Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial

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Summary

Background Standard treatment for locally advanced cervical cancer is chemoradiotherapy, but many patients relapse and die of metastatic disease. We aimed to determine the effects on survival of adjuvant chemotherapy after chemoradiotherapy.

Methods The OUTBACK trial was a multicentre, open-label, randomised, phase 3 trial done in 157 hospitals in Australia, China, Canada, New Zealand, Saudi Arabia, Singapore, and the USA. Eligible participants were aged 18 year or older with histologically confirmed squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma of the cervix (FIGO 2008 stage IB1 disease with nodal involvement, or stage IB2, II, IIIB, or IVA disease), Eastern Cooperative Oncology Group performance status 0–2, and adequate bone marrow and organ function. Participants were randomly assigned centrally (1:1) using a minimisation approach and stratified by pelvic or common iliac nodal involvement, requirement for extended-field radiotherapy, FIGO 2008 stage, age, and site to receive standard cisplatin-based chemoradiotherapy (40 mg/m² cisplatin intravenously once-a-week for 5 weeks, during radiotherapy with 45·0–50·4 Gy external beam radiotherapy delivered in fractions of 1·8 Gy to the whole pelvis plus brachytherapy; chemoradiotherapy only group) or standard cisplatin-based chemoradiotherapy followed by adjuvant chemotherapy with four cycles of carboplatin (area under the receiver operator curve 5) and paclitaxel (155 mg/m²) given intravenously on day 1 of a 21 day cycle (adjuvant chemotherapy group). The primary endpoint was overall survival at 5 years, analysed in the intention-to-treat population (ie, all eligible patients who were randomly assigned). Safety was assessed in all patients in the chemoradiotherapy only group who started chemoradiotherapy and all patients in the adjuvant chemotherapy group who received at least one dose of adjuvant chemotherapy. The OUTBACK trial is registered with ClinicalTrials.gov, NCT01414608, and the Australia New Zealand Clinical Trial Registry, ACTRN12610000732088.

Findings Between April 15, 2011, and June 26, 2017, 926 patients were enrolled and randomly assigned to the chemoradiotherapy only group (n=461) or the adjuvant chemotherapy group (n=465), of whom 919 were eligible (456 in the chemoradiotherapy only group and 463 in the adjuvant chemotherapy group; median age 46 years [IQR 37 to 55]; 663 [72%] were White, 121 [13%] were Black or African American, 53 [6%] were Asian, 24 [3%] were Aboriginal or Pacific islander, and 57 [6%] were other races) and included in the analysis. As of data cutoff (April 12, 2021), median follow-up was 60 months (IQR 45 to 65). 5-year overall survival was 72% (95% CI 67 to 76) in the adjuvant chemotherapy group (105 deaths) and 71% (66 to 75) in the chemoradiotherapy only group (116 deaths; difference 1% [95% CI –6 to 7]; hazard ratio 0·90 [95% CI 0·70 to 1·17]; p=0·81). In the safety population, the most common clinically significant grade 3–4 adverse events were decreased neutrophils (71 [20%] in the adjuvant chemotherapy group *vs* 34 [8%] in the chemoradiotherapy only group), and anaemia (66 [18%] *vs* 34 [8%]). Serious adverse events occurred in 107 (30%) in the adjuvant chemotherapy group versus 98 (22%) in the chemoradiotherapy only group, most commonly due to infectious complications. There were no treatment-related deaths.

Interpretation Adjuvant carboplatin and paclitaxel chemotherapy given after standard cisplatin-based chemoradiotherapy for unselected locally advanced cervical cancer increased short-term toxicity and did not improve overall survival; therefore, it should not be given in this setting.

Funding National Health and Medical Research Council and National Cancer Institute.

Research in context

Evidence before this study

We searched PubMed and Google Scholar for articles written in English from database inception to Oct 26, 2022, using the terms "cervical cancer", "cervix cancer", "locally-advanced", "radiotherapy" AND "adjuvant chemotherapy" and found only a small number of randomised trials and 2 prior meta-analyses. Although some previous individual trials have suggested a benefit from the addition of adjuvant chemotherapy to chemo-radiation, these data was considered controversial because of short follow-up times and increased adverse events, and the results of meta-analyses have not confirmed a survival benefit from this practise.

Added value of this study

OUTBACK is a large, adequately powered, randomised trial with mature follow-up and overall survival as the primary endpoint. This trial showed that adjuvant chemotherapy of carboplatin plus paclitaxel given after standard chemoradiotherapy for unselected locally advanced cervical cancer increases the occurrence of adverse events without improving overall-survival or progression-free survival. Our study also reinforced the value of strong multinational intergroup collaboration required to successfully complete randomised trials in cervical cancer and raises several questions about the optimal way to design future trials in this disease.

Implications of all the available evidence

Standard treatment for locally advanced cervical cancer should remain cisplatin-based external beam chemoradiotherapy plus brachytherapy. More efforts are needed to ensure that all women diagnosed with cervical cancer can receive standard cisplatin-based chemoradiotherapy globally. Adjuvant carboplatin and paclitaxel chemotherapy should not be used in this setting.

Introduction

Cervical cancer is a substantial global health issue with more than half a million women diagnosed worldwide each year. In high-income countries the incidence has decreased considerably following the widespread introduction of cervical screening programmes.[1] However, many women still die from cervical cancer, particularly in low-income and middle-income countries, making it the fourth leading cause of cancer-related death in women worldwide.[2]

For women presenting with early-stage disease, surgical approaches or treatment with chemoradiotherapy provide excellent outcomes. However, a substantial proportion of women, particularly those who have not participated in screening programmes, present with more locally advanced disease and have much lower cure rates.[3]

Use of chemoradiotherapy for cervical cancer is proven to improve survival, and became established as standard of care in 1999.[4–6] Subsequently, a meta-analysis of individual patient data from 18 randomised trials found that adding concurrent chemotherapy to radiotherapy increased 5-year overall survival by 6% (60% with radiotherapy alone *vs* 66% with chemoradiotherapy; hazard ratio [HR] 0·81 [95% CI 0·71–0·91]).[7] However, a 5-year disease-free survival rate of 58% in those who received chemoradiotherapy left many women not cured, with most deaths due to the subsequent development of distant metastatic disease.[7,8]

We hypothesised that giving additional adjuvant chemotherapy following chemoradiotherapy would reduce distant relapses and improve overall survival. The meta-analysis by the Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration found improved survival benefits in two trials that gave additional cycles of adjuvant chemotherapy following chemoradiotherapy.[7] Subsequently, a randomised trial done in South America compared standard cisplatin-based chemoradiotherapy with the same radiotherapy with concurrent cisplatin and gemcitabine, followed by two cycles of adjuvant cisplatin and gemcitabine.[9] The trial reported a 9% improvement in both progression-free survival and overall survival at 3 years, and was highly influential in changing practise at some centres.

However, criticisms of the trial included the short follow-up of 3 years and significantly increased toxicity in patients who received the additional concurrent and adjuvant chemotherapy. These limitations precluded the widespread acceptance of the findings as standard treatment. However, an analysis of the US National Cancer Database, presented in 2022, suggested that one in ten patients were receiving multidrug adjuvant chemotherapy in addition to chemoradiotherapy with no survival benefit.[10] There was also a lower rate of brachytherapy completion in those treated with adjuvant chemotherapy, which is known to result in inferior outcomes.[10] Consequently, the Gynecologic Cancer Intergroup (GCIG) envisaged the OUTBACK trial as a confirmatory study. We aimed to test the potential benefit of adjuvant chemotherapy following primary chemoradiotherapy for locally advanced cervical cancer.

Methods

Study design and participants

The OUTBACK (ANZGOG 0902, RTOG 1174, NRG 0274) trial was a multicentre, open-label, randomised, phase 3 trial done at 157 hospitals in seven countries (Australia, China, Canada, New Zealand, Saudi Arabia, Singapore, and the USA; appendix pp 2–9). The trial was done under the auspices of the GCIG, led by the Australia and New Zealand Gynaecological Oncology Group (ANZGOG), and coordinated by the National Health and Medical Research Council Clinical Trials Centre, University of Sydney (Sydney, NSW, Australia). Participating cooperative groups or countries were NRG

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See **Online** for appendix

Oncology (USA, Saudi Arabia, Canada, and China) and Singapore.

Patients aged 18 years or older with locally advanced cervical cancer suitable for primary treatment with chemoradiotherapy were considered for inclusion. Participants were eligible if they had histologically confirmed squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma of the cervix (International Federation of Gynecology and Obstetrics [FIGO] 2008 stage IB1 disease with nodal involvement, or stage IB2, IIA, IIB, IIIB, or IVA disease), Eastern Cooperative Oncology Group performance status of 0–2, and adequate bone marrow and organ function. Key exclusion criteria included previous hysterectomy, para-aortic nodal involvement above the level of the common iliac nodes or above L3 or L4 (if biopsy proven, positive on PET, or ≥15 mm short axis diameter on CT), FIGO stage IIIA disease, and disease assessed at presentation as requiring interstitial brachytherapy. A full list of eligibility criteria is in the protocol (appendix). All participants had baseline CT imaging of the chest, abdomen, and pelvis, with or without MRI imaging of the pelvis and PET or PET/CT if available at the treating centre.

