Are we making progress in curing advanced cervical cancer—again?

Jacob Christian Lindegaard ,[1] Primoz Petric,[2] Li-Tee Tan,[3] Peter Hoskin,[4] Maximilian P Schmid,[5] Ina Jürgenliemk-Schulz,[6] Umesh Mahantshetty,[7] Christian Kirisits,[5] Richard Pötter[5]

For numbered affiliations see end of article.

Correspondence to
Dr Jacob Christian Lindegaard, Department of Oncology, Aarhus University Hospital, 8200 Aarhus, Denmark; jacob.lindegaard@auh.rm.dk

Received 9 April 2024
Accepted 25 June 2024

To cite: Lindegaard JC, Petric P, Tan L-T, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-005572

ABSTRACT

Major improvements in radiotherapy over the past two decades in the definitive treatment of locally advanced cervical cancer have significantly improved loco-regional control and survival, whereas little progress has been made with chemotherapy since the implementation of concomitant cisplatin 25 years ago. However, the randomized study INTERLACE (A phase III multicenter trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer) of neoadjuvant chemotherapy presented recently, has shown significant improvement in survival with the use of six cycles of weekly carboplatin and paclitaxel. Although INTERLACE is yet to be published, neoadjuvant chemotherapy is already being advocated as the new standard, and studies are being designed with neoadjuvant chemotherapy followed by chemoradiation and brachytherapy as the standard arm. It is noteworthy that INTERLACE was initiated before the improvements in radiotherapy mentioned above were broadly implemented. The survival rate in the standard arm of INTERLACE was therefore inferior to the results obtained with the latest state-of-the-art external beam radiotherapy and image guided adaptive brachytherapy (EMBRACE, Magnetic Resonance Imaging (MRI)-Guided Brachytherapy in Locally Advanced Cervical Cancer). Moreover, patient selection impedes the comparison of INTERLACE with other studies as the patients included in INTERLACE were younger, had better performance status, and had less advanced disease than in other studies. Notably patients with involved para-aortic nodes were excluded. In this review, we discuss neoadjuvant chemotherapy in the frame of the EMBRACE studies and show how the impact of modern radiotherapy and patient selection affects the interpretation of the results of INTERLACE. This has led us to conclude that neoadjuvant chemotherapy is not needed for the majority of patients with cervical cancer treated with definitive modern radiotherapy, and may cause harm. However, it is possible that short course neoadjuvant chemotherapy may benefit a minor subgroup of patients who need to be identified. Comprehensive understanding, including cost utility analyses, are needed to draw conclusions regarding the potential benefit of neoadjuvant chemotherapy in low and middle income countries with limited access to modern radiotherapy.

During the past 20 years, there have been major improvements in definitive radiotherapy for cervical cancer. Implementation of magnetic resonance imaging based, image guided adaptive brachytherapy have resulted in unprecedented local control rates of >90% across all stages, while improving pelvic control and survival rates by about 10% without increasing toxicity.[1–4] Compared with three-dimensional conformal techniques, the implementation of intensity modulated radiotherapy, volumetric arc radiotherapy, and advanced treatment planning techniques have allowed more precise delivery of external beam irradiation and, in particular, applying higher doses to involved lymph nodes while decreasing the irradiated volume of normal tissue, which should further improve survival and decrease late effects.[2]

In contrast, there has been little progress with the chemotherapeutic aspects of treatment since randomized studies[5] led to the implementation of concomitant cisplatin with radiotherapy at the turn of the century. Certainly, the study by Dueñas-Gonzáles et al[6] comparing concomitant cisplatin with concomitant cisplatin and gemcitabine followed by adjuvant treatment with the same doublet (Table 1) did show significant improvement in progression free survival. However, for many reasons highlighted in the editorial 'Are we making progress in curing advanced cervical cancer' by Thomas from 2011,[7] the cisplatin and gemcitabine combination was never widely adopted, and concomitant cisplatin has remained standard of care for chemoradiation in locally advanced cervical cancer.[8]

