Chasing nodes, saving lives?

Lymph node metastases in cervical cancer

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Faculteit der Geneeskunde

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Chapter 1

General introduction

Uterine cervical cancer is one of the most common cancers in women worldwide, with approximately 604,000 new cases and 342,000 deaths in 2020.[1] Although most cases occur in low- and middle-income countries, in the Netherlands, about 800 relatively young women are diagnosed with cervical cancer each year and 250 die from it.[2, 3] The incidence peaks between the ages of 35 and 45.[3] Disturbingly, the incidence of cervical cancer in the Netherlands has increased by 57% in the last two decades (from 6.6 to 10.4 European Standardized Rate (ESR) per 100,000 women), while mortality has not further decreased (Figure 1).[4] The World Health Organization (WHO) has developed a global strategy to accelerate the elimination of cervical cancer as a public health problem through vaccination, screening, and treatment access for women worldwide.[5] Although prevention is a rational approach to cervical cancer, better treatment strategies are still urgently needed. Focusing on lymph node metastasis may be a good strategy, as the presence of nodal metastasis is one of the most important prognostic factors in cervical cancer.[6] The identification of tumour-positive nodes is essential to provide insight into the clinical situation and prognosis, and to tailor treatment, with the goal to improve locoregional tumour control, survival and health-related quality of life (HRQoL). However, the best way to identify and manage lymph node metastases in cervical cancer patients is still under debate.

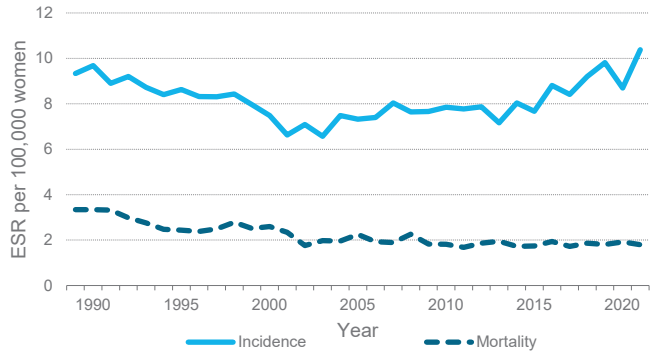

Figure 1. Incidence and mortality of cervical cancer in the Netherlands.[4]
Abbreviations: *ESR*, European Standardized Rate.

Diagnosis and staging

Staging is used to tailor treatment options and to provide prognostic information. At diagnosis, about 44% of patients have localised disease, 34% have regional disease, and 15% have distant metastases, with corresponding 5-year relative survival rates of 94%, 59% and 9%.[7] Cervical cancer usually spreads via direct extension into surrounding tissue or through lymphatic metastasis. The International Federation of Gynaecology and Obstetrics (FIGO) staging system is the most widely used classification system for cervical cancer, traditionally based on clinical examination alone. Since the 2018 revision, radiological and pathological assessments play a part in staging. The presence of lymph node metastasis has been defined as stage IIIC.[8, 9] Table 1 shows the 2009 and 2018 FIGO cervical cancer staging system.[8-10]

Table 1. The 2009 and 2018 International Federation of Gynaecology and Obstetrics (FIGO) cervical cancer staging system.

FIGO 2009		FIGO 2018	
I	Confined to the cervix	I	Confined to the cervix
IA	≤5 mm depth and ≤7 mm width, only diagnosed by microscopy	IA	≤5 mm depth, only diagnosed by microscopy
IA1	≤3 mm depth	IA1	≤3 mm depth
IA2	>3 mm and ≤5 mm depth	IA2	>3 mm and ≤5 mm depth
IB	Clinically visible lesion or >5 mm depth and >7 mm width	IB	Clinically visible lesion or >5 mm depth
IB1	≤4 cm tumour size	IB1	≤2 cm tumour size
IB2	>4 cm tumour size	IB2	>2 cm and ≤4 cm tumour size
		IB3	>4 cm tumour size
II	Invasion beyond the uterus but not onto lower 1/3 vagina or pelvic side wall	II	Invasion beyond the uterus but not onto lower 1/3 vagina or pelvic side wall
IIA	Upper 2/3 vagina	IIA	Upper 2/3 vagina
IIA1	Upper 2/3 vagina and ≤4 cm tumour size	IIA1	Upper 2/3 vagina and ≤4 cm tumour size
IIA2	Upper 2/3 vagina and >4 cm tumour size	IIA2	Upper 2/3 vagina and >4 cm tumour size
IIB	Parametrial invasion	IIB	Parametrial invasion
III	Involvement lower 1/3 vagina, pelvic sidewall, ureters	III	Involvement lower 1/3 vagina, pelvic sidewall, ureters, lymph nodes
IIIA	Lower 1/3 vagina	IIIA	Lower 1/3 vagina
IIIB	Pelvic sidewall	IIIB	Pelvic sidewall
		IIIC	Pelvic and para-aortic nodal involvement
		IIIC1	Pelvic nodal involvement
		IIIC2	Para-aortic nodal involvement
IV	Spread to adjacent and distant organs	IV	Spread to adjacent and distant organs
IVA	Spread to adjacent organs	IVA	Spread to adjacent organs
IVB	Spread to distant organs	IVB	Spread to distant organs

'Depth' is stromal invasion depth; 'width' concerns horizontal spread.
The tumour size is measured by maximum tumour diameter.
Imaging and pathology can be used for FIGO 2018 staging, with the notation of r (radiology) and p (pathology) to indicate the findings that were used to allocate stage.

