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Review Article

External beam radiotherapy boost versus surgical debulking followed by radiotherapy for the treatment of metastatic lymph nodes in cervical cancer: A systematic review and meta-analysis

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ABSTRACT

Objective: We aimed to assess disease-free survival (DFS), overall survival (OS) and treatment-related toxicity of two therapeutic strategies for treating bulky lymph nodes on imaging in patients with locally advanced cervical cancer (LACC): radiotherapy boost versus surgical debulking followed by radiotherapy.
Methods: We performed a systematic review of studies published up to October 2023. We selected studies including patients with LACC treated by external beam radiotherapy (EBRT) boost or lymph node debulking followed by EBRT (with or without boost).
Results: We included two comparative (included in the meta-analysis) and nine non-comparative studies. The estimated 3-year recurrence rate was 28.2% (95%CI:18.3–38.0) in the EBRT group and 39.9% (95% CI:22.1–57.6) in the surgical debulking plus EBRT group. The estimated 3-year DFS was 71.8% and 60.1%, respectively ($p = 0.19$). The estimated 3-year death rate was 22.2% (95%CI:11.2–33.2) in the EBRT boost group and 31.9% (95%CI:23.3–40.5) in the surgical debulking plus EBRT group. The estimated 3-year OS was 77.8% and 68.1%, respectively ($p = 0.04$). No difference in lymph node recurrence between the two comparative studies ($p = 0.36$). The meta-analysis of the two comparative studies showed no DFS difference ($p = 0.13$) but better OS in the radiotherapy boost group ($p = 0.006$). The incidence of grade≥3 toxicities (ranging 0–50%) was not different between the two approaches in the two comparative studies ($p = 0.31$).
Conclusion: No DFS and toxicity difference when comparing EBRT boost with surgical debulking of enlarged lymph nodes and EBRT in patients with cervical cancer was evident. Radiotherapy boost had better OS. Further investigation is required to better understand the prognostic role of surgical lymph node debulking in light of radiotherapy developments.

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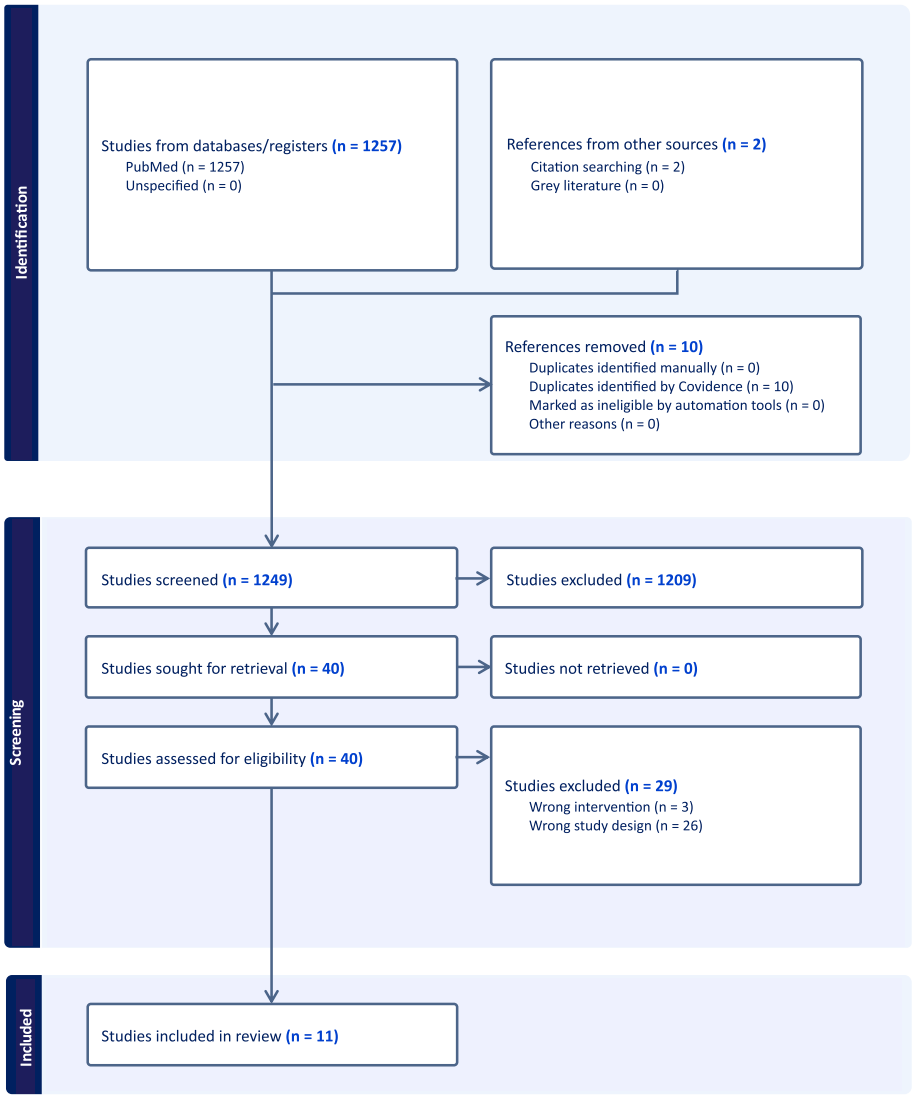


Fig. 1. PRISMA flow chart.