On this backdrop, it is understandable that a breakthrough in medical oncology would be highly appreciated. With the presentation of the INTERLACE study at ESMO 2023[9] showing a significant improvement in both progression free survival and overall survival with the use of a short course of neoadjuvant carboplatin and paclitaxel (Table 1), pressure is rising to adopt neoadjuvant chemotherapy as the new standard to be combined with definitive radiotherapy.[10] The full publication of the INTERLACE study is still pending; however, based on the available information, the encouraging results of this study are not consistent with existing evidence on the clinical outcome of advanced image guided definitive radiotherapy in cervical cancer,[2–4 8] raising the justifiable question of whether the demonstrated benefit of neoadjuvant chemotherapy in INTERLACE is only valid in comparison with less than optimal radiotherapy.

Table 1 Comparison of patient and treatment characteristics in the study of Duenas-Gonzales et al,[6] INTERLACE,[9] and EMBRACE-I[3] in relation to progression free survival and overall survival

	Dueñas-Gonzáles		INTERLACE		EMBRACE-I
	CRT	CRT+ACT	CRT	NACT-CRT	CRT
No of patients	256	259	250	250	1341
Age (years), median	46	45	46	46	49
Performance status (WHO) >0 (%)	Unknown	Unknown	12	14	28
$FIGO_{2009}$ III–IVA* (%)	39	38	14	13	20
N1 (pelvic)† (%)	NA	NA	43	42	43
N2 (para-aortic)† (%)	Excluded		Excluded		8
EBRT dose (Gy), median and range	50.4		40–50.4		45–50
Nodal EBRT boost	Not given		Unknown		Yes
Elective para-aortic EBRT	Not given		Unknown		Yes
BT technique	IC		IC		IC or IC/IS
BT target	Point A		Point A (70%)		CTV_{HR}
EBRT+BT dose (Gy), range, minimum, median	80–85		>78 EQD2‡		90 EQD2
PFS 3 year (%)	65	74	72	75	72§
PFS 5 year (%)	62	71	64	73	68§
OS 3 year (%)	70	78	80	86	81
OS 5 year (%)	64	75	72	80	74

*Stage according to $FIGO_{2009}$[38] which in this context is equivalent to T stage in the American Joint Committee on Cancer Tumor, Node, Metastasis system.
†N stage according to the American Joint Committee on Cancer, Tumor, Node, Metastasis system[39]
‡Equivalent dose in 2 Gy fractions.
§Disease free survival (events were persistent/recurrent disease or death from any cause). In EMBRACE-I, disease free survival was used as a substitute for progression free survival.
ACT, adjuvant chemotherapy; BT, brachytherapy; CRT, concomitant chemotherapy and radiotherapy; CTV_{HR}, high risk clinical target volume; EBRT, external beam radiotherapy; EMBRACE-1, Magnetic Resonance Imaging (MRI)-Guided Brachytherapy in Locally Advanced Cervical Cancer trial; FIGO, International Federation of Gynecology and Obstetrics; IC, intracavitary; INTERLACE, A phase III multicenter trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer; IS, interstitial; NA, not available; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression free survival.

Previous attempts with neoadjuvant chemotherapy followed by definitive radiotherapy in locally advanced cervical have largely failed.[8] Recently, two randomized phase III studies on neoadjuvant carboplatin and paclitaxel administered before surgery in stage IB–IIB were also negative.[11 12] The combination of carboplatin and paclitaxel in the adjuvant setting after chemoradiation likewise showed no benefit in the OUTBACK (Cisplatin and Radiation Therapy With or Without Adjuvant Carboplatin and Paclitaxel in Patients With Locally Advanced Cervical Cancer) study.[13] In addition, platinum–paclitaxel based chemotherapy without bevacizumab or immunotherapy had moderate activity in recurrent, persistent, or metastatic disease.[14–17]

