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Citation
Horeweg, N., Mittal, P., Gradowska, P. L., Boere, I., Nout, R. A., & Chopra, S. (2022). A systematic review and meta-analysis of adjuvant chemotherapy after chemoradiation for locally advanced cervical cancer. *Critical Reviews In Oncology/hematology*, *172*. doi:10.1016/j.critrevonc.2022.103638

Version:	Not Applicable (or Unknown)
License:	Leiden University Non-exclusive license
Downloaded from:	https://hdl.handle.net/1887/3566386

Note: To cite this publication please use the final published version (if applicable).

Critical Reviews in Oncology / Hematology 172 (2022) 103638

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

A systematic review and meta-analysis of adjuvant chemotherapy after chemoradiation for locally advanced cervical cancer

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ARTICLE INFO

Keywords:
Cervical cancer
Adjuvant chemotherapy
Chemoradiation
Meta-analysis
Systematic review

ABSTRACT

We investigated whether the addition of adjuvant chemotherapy to chemoradiation improves overall survival (OS) and progression-free survival (PFS) by conducting a systematic review and meta-analysis. Systematic searches in the databases of PubMed, Embase and Web of Science yielded 881 articles. Two reviewer authors independently selected 31 articles for full text review and deemed eight studies eligible for inclusion. Two were randomised controlled trials (RCT), one was a large (n = 609) matched-case study and the remaining were small retrospective cohort studies; in total 2150 patients. Risk of bias assessment showed that the RCTs were at low risk and all other studies were at high risk of bias. Pooled hazard ratios for OS and PFS were 0.78 (95%CI 0.45–1.33, p = 0.36) and 0.85 (95%CI 0.65–1.10, p = 0.22), respectively. Analysis stratified by study design and sensitivity analysis showed similar results. Funnel plots showed significant publication bias due to a lack of small studies with negative outcomes.

1. Introduction

Cervical cancer is the fourth most common cancer in women (Sung et al., 2021). The standard of care for locally advanced cervical cancer is external beam radiotherapy with concurrent platinum-based chemotherapy and brachytherapy since the National Cancer Institute alert in 1999 (Trimble et al., 2008). Further development of treatment for locally advanced cervical cancer has since mainly concerned improvements in radiation therapy techniques. Planning and delivery of external beam radiotherapy has evolved from conventional multiple field techniques to intensity-modulated radiotherapy. This resulted in significantly less toxicity and a better quality of life with better or similar tumour control and overall survival (Lin et al., 2018; Mohanty et al., 2018; Chopra et al., 2021). Also, conventional two-dimensional brachytherapy planning is increasingly replaced by image-guided (adaptive) brachytherapy as several studies have demonstrated improved local tumour control, reduced toxicity and possibilities for dose escalation (Sturdza et al., 2016; Lindegaard et al., 2013; Rijkmans et al., 2014). These modern radiotherapy techniques were standardized in 24 centres in Europe, Asia and North-America in the observational 'image-guided intensity modulated External beam radiochemotherapy and MRI-based adaptive BRAchytherapy in locally advanced CErvical cancer' (EMBRACE)-I study. Outcomes of this study, which included 1341 patients, are regarded as the benchmark for clinical practice and scientific studies: five-year local control was 92%, pelvic control 87%, overall survival 74% with 18% late grade 3 and higher toxicities (Potter et al., 2021).

Distant metastasis is nowadays the most common type of treatment

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https://doi.org/10.1016/j.critrevonc.2022.103638
Received 12 November 2021; Received in revised form 16 February 2022; Accepted 16 February 2022
Available online 18 February 2022
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failure and limits the overall survival of patients with locally advanced cervical cancer (Potter et al., 2021; Tan et al., 2019; Horeweg et al., 2019). The ability of current standard of care, chemoradiation and brachytherapy, to further impact on any micro-metastasis outside the radiotherapy fields seems limited (Tan et al., 2019). Addition of adjuvant chemotherapy after chemoradiation and brachytherapy may reduce the risk of disseminated disease and improve overall survival. Despite the fact that many studies have been conducted in the last two decades, none has been practice-changing.

The addition of neoadjuvant chemotherapy to chemoradiation and brachytherapy has been investigated in a single-arm phase II trial among 46 patients (McCormack et al., 2013). The addition of six cycles of neo-adjuvant carboplatin-paclitaxel resulted in a five-year progression-free survival and overall survival of 68% and 67%, respectively (McCormack et al., 2013). This strategy is currently under investigation in the phase III 'Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer' (INTERLACE) trial (University College London, 2019). A large randomised phase III trial showed that patients treated with neo-adjuvant carboplatin-paclitaxel followed by radical surgery had significantly worse disease-free survival then those treated with chemoradiation and brachytherapy (Gupta et al., 2018). Concerns with neo-adjuvant chemotherapy are the delayed start of the most effective treatment component, increased acute toxicity which may affect chemoradiation completion rates and possibly acquired chemotherapy resistance (McCormack et al., 2013; Gupta et al., 2018).

Our recent meta-analysis of studies published from 2000 to 2020 on adjuvant systemic therapy after chemoradiation and brachytherapy showed that most research in the last 20 years has focussed on chemotherapy, often combinations of platinum derivates with pyrimidine antagonists or taxanes, and that evidence on targeted therapies is still immature (Horeweg et al., 2021).