The protocol was approved by all participating groups and relevant institutional ethics review committees, and all participants gave written informed consent. The trial was done according to Good Clinical Practice guidelines of the International Conference on Harmonisation and the principles of the Declaration of Helsinki.

Randomisation and masking

Using a minimisation approach, participants were randomly assigned (1:1) to receive either standard chemoradiotherapy (chemoradiotherapy only group) or standard chemoradiotherapy followed by adjuvant chemotherapy (adjuvant chemotherapy group). Randomisation was stratified by pelvic or common iliac nodal involvement, or both (yes *vs* no *vs* unknown), requirement for extended-field radiotherapy (yes *vs* no), FIGO 2008 stage (IB or IIA *vs* IIB *vs* IIIB or IVA) age (<60 *vs* ≥60 years), and treating hospital or site. Random assignment was done by each site using a central web-based system. Nodal involvement was defined as any pelvic or common iliac nodes that were either PET positive, had a short axis diameter of more than 15 mm on CT or MRI, or were histologically positive after surgical sampling. Participants and investigators were not masked to treatment allocation given the alopecia associated with paclitaxel that was administered to patients in the adjuvant chemotherapy group.

Procedures

Participants in both groups received standard external beam radiotherapy to the pelvis plus brachytherapy. Cisplatin was given concurrently during radiotherapy at a dose of 40 mg/m² intravenously once-a-week for 5 weeks. Cisplatin was omitted or the dose reduced to 30 mg/m² if participants had adverse events specified in the protocol (appendix). External beam radiotherapy continued if cisplatin was withheld. Participants who had not recovered from adverse events within 21 days did not receive further cisplatin.

The standardised radiotherapy procedure used megavoltage energy with a source-to-surface distance of 80 cm or more. Use of linear accelerators or ^{60}Co units was allowed. A four-field box technique with parallel-opposed anterior-posterior and posterior-anterior and two opposing lateral fields was recommended and defined in the protocol; intensity modulated radiotherapy was not allowed. All patients received 45·0–50·4 Gy external beam radiotherapy delivered in fractions of 1·8 Gy to the whole pelvis. Participants with common iliac nodal disease received 45 Gy in 1·8 Gy fractions of extended field radiotherapy. Parametrial or nodal boost was allowed at the discretion of the treating radio-oncologist. The external beam target volume was to encompass, with adequate margins, the gross tumour volume, including the primary cervical tumour, any gross extension, and any grossly involved lymph nodes. The clinical target volume included the gross tumour volume; parametria; uterus; upper half of the vagina; the internal, external, and distal common iliac nodes; and the utero-sacral ligaments.

Intracavitary brachytherapy was delivered with standard applicators using either tandem and ovoids or tandem and ring. Brachytherapy could be delivered at either a high-dose rate or low-dose rate to deliver a total dose to the primary tumour of 80·0–86·4 Gy (equivalent dose in 2 Gy fractions), including external beam radiotherapy and brachytherapy. Brachytherapy could be prescribed either to point A or to image-guided target volumes.

Radiation quality assurance was monitored by the Imaging and Radiation Oncology Core administered by the American College of Radiology. Simulation films of digitally reconstructed radiographs (for all treatment fields and phases of treatment) were submitted and reviewed centrally for the first two participants at each participating site. If these were deemed acceptable, subsequent data from every tenth participant was submitted for central review. Centres with unsatisfactory results were required to send more participants for review until deemed compliant with the protocol.

Within 4 weeks of completing radiotherapy, including brachytherapy, and following recovery from any treatment-related adverse events, participants in the adjuvant chemotherapy received four 21-day cycles of adjuvant chemotherapy using carboplatin (areas under the receiver operator curve [AUC] 5, intravenously over 1 h) and paclitaxel (155 mg/m², intravenously over 3 h) administered on day 1 of each cycle. Hospira (Lake Forest, IL, USA) provided paclitaxel for sites in Australia and New Zealand. Before starting adjuvant chemotherapy,

any adverse events due to the previously completed concomitant chemoradiotherapy (regardless of whether ceased early because of toxicity) were required to be resolved to less than Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) grade 2 (except for lymphocyte count). Adjuvant chemotherapy doses could be delayed for up to 2 weeks or doses reduced, per protocol-defined guidelines (appendix).

After treatment, participants were followed up every 3 months for the first 2 years and then every 6 months for a minimum of 5 years. At each follow-up visit, a physical examination was done, and any laboratory-based monitoring was done as clinically indicted. Response rate using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was determined locally by the site investigator in those with measurable disease, based on pelvis CT or MRI at baseline and repeated 6 months after randomisation and if relapse was suspected. If PET or PET and CT was done at baseline, imaging was repeated 4–6 months after completing chemoradiotherapy. Metabolic PET response was assessed using Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST) version 1.0. There was no restriction on treatment given for relapse, which was as per investigator discretion.

Adverse events were classified and graded using the CTCAE (version 4.0), and assessed in person every week during chemoradiotherapy, before each cycle of adjuvant chemotherapy, and at the end of study treatment, then once every 3 months up to 2 years after randomisation, and then once every 6 months up to 5 years after randomisation. Health-related quality of life (HRQoL) was assessed at baseline, at the end of chemoradiotherapy, before each cycle of adjuvant chemotherapy, and then at each follow-up visit until 36 months after randomisation.

Outcomes

The primary endpoint was overall survival at 5 years, defined as the time from the date of randomisation to death from any cause or censoring at last known follow-up. The secondary endpoints were progression-free survival at 3 years and 5 years; adverse events within 1 year of randomisation (short-term safety) and after 1 year (long-term safety); the patterns of disease response and recurrence; radiation protocol compliance; and aspects of self-reported HRQoL related to both disease and treatment given. A tertiary endpoint was complete and partial metabolic response by PERCIST 1.0 criteria on a PET scan done 4–6 months after completion of chemoradiotherapy.

Progression-free survival was defined as the time from the date of randomisation to tumour progression or recurrence at any site, commencement of non-protocol anticancer therapy, or death from any cause, whichever occurred first. Recurrences were analysed according to the first site of recurrence, and defined as either persistent disease (present at treatment completion), locoregional, or distance recurrence.

All endpoints were determined by investigators at the study sites. Several HRQoL questionnaires were used as outlined in the protocol (appendix); we report the global health status and quality of life scale from the EORTC QLQ-C30. Due to the large amount of HRQoL data collected, a comprehensive analysis of HRQoL will be reported elsewhere.[11] The secondary endpoint of radiation protocol compliance will also be reported elsewhere.

Statistical analysis

The OUTBACK trial was originally powered to provide 80% power with a two-sided type 1 error rate of 5% if the true absolute difference in 5-year overall survival rates was 10% (range 63–73). This required 780 participants, assuming 3 years of accrual plus 3 years of additional follow-up. An Independent Data and Safety-Monitoring Committee (IDSMC) monitored the study and advised the trial steering committee on the safety and feasibility of the study. An interim analysis for efficacy, planned for after 120 deaths had occurred, was positive, and so the was trial continued. In 2016, after consideration of the lower-than-expected progression-free survival rate, and substantial non-adherence to prescribed adjuvant chemotherapy, the IDSMC recommended that the sample size be increased in a protocol amendment (version 5.0; May 9, 2016).

The revised sample size of 828 patients (414 per group) provided 80% power with a two-sided type 1 error rate of 5% if the true absolute difference in 5-year overall survival rates was 8% (range 72–80). This corresponded to a HR of 0·68 and assumed 48 months for accrual plus 42 months of additional follow-up. The study sample size was increased to 900 (450 per group) to allow for non-adherence and loss to follow-up.

All statistical analyses were done with SAS (version 9.4). Efficacy analyses were done in the intention-to-treat (ITT) population, which included all eligible patients who were randomly assigned to treatment and analysed according to their treatment allocation. The safety population included eligible patients in the chemoradiotherapy only group who started chemoradiotherapy and eligible patients in the adjuvant chemotherapy group who received at least one dose of adjuvant chemotherapy; patients were analysed according to their randomly assigned treatment group. Patterns of disease recurrence were measured in the ITT population. The secondary endpoints of acute and long-term safety were defined according to worst grade experienced within 1 year after randomisation (acute safety) and worst grade experienced at any time after 1 year (long-term saftery). For the acute and long-term safety analyses, participants in the safety population with no recorded safety assessment 1 year after randomisation were excluded from the analyses of long-term adverse events. For endpoints of response, these were calculated according to RECIST 1.1 in participants with measurable disease

at baseline, and patients who did not have a scan after baseline were treated as non-evaluable and excluded from this analysis.

The primary outcome of overall survival and its 95% CI at 3 and 5 years were estimated in each randomised treatment group using the Kaplan-Meier method, and SE was estimated using the Greenwood method. An unstratified log-rank test was used to quantify the evidence for overall survival differences between the two groups. For survival outcomes, patients who had not experienced the event of interest were censored at their last known event-free date.