1. Introduction

Cervical cancer is the fourth most common cancer in women, with an estimated 600,000 new cases and 340,000 deaths attributed to cervical cancer worldwide in 2020, accounting for 7.7% of all female cancer deaths [1]. The most important prognostic factors for cervical cancer are the stage of disease and lymph node involvement [2,3]. According to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging, the risk of metastatic lymph nodes increases with the tumor stage: for pelvic lymph nodes, this risk ranges from 2% in stage IA2 to 47% in stage IIB, and for para-aortic lymph nodes, it ranges from 5% in stage IB to 13%–30% in stage III [2]. It is also known that the number of metastatic lymph nodes is strictly related to survival [3,4]. Treatment of locally advanced cervical cancer (LACC) (FIGO 2018 stage IB3–IVA) is represented by definitive chemo-radiotherapy (CTRT) [5]. In cases of histologically proven or radiologically suspicious lymph node metastasis, the two main therapeutic strategies are external beam radiotherapy (EBRT) boost and nodal debulking prior to EBRT [5]. According to the most recent international guidelines for the management of patients with cervical cancer with lymph node involvement, surgical removal of large pathological pelvic and/or para-aortic nodes before definitive CTRT is not routinely recommended [6]. Although the role of surgery is debated, there is support for the rationale that removal of "bulky" lymph nodes (defined as lymph nodes with a short axis >1.5 cm at imaging) might increase the chance of complete response to CTRT. Indeed, the radiotherapy dose able to "sterilize" bulky lymph nodes might be too toxic for surrounding organs (such as the small bowel), and there is the need to balance tumor control and dose/volume constraints for organs at risk. In particular, a nodal tumor >2 cm requires at least 60 Gy to achieve tumor control; this dose increases toxicity for organs at risk [7–11]. On the other hand, the surgical removal of bulky nodes can represent a risk for intra- and post-operative complications with consequent delay in the start of RTCT.

In this systematic review and meta-analysis, we aimed to compare two therapeutic strategies for treating suspicious bulky lymph nodes on imaging in patients with cervical cancer (radiotherapy boost versus lymph node debulking followed by radiotherapy with or without boost). The primary outcome was disease-free survival (DFS). The secondary outcomes were overall survival (OS) and treatment-related toxicity.

2. Methods

2.1. Systematic review

We selected comparative studies and single-population (case series) studies: prospective or retrospective, multicentric or monocentric and

Table 1
Summary of the included studies.

Radiotherapy boost

First author and reference number	Title	Year	Number of patients	Journal	Study design
Lee et al. [17]	Prognostic factors of dose-response relationship for nodal control in metastatic lymph nodes of cervical cancer patients undergoing definitive radiotherapy with concurrent chemotherapy	2022	115 boost	*Journal of Gynecologic Oncology*	Monocentric retrospective study
Jayatilakebanda et al. [18]	High dose simultaneous integrated boost for node positive cervical cancer	2021	69 (23 boost)	*Radiation Oncology*	Monocentric retrospective study
Tiwari et al. [19]	Impact of nodal boost irradiation and MR-based brachytherapy on oncologic outcomes in node-positive cervical cancer	2021	161 (71 boost)	*Gynecologic Oncology*	Monocentric prospective study
Hata et al. [20]	Radiation therapy for para-aortic lymph node metastasis from uterine cervical cancer	2015	22 (8 boost)	*Anticancer Research*	Monocentric prospective study
Wakatsuki et al. [21]	Impact of boost irradiation on pelvic lymph node control in patients with cervical cancer	2014	245 (46 boost)	*Journal of Radiation Research*	Monocentric retrospective study
Ramlov et al. [22]	Impact of radiation dose and standardized uptake value of (18)FDG PET on nodal control in locally advanced cervical cancer	2015	84 boost	*Acta Oncologica*	Multicentric prospective study
Díaz-Feijoo et al. [14]	Laparoscopic debulking of enlarged pelvic nodes during surgical para-aortic staging in locally advanced cervical cancer: a retrospective comparative cohort study	2022	381 (217 boost)	*Journal of Minimally Invasive Gynecology*	Multicentric retrospective comparative cohort study
Olthof et al. [15]	Treatment of bulky lymph nodes in locally advanced cervical cancer: boosting versus debulking	2022	190 (101 boost)	*International Journal of Gynecological Cancer Cancers*	Nationwide retrospective comparative cohort study
Cheung et al. [16]	Simultaneous Integrated Boost for Dose Escalation in Node-Positive Cervical Cancer: 5-Year Experience in a Single Institution	2023	54 boost		Monocentric retrospective study