Pooled analysis of six studies on the addition of adjuvant platinum-pyrimidine antagonist to standard chemoradiation and brachytherapy showed no overall survival benefit (hazard ratio [HR] 0.76, 99% confidence interval [CI] 0.43–1.34 p = 0.22) (Horeweg et al., 2021; Duenas-Gonzalez et al., 2011; Kim et al., 2007, 2008; Kong et al., 2012; Fabri et al., 2019; Choi et al., 2011). Despite that a sub-analysis of only randomised trials indicate that there might be an overall survival benefit (HR 0.73, 99%CI 0.50–1.06, p = 0.020), this adjuvant therapy has not become standard of care for unselected patients due to the significant increase in acute and late toxicity (Horeweg et al., 2021; Duenas-Gonzalez et al., 2011; Kim et al., 2008). It is unlikely that new randomised trials will be conducted on adjuvant platinum-pyrimidine antagonist that are large enough to demonstrate benefit in subgroups of patients at high risk of recurrence.

Pooled analysis of the randomised 'Adjuvant Chemotherapy for Locally Advanced Cervical Cancer' (ACTLACC) trial (n = 259) and five small non-randomised studies (n = 363) on the addition of adjuvant platinum-taxane to standard chemoradiation with brachytherapy revealed no significant benefit for overall survival either (HR 0.47, 99% CI 0.12–1.86, p = 0.16) (Horeweg et al., 2021; Tangjitgamol et al., 2019; Yavas et al., 2019; Tu et al., 2018; Mabuchi et al., 2017; Manders et al., 2018; Abe et al., 2012). This chemotherapy combination appeared less toxic than platinum with a pyrimidine antagonist, but there was still a significant increase in acute toxicity compared to standard chemoradiation (Horeweg et al.,2021).

One randomised trial on the addition of adjuvant mitomycine C and 5-fluorouacil after standard chemoradiation with brachytherapy (n = 926) showed no significant difference in recurrence-free survival, distant metastasis-free survival, overall survival or toxicity (Lorvidhaya et al., 2003). All other studies on adjuvant chemotherapy after chemoradiation with brachytherapy did not have a control arm which impedes the interpretation of efficacy. Nonetheless, results on toxicity in these trials may help deciding whether an adjuvant therapy is feasible and should be taken further to larger randomised trials. In a series of articles investigators from Split University describe their experience with concurrent chemoradiation with cisplatin-ifosfamide followed by 2 cycles of adjuvant cisplatin-ifosfamide (Jelavic et al., 2015; Petric et al., 2015; Vrdoljak et al., 2005a,b, 2006). This regimen was completed by only 41% of the patients, possibly due to severe acute haematological (7% anaemia, 34% neutropenia and 15% thrombopenia) and gastrointestinal toxicity (12%) (Jelavic et al., 2015). Three other studies on adjuvant platinum derivates also reported high rates of acute severe haematological and gastro-intestinal toxicity (Dubay et al., 2004; Sood et al., 2002; Wilailak et al., 2003).

Since 2020, new important evidence has become available on the value of adjuvant chemotherapy after chemoradiation and brachytherapy for locally advanced cervical cancer. At the 2021 American Society of Clinical Oncology annual meeting, results of the randomised phase III OUTBACK trial (ANZGOG 0902/RTOG 1174/NRG 0274) have been presented (Mileshkin et al., 2021). In this trial, 919 women were randomised to standard chemoradiation followed by 4 cycles of adjuvant carboplatin-paclitaxel or standard chemoradiation (Mileshkin et al., 2021; NCT, 2017). Overall survival at five years was similar in the two arms (HR 0.91, 95%CI 0.70–1.18). Since the OUTBACK trial included more patients than all patients in the ACTLACC trial and 5 non-randomised studies combined, the results are of major importance for the conclusion on lack of added value of adjuvant platinum-taxane chemotherapy to the standard of care. Hence, an update of our previous systematic review and meta-analysis was performed (Horeweg et al., 2021).

Here, we present a systematic review and meta-analysis on the impact of adjuvant platinum-taxane chemotherapy after chemoradiation and brachytherapy on the overall survival of patients with locally advanced cervical cancer. The results of this study enable drawing a conclusion on the value of the addition of adjuvant chemotherapy to chemoradiation and brachytherapy in unselected patients with locally advanced cervical cancer.

2. Methods

This study was prospectively designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines and registered at PROSPERO (registration number: CRD42021259830) (Moher et al., 2009)). The protocol of this study is provided as Supplementary Material.

2.1. Article characteristics

Articles were eligible if chemoradiation with brachytherapy followed by adjuvant chemotherapy (consisting of a platinum derivate and a taxane) was compared to standard chemoradiation with brachytherapy in randomized and non-randomized prospective and retrospective studies. Articles of the following types were not eligible: guidelines, meta-analyses, reviews, editorials, letters to editor and case-reports. Since concurrent chemoradiation was not the standard of care before the 1999 National Cancer Institute alert, articles published before 2000 were excluded (Trimble et al., 2008).

2.2. Study population characteristics

Patients with a diagnosis of FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) stage IB2–IVA cervical cancer of the squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma histotype were eligible. This includes patients with para-aortic lymph node metastasis. Patients primarily treated with radical surgery or neo-adjuvant chemotherapy were not eligible, neither were patients with recurrent, persistent or metastatic cervical cancer.

2.3. Treatment characteristics

Chemoradiation had to consist of pelvic external beam radiotherapy with or without extended fields and/or integrated or sequential boosts, combined with concurrent chemotherapy which was preferably weekly cisplatin, but other agents and schedules were eligible too. In all patients the treatment intent had to be curative.

2.4. Outcome measures

Overall survival is the primary endpoint of this meta-analysis. As such, studies had to report on overall survival separately for the group treated with chemoradiation and adjuvant chemotherapy and the group treated with chemoradiation only. To enable the statistical analysis, the difference in overall survival between treatment groups had preferably to be reported as a hazard ratio with a measure of dispersion. If the publication did not report these, the study authors were contacted to provide them. If the study authors did not respond, the study could only be included if it was possible to impute the hazard ratio and its' variance using the reported information (see statistical methods). Progression-free survival was the secondary endpoint of this meta-analysis, data on this outcome was not an inclusion criterion.