Proportional hazards regression models were used to calculate HRs and 95% CIs for overall survival and progression-free survival at 3 years and 5 years. The proportional hazards assumption for overall survival and progression-free survival was tested with the method introduced by Li and colleagues[12] based on Martingale residuals. Calculations for progression-free survival used the same method. Tests of the proportional hazards assumption showed no evidence of non-proportionality for overall survival, but some evidence for progression-free survival. However, 20 patients had persistent disease (five in the adjuvant chemotherapy group and 15 in the chemoradiotherapy only group) whose progression was set to have occurred 0·5 days after randomisation. When these patients were removed, the proportional hazards assumption was upheld, but all participants are included in all survival analyses reported, unless otherwise indicated.

Given substantial rates of non-adherence in the adjuvant chemotherapy group, and our previous findings that non-completion of chemoradiation was the strongest predictor of not starting any adjuvant chemotherapy,[13] a prespecified sensitivity analysis for overall survival and progression-free survival was was done based on those who did or did not complete the initial chemoradiotherapy (appendix), using the Kaplan-Meier method to estimate survival outcomes and a proportional hazards regression model with randomised treatment, completion or non-completion of chemoradiotherapy and their interaction as predictors.

Subgroup analyses were done for the outcomes of 5 year overall survival and progression-free survival, according to prespecified baseline characteristics (ie, nodal involvement [yes *vs* no *vs* unknown], requirement for extended-field radiotherapy [yes *vs* no], FIGO 2008 stage [IB1 with nodal involvement or IB2 or IIA *vs* IIB *vs* IIIB or IVA], age [<60 *vs* ≥60 years], country [the USA and Canada *vs* Australia and New Zealand *vs* China, Saudi Arabia, and Singapore], and tobacco smoking status [never smoker *vs* current or former smoker or unknown]) and one post-hoc predictor (tumour histology [squamous or adenosquamous cell carcinoma *vs* adenocarcinoma]). The Cox proportional hazards regression models for these analyses included terms for the subgroup, randomised treatment group, and their interaction, with p values calculated.

Cervical cancer-specific mortality was compared between the two treatment groups was done with Gray's method. The HR and 95% CI was calculated using the Fine-Gray method, after masked central adjudication of the cause of death, before the primary analysis was done. For cervical-cancer-specific mortality, death from other causes was treated as a competing risk and patients alive at last follow-up were censored. A prespecified analysis in participants who underwent a PET scan 168 to 365 days after randomisation explored the association between PET response (complete metabolic response [CMR] *vs* any other result [non-CMR, progressive metabolic disease, result unknown]) and the outcomes of overall survival and progression-free survival. The Kaplan-Meier method was used to calculate survival estimates separately for participants with and without CMR in each treatment group. Proportional hazards regressions model tested for interaction between CMR and treatment group and calculated HRs for the effect of treatment and CMR in a multivariable model.

Changes in mean HRQoL scores from baseline for participants with at least one follow-up questionnaire were compared between groups using two-sample Student's *t* tests and described with difference and 95% CIs. Categorical outcomes were compared with the χ^2 test. The OUTBACK trial is registered with

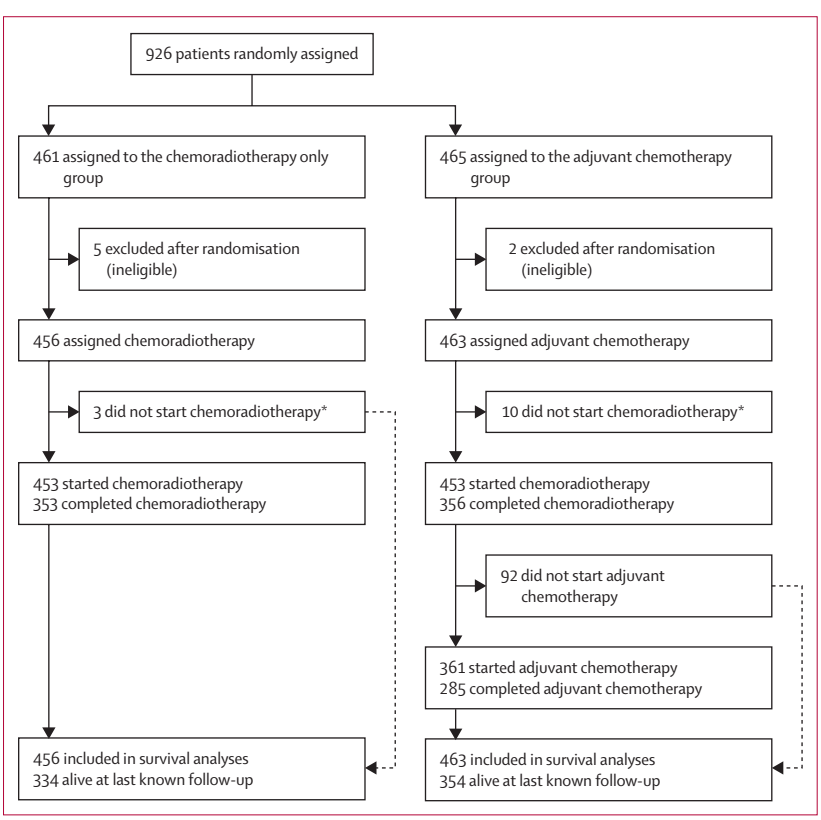


Figure 1: **Trial profile**
*The most common reason for not starting chemoradiotherapy in both groups was withdrawl of patient consent due to patient preference. In the adjuvant chemotherapy group, two patients were deemed to have disease not suitable for treatment with radiotherapy as per the study protocol, and one patient had a haemoglobin level too low for eligibility.

ClinicalTrials.gov, NCT01414608, and the Australia New Zealand Clinical Trial Registry, ACTRN12610000732088.

Role of the funding source

The funding bodies had no role in study design, data collection, data interpretation or analysis, or writing of the report.

Results

Between April 15, 2011, and June 26, 2017, 926 participants were randomly assigned to treatment. Seven participants were found to be ineligible after randomisation and were excluded from analyses (figure 1). 919 women (99%; median age 46 years [IQR 37–55]; 663 [72%] of 919 were White, 121 [13%] were Black or African American, 53 [6%] were Asian, 24 [3%] were Aboriginal or Pacific islander, and 57 [6%] were other races) were included in the ITT population (456 [50%] randomly assigned to the chemoradiotherapy only group and 463 [50%] to the adjuvant chemotherapy group. As of data cutoff (April 12, 2021), the median duration of follow-up was 60 months (IQR 45–65). Baseline characteristics are reported in table 1.

Adherence to the standard chemoradiotherapy protocol was similar in the two treatment groups. Dose modification or delays due to adverse events occurred for 162 (35%) of 463 patients in the adjuvant chemotherapy group and 144 (32%) of 456 patients in the chemoradiotherapy only group. One (<1%) participant in the adjuvant chemotherapy group received radiotherapy but no concurrent cisplatin. External beam radiotherapy was given without interruption in 92% of participants, and brachytherapy was delivered as planned in 95%. All components of chemo-radiation were completed by 77% of participants, including at least 45 Gy of external beam radiotherapy, all planned brachytherapy, and all 5 cycles of concurrent cisplatin (table 2).

102 (22%) of 465 patients in the adjuvant chemotherapy group did not initiate any adjuvant chemotherapy; the most common reason for which was patient preference (appendix p 72). 200 (70%) of 285 patients in the adjuvant chemotherapy who completed treatment completed all four cycles of carboplatin without dose reduction or delay, and 197 (69%) completed all four cycles of paclitaxel without dose reduction or delay (appendix p 10).

As of data cut-off, 109 (24%) of 463 patients in the adjuvant chemotherapy group and 123 (27%) of 456 patients in the chemoradiotherapy only group had died; median overall survival time was not reached in either group (figure 2). 5-year overall survival was 72% (95% CI 67 to 76; 105 deaths) in the adjuvant chemotherapy group versus 71% (66 to 75; 116 deaths) in the chemoradiotherapy only group (difference 1% [95% CI –6 to 7]; HR 0·90 [95% CI 0·70 to 1·17]; p=0·81).