Debulking + radiotherapy

First author and reference number	Title	Year	Number of patients	Journal	Radiotherapy to debulked lymph node site	Design
Cheung et al. [23]	Debulking metastatic pelvic nodes before radiotherapy in cervical cancer patients: a long-term follow-up result	2011	53 debulking	*International Journal of Clinical Oncology*	EBRT ± boost	Monocentric retrospective study
Hacker et al. [9]	Resection of bulky positive lymph nodes in patients with cervical carcinoma	1995	34 debulking	*International Journal of Gynecological Cancer*	EBRT	Monocentric retrospective study
Díaz-Feijoo et al. [14]	Laparoscopic debulking of enlarged pelvic nodes during surgical para-aortic staging in locally advanced cervical cancer: a retrospective comparative cohort study	2022	381 (164 debulking)	*Journal of Minimally Invasive Gynecology*	EBRT + boost	Multicentric retrospective comparative cohort study
Olthof et al. [15]	Treatment of bulky lymph nodes in locally advanced cervical cancer: boosting versus debulking	2022	190 (60 debulking)	*International Journal of Gynecological Cancer*	31 EBRT, 29 EBRT + boost	Nationwide retrospective comparative cohort study

EBRT = external beam radiotherapy.

including patients with LACC treated by EBRT boost or lymph node debulking followed by EBRT (with or without boost). We excluded studies reporting exclusive radiotherapy without lymph node boost, and studies with insufficient data for accurate identification of the target population. We included studies with patients with a histological diagnosis of cervical cancer and imaging (computed tomography [CT], magnetic resonance imaging [MRI] or positron emission tomography–computed tomography [PET-CT]) detection of lymph node metastasis (defined as a short axis >1.5 cm and avid [18F]fluorodeoxyglucose update). We excluded studies with patients undergoing systematic lymphadenectomy for staging purposes.

Two review authors (SDB and KB) extracted data independently, from studies identified through the MEDLINE (1946–October 2023) and Embase (1980–October 2023) electronic databases. A third reviewer author (BG) checked and resolved conflicts. We used Cochrane's assessment of risk of bias and the PRISMA 2020 checklist to edit the final manuscript. The search string was: "Cytoreductive" OR "Chemoradiotherapy" [MeSH] OR "Combined Modality Therapy" [MeSH] OR "Radiotherapy" [MeSH] OR "Lymphatic Metastasis" [MeSH] OR "Lymphatic Irradiation" [MeSH] OR "Boost" OR "Bulky lymph node" OR "Debulking") OR "extended-field radiation therapy" [MeSH] AND ("Lymph Nodes" [MeSH]) AND ("Uterine Cervical Neoplasms" [MeSH] OR "Cervical cancer").

We followed the PICO(T) model:

P = Population: LACC;
I = Intervention: surgical lymph node debulking + radiotherapy;
C = Control: radiotherapy boost;
O = Outcome: DFS and OS;
T = Time: survival analysis performed at least at 3 years.

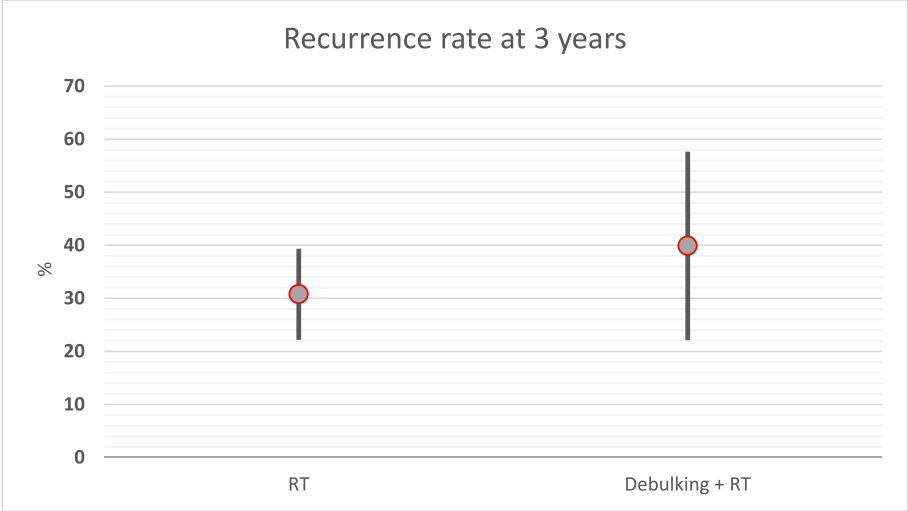
2.2. Meta-analysis of the comparative studies

