Gynecologic Oncology 164 (2022) 667–674

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Upstaging by para-aortic lymph node dissection in patients with locally advanced cervical cancer: A systematic review and meta-analysis

Annelou A.B. Thelissen [a], Ina M. Jürgenliemk-Schulz [a], Femke van der Leij [a], Max Peters [a], Cornelis G. Gerestein [b], Ronald P. Zweemer [b], Peter S.N. van Rossum [a,*]

[a] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Department of Gynecologic Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

HIGHLIGHTS

- Para-aortic lymph node (PALN) status in locally advanced cervical cancer has therapeutic and prognostic implications.
- Reported proportions in literature of upstaging by PALN dissection after negative PALN imaging were meta-analyzed.
- After negative PET or PET-CT, PALN dissection yielded pathologic PALNs in 12% of all patients.
- After negative MRI or CT, PALN dissection yielded pathologic PALNs in 11% of all patients.
- After PET-CT showed pelvic nodal (but no PALN) involvement, PALN dissection yielded pathologic PALNs in 21% of patients.

ARTICLE INFO

Article history:
Received 8 October 2021
Received in revised form 17 December 2021
Accepted 21 December 2021
Available online 27 December 2021

Keywords:
Cervical cancer
Para-aortic lymph nodes
PET
MRI
Lymphadenectomy

ABSTRACT

Background. Accurate staging of para-aortic nodal status in cervical cancer is of great importance for individualizing treatment and impacting outcomes. Three-dimensional imaging (i.e. PET, CT, MRI) may miss para-aortic lymph node (PALN) metastases. The aim of this study was to systematically review and meta-analyze the proportion of upstaging by PALN dissection in patients with locally advanced cervical cancer without suspicious PALNs on imaging.

Methods. PubMed/MEDLINE and Embase were systematically searched. The analysis included diagnostic studies that reported on 3D imaging and pre-therapeutic surgical assessment of PALN status in patients with cervical cancer. An overall pooled upstaging rate was calculated using a random-effects model.

Results. The search identified 16 eligible studies including 18 cohorts with a total of 1530 patients. Pooling of 12 cohorts demonstrated an upstaging rate of 12% (95% confidence interval [CI] 10–15%) by PALN dissection after negative PET or PET-CT. Pooling of 6 cohorts demonstrated a pooled upstaging rate of 11% (95% CI: 8–16%) by PALN dissection after negative MRI or CT. No significant heterogeneity in upstaging proportions across cohorts was observed ($I^2 = 0\%$ and 27%, respectively). In 7 cohorts including only patients with pelvic nodal metastases on imaging (but no suspicion of PALN involvement) a pooled upstaging rate by PALN dissection of 21% (95% CI: 17–26%) was found ($I^2 = 0\%$).

Conclusions. This meta-analysis demonstrates that in case of no suspicious PALN on PET-CT or MRI, PALN dissection still identifies lymph node metastases in a considerable amount of patients with locally advanced cervical cancer and especially in those patients with confirmed pelvic nodal metastases.

Contents

* Corresponding author at: Department of Radiation Oncology, Q00.3.11, University Medical Center Utrecht, PO Box 85500, 3508GA Utrecht, the Netherlands.
E-mail address: P.S.N.vanRossum-2@umcutrecht.nl (P.S.N. van Rossum).

https://doi.org/10.1016/j.ygyno.2021.12.026
0090-8258/

1. Introduction

Uterine cervical carcinoma remains the fourth most common cancer in women worldwide [1]. Cervical cancer spreads primarily to regional pelvic lymph nodes. Generally, the first extra-pelvic site of spread is the para-aortic area, which is involved in 12–25% of cases [2]. Metastasis to para-aortic lymph nodes (PALNs) represents an important prognostic factor for survival in patients with cervical cancer [3]. Extended para-aortic field radiotherapy, in addition to standard chemoradiation therapy, is recommended for patients with metastatic PALNs. However, such an extended radiation field from the pelvis to the upper abdomen significantly increases toxicity, such as radiation-induced enteritis [4–6]. Therefore, accurate determination of nodal status in cervical cancer significantly influences treatment burden and disease outcomes.

The stage of cervical cancer is based mainly on clinical examination and imaging, as recommended by the International Federation of Gynecology and Obstetrics (FIGO) guidelines [7]. However, there are known limitations of clinical staging using modern 3D imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT) and integrated ^{18}F-FDG positron emission tomography-CT (PET-CT) [8–11]. Regarding PALN involvement, several retrospective studies have demonstrated a significant rate of upstaging by pathologic staging after surgery when compared to staging by imaging of PALNs [3,12,13]. This suggests imaging techniques cannot completely fill the gap between clinical and histological staging. Staging surgery as alternative could be justified if the anticipated benefits of positive detection outweigh its possible morbidities [14]. Although complications seem low when laparoscopic surgery is performed by trained teams, consensus regarding the diagnostic and therapeutic benefit of surgical PALN dissection has not been established [3,15,16].

As a consequence of suboptimal staging by imaging, a significant number of patients with PALN metastases may remain undertreated, whereas an approach of treating all patients at the PALN site would lead to overtreatment in many cases. Hence, several experts advocate the use of pre-treatment laparoscopic surgical PALN assessment, at the cost of increased morbidity and treatment delay [16,17]. In order to balance increased morbidity with the benefit of surgery, selecting eligible patients for PALN dissection based on prognostic factors of PALN involvement is of significant value. Several studies have confirmed that an increased risk of PALN involvement exists in patients with pelvic lymph node metastases [15,18–20].

The primary objective of this systematic review and meta-analysis was to evaluate upstaging outcomes of surgical PALN dissection after negative para-aortic imaging in patients with cervical cancer, in order to assess the added diagnostic value of laparoscopic PALN dissection.

2. Methods

Reporting was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [21].

2.1. Search strategy

A systematic literature search was performed and last updated on 18 April 2021 to identify data investigating the role of pretherapeutic surgical PALN assessment and its impact on detection of metastases in patients with cervical cancer. Relevant articles were identified in databases of PubMed/MEDLINE and Embase using the search terms 'cervical', 'cancer', 'para-aortic', 'lymphadenectomy', and synonyms of these terms, according to the search strategy presented in Table 1.

2.2. Study selection

After removal of duplicates, all titles and abstracts were reviewed for eligibility. Subsequently, full texts of potentially relevant articles were retrieved and evaluated for inclusion. Eligibility criteria included diagnostic studies published from the year 2000 onward that reported on the accuracy of laparoscopic PALN dissection and imaging for detection of metastatic para-aortic lymph nodes in humans with cervical cancer using histology as reference standard. Both randomized and non-randomized, prospective and retrospective studies were eligible.