As of data cut-off, 151 progression-free survival events (20 deaths; 131 progressions) were reported in the adjuvant chemotherapy group versus 168 events (18 deaths; 150 progressions) in the chemoradiotherapy only group. The 3-year and 5-year progression-free survival are shown in figure 3. There were 84 cervical-cancer specific deaths and 25 with other or unknown cause in the adjuvant chemotherapy group versus 102 cervical cancer-specific deaths and

	Chemoradiotherapy only group (n=456)	Adjuvant chemotherapy group (n=463)
Age, years	45 (38–54)	46 (37–55)
ECOG performance status		
0	344 (75%)	337 (73%)
1	94 (21%)	117 (25%)
2	18 (4%)	9 (2%)
Race*		
White	326 (71%)	337 (73%)
Black or African American	68 (15%)	53 (11%)
Asian	22 (5%)	31 (7%)
Aboriginal or Pacific Islander	11 (2%)	13 (3%)
Other	28 (6%)	29 (6%)
Geographical region		
Australia and New Zealand	84 (18%)	81 (17%)
USA and Canada	366 (80%)	373 (81%)
China, Saudi Arabia, and Singapore	6 (1%)	9 (2%)
Tobacco smoking		
Never smoker	237 (52%)	224 (48%)
Current or former smoker or unknown	219 (48%)	239 (52%)
Histological type		
Squamous cell carcinoma	358 (79%)	383 (83%)
Adenocarcinoma	79 (17%)	68 (15%)
Adenosquamous cell carcinoma	19 (4%)	12 (3%)
FIGO 2008 stage		
IB1 (all node positive), IB2, or IIA	152 (33%)	154 (33%)
IIB	196 (43%)	197 (43%)
IIIB or IVA	108 (24%)	112 (24%)
Maximum tumour diameter, cm	5·0 (4·0–6·0)	5·0 (4·0–6·0)
Nodal involvement		
Pelvic alone	144 (32%)	149 (32%)
Common iliac alone	33 (7%)	31 (7%)
Pelvic and common iliac	44 (10%)	44 (10%)
Neither	225 (49%)	231 (50%)
Unknown	10 (2%)	8 (2%)
Extended field radiotherapy planned		
No	397 (87%)	404 (87%)
Yes	59 (13%)	59 (13%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. *Self-reported.

Table 1: **Baseline demographic and disease characteristics, intention-to-treat population**

	Chemoradiotherapy only group (n=456)	Adjuvant chemotherapy group (n=463)
Chemotherapy		
Number of cisplatin cycles commenced		
0–3	27 (6%)	49 (11%)
4	46 (10%)	32 (7%)
5	383 (84%)	382 (83%)
Cisplatin cycles completed at full dose with no delays		
Cycle one	450 (100%)	451 (99%)
Cycle two	438 (98%)	434 (96%)
Cycle three	431 (97%)	423 (95%)
Cycle four	420 (95%)	409 (93%)
Cycle five	383 (88%)	375 (87%)
Cisplatin dose intensity, mg/m^2 per week	28 (27–29)	28 (26–29)
Radiation technique		
Four field	413 (91%)	416 (92%)
Two field	7 (2%)	5 (1%)
Other	33 (7%)	33 (7%)
Radiotherapy		
Mean EBRT dose given, Gy	45·6	45·7
EBRT nodal boost given	145 (32%)	135 (30%)
EBRT parametrial boost given	161 (36%)	165 (36%)
EBRT without interruption	417 (92%)	418 (92%)
Brachytherapy given	429 (95%)	426 (94%)
Brachtherapy dose rate		
High-dose rate	393 (92%)	384 (90%)
Low-dose rate	25 (6%)	24 (6%)
Pulse-dose rate	9 (2%)	16 (4%)
Not recorded	1 (<1%)	4 (1%)
Brachytherapy prescription		
Point A	292 (64%)	292 (63%)
Image-guided	134 (29%)	131 (28%)
Not recorded	30 (7%)	40 (9%)
Duration of radiation		
<8 weeks	278 (63%)	281 (64%)
8–10 weeks	141 (32%)	143 (33%)
>10 weeks	19 (4%)	14 (3%)
Chemoradiotherapy completed		
Five cisplatin cycles, 45 Gy EBRT, and brachytherapy	353 (77%)	356 (77%)
Minimum four cisplatin cycles, 45 Gy EBRT, and brachytherapy	396 (87%)	383 (83%)

Data are median (IQR) or n (%), unless otherwise indicated. EBRT=external beam radiotherapy.

Table 2: **Chemoradiotherapy adherence in the intention-to-treat population**

21 with other or unknown cause in the chemoradiotherapy only group. The 5-year cumulative incidence of cervical cancer-specific death was also similar in in both groups (21% [95% CI 17–26] *vs* 24% [20–28]; p=0·21).

Forest plots and p values for interactions showed no evidence that adjuvant chemotherapy had different effects on 5-year overall survival or 5-year progression-free survival in prespecified subgroups defined by nodal status, requirement for extended field radiotherapy, FIGO stage, country, and smoking status, or post-hoc subgroup histological subtype (figure 4). A sensitivity analysis showed that in those who completed initial chemoradiotherapy, the 5-year overall survival was 74% in the adjuvant chemotherapy group versus 71% in the chemoradiotherapy only group, with an absolute difference of 3% (95% CI –4 to 11) in 5-year overall survival between the treatment groups (HR 0·81 [95% CI 0·60 to 1·08]; p=0·15). A similar pattern was seen for progression-free survival (appendix p 11).

Sites of disease recurrence were similar in the randomly assigned groups; most patients were disease free at last follow-up. In the ITT population, persistent disease after treatment was reported in five (1%) of 463 patients in the adjuvant chemotherapy group versus 15 (3%) of 456 patients in the chemoradiotherapy only group. Isolated locoregional recurrence was reported in 54 (12%) patients in the adjuvant chemotherapy group versus 50 (11%) in the chemoradiotherapy only group. Distant recurrence was reported in 61 (13%) patients in the adjuvant chemotherapy group versus 70 (15%) in the chemoradiotherapy only group. Sites of other or unknown recurrence were reported in 11 (2%) patients in the adjuvant chemotherapy group versus 15 (3%) in the chemoradiotherapy only group. There was no evidence of difference in sites of recurrence (none *vs* locoregional *vs* distant *vs* other or unknown) between the randomly assigned groups (p=0·12). Chemotherapy was the most common treatment given for recurrent disease (appendix p 73).

In the safety population, grade 2 or worse adverse events were reported in the first year after randomisation in 356 (99%) of 361 patients in the adjuvant chemotherapy group versus 409 (90%) of 453 patients in the chemoradiotherapy only group. Grade 3 or worse adverse events were reported in 292 (81%) patients in the adjuvant chemotherapy group versus 280 (62%) patients in the chemoradiotherapy only group (p<0·0001). Grade 1–2 adverse events reported in at least 10% of patients and grade 3–5 events reported in 1% of patients are shown in table 3. The most common grade 3–4 adverse events were decreased lymphocyte count (211 [58%] of 361 patients in the adjuvant chemotherapy group *vs* 208 [46%] of 453 in the chemoradiotherapy only group), decreased neutrophils (71 [20%] *vs* 34 [8%]), and anaemia (66 [18%] *vs* 34 [8%]; appendix pp 12–43). Serious adverse events occurred in 107 (30%) patients in the adjuvant chemotherapy group versus 98 (22%) in the chemoradiotherapy only group, with infectious adverse events being the most common. Established adverse events associated with carboplatin and paclitaxel, such as nausea, vomiting, haematological toxicity, alopecia, fatigue, myalgia, and