Treatment

Surgery, radiotherapy, and chemotherapy are the cornerstones of cervical cancer treatment. The type of treatment is mainly based on tumour stage, together with the patient's age, comorbidities, and preferences after counselling. The primary treatment of cervical cancer can be broadly categorised as follows:

- Early-stage cervical cancer

Early-stage cervical cancer, defined as FIGO 2018 stage IA-IB2 and IIA1, is mainly treated with surgery.[3, 11, 12] For stages IA1 and IA2, therapeutic options include loop electrosurgical excision, conisation, or simple hysterectomy.[3, 11] For stage IA2 with presence of lymphovascular space involvement (LVSI), simple or radical hysterectomy in combination with lymph node staging is recommended, because of an increased risk of lymph node metastasis.[13] The standard treatment for stages IB1, IB2 and IIA1 is a radical hysterectomy with pelvic lymphadenectomy.[3, 11, 12] Adjuvant radiotherapy should be considered for patients with ≥2 intermediate-risk factors according to the Sedlis criteria.[14] Adjuvant chemoradiotherapy, consisting of a combination of chemotherapy and radiotherapy, should be considered for patients with ≥1 high-risk factors, see Table 2.[3, 11, 12] In cases where surgery is not feasible, primary pelvic radiotherapy becomes an option.

- Advanced-stage cervical cancer

Locally advanced cervical cancer is defined as FIGO 2018 stage IB3 and IIA2-IVA, for which the standard treatment consists of chemoradiotherapy.[3, 11, 12] For stages IB3 and IIA2, which are still confined to the cervix and vagina, respectively, radical surgery with lymph node staging is an alternative treatment option. Radiotherapy comprises pelvic external beam radiotherapy (i.e., 45-50 Gy), including brachytherapy (i.e. 90 Gy). The use of advanced radiotherapy techniques, such as intensity-modulated and image-guided radiotherapy, is recommended by current guidelines as it may reduce treatment-related morbidity. In the case of chemoradiotherapy, radiotherapy is combined with concurrent chemotherapy (i.e., 5-6 cycles of cisplatin 40 mg/m2 weekly). Hyperthermia may be considered as an alternative treatment in case of contraindications to chemotherapy. Treatment for metastatic disease (i.e., FIGO stage IVB) is individualised, but usually consists of chemotherapy, which may be combined with targeted therapy, such as bevacizumab and pembrolizumab.[3, 11, 12]

Table 2. Postoperative pathological intermediate and high-risk factors with an indication for either adjuvant radiotherapy or chemoradiotherapy, respectively.

Intermediate-risk factors	High-risk factors
Lymphovascular space-invasion (LVSI)	Lymph node metastasis
>1/3 (or ≥15mm) depth of stromal invasion	Parametrial invasion
≥4 cm maximum tumour diameter	Positive or close resection margins

Lymph node involvement

The risk of pelvic lymph node involvement increases with FIGO stage, with prevalences ranging from 0.1% (stage IA1) to 43% (stage IIB).[3, 6, 15] Lymph node staging in early-stage cervical cancer is usually performed by a pelvic lymphadenectomy, which includes the removal of lymph nodes from the obturator fossa, external iliac regions, common iliac regions bilaterally (Figure 2).[3, 11] Staging of the para-aortic region is not part of standard care. An emerging alternative for nodal staging of tumours <4 cm is the sentinel lymph node procedure, which offers potential benefits such as improved metastatic detection through ultra-staging and reduced morbidity, especially lymphedema.[16-19] However, prospective trials are still ongoing to confirm these benefits and its long-term safety, before it can be fully integrated into the standard of care.[16, 19]

Nodal staging by imaging, in both early and advanced cervical cancer, is usually done by magnetic resonance imaging (MRI), computed tomography (CT) and/or 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission computed tomography ([^{18}F]FDG-PET/CT). In clinically early cervical cancer, MRI is recommended to assess the extent of the pelvic tumour and lymph node involvement. If lymph nodes are suspicious, PET-CT is recommended.[11] In locally advanced cervical cancer, PET-CT is the preferred modality for nodal staging and is recommended for treatment planning before chemoradiotherapy. Nevertheless, the accuracy of nodal imaging remains a subject of debate, because of inconsistent study results due to heterogeneity in study populations, imaging settings, and criteria for suspicious lymph nodes. Inaccurate imaging results can lead to over- or undertreatment due to false-positive or false-negative suspicious lymph nodes. In this context, pathological evaluation of these nodes (e.g., image-guided fine-needle cytology/biopsy or debulking) could be a strategy to reduce the risk of overtreatment.