There are several issues in the INTERLACE study which raise concerns about the applicability of the results in the context of state-of-the art radiotherapy. Brachytherapy was by the intracavitary technique only and mainly point A based (70%), with no optimization to the actual tumor volume, which is substantially inferior to the current standard, as defined in the multidisciplinary European guidelines.[8] We do not yet have detailed information about the external beam radiotherapy technique in INTERLACE but in 59% of patients it was delivered by a three-dimensional conformal technique, which does not comply with current recommendations.[8] Nevertheless, the investigators stated in their presentation that the radiotherapy used in both arms of INTERLACE reflected best clinical practice.

The investigators also stated that overall survival in the standard arm was similar to that reported in the recent published literature. However, the INTERLACE cohort had fewer locally advanced primary tumors and less extensive nodal disease than, for instance, in EMBRACE-I (Table 1). Moreover, patients with involved para-aortic nodes were excluded. Notably, the relative improvement of progression free survival in INTERLACE mirrors the results of the study of Dueñas-Gonzáles et al in 2011,[6] which more or less was based on the same technique, dose, and fractionation of external beam radiotherapy and brachytherapy, but performed in patients in a more advanced stage (Table 1). Comparison with state-of-the-art radiotherapy, as for example in EMBRACE-I, is difficult mainly due to patient selection. However, by excluding patients with para-aortic nodes (N2 stage) and by calibrating the local tumor stage by the use of the T-score,[18] it was possible to create an EMBRACE cohort with at least a comparable T and N stage distribution as in INTERLACE (Table 2). When viewed against this more comparable cohort, it is

Table 2 Comparison of INTERLACE[9] with EMBRACE-I[4 18] based on patient selection of INTERLACE-like patients in EMBRACE-I by excluding patients with para-aortic nodes (N2) and with T stage calibration by using the T-score (ie, INTERLACE-like: N2=0 and T-score <11)

	INTERLACE		EMBRACE-I	
	CRT	NACT+CRT	INTERLACE-like CRT	Other CRT
No of patients	250	250	1141	177
Age (years) (median)	46	46	49	53
Performance status >0 (WHO) (%)	12	14	25	44
Comorbidity (%)	Unknown	Unknown	28	31
T3-T4 ($FIGO_{2009}$ III–IVA)* (%)	14	13	14	63
N1 (pelvic)* (%)	43	42	48	25
N2 (para-aortic)* (%)	0		0	57
EBRT dose (Gy) (range/median)	40–50.4		45	45
Nodal EBRT boost (%)	Unknown		32	57
Elective para-aortic EBRT (%)	Unknown		11	52
EBRT+BT dose (Gy) (minimum/median)	>78 EQD2		90 EQD2	88 EQD2
Completed five weekly cisplatin (%)	79	68	71	55
Total local/pelvic relapse (%)	16	16	12	18
Total distant relapse† (%)	20	12	16	33
Total relapse (%)	28	22	23	41
PFS 3 year (%)	72	75	76‡	56‡
PFS 5 year (%)	64	73	72‡	47‡
OS 3 year (%)	80	86	84	68
OS 5 year (%)	72	80	78	57

For this exercise, a cohort of 1318 patients from EMBRACE-I with complete information on disease stage was used.[4] Overall survival was available for both INTERLACE and EMBRACE-I, whereas disease free survival was used as a substitute in EMBRACE-1 to compare with progression free survival in INTERLACE.
*T and N stage distribution according to the American Joint Committee on Cancer, Tumor, Node, Metastasis system, V.9.[39]
†Including para-aortic relapse.
‡Disease free survival (events were persistent/recurrent disease or death from any cause).
BT, brachytherapy; CRT, concomitant chemotherapy and radiotherapy; EBRT, external beam radiotherapy; EMBRACE-1, Magnetic Resonance Imaging (MRI)-Guided Brachytherapy in Locally Advanced Cervical Cancer trial; EQD2, equivalent dose in 2 Gy fractions; FIGO, International Federation of Gynecology and Obstetrics; INTERLACE, A phase III multicenter trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression free survival.