We used a random-effects model meta-analysis with the Der Simonian–Laird method to estimate the risk ratio and the 95% confidence interval (CI). We assessed the toxicity according to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria [12]. To test the overall effects, we used the Z-test, with $p < 0.05$ considered to be significant. We used Review Manager 5.4.1 for the analyses.

2.3. Analysis of the case series

For each study, including case series in the comparative studies, we calculated the proportion of patients who had recurrences or who died relative to the total number of patients. We combined the data across studies by using a weighted mean of these probabilities of recurrence/death. The WebPlotDigitizer software was used to extract data from published DFS and OS Kaplan-Meier curves [35]. We calculated summary mortality and morbidity rates in a similar manner. We used a

A.



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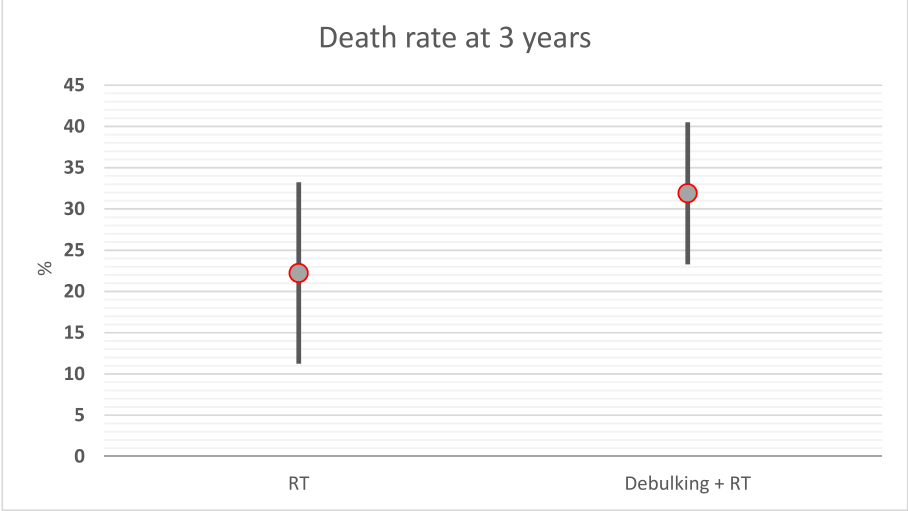

Fig. 2. The recurrence rate (A) and the death rate (B) at 3 years.

formula that has been described for the estimation of precision in cluster sampling to calculate the 95% CI of each summary probability [13]. The computation of this CI considers the sum of the inter- and the intra-study variances. We used Microsoft Excel for the calculations. We created the stock charts of probabilities of recurrence/death at 3 years, with the CI and linear curves, by using Microsoft Excel.

We generated Kaplan–Meier curves to show the survival trend for each treatment and compared them with the log-rank test. With this approach, we did not consider the inter-study variance. We considered $p < 0.05$ to be statistically significant.

3. Results

3.1. Search results

The database searches resulted in 1257 records (including two articles retrieved through references from citations). After removing duplicates, we assessed 1249 unique records. Of these, we excluded 1209 after analysis of the abstracts as not pertinent to the outcome of interest. Therefore, we assessed 40 studies for eligibility. We excluded 29 studies because they had the wrong study design (n = 26), or wrong intervention (n = 3), leaving 11 studies for the systematic review (Fig. 1). Of the included studies, two were comparative [14,15] and we included them in the meta-analysis, while the remaining nine studies did not compare the two treatments [9,16–23]. Table 1 shows the included studies on radiotherapy boost and surgical debulking followed radiotherapy.