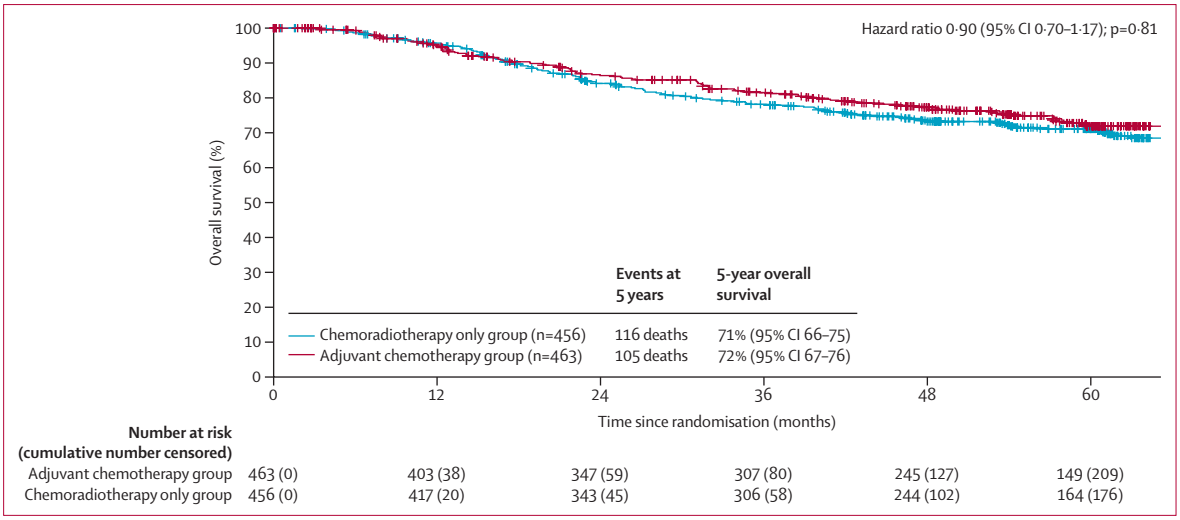


Figure 2: **Kaplan-Meier estimates of overall survival**

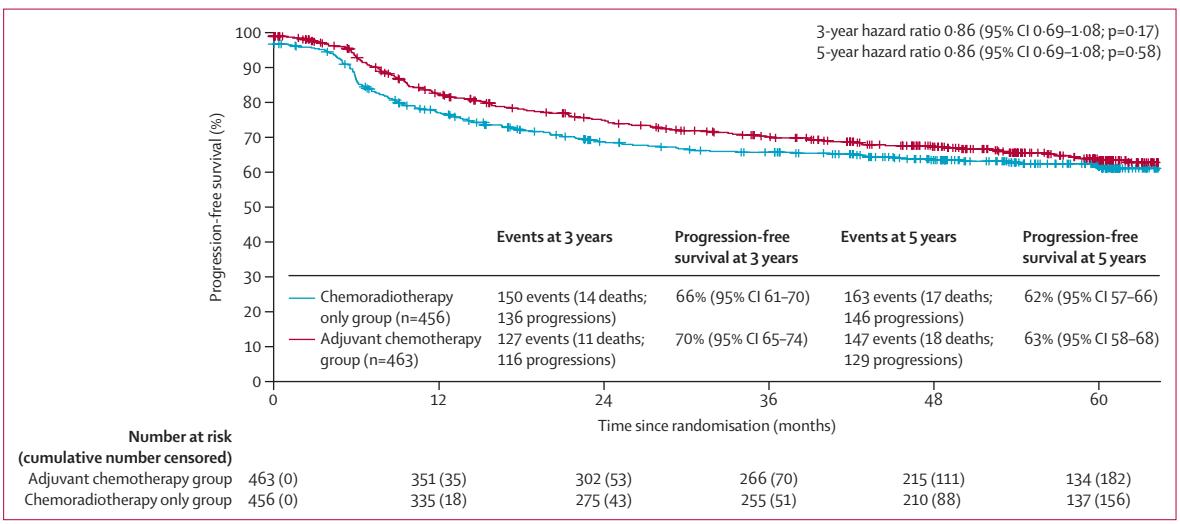


Figure 3: **Kaplan-Meier estimates of progression-free survival**

peripheral neuropathy, were more frequent in the adjuvant chemotherapy group and resulted in 84 serious adverse events in 56 (16%) participants. Febrile neutropenia occurred in nine (2%) patients in both treatment groups. There were no deaths attributed to study treatment.

Long-term safety data were available for 316 (88%) of 361 patients in the adjuvant chemotherapy group and 377 (83%) of 453 patients in the chemoradiotherapy group. Grade 2 sensory peripheral neuropathy, peripheral motor neuropathy, pain in extremity, hyperglycaemia, and fever related to chemotherapy were all significantly more common in the adjuvant chemotherapy group than in the chemotherapy alone group (appendix pp 44–58).

406 (88%) patients in the adjuvant chemotherapy group and 401 (88%) patients in the chemoradiotherapy group participated in HRQoL collection, of whom 369 (92%) and 369 (91%) completed a questionnaire at baseline (appendix p 70). Mean QLQ-C30 global health status and quality of life scores were worse in the adjuvant chemotherapy group versus the chemoradiotherapy only group for 3–6 months after completion of chemoradiotherapy; however, mean status and score were similar between the groups from months 12 to 36 (appendix pp 71, 74).

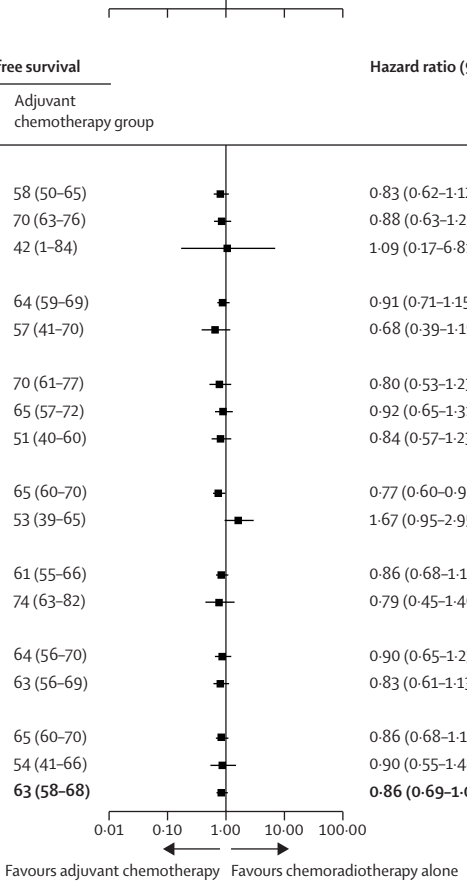
284 (61%) of 463 patients in the adjuvant chemotherapy group and 252 (55%) of 456 patients in the chemoradiotherapy only group had RECIST 1.1 measurable disease at baseline. 150 (53%) of 284 patients in the adjuvant chemotherapy group had a complete response and 77 (27%) had a partial response. 124 (49%) of 252 patients in the chemoradiotherapy only group had a complete response and 68 (27%) had a partial response (p=0·55). 244 (53%) of 463 patients in the adjuvant chemotherapy group and 223 (49%) of 456 in the

A

	Events/total		5-year overall survival		Hazard ratio (95% CI)	$p_{interaction}$
	Chemoradiotherapy only group	Adjuvant chemotherapy group	Chemoradiotherapy only group	Adjuvant chemotherapy group		
Pelvic or common iliac nodal involvement, or both						0·57
Yes	70/221	65/224	65 (57–71)	67 (59–73)	0·91 (0·65–1·27)	
No	51/225	42/231	76 (70–82)	78 (71–83)	0·84 (0·56–1·26)	
Unknown	2/10	2/8	90 (47–99)	40 (1–83)	4·32 (0·39–47·75)	
Requirement for EFRT						0·17
No	99/397	95/404	74 (69–78)	72 (67–77)	0·98 (0·74–1·30)	
Yes	24/59	14/59	53 (38–66)	69 (52–81)	0·60 (0·31–1·17)	
FIGO 2008 stage						0·38
Stage IB1 and node positive, stage IB2, or stage IIA	31/152	33/154	79 (71–85)	75 (66–82)	1·09 (0·67–1·78)	
Stage IIB	46/196	39/197	74 (66–80)	76 (68–82)	0·93 (0·61–1·43)	
Stage IIIB or stage IVA	46/108	37/112	55 (45–65)	62 (51–71)	0·71 (0·46–1·09)	
Age (years)						0·019
<60	109/390	86/393	70 (65–75)	74 (69–79)	0·79 (0·59–1·05)	
≥60	14/66	23/70	77 (64–86)	60 (45–72)	1·89 (0·97–3·68)	
Country						0·99
USA and Canada	102/366	88/373	70 (64–75)	71 (65–76)	0·88 (0·66–1·17)	
Australia and New Zealand	21/84	19/81	75 (64–83)	77 (66–85)	0·91 (0·49–1·69)	
Smoking						0·88
Never smoked	60/237	49/224	74 (67–79)	74 (67–80)	0·92 (0·63–1·34)	
Current or former smoker, or unknown	63/219	60/239	69 (61–75)	70 (63–76)	0·88 (0·62–1·25)	
Tumour histology (post hoc)						0·98
Squamous or adenosquamous cell carcinoma	102/377	91/395	71 (66–76)	72 (66–77)	0·90 (0·68–1·20)	
Adenocarcinoma	21/79	18/68	71 (58–81)	72 (59–82)	0·87 (0·46–1·64)	
Overall	**123/456**	**109/463**	**71 (66–75)**	**72 (67–76)**	**0·90 (0·70–1·17)**	

B

	Events/total		5-year progression-free survival		Hazard ratio (95% CI)	$p_{interaction}$
	Chemoradiotherapy only group	Adjuvant chemotherapy group	Chemoradiotherapy only group	Adjuvant chemotherapy group		
Pelvic or common iliac nodal involvement, or both						0·90
Yes	93/221	84/224	56 (49–63)	58 (50–65)	0·83 (0·62–1·12)	
No	72/225	65/231	66 (59–73)	70 (63–76)	0·88 (0·63–1·23)	
Unknown	3/10	2/8	70 (33–89)	42 (1–84)	1·09 (0·17–6·81)	
Requirement for EFRT						0·32
No	138/397	130/404	64 (59–69)	64 (59–69)	0·91 (0·71–1·15)	
Yes	30/59	21/59	45 (31–58)	57 (41–70)	0·68 (0·39–1·19)	
FIGO 2008 stage						0·87
Stage IB1 and node positive, stage IB2, or stage IIA	46/152	40/154	70 (61–76)	70 (61–77)	0·80 (0·53–1·23)	
Stage IIB	68/196	60/197	64 (57–71)	65 (57–72)	0·92 (0·65–1·31)	
Stage IIIB or stage IVA	54/108	51/112	45 (35–55)	51 (40–60)	0·84 (0·57–1·23)	
Age (years)						0·015
<60	148/390	121/393	61 (56–66)	65 (60–70)	0·77 (0·60–0·98)	
≥60	20/66	30/70	66 (51–77)	53 (39–65)	1·67 (0·95–2·95)	
Country						0·96
USA and Canada	142/366	127/373	59 (53–64)	61 (55–66)	0·86 (0·68–1·10)	
Australia and New Zealand	26/84	22/81	68 (57–77)	74 (63–82)	0·79 (0·45–1·40)	
Smoking						0·77
Never smoked	82/237	71/224	64 (57–70)	64 (56–70)	0·90 (0·65–1·23)	
Current or former smoker, or unknown	86/219	80/239	59 (51–65)	63 (56–69)	0·83 (0·61–1·13)	
Tumour histology (post hoc)						0·94
Squamous or adenosquamous cell carcinoma	135/377	122/395	63 (58–68)	65 (60–70)	0·86 (0·68–1·10)	
Adenocarcinoma	33/79	29/68	53 (40–65)	54 (41–66)	0·90 (0·55–1·48)	
Overall	**168/456**	**151/463**	**62 (57–66)**	**63 (58–68)**	**0·86 (0·69–1·08)**	