obvious that the results obtained in the standard arm of INTERLACE were inferior to EMBRACE-I.[3] Thus neoadjuvant chemotherapy is merely compensating for suboptimal radiotherapy (Figure 1), which will be further evident with the imminent results of EMBRACE-II[2], entailing full integration of intensity modulated external beam radiotherapy, including simultaneous integrated nodal boost and risk adapted elective para-aortic irradiation as well as magnetic resonance image guided adaptive brachytherapy with combined intracavitary/interstitial implantation techniques.

From the relapse pattern, it appears that the effect of neoadjuvant chemotherapy on survival in INTERLACE likely is due to a reduction in systemic relapse from 20% to 12%, whereas neoadjuvant chemotherapy had no impact on overall loco-regional control (Table 2). From the phase II study preceding INTERLACE, a 70% response rate is expected from dose dense neoadjuvant chemotherapy, as used in INTERLACE.[19] The lack of impact of response to chemotherapy on loco-regional control is in line with the preclinical observation of volume regression and accelerated repopulation of clonogenic cells occurring simultaneously after a limited dose of radiotherapy,[20] which is likely to also be relevant for chemotherapy.[21] In addition, for the 30% of patients with no response to or progressive disease after neoadjuvant chemotherapy, the outlook for obtaining loco-regional control with radiotherapy is clearly diminished in a tumor environment with acquired resistance and an increased number of clonogenic cells.

A reduction in the event rate of total systemic/para-aortic relapse from 16% in the 'Interlike' cohort of EMBRACE-I to 12%, as reported for the neoadjuvant chemotherapy arm in INTERLACE (Table 2), will require that 25 patients receiving optimal radiotherapy are treated with neoadjuvant chemotherapy to prevent one systemic/para-aortic event, and that neoadjuvant chemotherapy is needlessly given to 96% of patients.[22] From the EMBRACE-I data, subgroups with a very low risk of recurrence (including systemic) have been identified where treatment de-escalation is even being considered. For this low risk group, the percentage of needless use of neoadjuvant chemotherapy will likely approach 100%. As we can assume