The following article types were not eligible: reviews, editorials, letters to the editor, case reports and conference abstracts. If significant overlap of studies was found between multiple articles, only the most recent article describing the largest series was included. Publications written in other languages than English or Dutch were excluded. Also, articles were excluded when there was no full text available. Studies that included other outcome measures than upstaging, ten or less patients with cervical carcinoma or insufficient data in order to create a 2-by-2 contingency table were excluded. Studies in which reading of the staging PET, CT or MRI scans was not blinded to the results of pathology after PALN dissection were excluded. Finally, reference lists of included articles and related reviews were screened for other potentially suitable articles. For subsequent quantitative analyses only studies reporting on false negative and true negative cases of 3D imaging after PALN dissection in a patient-based analysis were eligible.

2.3. Data extraction and quality assessment

Study and patient characteristics as well as treatment- and outcome-related factors were extracted from each study, and 2-by-2 contingency tables were constructed including true-positive, false-positive, true-negative, and false-negative numbers. The methodological quality of the selected studies was critically appraised using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [22]. For each study the risk of bias and applicability concerns (i.e. 'low, 'moderate' or 'high') on 4 key domains (i.e. patient selection, index test, reference standard, and flow and timing) were determined. Each domain was assessed in terms of risk of bias and the first 3 domains also in terms of applicability concerns. The results of meta-analyses were interpreted in light of the risk of bias findings.

Table 1
Search strategy and results.

No.	Search query	PubMed	Embase
#1	Cervical OR cervix	273,410	294,621
#2	Cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumor OR tumors OR neoplasm OR neoplasms OR malignancy OR malignancies OR malignant	3,444,584	3,895,162
#3	Para-aortic OR paraaortic OR peri-aortic OR periaortic OR PALN OR retroperitoneal	37,396	44,205
#4	Laparoscopic OR laparoscopy OR node dissection OR nodal dissection OR node resection OR nodal resection OR node excision OR nodal excision OR lymphadenectomy	193,094	251,327
#5	#1 AND #2 AND #3 AND #4	1044	1726

2.4. Statistical analysis

The primary outcome was the proportion of patients in which upstaging was observed by PALN dissection by means of histologically proven metastatic para-aortic nodes after previous 3D imaging without suspicion of PALN metastases. This corresponds to the false-negative rate of the imaging modality in each cohort and was calculated as the number of false-negative para-aortic imaging cases divided by the total number of patients with para-aortic negative imaging. The utility of preoperative 3D imaging in detecting metastases to the para-aortic lymph nodes was further assessed by calculating the sensitivity, specificity, negative and positive predictive value (NPV and PPV) of the imaging modality for the identification of PALN metastases.

The reported upstaging rates were pooled using a random-effects model and the result was expressed as proportion with 95% confidence interval (95% CI). The I^2 statistic was used to detect heterogeneity across studies. An I^2 between 30 and 60% was considered moderate heterogeneity according to the Cochrane Handbook for Systematic Reviews [23]. To determine a potential difference between upstaging rates after PALN dissection ‘up to the left renal vein’ versus ‘up to the inferior mesenteric artery’, meta-regression analysis was performed. Statistical analysis was performed using R open-source software version 3.3.8 (http://www.R-project.org; ‘Rcurl’, ‘metafor’, and ‘meta’ packages).

3. Results

3.1. Identification of studies

The process of study selection is demonstrated in Fig. 1. The systematic search strategy identified 2770 references. After removal of duplicates 1934 unique references were screened on title and abstract. Among those references 196 met the inclusion criteria. In the full-text screening of these references 182 articles were excluded for various reasons (Fig. 1), including a lack of reporting on upstaging as outcome measure ($n = 54$) or a lack of sufficient data in conference abstracts ($n = 51$). Other main reasons for exclusion were insufficient data for a 2-by-2 contingency table ($n = 26$) or a language other than English or Dutch ($n = 13$). Finally, 1 study was excluded because nuclear medicine physicians were not blinded to pathological results when they evaluated the PET scans [24].

Cross-referencing identified 2 additional articles. These articles were not part of the initial search result, because the title nor abstract included the ‘lymphadenectomy’ search term or synonyms. The final analysis included 16 studies [14,15,18,19,25–36] reporting on 18 cohorts which were suitable for quantitative meta-analysis with pooling of upstaging outcomes.

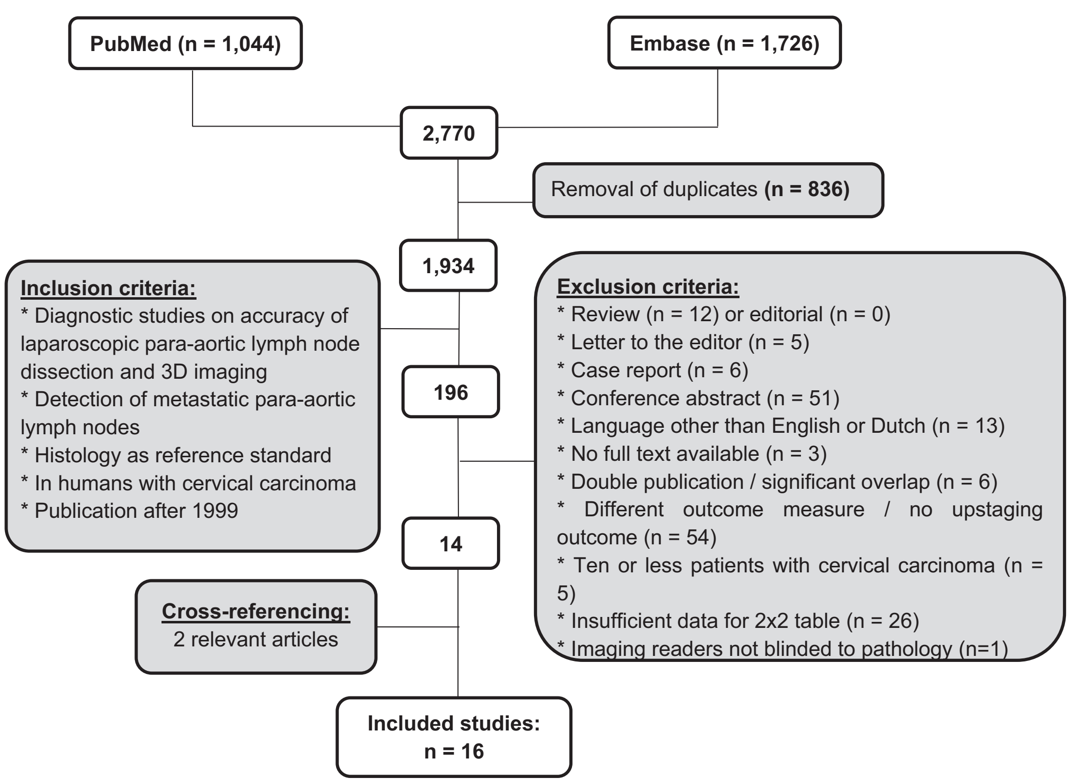

Fig. 1. Flowchart summarizing search results and study selection.