chemoradiotherapy only group were assessable for PET response according to PERCIST version 1.1. 138 (57%) of 244 patients in the adjuvant chemotherapy group versus 111 (50%) of 223 in the chemoradiotherapy only group had a complete metabolic response on PET or PET and CT 4 months or longer after completing chemoradiotherapy (p=0·14). A complete metabolic response on PET or PET and CT was associated with improved 5-year overall survival (HR 0·22 [95% CI 0·14–0·33]; p<0·0001) and 5-year progression-free survival (0·24 [0·17–0·33]; p<0·0001).

Discussion

The planned addition of four cycles of paclitaxel plus carboplatin following chemoradiotherapy with cisplatin for locally advanced cervical cancer did not improve overall survival or progression-free survival, but did increase the number of adverse events and diminish patient-reported health and quality of life during and up to 6 months after treatment. The survival results are somewhat surprising given the suggestive evidence for adjuvant cytotoxic therapy in this same patient population in previous trials.[6,10,23] This academic study, with its large sample size, mature follow-up, and multi-national accrual, provides opportunities to generate hypotheses for the results seen.

Despite the use of standard cisplatin-based chemoradiotherapy, treatment failures still occur. This led to the design of trials aiming to improve on chemoradiotherapy, which were largely focused on adding cytotoxic or novel drugs to chemoradiotherapy, and, since 2010, immune checkpoint inhibitors.[14–18] Of the trials with novels drugs reported to date, tirapazamine moved into a randomised phase 3 trial, but did not improve progression-free survival or overall survival.[19] Additionally, a presentation at the 2022 IGCS Annual Global Meeting indicated that adding adjuvant durvalumab to chemoradiotherapy did not improve progression-free survival.[20]

The rationale for adjuvant chemotherapy following chemoradiotherapy has its proof of concept in two of the original positive trials that lead to the US National Cancer Institute alert. RTOG 90-01[5] used one additional cycle of cisplatin and fluorouracil following radiotherapy, and the Gynecological Oncology Group (GOG) protocol 109[21] used two additional cycles of cisplatin and fluorouracil following radiotherapy after radical hysterectomy.[5,21] Subsequently, the trial by Dueñas-González and colleagues[9] evaluating the addition of gemcitabine to chemoradiotherapy followed by two additional cycles of cisplatin and gemcitabine showed improved progression-free survival, but the abridged follow-up time of 3 years prohibited any robust conclusion about the effect on overall survival. Our findings did not show a similar improvement in progression-free survival or overall survival to those reported by Dueñas-González and colleagues,[9] despite a larger sample size and 5 years of follow-up. Our results are consistent with a 2022 meta-analysis,[22] which included two randomised trials and eight matched case-control and retrospective studies. Both this meta-analysis and one done earlier did not find a survival benefit but showed increased toxicity with the addition of adjuvant chemotherapy.[22,23] Our results are also consistent with the similarly designed ACTLACC trial,[24] which used three cycles of adjuvant carboplatin and paclitaxel, but closed after interim analysis due to futility. Although we used carboplatin plus paclitaxel adjuvant chemotherapy, rather than cisplatin plus gemcitabine, this difference probably does not account for the different outcomes given that platinum plus paclitaxel is recommended as the most active regimen to treat metastatic disease.[25] The study by Dueñas-González and colleagues[9] also added additional gemcitabine chemotherapy to cisplatin during the standard chemoradiotherapy. However, a subsequent trial testing the effect of adding gemcitabine only during chemoradiotherapy was closed early due to futility.[16]

The OUTBACK trial had some limitations. First is the poor compliance with planned adjuvant chemotherapy, with 102 (22%) of 463 patients in the adjuvant chemotherapy group not receiving any planned adjuvant treatment. This is a substantial enough fraction to effect outcomes; as a result the sample was increased after the trial started to account for this. A similar non-compliance rate also occurred in previous trials of adjuvant chemotherapy (eg, 14% in the study by Dueñas-González and colleagues,[9] 32% in the RTOG 90-01 trial,[5] 23% in the ACTLACC trial,[24] and 29% in the GOG109 trial[21]). Patient preference was the most common reason for not commencing planned adjuvant chemotherapy, which probably resulted from residual adverse events after standard chemoradiotherapy, particularly fatigue. Before the primary analysis, we identified an association between older age (>60 years), non-White race, and not completing the initial standard chemoradiotherapy, with not proceeding to any adjuvant therapy.[13] This association suggests a subset of patients in this trial with additional susceptibilities that affected their ability to commence assigned adjuvant therapy, which might have included relatively young patients facing financial and social pressures, and those with concerns about alopecia. The poor compliance with adjuvant therapy in multiple trials, including OUTBACK, also raises the hypothesis of whether future trials of adjuvant systemic therapy should randomly assign patients to treatment after completion of standard chemoradiotherapy. However, our sensitivity analysis did not find clinically meaningful

Figure 4: **Subgroup analyses of 5-year overall survival (A) and progression-free survival (B)**
EFRT=extended field radiotherapy. FIGO=International Federation of Gynecology and Obstetrics. HR=hazard ratio.

	Chemoradiotherapy only group (n=453)				Adjuvant chemotherapy group (n=361)				p value*
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
Abdominal pain	179 (40%)	16 (4%)	0	0	175 (48%)	19 (5%)	0	0	0·0086
Alanine aminotransferase increased	77 (17%)	3 (1%)	1 (<1%)	0	98 (27%)	2 (1%)	0	0	0·0020
Alopecia	40 (9%)	0	0	0	284 (79%)	1 (<1%)	0	0	<0·0001
Anaemia	259 (57%)	34 (8%)	1 (<1%)	0	238 (66%)	66 (18%)	0	0	<0·0001
Anorexia	138 (30%)	5 (1%)	0	0	129 (36%)	2 (1%)	0	0	0·21
Anxiety	62 (14%)	0	1 (<1%)	0	76 (21%)	1 (<1%)	0	0	0·020
Arthralgia	40 (9%)	1 (<1%)	0	0	79 (22%)	1 (<1%)	0	0	<0·0001
Aspartate aminotransferase increased	46 (10%)	2 (<1%)	1 (<1%)	0	84 (23%)	2 (1%)	0	0	<0·0001
Back pain	111 (25%)	5 (1%)	0	0	96 (27%)	4 (1%)	0	0	0·79
Constipation	204 (45%)	1 (<1%)	1 (<1%)	0	192 (53%)	1 (<1%)	0	0	0·067
Creatinine increased	57 (13%)	4 (1%)	1 (<1%)	0	59 (16%)	3 (1%)	0	0	0·30
Cystitis non-infective	102 (23%)	6 (1%)	0	0	95 (26%)	6 (2%)	0	0	0·40
Dehydration	40 (9%)	14 (3%)	0	0	50 (14%)	9 (2%)	0	0	0·071
Depression	57 (13%)	1 (<1%)	0	0	70 (19%)	2 (1%)	1 (<1%)	0	0·012
Dermatitis radiation	64 (14%)	0	1 (<1%)	0	64 (18%)	1 (<1%)	0	0	0·37
Diarrhoea	323 (71%)	21 (5%)	0	0	277 (77%)	21 (6%)	0	0	0·064
Dizziness	53 (12%)	1 (<1%)	0	0	65 (18%)	2 (1%)	0	0	0·028
Dysgeusia	58 (13%)	0	0	0	60 (17%)	0	0	0	0·12
Dyspnoea	58 (13%)	3 (1%)	0	1 (<1%)	78 (22%)	3 (1%)	0	0	0·0037
Dysuria	54 (12%)	0	0	0	58 (16%)	0	0	0	0·088
Oedema limbs	49 (11%)	2 (<1%)	0	0	52 (14%)	0	0	0	0·14
Fatigue	361 (80%)	8 (2%)	0	0	327 (91%)	9 (2%)	0	0	<0·0001
Febrile neutropenia	0	8 (2%)	1 (<1%)	0	0	9 (2%)	0	0	0·63
Female genital tract fistula	10 (2%)	6 (1%)	2 (<1%)	0	6 (2%)	5 (1%)	0	0	0·78
Fever	32 (7%)	0	0	0	54 (15%)	3 (1%)	0	0	0·00017
Headache	94 (21%)	1 (<1%)	0	0	103 (29%)	0	0	0	0·025
Hearing impaired	47 (10%)	0	0	0	51 (14%)	4 (1%)	0	0	0·019
Haemorrhage bladder	76 (17%)	7 (2%)	0	0	54 (15%)	5 (1%)	0	0	0·76
Haemorrhage rectum	62 (14%)	2 (<1%)	0	0	65 (18%)	1 (<1%)	0	0	0·23
Hot flashes	106 (23%)	0	0	0	115 (32%)	2 (1%)	0	0	0·0066
Hyperglycaemia	41 (9%)	8 (2%)	3 (1%)	0	58 (16%)	7 (2%)	3 (1%)	0	0·0087
Hypertension	28 (6%)	17 (4%)	0	0	45 (12%)	12 (3%)	0	0	0·0077
Hypoalbuminaemia	54 (12%)	1 (<1%)	0	0	67 (19%)	2 (1%)	0	0	0·021
Hypocalcaemia	56 (12%)	3 (1%)	0	0	58 (16%)	1 (<1%)	0	0	0·24
Hypokalaemia	69 (15%)	11 (2%)	4 (1%)	0	65 (18%)	17 (5%)	0	0	0·30
Hypomagnesaemia	100 (22%)	2 (<1%)	2 (<1%)	0	111 (31%)	6 (2%)	0	0	0·0096
Hyponatraemia	62 (14%)	3 (1%)	0	0	46 (13%)	12 (3%)	0	0	0·019
Insomnia	96 (21%)	1 (<1%)	0	0	104 (29%)	0	0	0	0·030
Kidney infection	1 (<1%)	5 (1%)	0	0	0	3 (1%)	0	0	0·62
Lymphocyte count decreased	114 (25%)	167 (37%)	41 (9%)	0	77 (21%)	179 (50%)	32 (9%)	0	0·0012
Menopause	8 (2%)	12 (3%)	0	0	5 (1%)	16 (4%)	0	0	0·35
Myalgia	52 (11%)	0	0	0	141 (39%)	3 (1%)	0	0	<0·0001
Nausea	335 (74%)	14 (3%)	0	0	296 (82%)	11 (3%)	0	0	0·016
Neutrophil count decreased	84 (19%)	27 (6%)	7 (2%)	0	117 (32%)	61 (17%)	10 (3%)	0	<0·0001
Pain	41 (9%)	3 (1%)	0	0	44 (12%)	3 (1%)	0	0	0·33
Pain in extremity	94 (21%)	3 (1%)	0	0	123 (34%)	2 (1%)	0	0	0·00011
Pelvic pain	146 (32%)	11 (2%)	0	0	138 (38%)	8 (2%)	0	0	0·20
Peripheral motor neuropathy	19 (4%)	0	0	0	72 (20%)	4 (1%)	0	0	<0·0001
Peripheral sensory neuropathy	130 (29%)	1 (<1%)	0	0	271 (75%)	16 (4%)	0	0	<0·0001
Platelet count decreased	140 (31%)	3 (1%)	2 (<1%)	0	192 (53%)	14 (4%)	2 (1%)	0	<0·0001