2.5. Literature searches

Systematic searches were performed by N.H. in PubMed, Web of Science and Embase on July 8th 2021. Search strings are provided in Supplementary Materials S1 and were based on the terms: "cervical cancer", "chemoradiation" and "adjuvant therapy". Additionally, trial registries were searched for additional information on the identified trials.

2.6. Selection of studies

All articles identified by the searches in the three databases were deduplicated using a reference manager (EndNote version X9). The two reviewer authors (N.H. and P.M.) read titles and abstracts of all articles independently to select studies relevant for review of the full text. If full texts were not accessible the corresponding author of the study was contacted. In addition, the reference lists of the selected articles were screened for additional relevant publications. At each selection round, results of the review authors were compared. Disconcordances were discussed in consensus meetings, and if disagreement remained, the final decision was made by the third review author (S.C.). When multiple articles described a single trial or cohort, the most recent and complete article was used for analysis.

2.7. Risk of bias assessment

Risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews version 5.1.0 (Higgins et al., 2011). This system was extended for the evaluation of non-randomized trials according to the "Meta-analysis Of Observational Studies in Epidemiology" (MOOSE) consensus on the evaluation of observational studies (Stroup et al., 2000) as published previously (Horeweg et al., 2021). All risk of bias aspects were independently evaluated by two review authors (N.H. and P.M.), disconcordances were discussed in consensus meetings and a third review author (S.C.) was consulted in case if remaining disagreement. The overall risk of bias of a study was classified as: i) low, when risk of bias was low in all domains; ii) some concerns, when unclarities or some concerns of risk of bias were found in one domain; iii) high, when the risk of bias was high in one domain or more.

2.8. Data extraction

A data extraction protocol and electronic report forms were developed before start of the study (Supplementary Materials S2) to standardise collection of publication details, study design and population, treatment and survival outcomes. If survival outcomes were not reported in the text or tables, estimates at several time points were made using survival graphs. Data extraction was performed independently by two review authors (N.H, P.M.) and a third reviewer (S.C.) in case of disagreement.

2.9. Statistical methods

The primary and secondary endpoint of this meta-analysis was the impact of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation on overall survival and progression-free survival, respectively. If the HR and 95% CI of the endpoints were reported in the article, direct calculation of the natural logarithm of HR and its variance were performed (Supplementary Materials S3). If not, imputation according to the methodology of Tierney et al. (2007) was performed using other data provided in the article (Supplementary Materials S3).

Pooled estimates of the hazard ratios for overall survival and progression-free survival were calculated using random-effects models with the DerSimonian-Laird estimator for the amount of heterogeneity. Each study contributed to the meta-analysis according to their sample size using inverse variance weights. Statistical significance was pre-defined as (two-sided) p-values < 0.05.

Heterogeneity in effect size between studies was assessed using the I^2 and the Q-test. Statistical significance of heterogeneity was defined as $I^2 > 50\%$ combined with a Q-test $p < 0.05$. Pre-specified stratified analyses by study design (randomised controlled trials vs. non-randomized studies) were performed to address to the anticipated heterogeneity between studies. Pre-specified sensitivity analyses was performed to evaluate the impact of each study on the pooled estimates for overall and progression-free survival and consisted of re-estimating all pooled HRs according to the leave-one-out method using random effect models.

Publication bias was mapped for both overall and progression-free survival using funnel plots of the included studies' effect sizes vs. their standard error. Asymmetry in the distribution of study estimates, especially that of small studies in favour of an experimental treatment, indicates publication bias. A regression test for funnel plot asymmetry based on a mixed-effects meta-regression model using the standard error as predictor was used as formal test for publication bias.

Analyses were performed in R version 3.6.1 (http://www.r-project.org/) using the metafor package (https://cran.r-project.org/web/packages/metafor/index.html).

3. Results

3.1. Systematic searches

Systematic searches yielded 881 unique articles (Fig. 1). Thirty-one were selected for full-text review, of which 8 were eligible for inclusion. Hand searches of reference lists yielded no additional eligible articles.

3.2. Characteristics included studies

Table 1 shows the main characteristics of the eight included studies. Two of the eight studies were randomized controlled trials, the Thai ACTLACC trial and the Australian-led international OUTBACK trial, of which main outcomes were published in respectively 2019 and 2021 (Tangjitgamol et al., 2019; Mileshkin et al., 2021; NCT, 2017; ANZGOG, 2021). In 2021, a large retrospective study was published by Wu et al. wherein patients who had and had not received adjuvant chemotherapy after chemoradiation and brachytherapy were matched using a propensity score to correct for differences between the two groups (Wu et al., 2021) The remaining five studies described outcome in relatively small retrospective cohorts (Yavas et al., 2019; Tu et al., 2018; Mabuchi