Table 2
Characteristics of studies included for quantitative synthesis.

Study, year	Data acquisition	No. patients (total)	FIGO stage	Age (mean)	Upper level of dissection	Laparoscopic technique	No. dissected nodes[a]	Post-operative morbidity, No. (%)
Hertel, 2002 [25]	Prospective	91	IB2-IVB	49.7	NR	NR	10 [1–50]	2 (2%)
Wright, 2005 [26]	Retrospective	45	IA2-IIA	43.0	IMA	Retro	NR	NR
Yildirim, 2007 [27]	Prospective	16	IIB-IVA	48.7	IMA	Extra	17 [14–24]	0 (0%)
Mortier, 2008 [28]	Retrospective	90	IB2-IIIB	48.0	IMA	Retro/Trans	6 [1–24]	5 (6%)
Leblanc, 2011 [14]	Retrospective	125	IB2-IVA	48.3	LRV	Extra/Trans	17 [4–46]	7 (6%)
Ramirez, 2011 [29]	Prospective	60	IB2-IIIB	48.0	LRV	Extra	11 [1–39]	7 (12%)
Gil-Moreno, 2011 [30]	Prospective	87	IB2-IVA	51.0	LRV	Extra	16 [4–62]	6 (7%)
Uzan, 2011 [31]	Retrospective	95	IB1-IVA	45.0	≥IMA	Retro/Trans	13 [4–39]	15 (16%)
Fastrez, 2013 [32]	Retrospective	37	IB1-IVA	52.5	LRV and IMA	Retro/Trans	28 [1–54]	5 (14%)
Gouy, 2013 [15]	Prospective	237	IB2-IVA	46.0	LRV	Extra/Trans	NR	25 (11%)
Margulies, 2013 [33]	Retrospective	61	IB2-IVA	48.0	LRV	Extra/Trans	13 [2–42]	8 (13%)
Vázquez-Vicente, 2018 [34]	Retrospective	59	IB2-IVA	52.3	LRV	Retro/Trans	16 [1–37]	4 (6%)
Perez-Medina, 2019 [35]	Prospective	52	IB2-IVA	47.2	LRV	Trans	10 [NR]	NR
Mezquita, 2019 [36]	Retrospective	67	IB2-IVA	56.0	LRV	Trans	NR	7 (10%)
De Cuypere, 2020 [18]	Retrospective	168	IB2-IVA	52.0	LRV and IMA	Retro/Trans	19 [1–46]	22 (13%)
Gouy, 2021 [19]	Retrospective	240	IB2-IVA	45.0	LRV	Retro/Trans	15 [2–40]	NR

No: number of patients. NR: not reported. IMA: inferior mesenteric artery. LRV: left renal vein. Retro: retroperitoneal. Extra: extraperitoneal. Trans: transperitoneal.
[a] Reported mean of median [range].

3.2. Study characteristics

Characteristics of the 18 cohorts within 16 studies included in the quantitative synthesis are outlined in Table 2. Six studies [15,25,27,29,30,35] (38%) were prospective and 10 studies [14,18,19,26,28,31–34,36] (63%) were retrospective by design. All studies used laparoscopic procedures. In 2 studies [30,32], the laparoscopic procedure was robot-assisted. Surgical approaches were extraperitoneal or retroperitoneal in 4 studies [26,29–31], transperitoneal in 2 studies [35,36] and not reported in 1 study [25]. In 9 studies [14,15,18,19,28,31–34], both surgical approaches were used. In 9 studies [14,15,19,29,30,33–36], the upper level of dissection was the left renal vein, which is considered the golden standard. In 4 studies [26–28,31], the upper level of dissection was at least the inferior mesenteric artery. In 2 studies [18,32] both levels were used and 1 study [24] lacked reporting of the upper level of dissection. The average number of dissected PALNs was reported in 13 studies and varied from 6 to 28. Reported post-operative morbidity was observed in 0–16% of patients (Table 2).

Outcomes of the 18 cohorts within 16 studies including 1530 patients are outlined in Table 3. In 12 cohorts a total of 1180 patients received PET-CT or PET and 1138 (96%) of those patients had no suspicious PALNs on imaging. Six studies included a total of 436 patients who received CT and/or MRI for detecting PALN metastases and 354 (81%) of those patients had no suspicious PALN on imaging. A number of 86 patients besides PET also received MRI or CT and were included in both subgroups for further analyses. Seven studies [14,15,18,19,29,31,33] evaluated the rate of PALN metastases in 311 patients with metastatic pelvic nodes (but not para-aortic nodes) on PET-CT (Table S1).

3.3. Quality assessment

The results of the quality assessment are presented in Table 4. Overall, there was a moderate to good quality of included studies, with minor to no concerns regarding outcome measurement. Most studies included a consecutive series of patients with appropriate exclusions only. In general, the imaging procedures and pathologic assessments were sufficiently described and considered valid. Partial verification bias was of particular concern in most studies because often not all patients underwent surgical resection from below the left renal vein, which could have led to overestimation of sensitivity, specificity and negative predictive value estimates. The time interval between imaging and surgery was ≤2.5 weeks in 9 studies [14,15,18,19,27,29,31,33,35] and not reported in 7 studies [24,26,28,30,32,34,36].

3.4. Meta-analysis

Meta-analysis was performed for 18 cohorts reporting on surgical para-aortic nodal upstaging rates after any imaging. Subgroup analysis including 12 studies [14,15,18,19,26–29,31–33,35] showed an upstaging proportion by PALN dissection after negative PET or PET-CT among 1138 patients of 0.12 (95% CI: 0.10–0.15; Fig. 2). Similarly, subgroup analysis including 6 studies [25,28,30,34–36] showed an upstaging proportion by PALN dissection after negative MRI or CT among 354 patients of 0.11 (95% CI: 0.08–0.16; Fig. 3). No significant heterogeneity across studies on upstaging after PET and PET-CT ($I^2 = 0\%$) nor across studies on upstaging after MRI and CT ($I^2 = 27\%$) was observed.

Finally, meta-analysis was performed by pooling upstaging rates of cohorts that included only patients with positive pelvic lymph nodes (but negative PALN) on PET-CT. Pooled analysis across those 7 cohorts ($n = 311$) demonstrated an overall pooled upstaging proportion of 0.21 (95% CI: 0.17–0.26; Fig. 4). No statistical heterogeneity in upstaging proportions among these cohorts was observed ($I^2 = 0\%$).