Due to the significant negative prognostic impact, lymph node metastases require additional therapy. As mentioned above, pathological evidence of lymph node involvement after radical surgery (stage IIICp) is considered a high-risk factor and patients are therefore treated with adjuvant chemoradiotherapy.[3, 11, 12] In cases where suspicious lymph nodes are detected on imaging before surgery (stage IIICr), treatment strategy may be switched to primary chemoradiotherapy to avoid multimodality treatment. For all stages with suspicious nodes on imaging, chemoradiotherapy may be combined with additional nodal treatment (i.e., extended-field radiotherapy, nodal boosting and nodal debulking), as the standard dose of external beam radiotherapy may not be sufficient for tumour sterilisation. Extended-field radiotherapy may be recommended if ≥3 pelvic lymph nodes or the common iliac/para-aortic regions are involved, as was recommended in the EMBRACE study.[20] Nodal boosting can be applied as simultaneous integrated or sequential boost, with a total dose of 55 to 60 Gy (equi-effective dose to 2 Gy per fraction (EQD2)). Alternatively, surgical resection may be considered for suspicious bulky nodes, often defined as nodes ≥1.5 or ≥2.0 cm, although a clear definition is lacking.[21-25]

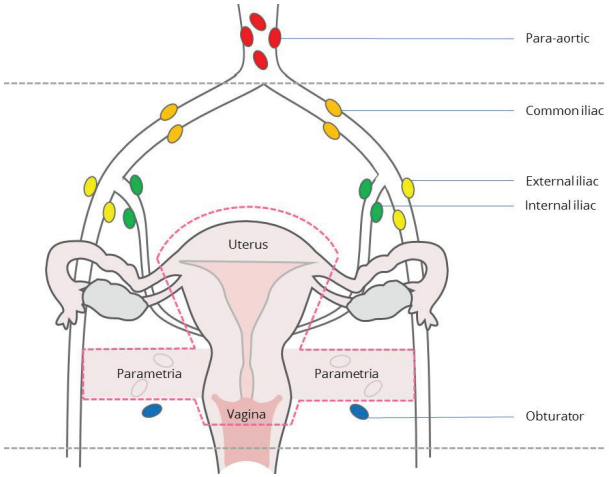

Figure 2. Loco-regional lymph nodes of cervical cancer with corresponding regions.

Health-related Quality of life

HRQoL is increasingly important in cancer research and clinical practice. As cervical cancer is commonly diagnosed at a relatively young age and at an early, usually curable stage, a substantial number of cervical cancer survivors have to deal with the consequences of the disease and treatment-related morbidity.[26] These morbidities vary across treatment strategies (e.g., surgery, primary (chemo)radiotherapy, adjuvant therapy) and can affect patients' HRQoL and sexual functioning to different degrees.[27-31] Well-informed patients have been shown to cope better with the disease and its consequences.[32] It is therefore important to provide adequate information during treatment counselling and to balance the potential benefits of treatment against the potential reduction in HRQoL.

Objective and outline

The aim of this thesis is to improve the survival and HRQoL of women with cervical cancer and lymph node metastases. We will contribute to this goal by evaluating the accuracy of imaging-based lymph node staging and tailoring treatment to each individual patient with suspicious lymph nodes or proven lymph node metastases. This could potentially reduce unnecessary procedures and avoid disabling complications and adverse events. The content of this thesis is described in two parts with the following sub-studies:

Part I – Identification of lymph node metastases

Chapter 2 describes the incidence and identification of lymph node metastases through a literature review. In this review, we have provided an update of the current knowledge on the incidence and prognostic value of lymph node metastases and of other clinical risk factors, biomarkers, imaging modalities and composite prediction models published since the review by Sakuragi et al. (2007).[6]

In *Chapter 3,* we compared the diagnostic accuracy of MRI, CT, and PET-CT in detecting lymph node metastases in clinically early-stage cervical cancer, based on a nationwide Dutch cohort study of 2,236 patients. This study provides insight into the diagnostic performance of pretreatment imaging in the current Dutch clinical practice.

In *Chapter 4,* we evaluated how often [^{18}F]FDG-PET/CT lymph node information is used in the management of advanced-stage cervical cancer, focusing on treatment with nodal boosting, extended-field radiotherapy and/or debulking. This study offers insight into the implementation of current guidelines with an appraisal of its consequences for the treatment of [^{18}F]FDG-positive nodes.

Part II – Treatment of lymph node metastases

Chapter 5 assesses the prognostic value of the number of positive lymph nodes and the lymph node ratio in patients with node-positive early-stage cervical cancer after radical hysterectomy. In this chapter, we determined optimal cut-offs to stratify patients into low-risk or high-risk groups for further risk stratification by both parameters in terms of survival.

In *Chapter 6,* we performed a retrospective analysis comparing the oncological outcome and therapy-related morbidity after radical hysterectomy and primary chemoradiotherapy for clinically early-stage cervical cancer with suspicious lymph nodes on imaging. Additionally, we evaluated preoperative clinicopathologic characteristics that may help to select patients at risk for multimodality treatment.

In *Chapter 7,* we directly compared the oncological outcome and therapy-related morbidity after different treatment strategies for suspicious bulky lymph nodes (short-axis ≥1.5 cm) in a patient cohort with locally advanced cervical cancer scheduled for definitive (chemo)radiotherapy. The treatment strategies included nodal boosting, debulking, or neither form of additional nodal treatment.