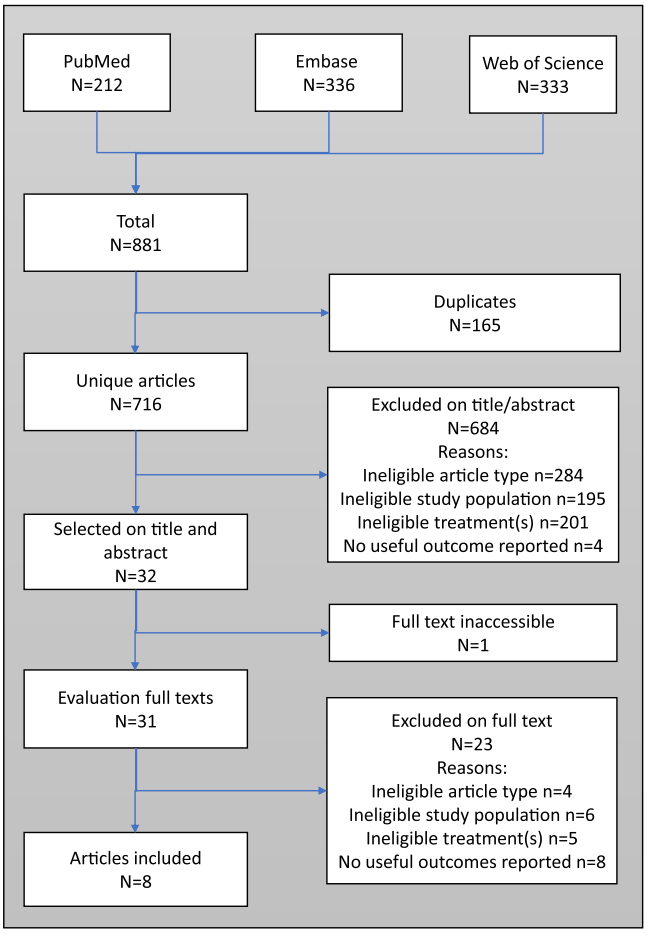

Fig. 1. Overview of article selection for meta-analysis, Flowchart describing systematic search and article selection process.

et al., 2017; Manders et al., 2018; Abe et al., 2012).

Supplementary Table S4 shows the agents, doses and schedules of concurrent and adjuvant chemotherapies. In 6 of 8 studies, concurrent chemotherapy was weekly cisplatin and adjuvant chemotherapy cis/carboplatin with paclitaxel (Tangjitgamol et al., 2019; Yavas et al., 2019; Manders et al., 2018; Abe et al., 2012; Mileshkin et al., 2021; NCT, 2017; ANZGOG, 2021; Wu et al., 2021). In the small retrospective cohort study by Mabuchi et al. patients in the experimental group received 5 weekly cycles of carboplatin-paclitaxel during radiotherapy followed by 3 adjuvant cycles of carboplatin-paclitaxel, and those in the control group received 5 weekly cycles of nedaplatin during radiotherapy (Mabuchi et al., 2017). In the small retrospective cohort study by Tu et al. patients in the experimental group were treated with 3 cycles of carboplatin-paclitaxel during radiotherapy and 3 cycles of adjuvant carboplatin-paclitaxel, while patients in the standard arm were treated with 3 cycles of carboplatin-paclitaxel during radiotherapy (Tu et al., 2018).

Supplementary Table S5 describes the radiotherapy techniques used in the included studies. Generally, external beam radiotherapy was conventionally planned using computed tomography. Radiotherapy delivery was performed by parallel opposing, 3–4 field or intensity modulated techniques. The use of extended field external beam radiotherapy was allowed in 50% of the studies. The dose to the pelvis was 45–50.4 Gy in fractions of 1.8–2.0 Gy in all studies. Brachytherapy was offered to all in patients in all studies, except the OUTBACK trial wherein this decision was at the discretion of the treating physician (NCT, 2017). In all studies that provided details on brachytherapy high dose rate equipment was used. Intracavitary brachytherapy was the standard, only Mabuchi et al. reported to have used interstitial needles in addition to intracavitary brachytherapy in some of their patients (Mabuchi et al., 2017) Brachytherapy dose schedules varied and delivered an additional 15–30 Gy in fractions of 5–10 Gy.

3.3. Risk of bias assessment

Results of the risk of bias assessment are presented in Table 2. The randomized ACTLACC and OUTBACK studies were both classified as at low risk of bias in all domains (Tangjitgamol et al., 2019; Mileshkin et al., 2021; NCT, 2017; ANZGOG, 2021). As many types of bias are inherent to retrospective study designs, such as registration bias and confounding by indication, the 6 remaining studies were all classified as at high risk of bias (Yavas et al., 2019; Tu et al., 2018; Mabuchi et al., 2017; Manders et al., 2018; Abe et al., 2012; Wu et al., 2021).

3.4. Meta-analysis

The impact of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy on overall survival is presented in Fig. 2. Meta-analysis of all eight studies, including a total of 2150 patients, showed no significant benefit for overall survival: HR 0.78 (95%CI 0.45–1.33), p = 0.36. Post-hoc tests showed that there was significant heterogeneity between studies. Pre-specified sub-analysis of only the randomised controlled trials (n = 1178) were not affected by heterogeneity and did not show any impact on overall survival: HR 1.00 (95%CI 0.66–1.53), p = 0.99 (Tangjitgamol et al., 2019; Mileshkin et al., 2021). Pooling of only the non-randomised studies was affected by significant heterogeneity and resulted in a non-significant benefit for overall survival: HR 0.57 (95%CI 0.20–1.66), p = 0.30 (Yavas et al., 2019; Tu et al., 2018; Mabuchi et al., 2017; Manders et al., 2018; Abe et al., 2012; Wu et al., 2021). The impact of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy

Table 1
Characteristics of the included studies.

Study	Country	Year	Design	N	Histotypes	Stage	Pelvic LN	PAO LN
ACTLACC trial	Thailand	2019	RCT	259	SQ, AC, ASQ	IIB–IVA	Yes	No
OUTBACK trial	International[2]	2021	RCT	919	SQ, AC, ASQ	IB-IV	Yes	No
Abe et al.	Japan	2012	Retro	37	SQ	IB–IVA	Yes	Yes
Mabuchi et al.	Japan	2017	Retro	82	SQ	IIIB–IVA	Yes	NR
Manders et al.	USA	2018	Retro	51	SQ, AC, ASQ	IB–II, IIIB–IVA	Yes	Yes
Tu et al.	China	2017	Retro	84	SQ, AC, ASQ	IBM IIB–IIIB	No	No
Wu et al.	China	2021	Match	609	SQ, AC, other[2]	IB-IV	Yes	Yes
Yavas et al.	Turkey	2019	Retro	109	SQ, AC, ASQ, SCC, LC	IB–IVA	Yes	Yes

Definition of abbreviations: AC = adenocarcinoma; ASQ; adenosquamous carcinoma; Match = propensity score matched pair study; LC = large cell carcinoma; NR = not reported; PAO LN = involved para-aortic lymph nodes allowed; Pelvic LN = involved pelvic lymph nodes allowed; RCT = randomised controlled trial; Retro = retrospective study; SQ = squamous cell carcinoma; SCC = small cell carcinoma.
[1]Australia-led international multicenter trial.
[2]Other histotypes were included but not specified by the study authors.