In the group of studies on PALN dissection after negative PET or PET-CT, further subdivision into 6 versus 4 studies that performed dissection ‘up to the left renal vein’ versus ‘up to the inferior mesenteric artery’ resulted in pooled upstaging rates by PALN dissection of 0.12 (95% CI: 0.10–0.14) versus 0.10 (95% CI: 0.06–0.15). The difference was not statistically significant in meta-regression analysis ($p = 0.475$). As such subdivision in the other groups of studies (i.e. after negative MRI or CT, or after PET-CT only in patients with positive pelvic nodes) led to too small subgroups, no meta-regression analyses were performed in these groups of studies.

4. Discussion

Increasing evidence suggests imaging techniques cannot completely fill the gap between radiological and histological lymph node staging in cervical cancer. This meta-analysis demonstrates that in case of no suspicious PALNs on PET-CT or MRI, PALN dissection still identifies lymph node metastases in 11–12% of all patients with locally advanced cervical cancer, and in up to 21% of patients with pelvic nodal metastases. This finding quantifies the added diagnostic value of laparoscopic PALN dissection. The result that patients with pelvic nodal metastases have a significantly higher upstaging rate after PALN dissection than a more unselected group of cervical cancer patients (21% versus 11–12%) validates the predictive power of pelvic nodal involvement for the PALN status. Also, this finding suggests that patients with pelvic nodal

Table 3
Outcomes of studies included for quantitative synthesis.

Study, year	No. (%) negative imaging	No. TN	No. FN	Up-staging	Sens-itivity	Spec-ificity	PPV	NPV	Imaging technique
Hertel, 2002 [25]	79 (87)	66	13	16%	19%	88%	25%	84%	CT
Wright, 2005 [26]	43 (96)	40	3	7%	25%	98%	50%	93%	PET
Yildirim, 2007 [27]	12 (75)	10	2	17%	50%	83%	50%	83%	PET-CT
Mortier, 2008 [28]	41 (93)	36	5	12%	38%	100%	100%	88%	PET
	73 (91)	67	6	8%	40%	96%	57%	92%	CT
Leblanc, 2011 [14]	112 (90)	98	14	13%	33%	94%	54%	88%	PET-CT
Ramirez, 2011 [29]	53 (88)	44	9	17%	36%	96%	71%	83%	PET-CT
Gil-Moreno, 2011 [30]	66 (76)	58	8	12%	38%	78%	24%	88%	MRI
Uzan, 2011 [31]	95 (100)	87	8	8%	NR	NR	NR	92%	PET-CT
Fastrez, 2013 [32]	35 (95)	31	4	11%	20%	97%	50%	89%	PET-CT
Gouy, 2013 [15]	237 (100)	208	29	12%	NR	NR	NR	88%	PET-CT
Margulies, 2013 [33]	61 (100)	54	7	11%	NR	NR	NR	89%	PET-CT
Vázquez-Vicente, 2018 [34]	46 (78)	44	2	4%	75%	86%	46%	95%	CT
Perez-Medina, 2019 [35]	36 (69)	32	4	11%	78%	94%	88%	88%	PET
	38 (73)	32	6	16%	67%	94%	86%	84%	MRI
Mezquita, 2019 [36]	52 (78)	49	3	6%	75%	89%	60%	94%	MRI/CT
De Cuypere, 2020 [18]	151 (90)	125	26	17%	24%	93%	47%	83%	PET-CT
Gouy, 2021 [19]	240 (100)	218	22	9%	NR	NR	NR	91%	PET-CT

No: number of patients. TN: true negatives. FN: false negatives. PPV: positive predictive value. NPV: negative predictive value. NR: not reported.

metastases may be the most eligible for PALN dissection as diagnostic procedure, considering that the benefits of staging surgery should outweigh its possible morbidities [14].

On the other hand, according to the current meta-analysis only using pelvic nodal metastasis as selection factor for PALN dissection would still reveal absence of para-aortic lymph node metastases in 79% of patients. Therefore, further elucidation of which patients carry the highest risk of PALN metastases is desired. A phase III trial, conducted by MD Anderson Cancer Center, demonstrated that the presence of pelvic uptake on PET imaging (but not histologic tumor type, tumor volume, age or FIGO disease stage) was associated with PALN involvement [20]. However, other studies suggested that histologic tumor type and FIGO disease stage are also predictive factors of PALN involvement and should be included in future research [15].

The introduction of PET-CT was believed to improve sensitivity in detecting small-sized PALN metastases [3,17,18]. However, this meta-analyses reveals that the pooled rate of upstaging by PALN dissection after both PET-CT and MRI or CT are comparable (i.e. 11–12%). The size of metastasis is strongly correlated to the detection ability by PET, since the detection threshold of PET-CT imaging for accurately detecting tumor tissue is approximately 5 mm [15,37]. Indeed, some studies reported that nearly 40% of patients with false-negative PET-CT results had nodal metastases smaller than 5 mm [28,29]. As such, negative para-aortic PET-CT (or MRI/CT) does not make PALN dissection obsolete and cannot be fully trusted to determine the appropriate extent of radiotherapy fields. Extending pelvic radiotherapy fields to the PALN region in patients with no suspicious PALNs has not been studied in a modern randomized trial. Such 'prophylactic' PALN irradiation resulted in improved progression-free survival in some cohort studies [38,39], but not in others [40,41], and its role is therefore not clearly established.

Regarding the surgical dissection, particular attention must be paid to PET-CT positivity in the common iliac region. It has been recommended that the multidisciplinary team must define the inferior boundaries of the surgical dissection per patient, taking precisely into account the upper limit of the planned pelvic radiation field [18]. In addition, the superior level of PALN dissection remains a matter of debate [42,43]. The majority of studies in this literature review defined the left renal vein as the upper limit for a thorough dissection. Although rare, skip metastases may be found above the inferior mesenteric artery, and isolated recurrences were also reported above the inferior mesenteric artery [3,14]. Indeed, our meta-regression analysis revealed a slightly higher pooled upstaging rate among studies with dissection up to the left renal vein (12%) versus studies with dissection up to the inferior mesenteric artery (9%), but this difference was not statistically significant.

Taking post-operative complication rates into account is important in the light of reported toxicity of alternatively extending the (para-aortic) radiotherapy field [29]. This is demonstrated to be approximately doubled compared to toxicity rates of not extending the (pelvic) radiotherapy field [5]. Most of the excess in complication rates (grade ≥ 3) is

Table 4
Quality assessment of included studies according to the QUADAS-2 tool [21].