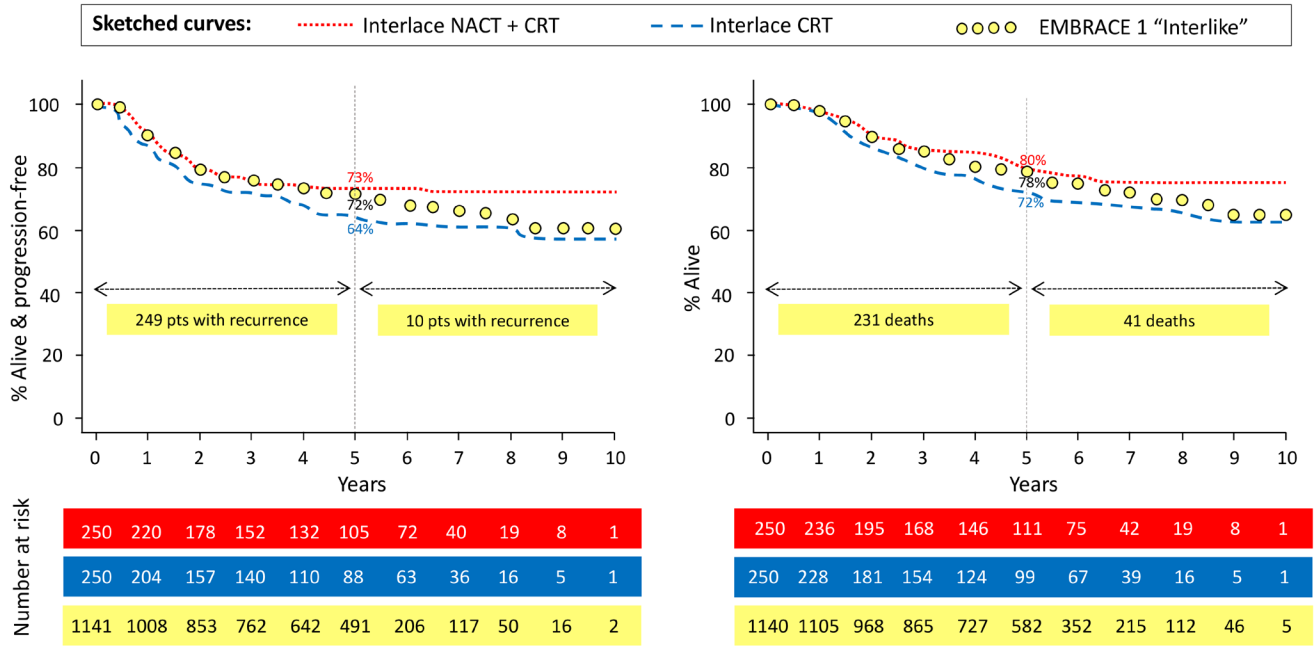

Figure 1 Progression free survival and overall survival in INTERLACE (a phase III multicenter trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer), reconstructed from the graphics presented at the 2023 ESMO congress. The reconstructed curves are not based on actual numeric data. Data points of the EMBRACE 1 (Magnetic Resonance Imaging (MRI)-Guided Brachytherapy in Locally Advanced Cervical Cancer) 'Interlike' cohort are projected over the INTERLACE curve sketches. The EMBRACE 1 'Interlike' cohort was selected to mirror the INTERLACE patients, specifically with regard to the absence of para-aortic nodal metastases. However, the 'Interlike' patients were older, and had more advanced stages and worse performance status than INTERLACE patients. Nevertheless, the EMBRACE 1 'Interlike' data points overlap with the sketched INTERLACE curve for induction chemotherapy up to the 5 year mark, before deviating downwards. Notably, the number of patients remaining for analysis after 5 years is low, and only a small proportion of events occurred after 5 years in EMBRACE 1. It can be argued that the neoadjuvant chemotherapy is merely compensating for suboptimal radiotherapy of the INTERLACE study. NACT, neoadjuvant chemotherapy; CRT, chemoradiation; pts, patients.

that para-aortic recurrences are included as systemic in INTERLACE and knowing that para-aortic recurrence was a common site of recurrence in EMBRACE-I,[23] it is also likely that the increased use of elective para-aortic radiotherapy in high risk N1 patients in EMBRACE-II will address this problem in a more selective and better tolerated way.[24] Thus preliminary data from EMBRACE-II are showing a 5% reduction in the event rate of extra-pelvic recurrences compared with EMBRACE-I. Results for distant control after optimal radiotherapy, as in EMBRACE-II, are then comparable with those achieved in the experimental arm of INTERLACE.

We acknowledge that it is unusual to comment on a study which at the moment is available only as an abstract[9] and from a meeting presentation. But there is increasing pressure in our clinical practice to immediately incorporate neoadjuvant chemotherapy as the new standard before the publication of INTERLACE.[10] In our view, this is a premature and retrograde step which is not consistent with evidence based medicine. Like many trials, the INTERLACE cohort was a highly selected cohort of young patients with good performance status and limited tumor load. Despite this, there was a 11% drop in the percentage of patients being able to complete five cycles of concomitant cisplatin after neoadjuvant chemotherapy. In the real world, use of concomitant cisplatin in patients not participating in studies is highly variable (40–77%) and there is a high dropout rate (30–60%) depending on age, performance status, comorbidity, and local tumor burden,[25–27] as is also demonstrated by the 'non-INTERLACE like' EMBRACE-I cohort (Table 2). Thus normal tissue reserves, including bone marrow, are limited in real world patients. By expending these reserves on unnecessary neoadjuvant chemotherapy, we run the risk of compromising the curative treatment for the many patients who are not fit for trials. In addition, prolonged leukopenia and thrombocytopenia may prevent timely delivery of image guided brachytherapy with interstitial needles, leading to further prolongation of overall treatment time with additional negative impact on local tumor control.