(Table 3 continues on next page)

	Chemoradiotherapy only group (n=453)				Adjuvant chemotherapy group (n=361)				p value*
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
(Continued from previous page)									
Premature menopause	..	11 (2%)	0	0	1 (<1%)	17 (5%)	0	0	0·11
Proctitis	49 (11%)	2 (<1%)	0	0	34 (9%)	0	0	0	0·36
Sepsis	0	1 (<1%)	8 (2%)	0	0	1 (<1%)	3 (1%)	0	0·32
Small intestinal obstruction	1 (<1%)	5 (1%)	0	0	1 (<1%)	8 (2%)	1 (<1%)	0	0·31
Syncope	2 (<1%)	5 (1%)	0	0	4 (1%)	5 (1%)	0	0	0·51
Thrombosis, thrombus, or embolism	19 (4%)	7 (2%)	0	0	18 (5%)	5 (1%)	2 (1%)	0	0·78
Tinnitus	84 (19%)	0	0	0	87 (24%)	1 (<1%)	0	0	0·079
Urinary frequency	92 (20%)	0	0	0	84 (23%)	0	0	0	0·31
Urinary incontinence	69 (15%)	0	0	0	68 (19%)	1 (<1%)	0	0	0·20
Urinary tract infection	63 (14%)	17 (4%)	1 (<1%)	0	51 (14%)	17 (5%)	0	0	0·87
Urinary tract obstruction	1 (<1%)	10 (2%)	0	0	1 (<1%)	8 (2%)	0	0	0·99
Urinary tract pain	45 (10%)	1 (<1%)	0	0	56 (16%)	0	0	0	0·039
Urinary urgency	40 (9%)	0	0	0	44 (12%)	0	0	0	0·12
Vaginal discharge	167 (37%)	0	0	0	147 (41%)	0	0	0	0·26
Vaginal dryness	56 (12%)	0	0	0	53 (15%)	1 (<1%)	0	0	0·33
Vaginal haemorrhage	164 (36%)	8 (2%)	1 (<1%)	0	133 (37%)	7 (2%)	1 (<1%)	0	0·95
Vaginal pain	65 (14%)	3 (1%)	0	0	47 (13%)	2 (1%)	0	0	0·84
Vaginal stricture	57 (13%)	10 (2%)	0	0	39 (11%)	5 (1%)	0	0	0·49
Vomiting	165 (36%)	11 (2%)	0	0	166 (46%)	15 (4%)	0	0	0·0042
Weight loss	46 (10%)	6 (1%)	0	0	52 (14%)	6 (2%)	0	0	0·16
White blood cell decreased	80 (18%)	16 (4%)	3 (1%)	0	74 (20%)	31 (9%)	7 (2%)	0	0·00066

Data are n (%). Data are for adverse events grade 1–2 occurring in at least 10% of patients and grade 3–5 events in at least 1% of patients. *χ^2 test comparing none versus mild (grade 1–2) versus severe (grade 3–5) between the treatment groups. Data are for adverse events grade 1–2 occurring in at least 10% of patients and all grade 3–5 events are in the appendix (pp 59–68).

Table 3: **Summary of adverse events, safety population**

improvements in survival, even in the subset of patients who completed initial chemoradiotherapy, which was the group most likely to complete assigned adjuvant therapy. The ongoing INTERLACE trial (NCT01566240) aims to answer the question about whether giving a short course of once-a-week chemotherapy before chemoradiotherapy could improve patient outcomes and be more deliverable

Second, we used four-field radiotherapy and brachytherapy to help generalise radiation availability for this global trial. Athough clinical practise in some high-income countries is now moving to more sophisticated radiotherapy planning, such as intensity-modulated radiation therapy (IMRT), the type of radiotherapy used in the OUTBACK trial is still widely used and accepted standard treatment in the 2023 National Comprehensive Cancer Network guidelines. Only 77% of patients in this trial completed planned chemoradiotherapy (all five doses of cisplatin), irrespective of allocated treatment. Radiotherapy was completed within 8 weeks in approximately 65% of patients with a mean dose of 45·6 Gy, indicating room for improvement. Impressively, brachytherapy was given to 95% of patients in the chemoradiotherapy only group and 94% in the adjuvant chemotherapy group. By comparison, in the study by Dueñas-González and colleagues,[9] the mean external beam dose was 50·4 Gy with a median duration of overall radiation of 49 days in the adjuvant chemotherapy group and 45 days in the control group. Because adherence to radiotherapy was similar between the adjuvant chemotherapy and chemoradiotherapy only group these differences are unlikely to have affected the primary endpoint of the OUTBACK trial. Additionally, 3-year progression-free survival rates were the same in the chemoradiotherapy only group of our study and in the control group of the study by Dueñas-González and colleagues[9] suggesting that the differences in radiation adherence do not explain the discordant findings between the two trials.

Emerging data suggest that improved imaging and radiotherapy delivery might identify tumours at increased risk for treatment failure and that might benefit from additional therapy. The EMBRACE I multicentre, prospective cohort study[26] confirmed the benefit of image-guided brachytherapy for locally advanced cervical cancer, which was given to approximately a third of patients in the OUTBACK trial. In subset analysis of EMBRACE I, clinical and pathological factors associated with local treatment failure, included having any positive common iliac lymph nodes (but negative para-aortic

nodes). Use of elective para-aortic radiation in this higher risk group decreased para-aortic treatment failures.[26] The ongoing EMBRACE II study (NCT03617133) is evaluating IMRT and volumetric modulated arc therapy (VMAT) for elective para-aortic radiotherapy and integrating radiation boost for cervical cancer to improve local control and decrease distant failures. An important question is whether there is more to be gained by adding more drugs to chemoradiotherapy, or instead ensuring that excellent quality primary chemoradiotherapy is available to all women with cervical cancer. Furthermore, new less-toxic radiation techniques could make testing the benefit of giving additional systemic therapies more feasible.