Study, year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference test
Hertel, 2002 [25]	Low	Moderate	Moderate	Unclear	Low	Low	Moderate
Wright, 2005 [26]	Low	Moderate	High	Unclear	Moderate	Low	Moderate
Yildirim, 2007 [27]	High	Low	Low	Low	Moderate	Low	Moderate
Mortier, 2008 [28]	Low	Low	Moderate	Unclear	Low	Low	Moderate
Leblanc, 2011 [14]	Low	Low	Low	Low	Low	Low	Low
Ramirez, 2011 [29]	Low	Low	Low	Low	Low	Low	Low
Gil-Moreno, 2011 [30]	Low	Low	Low	Unclear	Low	Low	Low
Uzan, 2011 [31]	Moderate	Low	Moderate	Low	Low	Low	Moderate
Fastrez, 2013 [32]	Low	Low	Low	Unclear	Low	Low	Low
Gouy, 2013 [15]	Low	Low	Low	Low	Low	Low	Low
Margulies, 2013 [33]	Low	Low	Low	Low	Low	Low	Low
Vázquez-Vicente, 2018 [34]	Low	Low	Low	Unclear	Low	Low	Low
Perez-Medina, 2019 [35]	Low	Low	Low	Low	Low	Low	Low
Mezquita, 2019 [36]	Low	Low	Low	Unclear	Low	Low	Low
De Cuypere, 2020 [18]	Low	Low	Low	Low	Low	Low	Low
Gouy, 2021 [19]	Moderate	Low	Low	Low	Moderate	Low	Low

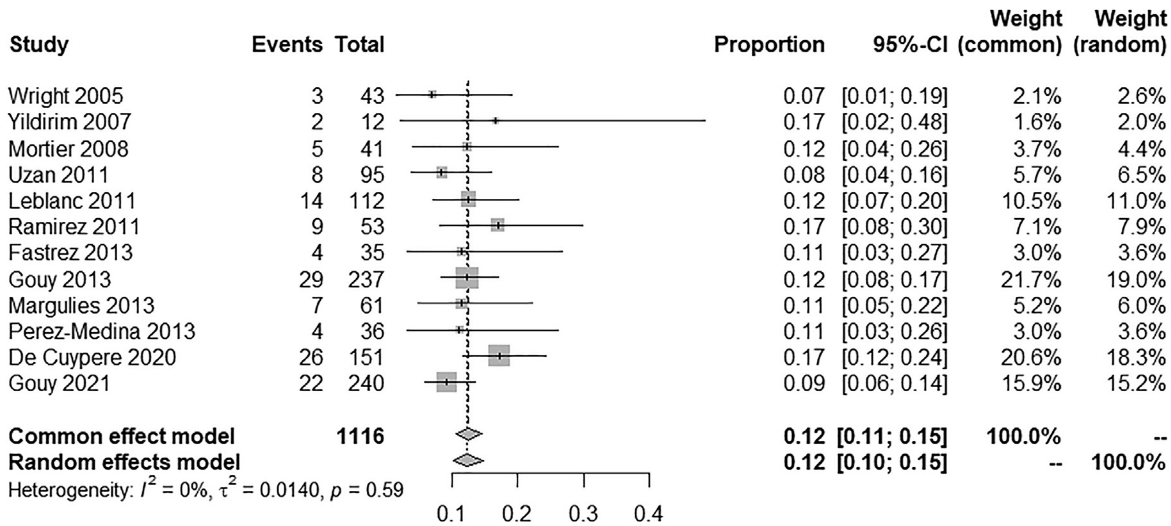

Fig. 2. Forest plot of the pooled analysis in 12 cohorts of upstaging proportion by PALN dissection after para-aortic negative PET(-CT) imaging.

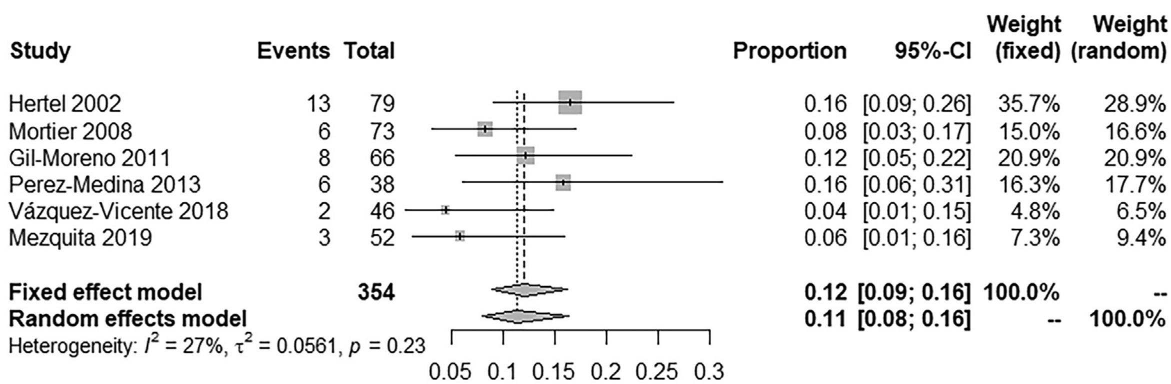

Fig. 3. Forest plot of the pooled analysis in 6 cohorts of upstaging proportion by PALN dissection after para-aortic negative MRI or CT imaging.

determined by gastrointestinal toxicity (i.e. radiation-induced enteritis) of up to 10% [5]. Various studies have shown that laparoscopic surgical staging is safe and feasible [3,14,17,25,30]. Complication rates of 0–16% have been reported [2]. Of all complications lymphocyst formation (grade 3) is the most common, but generally does not delay the start of radiotherapy [15].

Several studies on PALN dissection included patients with suspicious PALNs on imaging and reported significant rates of false-positive cases [14,18,25,30,34,36]. However, the interest of staging surgery is limited in patients with obvious PALN uptake on PET-CT because of the possible and unnecessary morbidity. Most of the false-positive findings are related to well-known conditions, such as ovarian follicles, urinary tract fixations,