The notion of using neoadjuvant chemotherapy as a strategy to bridge long waiting times for radiotherapy and/or compensate for the absence of advanced external beam radiotherapy and brachytherapy in low and middle income countries, but also some high income countries, is appealing. The INTERLACE study concluded that neoadjuvant chemotherapy was feasible in all countries, including low and middle income countries.[9] However, INTERLACE was not designed to address the question of worldwide feasibility of neoadjuvant chemotherapy. Only 112 (22%) of the included patients were from low and middle income countries and 100 (89%) of them were from the National Cancer Institute in Mexico (upper middle income country). In fact, the outcome of neoadjuvant chemotherapy in the real world settings of low and middle income countries would likely be inferior to standard

treatment, since the success of neoadjuvant chemotherapy critically depends on chemotherapy compliance and uninterrupted transition from neoadjuvant chemotherapy to chemoradiation, which are both more than challenging in low and middle income countries.[28 29]

Furthermore, the INTERLACE study did not address cost utility aspects. Access to external beam radiotherapy and brachytherapy is essential for cervical cancer treatment but remains restricted in low and middle income countries despite international efforts[28 30] and the fact that even simple external beam radiotherapy and brachytherapy with optimal overall treatment time can yield good results.[31] Likewise, in our experience with educational work through the European Society for Radiotherapy and Oncology (https://www.estro.org), the Groupe Européen de Curiethérapie (https://www.estro.org/About/ESTRO-Organisation-Structure/Committees/GEC-ESTRO-Committee), EMBRACE,[32] International Commission on Radiation Units and Measurements,[1] and BrachyTerra (https://brachyterra.thinkific.com/), experts from low and middle income countries are keen and able to adopt modern external beam radiotherapy and brachytherapy, achieving excellent outcomes and cost effectiveness,[33 34] but often face the barrier of costly and scarce training opportunities.[35] In this context, and despite the comparatively low per patient cost of the INTERLACE drug regimen, the cumulative expenditure due to the high incidence of cervical cancer could strain the already limited oncology budgets of low and middle income countries. Therefore, the use of neoadjuvant chemotherapy to bridge waiting times, compensate for suboptimal radiotherapy, or as a shortcut to bypass training, introduces the risk of diverting funds from the critically needed long term investments into radiotherapy infrastructure and education. Moreover, in regions with sparse or non-existent radiotherapy, medical oncologists are also scarce and concentrated in private rather than government or academic institutions where most patients seek treatment.[36 37] Expanding the indications for neoadjuvant chemotherapy could overburden the limited medical oncology capacities even more, compromising standard oncological treatment quality further.

In conclusion, we do not find convincing evidence for a survival benefit of neoadjuvant chemotherapy in INTERLACE compared with state-of-the-art chemoradiation and image guided adaptive brachytherapy. In contrast, neoadjuvant chemotherapy will prolong overall treatment time, reduce compliance with concomitant cisplatin, increase treatment cost, and may lead to increased overall morbidity. However, it is likely that short course neoadjuvant chemotherapy will benefit a small subgroup of patients. We therefore look forward to seeing the full data published and would urge the INTERLACE investigators to maximize the use of this dataset in seeking predictive factors, including biomarkers, to justify the use of neoadjuvant chemotherapy in highly selected cases. In addition, more comprehensive understanding of settings in low and middle income countries is mandatory (ie, cost utility analyses tailored to regional socioeconomic circumstances) before conclusions about the potential benefit of neoadjuvant chemotherapy in these countries can be drawn. Current efforts should prioritize enhancing access to the necessary infrastructure and education for the backbone of treatment which remain external beam radiotherapy, concomitant chemotherapy, and brachytherapy.