Like our study, the EMBRACE I trial[26] recruited a population of patients that was felt to be at high risk for recurrence, but ultimately was not found to be particularly high risk. A 2022 exploratory analysis of the OUTBACK trial[27] re-evaluated outcomes when the tumours were restaged on the basis of FIGO 2018 staging criteria, which now incorporates nodal status. In this analysis, the FIGO 2008 stage III and IV (T3 and T4 lesions) had a 5-year progression-free survival rate of 48% and 5-year overall survival rate of 58%.[27] These more advanced tumours do appear to be at the highest risk of recurrence, and patients with these tumours might benefit from any addition to chemoradiotherapy. However, in our study and others,[24] those with higher stage tumours or node-positive disease received no benefit from the addition of adjuvant chemotherapy.

Finally, in the past, when no effective interventions were available after systemic chemotherapy with or without bevacizumab for advanced or recurrent disease, overall survival was the best endpoint because no interventions were expected to confound the results.[28] With the approval of immune checkpoint inhibitors used concomitantly with systemic chemotherapy with or without bevacizumab for advanced or metastatic disease and approvals for monotherapy use for second-line treatment of metastatic disease, the expected overall survival has improved and these drugs could confound outcomes depending on use and availability.[29,30] With new drugs in the pipeline, one has to consider whether progression-free survival might be an appropriate primary endpoint in lieu of or in combination with overall survival for future studies. However, these newer therapies are unlikely to have confounded overall survival in OUTBACK because they were not available to patients in study sites during the study timeframe.

Future studies should focus on participants with high risk disease who have the most to gain from additional treatment, and avoid over-treating patients who do well with standard of care treatments. Subsequent translational research from the OUTBACK trial will be important to improve understanding of which groups of patients are most at risk of disease recurrence. Furthermore, benchmarks for studies moving forward will have to account for the stage migration that occurred with the FIGO 2008 to FIGO 2018 staging transition. For example, in a previous OUTBACK analysis the 5-year progression-free survival rate for FIGO 2008 stage III and IVA disease was 48%, but the 5-year overall survival rate for FIGO 2018 stage III and IVA disease was 56%.[27] The OUTBACK re-analysis provides helpful information for benchmarking control group expectations for future studies using the 2018 staging system.

In conclusion, adjuvant chemotherapy with four cycles of carboplatin and paclitaxel did not improve overall survival or progression-free survival after chemoradiotherapy with once-a-week cisplatin for locally advanced cervical cancer. Use of adjuvant carboplatin and paclitaxel following chemoradiotherapy should not be used in this disease setting. Future studies should select participants with high-risk disease and overcome barriers to adherence with treatment.

Contributors

LRM, KNM, VG, KN, MTK, DR, MQ, MRS, and BJM conceptualised the study. LRM, EHB, VG, KN, MTK, NB, YCL, and KD curated and verified the study data. EHB and VG did the formal analysis. LRM, KNM, KN, DR, MQ, VG, and MRS acquired the funding. LRM and KNM wrote the original draft of the manuscript. LRM, KNM, MQ, DR, MRS, BJM, DKG, WSJ, VG, and EHB refined the methods. LRM, KNM, NB, and KD were project administrators. EHB and VG did the statistical analysis. LRM, KNM, MQ, DR, MRS, BJM, KN, MTK, and VG supervised the study. LRM, KNM, MRS, BJM, EHB, VG, KN, and SVD validated the data. LRM, EHB, YCL, and KD visualised the data. LRM, KNM, EHB, VG, KN, MTK, NB, YCL, KD, AWF, WSJ, DKG, PK, SB, JST, WKH, CAM, MB, AS, TEL, IJB, CHH, SVD, MQ, DR, BJM, and MRS participated in the investigation, collected resources, and reviewed and edited the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

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Data sharing

Deidentified study data are available for sharing. To request access to the deidentified study data, please contact the corresponding author. Requests will be reviewed by the Trial Management Committee and written applications from investigators with the academic capability and credibility to undertake the work proposed will be considered. The scientific merit of the proposal, including the appropriate methods, analysis, and publication plan will be assessed. Consideration will be taken of any overlap with analyses already undertaken or planned to be undertaken by the study team. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

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References

1 Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24:** 2137–50.

2 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

3 Spayne J, Ackerman I, Milosevic M, Seidenfeld A, Covens A, Paszat L. Invasive cervical cancer: a failure of screening. *Eur J Public Health* 2008; **18:** 162–65.

4 Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999; **340:** 1154–61.

5 Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; **340:** 1137–43.

6 Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; **340:** 1144–53.

7 Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008; **26:** 5802–12.

8 Narayan K, Fisher RJ, Bernshaw D, Shakher R, Hicks RJ. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. *Int J Gynecol Cancer* 2009; **19:** 912–18.

9 Dueñas-González A, Zarbá JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011; **29:** 1678–85.

10 Nasioudis D, Smith AJ, Latif N. Adjuvant chemotherapy for patients with locally advanced cervical carcinoma receiving definitive chemoradiation: utilization and outcomes before the OUTBACK trial. 2022 Society of Gynaecological Oncology Annual Meeting; March 18–21, 2022 (abstr 361).

11 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

12 Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. *Biometrika* 1993; **80:** 557–72.

13 Mileshkin L, Barnes E, Moore K, et al. Disparities starting adjuvant chemotherapy for locally advanced cervix cancer in the international, academic, randomised, phase 3 OUTBACK trial (ANZGOG 0902, RTOG 1174, NRG 0274). ESMO Congress; Sept 16–21, 2021 (abstr 1923).

14 Duska LR, Scalici JM, Temkin SM, et al. Results of an early safety analysis of a study of the combination of pembrolizumab and pelvic chemoradiation in locally advanced cervical cancer. *Cancer* 2020; **126:** 4948–56.

15 Rose PG, Sill MW, McMeekin DS, et al. A phase I study of concurrent weekly topotecan and cisplatin chemotherapy with whole pelvic radiation therapy in locally advanced cervical cancer: a gynecologic oncology group study. *Gynecol Oncol* 2012; **125:** 158–62.

16 Wang CC, Chou HH, Yang LY, et al. A randomized trial comparing concurrent chemoradiotherapy with single-agent cisplatin versus cisplatin plus gemcitabine in patients with advanced cervical cancer: an Asian Gynecologic Oncology Group study. *Gynecol Oncol* 2015; **137:** 462–67.

17 Rischin D, Narayan K, Oza AM, et al. Phase 1 study of tirapazamine in combination with radiation and weekly cisplatin in patients with locally advanced cervical cancer. *Int J Gynecol Cancer* 2010; **20:** 827–33.

18 Kunos CA, Sherertz TM. Long-term disease control with triapine based radiochemotherapy for patients with stage IB2-IIIB cervical cancer. *Front Oncol* 2014; **4:** 184.

19 DiSilvestro PA, Ali S, Craighead PS, et al. Phase III randomized trial of weekly cisplatin and irradiation versus cisplatin and tirapazamine and irradiation in stages IB2, IIA, IIB, IIIB, and IVA cervical carcinoma limited to the pelvis: a Gynecologic Oncology Group study. *J Clin Oncol* 2014; **32:** 458–64.

20 Monk BJ, Toita T, Wu X, Carlos J. Durvalumab, in combination with and following chemoradiotherapy, in locally advanced cervical cancer: results from the phase 3 international, randomized, double-blind, placebo-controlled CALLA trial. IGCS Annual Global Meeting; Sept 29 to Oct 1, 2022 (abstr Plenary 01).

21 Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000; **18:** 1606–13.

22 Horeweg N, Mittal P, Gradowska PL, Boere I, Nout RA, Chopra S. A systematic review and meta-analysis of adjuvant chemotherapy after chemoradiation for locally advanced cervical cancer. *Crit Rev Oncol Hematol* 2022; **172:** 103638.

23 Tangjitgamol S, Katanyoo K, Laopaiboon M, Lumbiganon P, Manusirivithaya S, Supawattanabodee B. Adjuvant chemotherapy after concurrent chemoradiation for locally advanced cervical cancer. *Cochrane Database Syst Rev* 2014; **12:** CD010401.

24 Tangjitgamol S, Tharavichitkul E, Tovanabutra C, et al. A randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients: ACTLACC trial. *J Gynecol Oncol* 2019; **30:** e82.

25 Kitagawa R, Katsumata N, Shibata T, et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. *J Clin Oncol* 2015; **33:** 2129–35.

26 Peters M, de Leeuw AAC, Nomden CN, et al. Risk factors for nodal failure after radiochemotherapy and image guided brachytherapy in locally advanced cervical cancer: an EMBRACE analysis. *Radiother Oncol* 2021; **163:** 150–58.

27 Mileshkin L, Moore KN, Barnes EH, et al. Staging locally advanced cervical cancer with FIGO 2018 versus FIGO 2008: impact on overall survival and progression-free survival in the OUTBACK trial (ANZGOG 0902, RTOG 1174, NRG 0724). *Proc Am Soc Clin Oncol* 2022; **40:** 5531 (abstr).

28 Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017; **390:** 1654–63.

29 Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021; **385:** 1856–67.

30 Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. *N Engl J Med* 2022; **386:** 544–55.