Table 2
Risk of bias assessment.

Study	Year of publication	Design	Number of patients[a]	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Registration bias	Confounding by indication	Other bias	Overall risk of bias
ACTLACC trial	2019	RCT	259	LR	LR	LR	LR	LR	LR	LR	LR	LR
OUTBACK trial	2021	RCT	919	LR	LR	LR	LR	LR	LR	LR	LR	LR
Abe et al.	2012	Retro cohort	37	HR	HR	?	LR	HR	HR	HR	LR	HR
Mabuchi et al.	2017	Retro cohort	82	HR	HR	LR	?	HR	HR	HR	LR	HR
Manders et al.	2018	Retro cohort	51	HR	LR	?	LR	HR	HR	HR	LR	HR
Tu et al.	2017	Retro cohort	84	HR	LR	LR	LR	HR	HR	HR	LR	HR
Wu et al.	2021	Match	609[1]	HR	HR	LR	HR	HR	HR	HR	LR	HR
Yavas et al.	2019	Retro cohort	109	HR	HR	LR	LR	HR	HR	HR	LR	HR

Definition of abbreviations: ? = unclear risk; HR = high risk; LR = low risk; Match = retrospective study with two propensity score-matched study arms; RCT = randomised controlled trial.
[1]Number of patients included after propensity score matching.

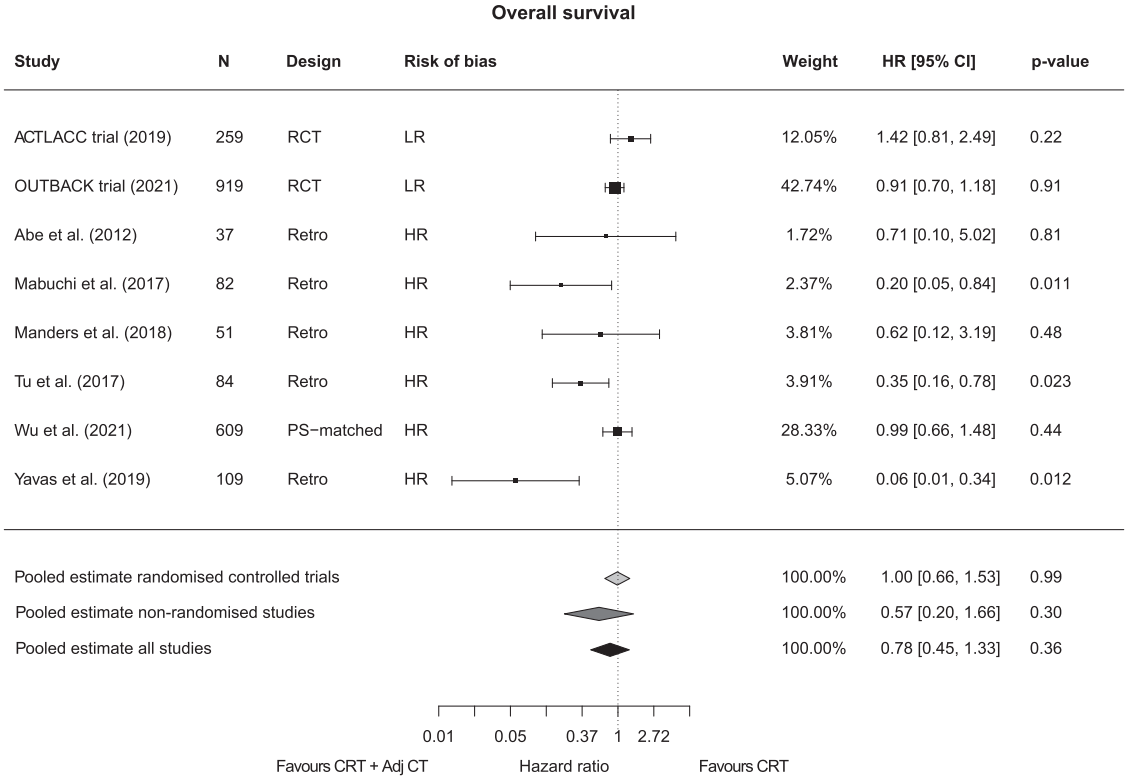

Fig. 2. Impact on overall survival of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy for locally advanced cervical cancer, The forest plot displays the studies' hazard ratios and 95% confidence intervals by a square with horizontal bars. The size of the square is relative to the size of the study and their weight in the meta-analysis. The pooled estimates and the associated 95% confidence intervals of all studies combined and subgroup analysis by study type are represented by the diamonds at the bottom of the figure. Post-hoc tests for heterogeneity: all studies combined I^2 67.7%, Q-test p = 0.0029, sub-analysis of randomised controlled trials I^2 49.6%, Q-test p = 0.16, sub-analysis of non-randomised studies I^2 68.9%, Q-test p = 0.0066.Definition of abbreviations: N = number, CI = confidence interval, RCT = randomized controlled trial, Retro = retrospective cohort study, PS-matched = retrospective propensity score matched study, LR = low risk of bias, HR = high risk of bias, CRT = chemoradiation and brachytherapy, Adj CT = adjuvant platinum-taxane chemotherapy.

on progression-free survival is presented in Fig. 3. Meta-analysis of all eight studies, showed no significant benefit for overall survival: HR 0.85 (95%CI 0.65–1.10), p = 0.22. Sub-analysis by study design showed no benefit either for pooled analysis of randomised controlled trials (HR 0.94, 95%CI 0.66–1.36, p = 0.76) (Tangjitgamol et al., 2019; Mileshkin et al., 2021) or non-randomised trials (HR 0.75, 95%CI 0.46–1.22, p = 0.24). Post-hoc tests showed no significant heterogeneity (Yavas et al., 2019; Tu et al., 2018; Mabuchi et al., 2017; Manders et al., 2018; Abe et al., 2012; Wu et al., 2021).