Author affiliations
[1]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Radiation Oncology, University Hospital Zürich, Zürich, Switzerland
[3]Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[4]Mount Vernon Cancer Centre, Northwood, UK
[5]Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
[6]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, Netherlands
[7]Radiation Oncology, Homi Bhabha Cancer Hospital and Research Center, Visakhapatnam, India

Contributors Planning of the manuscript was done by JCL, PP, and RP. Figure 1 was drawn by PP and JCL. The tables were produced by JCL, RP, and CK. The manuscript was written by JCL with substantial contribution and support from all co-authors: PP, LTT, PH, MPS, IJ-S, UM, CK, and RP.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Jacob Christian Lindegaard http://orcid.org/0000-0003-2426-7255

REFERENCES

1 13. Recording, and reporting Brachytherapy for cancer of the Cervix. ICRU Report 89. *Journal of the ICRU*; 2013.
2 Pötter R, Tanderup K, Kirisits C, *et al*. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018;9:48–60.
3 Pötter R, Tanderup K, Schmid MP, *et al*. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. *Lancet Oncol* 2021;22:538–47.
4 Schmid MP, Lindegaard JC, Mahantshetty U, *et al*. Risk factors for local failure following chemoradiation and magnetic resonance image-guided brachytherapy in locally advanced cervical cancer: results from the EMBRACE-I study. *J Clin Oncol* 2023;41:1933–42.
5 Vale C, Tierney JF, Stewart LA. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *JCO* 2008;26:5802–12.
6 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.
7 Thomas G. Are we making progress in curing advanced cervical cancer *J Clin Oncol* 2011;29:1654–6.
8 Cibula D, Raspollini MR, Planchamp F, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer - update 2023*. *Int J Gynecol Cancer* 2023;33:649–66.
9 McCormack M, Gallardo Rincón D, Eminowicz G, *et al*. A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: the GCIG INTERLACE trial. *Ann Oncol* 2023;34.
10 García E, Ayoub N, Tewari KS. Recent breakthroughs in the management of locally advanced and recurrent/metastatic cervical cancer. *J Gynecol Oncol* 2024;35:e30.
11 Gupta S, Parab P, Kerkar R, *et al*. Neoadjuvant chemotherapy followed by surgery (NACT-surgery) versus concurrent cisplatin and radiation therapy (CTRT) in patients with stage Ib2 to IIB squamous