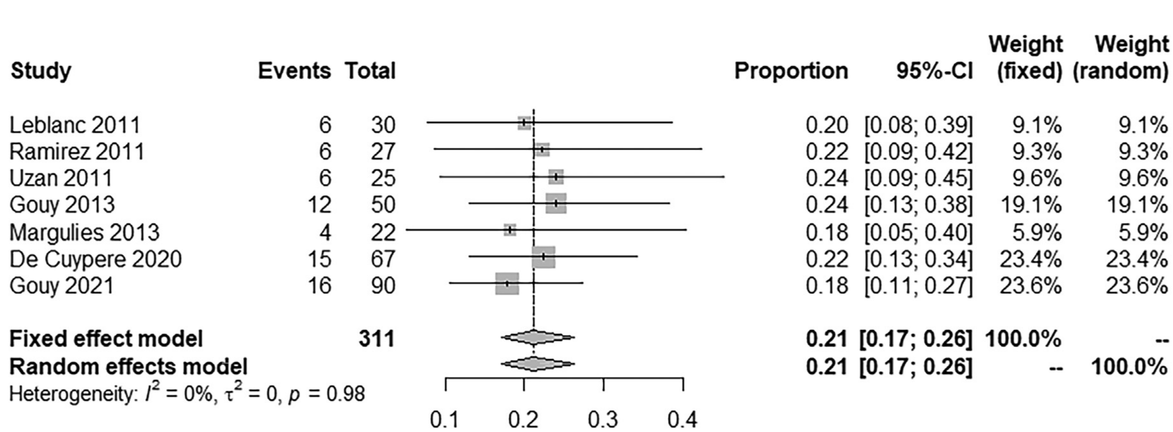

Fig. 4. Forest plot of the pooled analysis in 7 cohorts of upstaging proportion by PALN dissection after para-aortic negative PET-CT imaging and pelvic lymph nodes metastases.

bowel-loop fixations or inflammatory processes [27]. Although difficulty in differentiating between metastatic and inflammatory lymph nodes exists, experts have stated that most false positive-findings should be preventable [24].

A few limitations apply to this meta-analysis. First, it would be desirable to know what proportion of upstaging by PALN dissection is due to micrometastases (i.e. <5 mm) to find out to what extent the detection threshold of imaging is responsible for the false-negative results. However, the studies generally did not report on such detailed histopathologic level, which might in part be explained by the lack of routine serial sectioning. Finally, true clinical usefulness of PALN cannot be claimed by the results of this meta-analysis and would ideally require prospective controlled trials of laparoscopic PALN dissection versus no PALN dissection with clinically relevant patient outcomes such as progression-free and overall survival, toxicity and quality of life. However, this meta-analysis is strengthened by the reasonable number of studies and a moderate to good quality of the individual studies.

In conclusion, this meta-analysis of 18 cohorts in 16 studies demonstrates a significant rate of upstaging in patients with cervical cancer by laparoscopic PALN dissection after imaging suggested no PALN metastases, particularly in patients with pelvic nodal metastases. The false-negative rate of PET-CT and MRI or CT imaging for the detection of PALN metastasis should be considered in clinical practice. The higher rate of PALN metastases in patients with pelvic nodal metastasis could help select patients eligible for diagnostic PALN dissection.

Conflicts of interest

All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.12.026.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (8) (2018) 394–424, https://doi.org/10.3322/caac.21492.

[2] S. Gouy, P. Morice, F. Narducci, C. Uzan, J. Gilmore, H. Kolesnikov-Gauthier, D. Querleu, C. Haie-Meder, E. Leblanc, Nodal-staging surgery for locally advanced cervical cancer in the era of PET, Lancet Oncol. 13 (5) (2012) 212–220, https://doi.org/10.1016/S1470-2045(12)70011-6.

[3] S. Marnitz, C. Köhler, C. Roth, J. Füller, W. Hinkelbein, A. Schneider, Is there a benefit of pretreatment laparoscopic transperitoneal surgical staging in patients with advanced cervical cancer? Gynecol. Oncol. 99 (3) (2005) 536–544, https://doi.org/10.1016/j.ygyno.2005.07.005.

[4] M. Rotman, T.F. Pajak, K. Choi, M. Clery, V. Marcial, P.W. Grigsby, J. Cooper, M. John, Prophylactic extended-field irradiation of Para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20, JAMA. 274 (5) (1995) 387–393 (PMID: 7616634).

[5] C. Haie, M.H. Pejovic, A. Gerbaulet, J.C. Horiot, H. Pourquier, J. Delouche, J.F. Heinz, D. Brune, J. Fenton, G. Pizzi, et al., Is prophylactic Para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group, Radiother. Oncol. 11 (2) (1988) 101–112, https://doi.org/10.1016/0167-8140(88)90245-9.

[6] S. Kuku, C. Fragkos, M. McCormack, A. Forbes, Radiation-induced bowel injury: the impact of radiotherapy on survivorship after treatment for gynaecological cancers, Br. J. Cancer 109 (6) (2013) 1504–1512, https://doi.org/10.1038/bjc.2013.491.

[7] N. Bhatla, D. Aoki, D.N. Sharma, R. Sankaranarayanan, Cancer of the cervix uteri, Int. J. Gynaecol. Obstet. 143 (Suppl. 2) (2018) 22–36, https://doi.org/10.1002/ijgo.12611.

[8] H.J. Choi, J.W. Roh, S.S. Seo, S. Lee, J.Y. Kim, S.K. Kim, K.W. Kang, J.S. Lee, J.Y. Jeong, S.Y. Park, Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study, Cancer. 106 (4) (2006) 914–922, https://doi.org/10.1002/cncr.21641.

[9] H.H. Chung, S. Lee, J.S. Sim, J.Y. Kim, S.S. Seo, S.Y. Park, J.W. Roh, Pretreatment laparoscopic surgical staging in locally advanced cervical cancer: preliminary results in Korea, Gynecol. Oncol. 97 (2) (2005) 468–475, https://doi.org/10.1016/j.ygyno.2005.01.005.

[10] M. Boughanim, S. Leboulleux, A. Rey, C.T. Pham, Y. Zafrani, P. Duvillard, J. Lumbroso, C. Haie-Meder, M. Schlumberger, P. Morice, Histologic results of para-aortic lymphadenectomy in patients treated for stage IB2/II cervical cancer with negative [18F]fluorodeoxyglucose positron emission tomography scans in the para-aortic area, J. Clin. Oncol. 26 (15) (2008) 2558–2561, https://doi.org/10.1200/JCO.2007.14.3933.

[11] R.M. Smits, P.L. Zusterzeel, R.L. Bekkers, Pretreatment retroperitoneal Para-aortic lymph node staging in advanced cervical cancer: a review, Int. J. Gynecol. Cancer 24 (6) (2014) 973–983, https://doi.org/10.1097/IGC.0000000000000177.

[12] M. Del Pino, P. Fusté, J. Pahisa, A. Rovirosa, M.J. Martínez-Serrano, S. Martínez-Román, I. Alonso, L. Vidal, J. Ordi, A. Torné, Laparoscopic lymphadenectomy in advanced cervical cancer: prognostic and therapeutic value, Int. J. Gynecol. Cancer 23 (9) (2013) 1675–1683, https://doi.org/10.1097/IGC.0000000000000000.

[13] C. Köhler, A. Mustea, S. Marnitz, A. Schneider, V. Chiantera, U. Ulrich, J.P. Scharf, P. Martus, M.A. Vieira, A. Tsunado, Perioperative morbidity and rate of upstaging after laparoscopic staging for patients with locally advanced cervical cancer: results of a prospective randomized trial, Am. J. Obstet. Gynecol. 213 (4) (2015) 1–7, https://doi.org/10.1016/j.ajog.2015.05.026.