Chapter 8 evaluates the effect of surgery and primary chemoradiotherapy on long-term HRQoL and short-term toxicity among early-stage cervical cancer survivors using results from the population-based PROFILES registry. Within this context, we also conducted an analysis of the relationship between HRQoL and toxicities, along with a subgroup analysis focused on cases involving surgery with adjuvant therapy.

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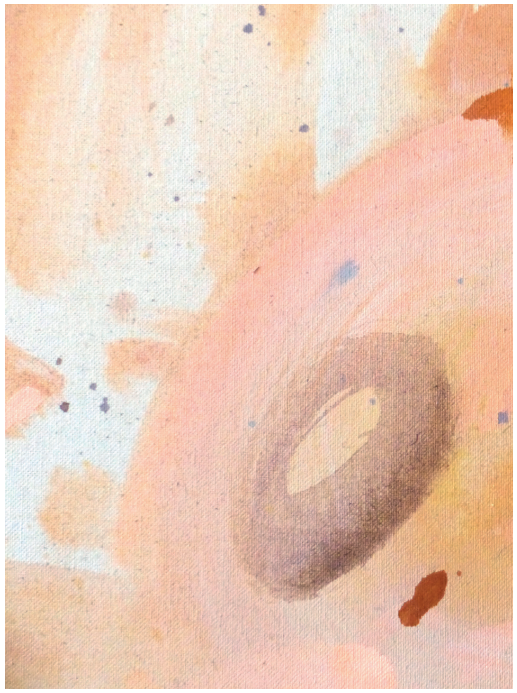
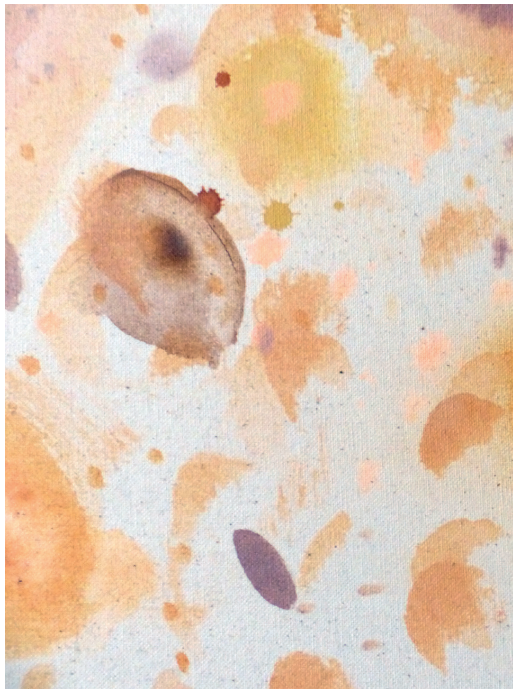


Part 1

Identification of lymph node metastases



Chapter 2

The role of lymph nodes in cervical cancer: incidence and identification of lymph node metastases - a literature review

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ABSTRACT

Correct identification of patients with lymph node metastasis from cervical cancer prior to treatment is of great importance, because it allows more tailored therapy. Patients may be spared unnecessary surgery or extended field radiotherapy if the nodal status can be predicted correctly. This review captures the existing knowledge on the identification of lymph node metastases in cervical cancer. The risk of nodal metastases increases per 2009 FIGO stage, with incidences in the pelvic region ranging from 2% (stage IA2) to 14–36% (IB), 38–51% (IIA) and 47% (IIB); and in the para-aortic region ranging from 2 to 5% (stage IB), 10–20% (IIA), 9% (IIB), 13–30% (III) and 50% (IV). In addition, age, tumor size, lymph vascular space invasion, parametrial invasion, depth of stromal invasion, histological type, and histological grade are reported to be independent prognostic factors for the risk of nodal metastases. Furthermore, biomarkers can contribute to predict a patient's nodal status, of which the squamous cell carcinoma antigen (SCC-Ag) is currently the most widely used in squamous cell cervical cancer. Still, pre-treatment lymph node assessment is primarily performed by imaging, of which diffusion-weighted
magnetic resonance imaging has the highest sensitivity and 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission computed tomography the highest specificity. Imaging results can be combined with clinical parameters in nomograms to increase the accuracy of predicting positives nodes. Despite all the progress regarding pre-treatment prediction of lymph node metastases in cervical cancer in recent years, prediction rates are not robust enough to safely abandon surgical staging of the pelvic or
para-aortic region yet.

INTRODUCTION

Uterine cervical cancer is one of the most common cancers among women worldwide with approximately 570,000 new cases and 311,000 deaths in 2018.[1] The most important prognostic factors for cervical cancer are the stage of disease and lymph node involvement. The overall survival (OS) of patients with cervical cancer decreases with an increasing number of positive lymph nodes.[2] Lymph node metastases (LNM) were not included in the staging until the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification. In this latest classification, assessment of lymph nodes by imaging and/or pathological examination is integrated as stage IIIC disease with the annotation 'r' or 'p'. Stage IIIC1 reflects the presence of LNM in the pelvic region and IIIC2 in the para-aortic region.[3, 4]