3.2. Recurrence rate and disease-free survival

In the radiotherapy boost without surgery group, considering the results of the nine included studies [14–22], the estimated overall 3-year recurrence rate was 28.2% (95% CI: 18.3–38.0) (Fig. 2A). The estimated 3-year DFS was 71.8%. In the surgical debulking + radiotherapy group, considering the results of the four included studies [9,14,15,23], the estimated overall 3-year recurrence rate was 39.9% (95% CI: 22.1–57.6) and the estimated 3-year DFS was 60.1%. The log-rank test showed no significant difference in terms of 3-year DFS in patients undergoing radiotherapy boost versus debulking + radiotherapy (p = 0.19). Fig. 3A

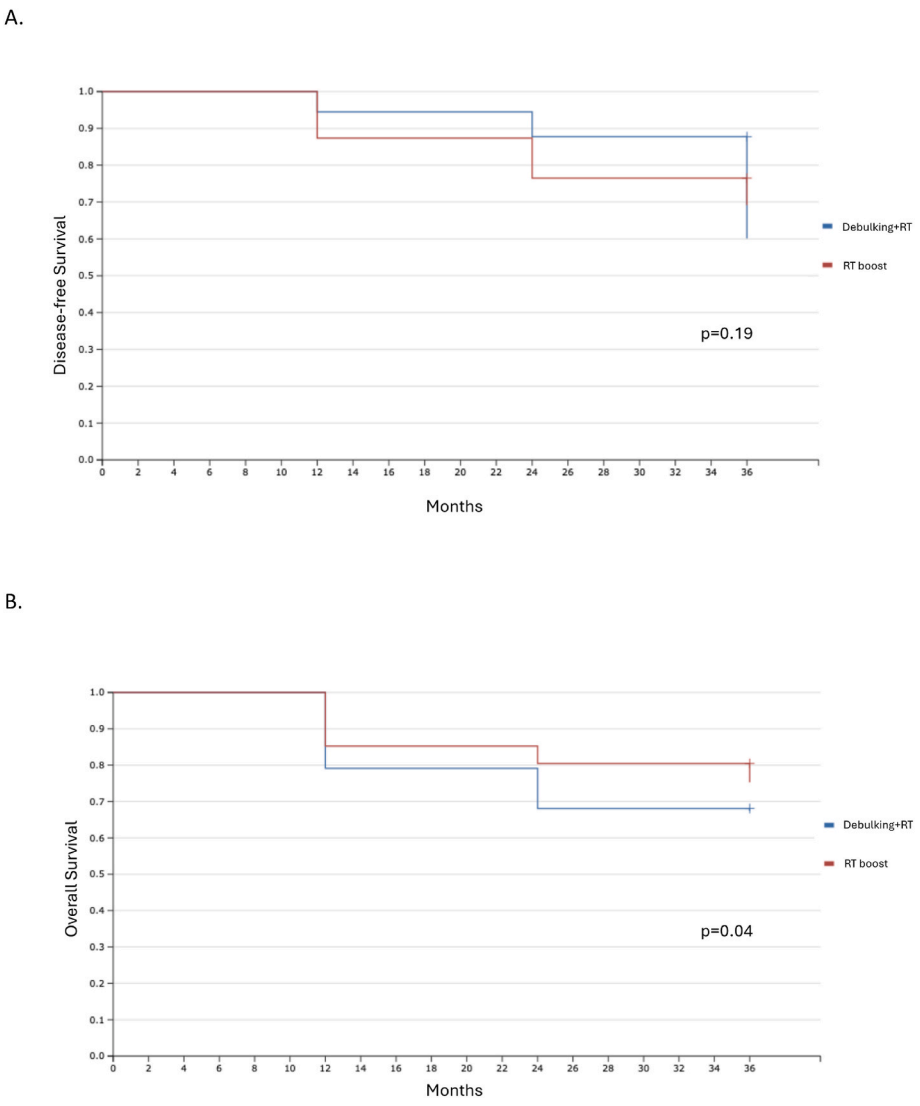

Fig. 3. Disease-free survival (DFS, A) and overall survival (OS, B).

shows the results of the meta-analysis as a standard Kaplan–Meier curve with data from the 11 included studies. The meta-analysis of the two comparative studies did not show a significant difference in DFS between the treatment approaches (p = 0.13; Fig. 4A).

3.3. Pattern of recurrence

When we analyzed the pattern of recurrence, the incidence of lymph node recurrence was superposable between the two study groups for the studies that reported this data (25% in the radiotherapy boost versus 26% in the debulking group; Supplementary Table 1). The meta-analysis of the two comparative studies showed no difference in lymph node, pelvic and extra-pelvic recurrence between the treatment approaches (p = 0.36, p = 0.46 and p = 0.52, respectively; Fig. 4B–D).

3.4. Death rate and overall survival

In the radiotherapy boost without surgery group, considering the results of the nine included studies [14–22], the estimated overall 3-year death rate was 22.2% (95% CI: 11.2–33.2) and the estimated 3-year OS was 77.8%. In the debulking + radiotherapy group, considering the results of the four included studies [9,14,15,23], the estimated overall 3-year death rate was 31.9% (95% CI: 23.3–40.5) and the estimated 3-year OS was 68.1% (Fig. 2B). The log-rank test showed a better OS in patients undergoing radiotherapy boost (p = 0.04; Fig. 3B). The meta-analysis of the two comparative studies showed better OS in patients undergoing radiotherapy boost (p = 0.006; Fig. 4E).