carcinoma of cervix: a randomized controlled trial (RCT). *Ann Oncol* 2017;28:v627.
12 Kenter GG, Greggi S, Vergote I, *et al*. Randomized phase III study comparing neoadjuvant chemotherapy followed by surgery versus chemoradiation in stage Ib2-IIB cervical cancer: EORTC-55994. *J Clin Oncol* 2023;41:5035–43.
13 Mileshkin LR, Moore KN, Barnes EH, *et al*. Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24:468–82.
14 Colombo N, Dubot C, Lorusso D, *et al*. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021;385:1856–67.
15 Monk BJ, Sill MW, McMeekin DS, *et al*. Phase III trial of four cisplatin-containing doublet combinations in stage Ivb, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2009;27:4649–55.
16 Tewari KS, Sill MW, Long HJ 3rd, *et al*. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;370:734–43.
17 Oaknin A, Gladieff L, Martínez-García J, *et al*. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATCC): a randomised, open-label, phase 3 trial. *Lancet* 2024;403:31–43.
18 Lindegaard JC, Petric P, Schmid MP, *et al*. Prognostic implications of uterine cervical cancer regression during chemoradiation evaluated by the T-score in the multicenter EMBRACE I study. *Int J Radiat Oncol Biol Phys* 2022;113:379–89.
19 McCormack M, Kadalayil L, Hackshaw A, *et al*. A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. *Br J Cancer* 2013;108:2464–9.
20 Hermens AF, Barendsen GW. Changes of cell proliferation characteristics in a rat rhabdomyosarcoma before and after X-irradiation. *Eur J Cancer* 1969;5:173–89.
21 Davis AJ, Tannock JF. Repopulation of tumour cells between cycles of chemotherapy: a neglected factor. *Lancet Oncol* 2000;1:86–93.
22 Bogaty P, Brophy J. Numbers needed to treat (needlessly). *Lancet* 2005;365:1307–8.
23 Nomden CN, Pötter R, de Leeuw AAC, *et al*. Nodal failure after chemo-radiation and MRI guided brachytherapy in cervical cancer: patterns of failure in the EMBRACE study cohort. *Radiother Oncol* 2019;134:185–90.
24 Jürgenliemk-Schulz I-M, Beriwal S, de Leeuw AAC, *et al*. Management of nodal disease in advanced cervical cancer. *Semin Radiat Oncol* 2019;29:158–65.
25 Sturdza A, Pötter R, Fokdal LU, *et al*. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in retroembrace, a multicenter cohort study. *Radiother Oncol* 2016;120:428–33.
26 Lindegaard JC, Kirisits C, Schmid MP, *et al*. Real-world clinical outcome from using the EMBRACE-II protocol in locally advanced Cervical cancer. *Radiother Oncol* 2024;194:262–3.
27 Xiang M, Kidd EA. Benefit of cisplatin with definitive radiotherapy in older women with cervical cancer. *J Natl Compr Canc Netw* 2019;17:969–75.
28 Christ SM, Willmann J. Measuring global inequity in radiation therapy: resource deficits in low- and middle-income countries without radiation therapy facilities. *Adv Radiat Oncol* 2023;8:101175.
29 Zamorano AS, Barnoya J, Gharzouzi E, *et al*. Treatment compliance as a major barrier to optimal cervical cancer treatment in guatemala. *J Glob Oncol* 2019;5:1–5.
30 Rodin D, Burger EA, Atun R, *et al*. Scale-up of radiotherapy for cervical cancer in the era of human papillomavirus vaccination in low-income and middle-income countries: a model-based analysis of need and economic impact. *Lancet Oncol* 2019;20:915–23.
31 Mahantshetty U, Lavanya G, Grover S, *et al*. Incidence, treatment and outcomes of cervical cancer in low- and middle-income countries. *Clin Oncol* 2021;33:e363–71.
32 Tan L-T, Tanderup K, Kirisits C, *et al*. Education and training for image-guided adaptive brachytherapy for cervix cancer—the (GEC)-ESTRO/EMBRACE perspective. *Brachytherapy* 2020;19:827–36.
33 Chakraborty S, Mahantshetty U, Chopra S, *et al*. Income generated by women treated with magnetic resonance imaging-based brachytherapy: a simulation study evaluating the macroeconomic benefits of implementing a high-end technology in a public sector healthcare setting. *Brachytherapy* 2017;16:981–7.
34 Mahantshetty U, Krishnatry R, Hande V, *et al*. Magnetic resonance image guided adaptive brachytherapy in locally advanced cervical cancer: an experience from a tertiary cancer center in a low and middle income countries setting. *Int J Radiat Oncol Biol Phys* 2017;99:608–17.
35 Gospodarowicz M. Global access to radiotherapy—work in progress. *JCO Glob Oncol* 2021;7:144–5.
36 Fundytus A, Sullivan R, Vanderpuye V, *et al*. Delivery of global cancer care: an international study of medical oncology workload. *J Glob Oncol* 2018;4:1–11.
37 Sengar M, Fundytus A, Hopman WM, *et al*. Medical oncology in India: workload, infrastructure, and delivery of care. *Indian J Med Paediatr Oncol* 2019;40:121–7.
38 Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105:103–4.
39 Olawaiye AB, Baker TP, Washington MK, *et al*. The new (version 9) American Joint committee on cancer tumor, node, metastasis staging for cervical cancer. *CA Cancer J Clin* 2021;71:287–98.