Sensitivity analyses demonstrated robustness of the meta-analysis. All alternative meta-analyses wherein subsequently each study was excluded once, would have had the same result: no significant impact of adjuvant chemotherapy on overall and progression-free survival (Supplemental Materials Table S5).

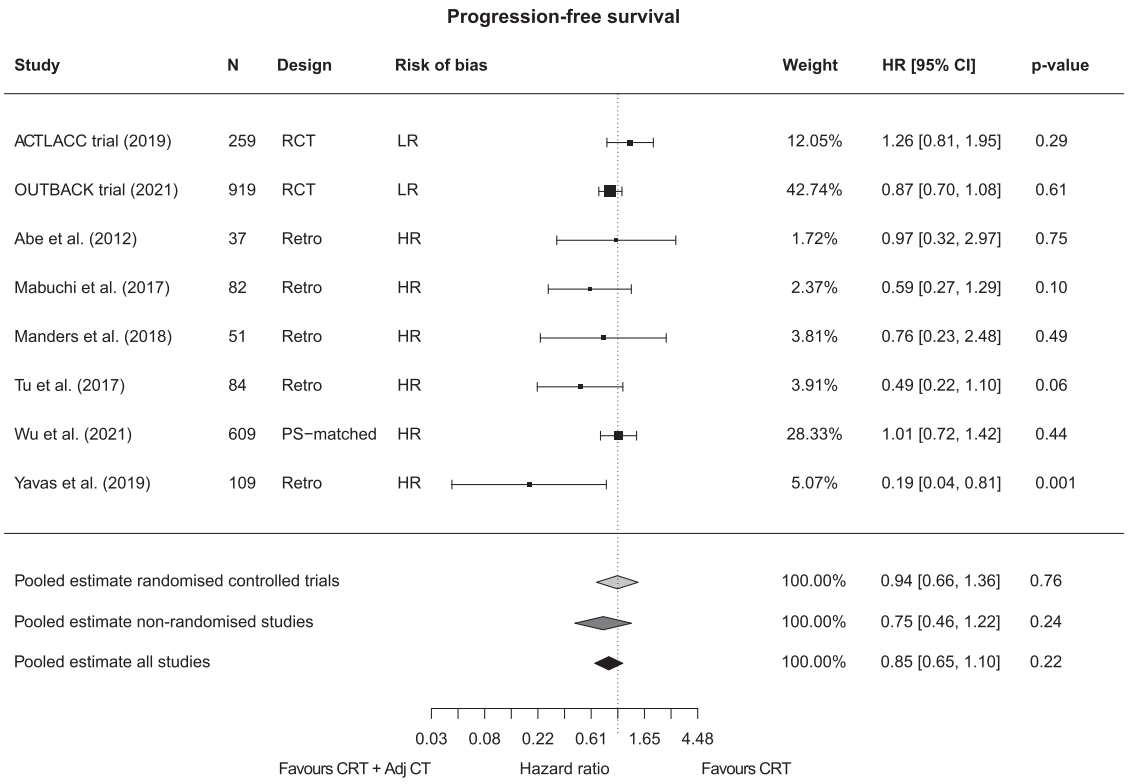

Fig. 3. Impact on progression-free survival of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy for locally advanced cervical cancer, The forest plot displays the studies' hazard ratios and 95% confidence intervals by a square with horizontal bars. The size of the square is relative to the size of the study and their weight in the meta-analysis. The pooled estimates and the associated 95% confidence intervals of all studies combined and subgroup analysis by study type are represented by the diamonds at the bottom of the figure.Post-hoc tests for heterogeneity: all studies combined I^2 34.4%, Q-test p = 0.15, sub-analysis of randomised controlled trials I^2 55.0%, Q-test p = 0.14, sub-analysis of non-randomised studies I^2 35.6%, Q-test p = 0.17. Definition of abbreviations: N = number, CI = confidence interval, RCT = randomized controlled trial, Retro = retrospective cohort study, PS-matched = retrospective propensity score matched study, LR = low risk of bias, HR = high risk of bias, CRT = chemoradiation and brachytherapy, Adj CT = adjuvant platinum-taxane chemotherapy.

Assessment of the risk of publication bias by funnel plots (Fig. 4) and formal tests showed a lack of small studies with a non-significant or negative outcome which may have biased the meta-analysis in favour of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy.

4. Discussion

This systematic review and meta-analysis on the addition of adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy included studies published since the year 2000. Two of these eight studies were high-quality randomised controlled trials (Tangjitgamol et al., 2019; Mileshkin et al., 2021), one was a large retrospective matched-case study (Wu et al., 2021) and the remaining five were relatively small retrospective studies at high risk of bias (Yavas et al., 2019; Tu et al., 2018; Mabuchi et al., 2017; Manders et al., 2018; Abe et al., 2012). A total of 2150 patients with locally advanced cervical cancer were included for analysis and it was shown that there was no benefit for overall survival and progression-free survival.