3.5. Toxicity

Table 2 presents the toxicity profile in the included studies. The incidence of major toxicities (grade ≥3) ranged from 0% to 50%. When analyzing only the two comparative studies, there was a similar toxicity profile in both treatment groups in one study [14] and a trend towards a higher incidence of complications in the debulking + radiotherapy group in the other study [15]. Based on the meta-analysis of the two comparative studies [14,15], there was not a significant difference between the two treatment approaches (p = 0.31; Supplementary Fig. 1).

4. Discussion

In this systematic review and meta-analysis, we collected 11 studies looking at radiotherapy boost versus surgical debulking of bulky nodes followed by radiotherapy in cervical cancer. The quality of the evidence was low, but there were no DFS and toxicity differences between the two treatments. Based on the meta-analysis of the two comparative studies,

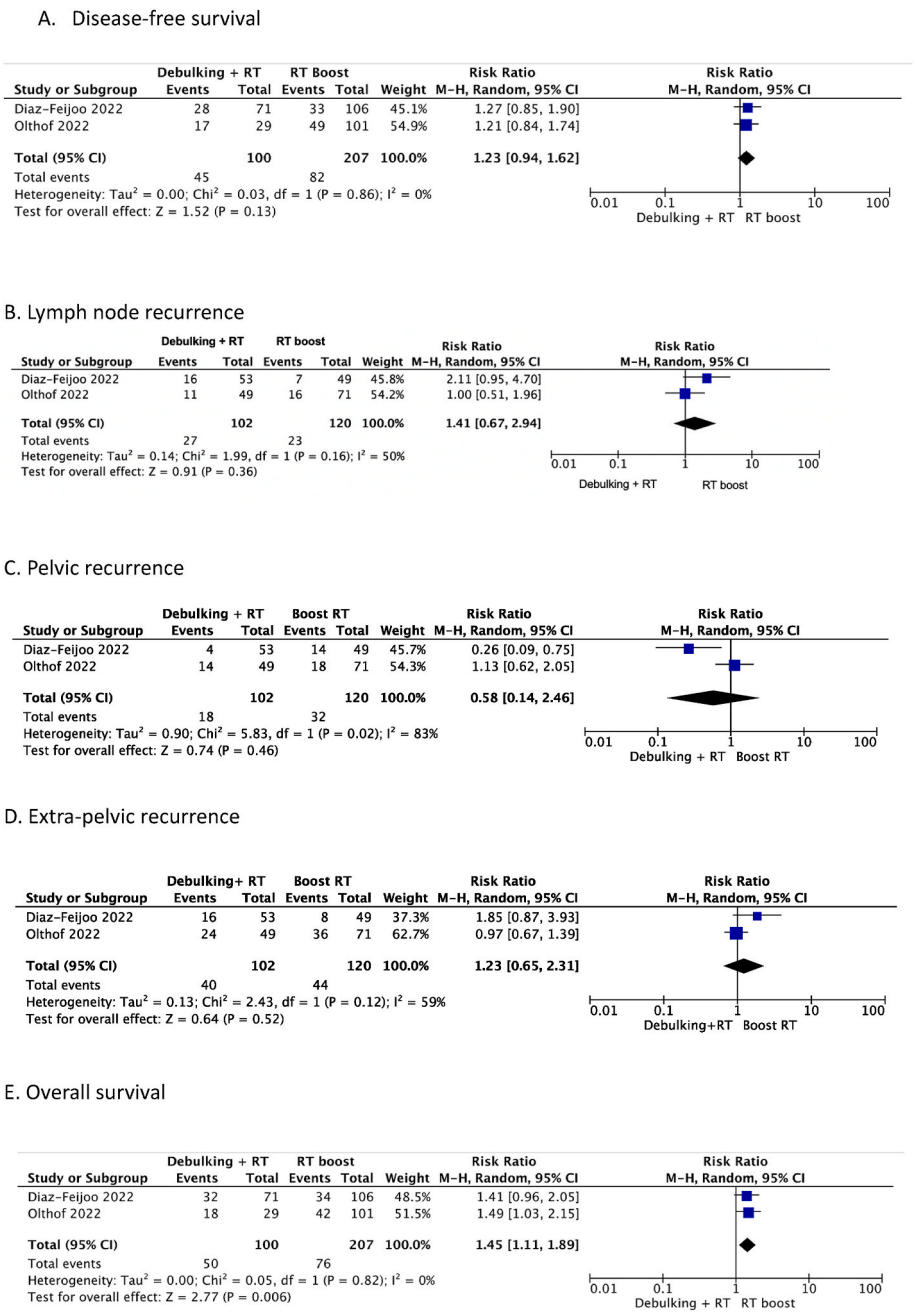

Fig. 4. Forest plots showing the meta-analysis of the two comparative studies. Disease-free survival (A), lymph node recurrence (B), pelvic recurrence (C), extra-pelvic recurrence (D), overall survival (E).

radiotherapy boost had better OS (which was confirmed when all 11 included studies were analyzed).