The ability to accurately predict LNM prior to treatment could potentially be of benefit for all patients with cervical cancer, because it facilitates tailoring of therapy. If correct prediction of LNM at primary staging is possible, patients with early stage cervical cancer (ECC) and nodal metastases can be spared radical surgery with pelvic and/or paraaortic lymphadenectomy. For patients with locally advanced cervical cancer (LACC), radiotherapy target volumes can be set more precisely and thereby, the associated morbidity can be reduced. Nowadays, pre-treatment lymph node status is primarily assessed by computed tomography (CT), magnetic resonance imaging (MRI), and/or 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission computed tomography ([^{18}F]FDG-PET/CT) scan. However, there is a debate on the accuracy of the various imaging techniques for the detection of lymph node metastases.[5] Imaging can lead to both false-positive and false-negative results resulting in over- or undertreatment. Combining imaging results with clinicopathological parameters and/or biomarkers in nomograms may help to increase the accuracy of predicting LNM in patients with cervical cancer.[6]

Because of the prognostic significance of LNM in cervical cancer, accurate identification and appropriate treatment of these metastases is crucial. Sakuragi et al. gave an overview of the available literature on cervical cancer and lymph node metastases in 2007.[7] Since then, many new studies have been published on the incidence and prognostic value of LNM, and of other clinical risk factors, biomarkers, imaging methods and composite prediction models. In the present review, we aim to give an update of the current knowledge on the pre-treatment identification of lymph node metastases in cervical cancer.

MATERIALS AND METHODS

Data for this review were identified by searches of PubMed database, by 'similar articles' via PubMed and by hand searches of reference lists. Articles were selected when published in English between 2007 and October 2020. The electronic searches strategy incorporated the following keywords, including various synonyms: "Uterine Cervical Neoplasms", "Lymph Nodes", "Incidence", "Risk factors", "Prognostic Factors", "Metabolic tumor volume", "Biomarkers", "Diagnostic Imaging", "Magnetic
Resonance Imaging", "Diffusion Magnetic Resonance Imaging", "Positron Emission Tomography Computed Tomography", "Nomogram", "Prediction Model". See supplementary Table 1 for the complete list of search terms. Eligibility of the identified reports by electronic searches was assessed by titles
and abstracts.

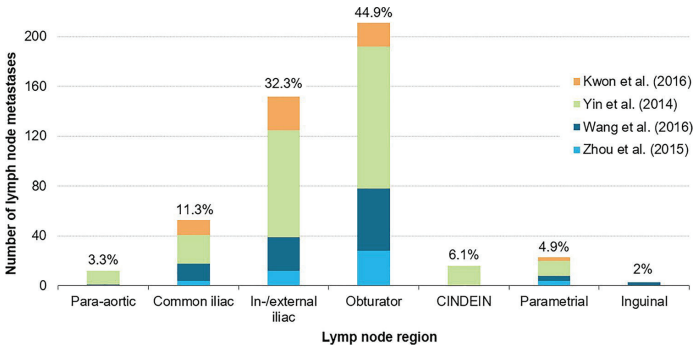

Figure 1. Number of lymph node metastases per region in stage IA–IIA, summarized per study.
Abbreviations: *CINDEIN*, circumflex iliac node distal to the external iliac node.

RESULTS

Incidence of lymph node metastases

The incidence of positive lymph nodes increases with 2009 FIGO stage, but varies greatly within prospective and retrospective studies. Sakuragi et al. reported the incidences of pelvic LNM in 2009 FIGO stage IB, IIA, and IIB cervical carcinoma to be 12–22%, 10–27%, and 34–43%, respectively.[7] We summarized more recently published studies on incidences of pathologically confirmed LNM per tumor stage and lymph node station. In Table 1, the incidence of nodal metastases in the pelvic region vary per 2009 FIGO stage from 2% (stage IA2) to 14–36% (IB), 38–51% (IIA) and 47% (IIB). In the para-aortic region, metastases have been reported in 2–5% (stage IB), 10–20% (IIA), 9% (IIB), 13–30% (III) and 50% (IV) of patients. The most frequently detected locations of LNM in stage IA–IIB cervical cancer were the obturator region (45%) and the internal and external iliac region (32%), illustrated in Fig. 1.[17, 22, 24, 39]

In the literature, some studies report only clustered incidence rates instead of per substage and could, therefore, not be included in Table 1. Non-surgical series were also excluded, and therefore, incidence rates for pelvic LNM in advanced stage III and IV are not reported. Furthermore, only a few studies were found on reporting LNM incidence rates in stage IA1, since pelvic lymphadenectomy is not a standard procedure for this stage of disease according to the guidelines.[40] The reported incidence rates of 3–5% for pelvic LNM in stage IA1 are higher than expected, compared with previous literature, making the representativeness of these patient cohorts questionable.[10, 17, 41] For example, Buchanan et al. (2017) in a review on lymphadenectomy in ECC, reported incidences of LNM of 0.13% (13/1033) for stage IA1 and 1.3% (10/787) for stage IA2.[41] All percentages in Table 1 should be cautiously interpreted, since most of the studies had a retrospective design with few patients.

Table 1. Incidence of patients with lymph node metastases (nodal positive/total patients) per study, represented by 2009 FIGO stage and lymph node station.

