on a large number of data. In order to decrease heterogeneity, the researcher performed a comparison between the results in terms of survival of neoadjuvant chemotherapy and other treatments for the included phase III trials. The researcher performed such comparison in order to confirm the conclusion based on a less heterogeneous sample. Furthermore, the quality of the included trials was assessed using the Newcastle-Ottawa quality assessment scale. This scale provided good information about the quality of non-randomized trials in the meta-analysis and was arguably used for this study that included a large number of trials with a small number of patients.

The quality of this systematic review was assessed on the basis of the PRISMA 2009 checklist criteria by an independent reviewer, and found to meet the criteria of systematic reviews.[22] Furthermore, the statistical analysis performed in this study was considered advanced as defined by Garg *et al*.[42]

The neoadjuvant chemotherapy represents a reasonable treatment option for locally advanced cancer cervix. It achieved a mean ORR of 84%, a 5-year PFS of 61.9%, and a 5-year OS of 72.8%. Chemotherapy had a mild toxicity profile. Furthermore the neoadjuvant chemotherapy had also a mild late toxicity profile.

Considering that many chemotherapy regimens are available with many combinations and with cisplatin as main agent, this systematic review failed to identify the combination offering the best result. However, all the regimens achieved comparable results. It would be reasonable to recommend further trials to solve this unclear point. One should also take into consideration the recent systematic review by Lorusso *et al*., which showed that cisplatin-based chemotherapy achieved better survival results compared with carpoplatin-based chemotherapy in cancer cervix.[44]

For the purpose of the analysis of survival, relapses and late toxicity, both studies that did not include survival data were excluded. This study excluded also studies with postoperative radiotherapy, as they may affect the results in terms of survival and toxicity, but were included only in the calculation of the response data to the neoadjuvant chemotherapy.

Conclusions

The neoadjuvant chemotherapy is a reasonable treatment option for locally advanced cancer cervix. It achieved comparable survival benefits to CCRT, and was associated with fewer side effects. More trials are needed to clarify many unclear points, including the best chemotherapeutic regimen, and late side effects preferably in comparison with CCRT.

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