According to the ESGO/ESTRO/ESP guidelines for cervical cancer management, definitive CTRT and brachytherapy should be the preferred treatment for patients with LACC and unequivocally positive lymph nodes on imaging [5]. Nevertheless, the rationale behind the use of surgery to remove bulky lymph nodes is supported by basic radiobiological principles suggesting that at least 60 Gy is necessary to control 90% of lesions measuring 2 cm [24]. When producing dose-response curves, the impact of the dose on normal tissues should be evaluated impartially. Intestinal structures, particularly the small bowel, are inevitably included in the irradiated space, with a maximum tolerance of 2 cm^3 below 65 Gy, and a 5% risk of complications at 5 years (TD5/5) from severe toxicity after a 50 Gy dose to one third of the small bowel [25]. In patients with bulky pelvic or para-aortic lymph nodes (>2 cm), the dose administered may fail to achieve effective tumor control [21,25,26]. Given that the dose required to sterilize this tumor volume is excessive for the surrounding organs, a reduction in the tumor burden can be considered [25]. Moreover, earlier trials have established that bulky pelvic and/or para-aortic nodes (>2 cm) are resistant to chemotherapy and/or radiotherapy, and hence pose a significant challenge [27,28]. In a few studies, there was a significant survival benefit in patients submitted to complete debulking of tumor-involved pelvic and/or para-aortic lymph nodes compared with patients in whom debulking was not performed. Moreover, women with microscopically positive pelvic and para-aortic lymph nodes had the same relapse-free survival and OS as those with grossly positive but completely resected metastases [8–10,29,30]. However, most of these studies are out of date and PET/CT-scan was not used as part of the radiological staging. For this reason, surgical debulking might not give the same advantage in the

Table 2
Toxicities related to the different treatments.

Study	Acute grade ≥3[a] toxicities		
	Debulking + radiotherapy	Radiotherapy	Type of toxicity
Lee et al. [17]	–	14/115 (12.2%)	6 urinary toxicities 8 bowel toxicities
Jayatilakebanda et al. [18]	–	5/23 (21.7%)	5 fatigue
Tiwari et al. [19]	–	5/71 (7.0%)	5 bowel and urinary toxicities
Hata et al. [20]	–	11/22 (50.0%)	11 haematologic toxicities
Wakatsuki et al. [21]	–	0/46	
Ramlov et al. [22]	–	NA	
Cheung et al. [16]	–	1/54 (1.8%)	1 bowel toxicity
Cheung et al. [23]	NA	–	
Hacker et al. [9][b]	5/34 (14.7%)	–	1 lacerated external iliac vein 1 necrotizing fasciitis 1 postoperative cytomegalovirus hepatitis 2 infected lymphocysts
Díaz-Feijoo et al. [14]	13/71 (18.3%)	19/106 (17.9%)	4 versus 5 bowel toxicities 1 versus 0 urinary toxicities 8 versus 14 haematologic toxicities
Olthof et al. [15]	10/29 (34.4%)	15/101 (14.8%)	NA for debulking + radiotherapy Radiotherapy: 4 urogenital toxicities 9 bowel toxicities 2 other toxicities

NA = not available.
[a] Using the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria.
[b] Surgical complications.

era of modern imaging.