Station	Study	*n*	Stage I				Stage II				Stage III		Stage IV
			IA2	IB	IB1	IB2	IIA	IIA1	IIA2	IIB	IIIA	IIIB	IVA
Pelvic	Siu[6]	163	0/9	27/143	23/139	4/4	7/11						
	Martinez[9] a	41	0/4	5/37	5/36	0/1							
	Reynolds[10] b	12	0/12										
	Garg[11]	259					111/259	59/146	52/113				
	Sun[12]	207		40/167			12/40						
	Li[13]	404			26/222		38/182						
	Yan[14]	148			27/148								
	Hongladaromp[15]	133					52/133	39/101	13/32				
	Kim[6]	493	0/49	88/416	44/325	44/91	11/28	8/20	3/8				
	Togami[16]	163	0/12	19/103	13/76	6/27	8/24			15/24			
	Yin[17]	451	0/7	54/185	26/113	28/72	107/259	51/140	56/119				
	Zaal[18] acd	535		126/535	106/477	20/58							
	Bai[19]	1629	2/84		134/1545								
	Liu[20] e	263		25/143			15/61			20/59			
	Yoneda[21]	40	2/40										
	Zhou[22]	192	0/6		20/144			16/42					
	Tsuruga[23]	172				33/75			11/26	38/71			
	Wang[24]	276	0/8		36/207			18/61					
	Han[25]	723		123/365	85/275	38/90	175/358	90/215	85/143				
	Du[26] e	406		55/406	33/277	22/129							
	Nanthamongkolku[27]	496	1/52		22/444								
	Yu[28] f	153		28/110			26/43						
	Wu[29]	189		20/90			18/77			11/22			
	Hou[30]	168		29/128			10/40						
	Wu[31]	479		50/276			38/169			15/34			
	Xiao[32]	233		48/160	31/121	17/39	33/72	19/50	14/22	1/1			
	Total %		5/283 1.8%	737/3264 22.6%	631/4549 13.9%	212/586 36.2%	66 1/1756 37.6%	300/775 38.7%	234/4 50.5%	100/211 47.4%			
Common iliac	Siu, 2006[6]	163	0/9	7/143	6/139	1/4	1/11						
	Du, 2018[26]	406		14/406	8/277	6/129							
	Total		0/9	21/549	14/416	7/133	1/11						
	%		0%	3.8%	3.4%	5.3%	9.1%						

Table 1. (continued)

Station	Study	*n*	Stage I				Stage II				Stage III			Stage IV
			IA2	IB	IB1	IB2	IIA	IIA1	IIA2	IIB	IIIA	IIIB		IVA
Para-aortic	Leblanc[33]	176				12/58	2/9			7/43	1/8	20/57		1/1
	Mortier[34] d	80				2/12	4/32			3/25	1/7	0/7		
	Gil-Moreno[35]	87				3/30				6/30	0/2	2/10		0/1
	Margulies[36] d	61				1/11	1/14			4/30	0/1	0/3		1/2
	Del Pino[37] d	109				0/12				10/58		13/39		
	Tsuruga[22]	136				3/42				9/80				
	Matsuo[38]	4513		38/3414	27/2836	11/578	7/434			42/665				
	Han[25]	723		33/365	23/275	10/90	68/358	37/215	31/143					
	Du[26]	406		19/406	10/277	9/129								
	Total			90/4185	60/3388	51/962	82/514			81/931	2/15	35/116		2/4
	%			2.2%	1.8%	5.3%	9.7%			8.7%	13.3%	30.2%		50.0%

Data are nodal positive/total patients or %
[a]Sentinel node biopsy followed by pelvic lymphadenectomy
[b]Adenocarcinomas only
[c](adeno)squamous cell carcinoma and adenocarcinoma only
[d]No evidence of extra pelvic disease on preoperative imaging
[e]Including patients treated with neoadjuvant therapy
[f]Squamous cell carcinoma only

Clinical and histological risk factors

There are several clinical and pathological parameters correlated with the presence of LNM (Table 2). Since pathological examination is considered as the golden standard for LNM, and most histopathological risk factors can only be examined after surgery, nearly all studies on this topic concern FIGO (2009) stages IA–IIB. The multivariable models that are presented in Table 2 correct for different covariates, leading to inconsistent outcomes with regard to the various clinicopathological parameters that are identified as independent risk factor for LNM. For example, the clinical parameters age and tumor size seem to be independent prognostic factors for LNM in patients with cervical cancer.[6, 16, 42, 43] Togami et al. and Gulseren et al. both showed that tumor size greater than 2 cm was independently associated with LNM.[16, 43] This was confirmed by Kim et al., who found that a larger tumor size assessed by MRI was an independent predictor of nodal metastases.[6] However, other studies were unable to demonstrate a correlation between tumor size and LNM by univariable and/or multivariable analysis.[22, 24, 42, 44] In addition, Kim et al. showed that age can be used as an independent clinical predictor of nodal metastases. Most other studies in Table 2 on the other hand were unable to demonstrate this correlation, even in univariable analysis.[16, 19, 20, 22, 24, 27, 43]