[14] E. Leblanc, H. Gauthier, D. Querleu, G. Ferron, S. Zerdoud, P. Morice, C. Uzan, S. Lumbroso, F. Lecuru, A.S. Bats, N. Ghazzar, M. Bannier, G. Houvenaeghel, I. Brenot-Rossi, F. Narducci, Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult Para-aortic node involvement in patients with a locally advanced cervical carcinoma, Ann. Surg. Oncol. 18 (8) (2011) 2302–2309, https://doi.org/10.1245/s10434-011-1583-9.

[15] S. Gouy, P. Morice, F. Narducci, C. Uzan, A. Martinez, A. Rey, E. Bentivegna, P. Pautier, D. Deandreis, D. Querleu, C. Haie-Meder, E. Leblanc, Prospective multicenter study evaluating the survival of patients with locally advanced cervical cancer undergoing laparoscopic Para-aortic lymphadenectomy before chemoradiotherapy in the era of positron emission tomography imaging, J. Clin. Oncol. 31 (24) (2013) 3026–3033, https://doi.org/10.1200/JCO.2012.47.3520.

[16] C.H. Lai, K.G. Huang, J.H. Hong, C.L. Lee, H.H. Chou, T.C. Chang, S. Hsueh, H.J. Huang, K.K. Ng, C.S. Tsai, Randomized trial of surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer, Gynecol. Oncol. 89 (1) (2003) 160–167, https://doi.org/10.1016/s0090-8258(03)00064-7.

[17] E. Leblanc, F. Narducci, M. Frumovitz, A. Lesoin, B. Castelain, M.C. Baranzelli, S. Taieb, C. Fournier, D. Querleu, Therapeutic value of pretherapeutic extraperitoneal laparoscopic staging of locally advanced cervical carcinoma, Gynecol. Oncol. 105 (2) (2007) 304–311, https://doi.org/10.1016/j.ygyno.2006.12.012.

[18] M. De Cuypere, P. Lovinfosse, F. Goffin, C. Gennigens, R. Rovira, J. Duch, M. Fastrez, G. Gebhart, J.L. Squifflet, M. Luyckx, G. Charaf, K. Crener, F. Buxant, D. Bucella, M. Jouret, R. Hustinx, F. Kridelka, Added value of Para-aortic surgical staging compared to 18F-FDG PET/CT on the external beam radiation field for patients with locally advanced cervical cancer: an ONCO-GF study, Eur. J. Surg. Oncol. 46 (5) (2020) 883–887, https://doi.org/10.1016/j.ejso.2019.11.496.

[19] S. Gouy, V. Seebacher, C. Chargari, M. Terroir, S. Grimaldi, A. Ilenko, A. Maulard, C. Genestie, A. Leary, P. Pautier, P. Morice, D. Deandreis, False negative rate at ^{18}F-FDG PET/CT in Para-aortic lymphnode involvement in patients with locally advanced cervical cancer: impact of PET technology, BMC Cancer 21 (1) (2021) 135, https://doi.org/10.1186/s12885-021-07821-9.

[20] M. Frumovitz, D. Querleu, A. Gil-Moreno, P. Morice, A. Jhingran, M.F. Munsell, H.A. Macapinlac, E. Leblanc, A. Martinez, P.T. Ramirez, Lymphadenectomy in locally advanced cervical cancer study (LiLACS): phase III clinical trial comparing surgical with radiologic staging in patients with stages IB2-IVA cervical cancer, J. Minim. Invasive Gynecol. 21 (1) (2014) 3–8, https://doi.org/10.1016/j.jmig.2013.07.007.

[21] D. Mother, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA group preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement, PLoS Med. 6 (7) (2009) 1000097, https://doi.org/10.1371/journal.pmed.1000097.

[22] P.F. Whiting, A.W. Rutjes, M.E. Westwood, S. Mallet, J.J. Deeks, J.B. Reitsma, M.M. Leeflang, J.A. Sterne, P.M. Bossuyt, QUADAS-2 group: QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies, Ann. Intern. Med. 155 (8) (2011) 529–536, https://doi.org/10.7326/0003-4819-155-8-201110180-00009.

[23] J. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. Page, V. Welch (Eds.), Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021), Cochrane, 2021.

[24] W.C. Lin, Y.C. Hung, L.S. Yen, C.H. Kao, R.F. Yen, Y.Y. Shen, Usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography to detect Para-aortic lymph nodal metastasis in advanced cervical cancer with negative computed tomography findings, Gynecol. Oncol. 89 (1) (2003) 73–76, https://doi.org/10.1016/s0090-8258(03)00058-1.

[25] H. Hertel, C. Köhler, T. Elhawary, W. Michels, M. Possover, A. Schneider, Laparoscopic staging compared with imaging techniques in the staging of advanced cervical cancer, Gynecol. Oncol. 87 (1) (2002) 46–51, https://doi.org/10.1006/gyno.2002.6722.

[26] J.D. Wright, F. Dehdashti, T.J. Herzog, D.G. Mutch, P.C. Huettner, J.S. Rader, R.K. Gibb, M.A. Powell, F. Gao, B.A. Siegel, P.W. Gribsby, Preoperative lymph node staging of early-stage cervical carcinoma by [^{18}F]-fluoro-2-deoxy-D-glucose-positron emission tomography, Cancer. 104 (11) (2005) 2484–2491, https://doi.org/10.1002/cncr.21527.

[27] Y. Yildirim, S. Sehirali, M.E. Avci, C. Yilmaz, K. Ertopcu, S. Tinar, Y. Duman, S. Sayhan, Integrated PET/CT for the evaluation of Para-aortic nodal metastasis in locally advanced cervical cancer patients with negative conventional CT findings, Gynecol. Oncol. 108 (1) (2008) 154–159, https://doi.org/10.1016/j.ygyno.2007.09.011.

[28] D.G. Mortier, S. Stroobants, F. Amant, P. Neven, E. Van Limbergen, I. Vergote, Laparoscopic Para-aortic lymphadenectomy and positron emission tomography scan as staging procedures in patients with cervical carcinoma stage IB2-IIIB, Int. J. Gynecol. Cancer 18 (4) (2008) 723–729, https://doi.org/10.1111/j.1525-1438.2007.01061.x.