The most common type of treatment failure for locally advanced cervical cancer is distant metastasis, which limits survival up to a third of the patients. The addition of chemotherapy after chemoradiation and brachytherapy was hypothesised to eliminate micro-metastasis and improve overall survival. Our previous meta-analysis summarised all evidence published until September 2020 on the addition of adjuvant systemic therapy (Horeweg et al., 2021). Disappointingly, none of the chemotherapy (combinations) had a significant benefit for overall survival, while acute and/or late toxicity were significantly increased for most agents. For the current meta-analysis, an update of the systematic search was performed to include the latest large randomised controlled trial on adjuvant carboplatin-paclitaxel, the OUTBACK trial (Mileshkin et al., 2021; NCT, 2017; ANZGOG, 2021). The combination of the outcomes of the previous and current meta-analysis lead to the rejection of the hypothesis that adjuvant chemotherapy after chemoradiation and brachytherapy improves survival in unselected patients with locally advanced cervical cancer.

The current meta-analysis included both randomised controlled trials and non-randomized and retrospective studies to provide a complete overview of all evidence on adjuvant platinum-taxane chemotherapy to chemoradiation and brachytherapy. Since non-randomised studies are inherently subject to a number of biases that could affect outcomes, it was predefined to perform a sub-analysis by study design.

Systematic searches in the PubMed, Embase and Web of Science databases yielded 881 articles, of which eight were deemed eligible for inclusion. Heterogeneity between studies in inclusion criteria and the quality of radiotherapy techniques and dose delivery was observed. Most studies compared cisplatin-based chemoradiation followed by adjuvant cis/carboplatin-paclitaxel to cisplatin-based chemoradiation. However, in a small retrospective study by Mabuchi et al., concurrent chemotherapy consisted of weekly carboplatin-paclitaxel in experimental group and of weekly nedaplatin only in the control group, introducing performance bias (Mabuchi et al., 2017). Serious concerns of performance bias, but also selection bias, registration bias and confounding by indication were identified in all six retrospective studies (Yavas et al., 2019; Tu et al., 2018; Mabuchi et al., 2017; Manders et al., 2018; Abe et al., 2012; Wu et al., 2021). In only one of these studies propensity score matching was used to correct for differences between treatment groups (Wu et al., 2021). The risk of bias assessment showed a

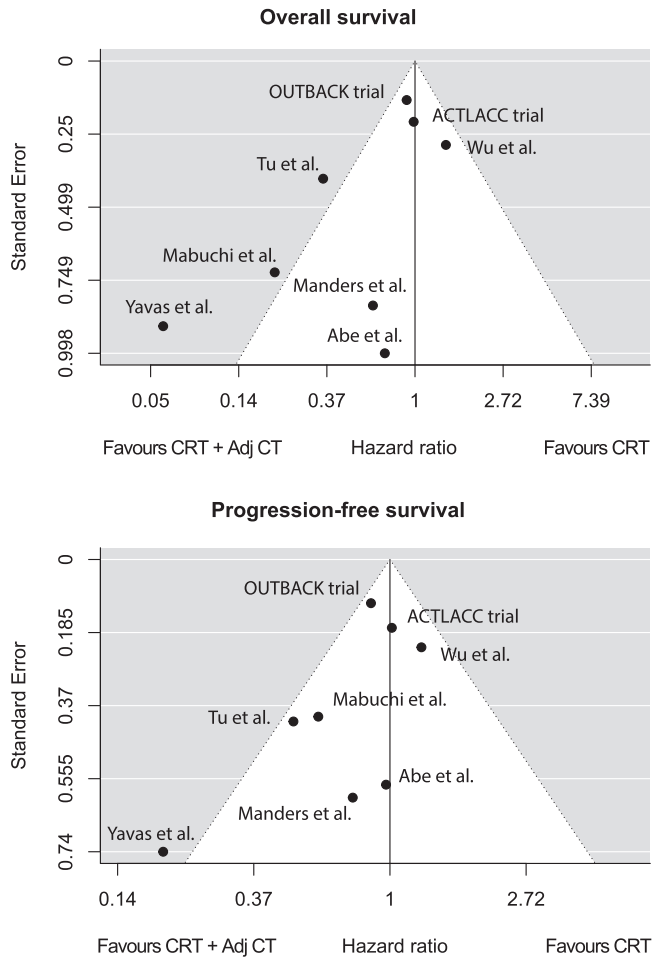

Fig. 4. Funnel plot of study effect size by uncertainty to assess publication bias, Funnel plots showing on the x-axis the estimated impact of the addition of adjuvant platinum-taxane chemotherapy to chemoradiation in the eight included studies on overall survival (panel A) and progression-free survival, and the uncertainty on the y-axis (lower values indicate less uncertainty). The white pyramids represent the 95% confidence interval of the null-hypothesis that there is no benefit of the addition of adjuvant chemotherapy. Regression test for funnel plot asymmetry: overall survival p = 0.010, progression-free survival p = 0.043. Definition of abbreviations: CRT = chemoradiation with brachytherapy, Adj CT = adjuvant platinum-taxane chemotherapy.

low risk of bias for the randomised ACTLACC and OUTBACK trials (Tangjitgamol et al., 2019; Mileshkin et al., 2021; NCT, 2017; ANZGOG, 2021).