Several pathological characteristics were independent prognostic factors for LNM in one or more studies, such as lymph vascular space invasion (LVSI), histologically confirmed parametrial invasion, depth of stromal invasion and histological grade.[16, 19, 20, 22, 24, 26, 27, 44, 45] A retrospective review of 296 patients with stage IA–IIB cervical squamous cell carcinoma concluded that patients with parametrial invasion had a nine times higher risk of pelvic LNM compared to patients without parametrial invasion.[20] The association between parametrial invasion and LNM was confirmed by others (odds ratios (OR) ranging from 3.0 to 5.8).[16, 20, 24, 27] Li and colleagues demonstrated in a group of 665 patients that LVSI and deep stromal invasion increased the risk of lymph node metastases.[42] One of the largest studies on this topic, with 1632 ECC patients, reported correlations between LNM and tumor grade, stromal invasion and LVSI.[19] However, an (independent) relation between LNM and tumor grade was not found in all studies in Table 2.[22, 24, 42] This also applies to FIGO stage and stromal invasion.[20, 24, 27, 42]

Table 2. Clinicopathological parameters that are independently associated with lymph node metastases in cervical cancer, listed by corresponding studies with first authors name.

Study	Liu[20]	Dai[44]	Li[42]	Zhou[22]	Wang[24]	Bai[19]	Gulseren[43]	Nanthamongkolkul[27]	Du[26]	Togami[16]	Kim[6]
(n)	296	302	665	192	276	1632	283	496	406	163	493
Factors											
LVSI	OR 4.86 (2.35–10.03)	RR 0.42 (0.19–0.95)	OR 3.97 (2.36–6.67)	HR 2.94 (1.22–7.08)	OR 2.97 (1.41–6.24)	$p < 0.001$	OR 11.3 (5.2–24.3)				
Stromal invasion	OR 3.35 (1.51–7.44)	RR 2.66 (1.41–5.01)	OR 2.93 (2.01–4.28)	HR 4.49 (1.44–14.01)	OR 2.16 (1.25–3.73)	$p = 0.015$		OR 3.5 (1.4–9.1)			
Parametrial invasion	OR 8.56 (1.24–58.98)							OR 5.8 (1.8–18.7)	OR 5.1 (2.1–12.1)	OR 3.6 (1.4–9.9)	
Age			OR 0.98 (0.96–1.00)								OR 0.97 (0.94–1.00)
Tumor size							OR 3.2 (1.4–7.2)			OR 4.7 (1.4–20.9)	OR 1.58 (1.29–1.95)
Tumor grade						$p = 0.009$					
FIGO stage		RR 2.06 (1.03–4.11)									
Non-significant variables in the model	Clinical stage, uterine invasion, tumor grade, tumor size, NACT	Tumor grade, uterine body involvement, parametrial involvement	Tumor size, macroscopic type, FIGO stage, histological type, tumor grade, pathological morphology type	FIGO stage, tumor size	SCC-Ag, tumor size		Age, hemoglobin, histological type		Conization, tumor grade	Tumor markers	LNM on [^{18}F] FDG]-PET/CT

Effect size is indicated by *OR* (odds ratio), *RR* (relative risk), *HR* (hazard ratio), and 95% confidence intervals, or *p* value.

Biomarkers

Biomarkers are substances or processes that can be indicative of the presence of cancer and used in the diagnostic process and/or follow-up of patients with cervical cancer. Regarding the prediction of LNM, many markers have been evaluated, of which the squamous cell carcinoma antigen (SCC-Ag) is currently most widely used for squamous cell carcinoma of the cervix.[16, 45-49] In a pooled analysis by Zhou et al. of 4000 cervical cancer patients, a sensitivity of 70% and a specificity of 63% of the SCC-Ag was found for the detection of LNM, indicating an average diagnostic power.[48] In addition, the authors summarized results of eight articles on the relationship between SCC-Ag values and the risk of pelvic nodal metastases. Different SCC-Ag cutoff values varying from 1.5 to 40.0 ng/mL were used with corresponding risk ratios varying from 2 to 40, reflecting heterogeneity between studies and the need for an optimal and standardized SCC-Ag cutoff point. A more recent study, of nearly 800 patients with squamous cell cervical carcinoma treated by radical hysterectomy with pelvic lymphadenectomy, showed that a preoperative SCC-Ag of > 3.26 ng/mL was found to increase the likelihood of positive lymph nodes fourfold.[49] Nevertheless, the association was insufficient for a reliable diagnosis of pelvic LNM with a corresponding sensitivity of 55%.

Another group of biomarkers that has been suggested to predict LNM in patients with cervical cancer are microRNAs, small non-coding ribonucleic acids that can regulate gene expression, either detectable in blood or tumor tissue.[50-52] Studies on this subject are based on small cohort sizes, do not correct for confounders and/or do not include validation cohorts. Therefore, it is not possible to draw meaningful conclusions on the predictive value of microRNAs. Although, results on biomarkers for LNM in cervical cancer might look promising, larger, prospective studies are required to confirm and validate the correlation between biomarkers and nodal metastases in patients with cervical cancer.