[29] P.T. Ramirez, A. Jhingran, H.A. Macapinlac, E.D. Euscher, M.F. Munsell, R.L. Coleman, P.T. Soliman, K.M. Schmeler, M. Frumovitz, L.M. Ramondetta, Laparoscopic extraperitoneal Para-aortic lymphadenectomy in locally advanced cervical cancer:

a prospective correlation of surgical findings with positron emission tomography/computed tomography findings, Cancer. 117 (9) (2011) 1928–1934, https://doi.org/10.1002/cncr.25739.
[30] A. Gil-Moreno, S. Franco-Camps, S. Cabrera, A. Pérez-Benavente, X. Martínez-Gómez, A. Garcia, J. Xercavins, Pretherapeutic extraperitoneal laparoscopic staging of bulky or locally advanced cervical cancer, Ann. Surg. Oncol. 18 (2) (2011) 482–489, https://doi.org/10.1245/s10434-010-1320-9.
[31] C. Uzan, A. Souadka, S. Gouy, T. Debaere, J. Duclos, J. Lumbroso, C. Haie-Meder, P. Morice, Analysis of morbidity and clinical implications of laparoscopic Para-aortic lymphadenectomy in a continuous series of 98 patients with advanced-stage cervical cancer and negative PET–CT imaging in the Para-aortic area, Oncologist. 16 (7) (2011) 1021–1027, https://doi.org/10.1634/theoncologist.2011-0007.
[32] M. Fastrez, F. Goffin, I. Vergote, J. Vandromme, P. Petit, K. Leunen, M. Degueldre, Multi-center experience of robot-assisted laparoscopic Para-aortic lymphadenectomy for staging of locally advanced cervical carcinoma, Acta Obstet. Gynecol. Scand. 92 (8) (2013) 895–901, https://doi.org/10.1111/aogs.12150.
[33] A.L. Margulies, A. Peres, E. Barranger, I. Perreti, J.F. Brouland, E. Troubet, L.E. Sarda-Mantel, A. Thoury, C. Chis, F. Walker, D. Luton, Y. Delpech, M. Koskas, Selection of patients with advanced-stage cervical cancer for Para-aortic lymhpadenectomy in the era of PET/CT, Anticancer Res. 33 (1) (2013) 283–286.
[34] D. Vázquez-Vicente, B. Fernández Del Bas, J. García Villayzán, H.A. Di Fiore, J. Luna Tirado, V. Cascado Echarren, J. García-Foncillas, J. Plaza Arranz, L. Chiva, Laparoscopic paraaortic surgical staging in locally advanced cervical cancer: a single center experience, Clin. Transl. Oncol. 20 (11) (2018) 1455–1459, https://doi.org/10.1007/s12094-018-1878-4.
[35] T. Perez-Medina, A. Pereira, J. Mucientes, M. García-Espantaleón, J.S. Jiménez, L. Calles, B. Rodríguez, E. Iglesias, Prospective evaluation of 18-fluoro-2-deoxy-D-glucose positron emission tomography for the discrimination of paraaortic nodal spread in patients with locally advanced cervical carcinoma, Int. J. Gynecol. Cancer 23 (1) (2013) 170–175, https://doi.org/10.1097/IGZ.0b013e3182784289.
[36] G. Mezquita, J.C. Muruzabal, B. Perez, S. Aguirre, E. Villafranca, M. Jurado, Para-aortic plus pelvic lymphadenectomy in locally advanced cervical cancer: a single institutional experience, Eur. J. Obstet. Gynecol. Reprod. Biol. 236 (2019) 79–83, https://doi.org/10.1016/j.ejogrb.2019.02.033.
[37] J.W. Roh, S.S. Seo, S. Lee, K.W. Kang, S.K. Kim, J.S. Sim, J.Y. Kim, E.K. Hong, D.S. Cho, J.S. Lee, S.Y. Park, Role of positron emission tomography in pretreatment lymph node staging of uterine cervical cancer: a prospective surgicopathologic correlation study, Eur. J. Cancer 41 (14) (2005) 2086–2092, https://doi.org/10.1016/j.ejca.2005.05.013.
[38] M. Peters, A.A.C. de Leeuw, C.N. Nomden, K. Tanderup, K. Kirchheiner, J.C. Lindegaard, C. Kirisits, C. Haie-Meder, A. Sturdza, L. Fokdal, U. Mahantshetty, P. Hoskin, B. Segedin, K. Bruheim, B. Rai, F. Huang, R. Cooper, E. van der Steen-Banasik, E. van Limbergen, B.R. Pieters, L.T. Tan, P.S.N. van Rossum, N. Nesvacil, R. Nout, M.P. Schmid, R. Pötter, I.M. Jürgenliemk-Schulz, EMBRACE collaborative group, risk factors for nodal failure after radiochemotherapy and image guided brachytherapy in locally advanced cervical cancer: an EMBRACE analysis, Radiother. Oncol. 163 (2021) 150–158, https://doi.org/10.1016/j.radonc.2021.08.020.
[39] Y. Ouyang, Y. Wang, K. Chen, X. Cao, Y. Zeng, Clinical outcome of extended-field irradiation vs. pelvic irradiation using intensity-modulated radiotherapy for cervical cancer, Oncol. Lett. 14 (6) (2017) 7069–7076, https://doi.org/10.3892/ol.2017.7077.
[40] W. Wang, X. Liu, Q. Meng, F. Zhang, K. Hu, Prophylactic extended-field irradiation for patients with cervical cancer treated with concurrent chemoradiotherapy: a propensity-score matching analysis, Int. J. Gynecol. Cancer 28 (8) (2018) 1584–1591, https://doi.org/10.1097/IGC.0000000000001344.
[41] M.L. Yap, J. Cuartero, J. Yan, M. Pintilie, A. Fyles, W. Levin, L. Manchul, M. Milosevic, The role of elective Para-aortic lymph node irradiation in patients with locally advanced cervical cancer, Clin. Oncol. (R Coll. Radiol.). 26 (12) (2014) 797–803, https://doi.org/10.1016/j.clon.2014.08.008.
[42] E. Leblanc, N. Katdare, F. Narducci, L. Bresson, S. Gouy, P. Morice, G. Ferron, D. Querleu, A. Martinez, Should systematic infrarenal para-aortic dissection be the rule in the pretherapeutic staging of primary or recurrent locally advanced cervix cancer patients with a negative preoperative para-aortic PET imaging? Int. J. Gynecol. Cancer 26 (1) (2016) 169–175, https://doi.org/10.1097/IGC.0000000000000588.
[43] C. Petitnicolas, H. Azaïs, L. Ghesquière, E. Tresch-Bruneel, A. Cordoba, F. Narducci, L. Bresson, E. Leblanc, Morbidity of staging Inframesenteric paraaortic lymphadenectomy in locally advanced cervical cancer compared with infrarenal lymphadenectomy, Int. J. Gynecol. Cancer 27 (3) (2017) 575–580, https://doi.org/10.1097/IGC.0000000000000921.