The meta-analysis of overall survival outcomes of all eight studies included 2150 patients and showed no significant benefit of carboplatin-paclitaxel after chemoradiation and brachytherapy (HR 0.78, 95%CI 0.45–1.33, p = 0.36). This analysis was affected by significant heterogeneity between studies and publication bias (lack of negative small studies). Hence, the pooled hazard ratio is probably too optimistic. This is supported by the fact that the effect estimates of most robust studies are around 1: ACTLACC trial HR 1.42 (95%CI 0.81–2.49), OUTBACK trial HR 0.91 (95%CI 0.70–1.18) and the matched-case study by Wu et al. HR 0.99 (95%CI 0.66–1.48) (Tangjitgamol et al., 2019; Mileshkin et al., 2021; Wu et al., 2021). The pre-defined sub-analysis of only randomised trials showed a pooled hazard ratio for overall survival of 1.00 (95%CI 0.66–1.53, p = 0.99) (Tangjitgamol et al., 2019; Mileshkin et al., 2021). This analysis was not affected by heterogeneity.

Meta-analysis of progression-free survival of all eight studies combined did not show a significant benefit of the addition of adjuvant platinum-taxane chemotherapy either: HR 0.85 (95%CI 0.65–1.10), p = 0.22. This time, the analysis was not affected by between-study heterogeneity, but the lack of published small negative studies could still have biased the pooled estimate in favour of the addition of adjuvant chemotherapy. The outcomes of the sub-analysis of the two randomised trials were accordingly: HR 0.75, 95%CI 0.46–1.22, p = 0.24 (Tangjitgamol et al., 2019; Mileshkin et al., 2021). Hence, lack of benefit of adjuvant platinum-taxane chemotherapy even for progression-free survival, which should be impacted directly and more substantially than overall survival, reinforces the conclusion that this treatment strategy is not effective. Moreover, sensitivity analyses for both overall survival and progression-free survival demonstrated that the results of this meta-analysis were robust and not influenced by the impact of any individual study.

Considering this and our previous meta-analysis (Horeweg et al., 2021), we can only conclude that there is no benefit of adjuvant chemotherapy to chemoradiation and brachytherapy in unselected locally advanced cervical cancer patients. Now, the focus of research locally advanced cervical cancer has moved to targeted therapies such as anti-PD(L)1 (Mayadev et al., 2020; Merck Sharp & Dohme Corp. et al., 2020; Duska et al., 2020; Institute Curie and Bristol-Myers Squibb, 2017; Gustave Roussy, 2018; Grupo Español de Investigación en Cáncer de Ovario et al., 2019), anti-CTLA-4 (Mayadev et al., 2019; NCT, 2021), anti-VEGF (National Cancer Institute and Radiation Therapy Oncology Group, 2006; Air Force Military Medical University, China, 2019; Schefter et al., 2014; Lu et al., 2021) and anti-EGFR agents (Zhujiang Hospital, 2018; Chen et al., 2017; Qu et al., 2019; Rawat et al., 2020). Nonetheless, the cervical cancer research community should learn from the message hidden in the outcomes of all trials on adjuvant chemotherapy: non-selective allocation of adjuvant systemic treatment was not successful. This does not mean that adjuvant chemotherapy is not beneficial for some patients. Some might be at sufficiently high risk to benefit and others may have tumour that is particularly sensitive to chemotherapy. A therapeutic window for adjuvant chemotherapy might exists in some subgroups, but the trials that have been conducted were not designed to prove this. Results of the randomised INTERLACE trial wherein the addition of carboplatin-paclitaxel before start of chemoradiation is investigated, are awaited (University College London, 2019). Although the 6 neoadjuvant cycles are given in a weekly schedule in this trial, which may addresses to some concerns of delay and insufficient dose density, the patient selection is not limited to those who may benefit most (University College London, 2019).

To be more successful in future trials, a paradigm shift needs to be made. Experimental treatments should be allocated after more accurate assessment of the patients' risk of metastasis and reliable predictors of response to therapy should be employed. This requires more translational research on (bio)markers of response to therapy and clinical outcomes. To achieve this, data and tumour material of patients included in studies that have been conducted should be reanalysed and new studies should be designed in such a way that we cannot only learn whether a new therapy works but also why and in whom. Simple measures such as by design obtaining permission for use of the collection of additional data and patient material, perform secondary analysis and sharing with other research groups are crucial. Especially the latter is important because trials are often not powered for sub-analysis. Hence, international research collaborations are needed to acquire databanks and biobanks that are large enough to conduct such studies.

Concluding, this meta-analysis confirmed that the addition of platinum-taxane chemotherapy to chemoradiation and brachytherapy is not effective for improving overall survival and progression-free survival. This meta-analysis completes the overview of the literature on adjuvant chemotherapy and leads to the conclusion that adjuvant chemotherapy is not recommended for unselected patients with locally advanced cervical cancer. Re-analysis of published studies to identify (bio)markers of response to therapy and risk of distant metastasis and death are encouraged. Future clinical trials should, by design, allocate new (targeted) treatment strategies based on available evidence for

response and include translational research programs to move towards more personalised treatment.

CRediT authorship contribution statement

Nanda Horeweg: Conceptualization, Methodology, Formal analysis, Systematic search, Article selection, data extraction and risk of bias assessment, Writing – original draft, Writing – review & editing. **Prachi Mittal:** Article selection, data extraction and risk of bias assessment, Writing – review & editing. **Patrycja L. Gradowska:** Methodology, Formal analysis, Writing – review & editing. **Ingrid Boere:** Writing – review & editing. **Remi A. Nout:** Conceptualization, Writing – review & editing. **Supriya Chopra:** Conceptualization, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest statement

N.H. reports having received funding for research other that the current study from the Dutch Cancer Foundation. S.C. reports having received funding for research other than the current work from Varian International, Terry Fox Foundation, Department of Atomic Energy Clinical Trials Centre India, Department of Science and Technology India and International Atomic Energy Agency. R.N. reports having received funding for research other than the current work from the Dutch Cancer Foundation, Dutch Research Council, Elekta, Varian, Accuray and Merck Radiation Therapy Advisory Board Meeting on November 6th, 2020. The other others have declared no conflicts of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2022.103638.

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