There are a few necessary considerations regarding surgical node debulking. Surgery-related morbidity must be as low as possible because debulking is performed before the start of CTRT, which represents the actual treatment for cervical cancer. A minimally invasive approach might also be considered to reduce the time to start CTRT, always keeping in mind the basic principles of oncological surgery, namely careful tumor manipulation, endobag extraction and no tumor spillage. The site and the number of involved nodes should be considered as selection criteria. The majority of the studies supporting the role of surgical debulking are old, and the most recent advances in radiotherapy techniques might represent a way to overcome the dose constraint limitation. For this reason, the updated ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer do not recommend routine surgical removal of large pathological pelvic and/or para-aortic nodes before definitive CTRT [6]. In fact, when looking at the results of the two comparative studies we included in the meta-analysis [14,15], they both found that there was no survival improvement when performing debulking of enlarged lymph nodes before radiotherapy, and there was a potential higher risk of major complications. Very recently, two studies analyzed clinical outcomes of patients with bulky nodes undergoing radiotherapy boost and found that complete response was achieved in all cases (even those with larger lymph node diameter) with no lymph node recurrence reported, thus demonstrating the efficacy of modern radiation techniques [31,32]. The meta-analysis of the two comparative studies also confirmed the lack of a DFS advantage when performing surgical node debulking, with better OS in the radiotherapy boost group. Nevertheless, it should be noted that the number of patients with lymph nodes >2 cm in the short axis receiving nodal debulking was low in both studies, thus limiting the results in the sub-group of patients who might benefit the most from this approach. In addition, Berta-Diaz et al. [14] only included patients undergoing pelvic node debulking, and the authors did not report survival outcomes for patients with para-aortic bulky nodes. Better OS in the radiotherapy boost group in our study 3 might be explained by the different rate of extra-pelvic recurrences (even though the difference was not significant based on the meta-analysis of the two comparative studies), by the potential delay in starting concomitant chemotherapy due to surgery (even though in most of the series the delay was not considered significant) and by the potential lack of chemotherapy in older debulking studies [9].

In 2020, a randomized trial comparing the role of surgical lymph node staging versus clinical staging followed by primary CTRT in LACC was published [33]. This study did not show a difference in DFS between the two study groups. However, there was a significant DFS benefit for patients with FIGO stage IIB and, in a post hoc analysis, there was a cancer-specific survival benefit in favor of surgical staging. This last result might be justified by the fact that patients with bulky nodes at imaging were also included in the study and the surgical removal of these nodes could have contributed to the survival advantage found in the post hoc analysis of the surgical arm. Nevertheless, the lack of radiological staging with PET/CT-scan has to be reported a limitation of the UTERUS-11.

Recently, a phase III randomized trial aiming to assess the therapeutic effect of surgical debulking of metastatic lymph nodes in cervical cancer FIGO 2018 Stage IIICr has been launched (KGOG-1047/DEBULK, NCT05421650), the results of which will finally answer the question about the role of surgical lymph node debulking before radiation therapy [34].

We have to acknowledge a few limitations of the present study. First, although we included 11 included articles, only two (18.2%) [14,15] were comparative studies analyzing both treatments in the same study and could be used for meta-analysis. Moreover, we did not consider the advances in radiotherapy treatment that might lead to different performance in patients with bulky lymph nodes. The broad time frame we selected to include studies might represent a bias in terms of both surgical and radiotherapy treatment (e.g. patients treated in older studies might have received radiotherapy without systemic chemotherapy). The fact that the surgical group might have received radiotherapy boost in addition to EBRT could be misleading. However, to the best of our knowledge, this is the first systematic review and meta-analysis that has evaluated the role of surgical debulking of lymph nodes in cervical cancer.

5. Conclusion

We identified two comparative studies assessing the prognostic role of EBRT boost versus surgical debulking plus radiotherapy in the treatment bulky lymph nodes in patients with cervical cancer. The remaining nine studies were limited to separate treatments and thus precluded meaningful comparisons. There was no significant DFS difference when assessing EBRT boost versus surgical debulking of enlarged lymph nodes followed by radiotherapy in patients with cervical cancer. A meta-analysis of two comparative studies revealed that radiotherapy boost provided a superior OS rate. Although surgical debulking appeared to pose a higher risk of major toxicity, this was not significant in the comparative studies. Further investigation is required to better understand the prognostic role of surgical lymph node debulking in light of radiotherapy developments.

Author contributions

NB: Conceptualization, Methodology. Writing – original draft preparation. Writing- Reviewing and Editing. SDB: Conceptualization, Methodology. Software, Data curation. Writing- Reviewing and Editing.

BG: Conceptualization, Methodology. Writing – original draft preparation. Writing- Reviewing and Editing. KB: Software, Data curation. Writing- Reviewing and Editing. VB: Visualization, Investigation. Software, Validation. Writing- Reviewing and Editing. MAG: Visualization, Investigation. Software, Validation. Writing- Reviewing and Editing. MB: Software, Data curation. Writing- Reviewing and Editing. AF: Visualization, Investigation. Software, Validation. Writing- Reviewing and Editing. PM: Visualization, Investigation. Supervision. Software, Validation. Writing- Reviewing and Editing. FL: Visualization, Investigation. Software, Validation. Supervision. Writing- Reviewing and Editing. DQ: Visualization, Investigation. Supervision. Software, Validation. Writing- Reviewing and Editing. GF: Visualization, Investigation. Software, Validation. Writing- Reviewing and Editing. GS: Visualization, Investigation. Supervision. Software, Validation. Writing-Reviewing and Editing.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.108013.

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