Imaging of lymph node metastases

CT, MRI and [^{18}F]FDG-PET/CT are the most commonly used imaging techniques in the detection of LNM in patients with cervical cancer.[7] The performance of these techniques has been well studied with pathological confirmation of LNM as reference standard in all the referred papers, except for Shen et al.[60] Recently, the sensitivities and specificities for CT, MRI, PET-CT and ultrasound were calculated in a meta-analysis, to evaluate and compare performance.[61] Both conventional and diffusion-weighted (DW)-MRI - an advanced MRI technique involving the diffusion motion of water protons to assess tissue contrast - were included.[62] In this meta-analysis, the pooled sensitivities (51–57%) among all stages were poor, whereas the pooled specificities (87–95%) were high; in which PET-CT outperformed other modalities in detecting LNM.

In one of the largest meta-analyses on detecting LNM, the accuracy of CT, conventional MRI, DW-MRI, and [^{18}F] FDG-PET/CT were compared to pathology in women with cervical cancer of any histological type or stage.[62] The authors concluded that DW-MRI had the highest sensitivity (87%) and [^{18}F]FDG-PET/CT the highest specificity (97%) for the detection of LNM. Results on DW-MRI performance in this paper were consistent with the findings from the meta-analysis by Shen et al. (2015) (pooled sensitivity 86% and specificity 84%).[60] Another large meta-analysis, reported the accuracy for CT, conventional MRI, and [^{18}F]FDG-PET-CT in detecting LNM in women with cervical cancer of all stages.[63] They found a sensitivity of 58%, 56% and 75% for CT, conventional MRI, and PET-CT, and a specificity of 92%, 93%

and 98%, respectively. The higher accuracy of PET-CT compared to CT and MRI can result from its benefits of functional imaging.[64] Unlike the other imaging methods, that mostly rely on size (≥ 1 cm) and morphological characteristics of the lymph node to determine its status, [^{18}F]FDG-PET-CT detects increased glucose metabolism. This may, on the other hand, also increase false-positive results on PET-CT by showing reactive lymph nodes as a result of tumor necrosis or inflammation.[64]

In the previously mentioned meta-analysis by Liu et al. (2017) subgroup analysis of [^{18}F]FDG-PET/CT and conventional MRI stratified by stage of disease (ECC versus LACC) barely affected the specificity, which remained above 90% for both imaging methods.[62] On the contrary, sensitivities were substantially lower in patients with ECC compared to LACC for [^{18}F]FDG-PET/CT (41% vs. 83%) and MRI (52% vs. 88%) since the sensitivity is affected by the incidence of LNM, which increases per stage. Subgroup analysis on lymph node region (pelvic versus para-aortic), again, marginally influenced the specificity (≥ 90%) of all three imaging methods. Where is the sensitivity was higher in the para-aortic region compared to the pelvic region for both CT (68% vs 48%) and PET-CT (81% vs. 55%), this was not the case for MRI (54% vs. 62%). These differences per lymph node region may be caused by selection bias: there were more LACC patients in the para-aortic group. Since nodal metastases are more common and often larger in size in advanced stages of disease, they are more easily detected in this subgroup.

To overcome the influence of stage, one of the few prospective studies in this field reported the detection of LNM per region by [^{18}F]FDG-PET/CT solely in patients with LACC.[65] In contrast to the meta-analyses, this study reported a higher sensitivity (83%) in the pelvic region compared to the para-aortic/common iliac region (50%), with corresponding specificities of 63% and 85%, respectively. Two possible explanations for the lower sensitivity observed in the para-aortic region are nodal size and selection bias. Since the para-aortic region is a secondary lymphatic draining station, the size of para-aortic LNM may be smaller, and therefore, the LNM may be harder to detect. Furthermore, the study cohort might have contained a lower prevalence of para-aortic LNM in comparison to the real population because in LACC, a para-aortic lymphadenectomy is generally not performed to confirm suspicious nodes on imaging, but rather to exclude false negatives.

In conclusion, there has been considerable interest in imaging techniques to determine lymph node status in patients with cervical cancer. Heterogeneity of populations within and between studies, imaging settings, and various criteria for suspicious lymph nodes on imaging all contribute to inconsistent results. Overall, the highest sensitivity for detecting LNM in patients with cervical cancer was found for DW-MRI, and the highest specificity for [^{18}F]FDG-PET/CT. Imaging performance improves with higher stages of disease, when the likelihood and size of LNM increase.

Prediction models

Multiple prognostic factors can be combined in statistical models to predict the risk of a certain future outcome. These models are called prediction models or nomograms.[66] Potentially, all of the above-mentioned parameters can be used in a prediction model for LNM in cervical cancer because of their association with an increased risk on LNM. However, many histopathological parameters are unsuitable because they are assessed postoperatively.

The majority of prediction models for LNM in cervical cancer were developed in the past few years, but the quality of the studies in which they were analyzed varies considerably. Some models are based on

a small and/or heterogenic study population without verification in a validation cohort.[12, 53, 54, 57-59] Prediction models can be useful for preoperative decision-making, and therefore, concern mostly ECC (Table 3). An example is the model that was developed by Kim et al. (2014).[6] This model, including age, tumor size measured by MRI and LNM assessed by [^{18}F]FDG-PETCT, was designed to select ECC patients with a low risk (< 5%) on LNM. Within a cohort of 493 patients, the model had a C-index of 0.83 (95% CI 0.74–0.90), a sensitivity of 96% and a negative predictive value of 98% with a LNM prevalence of 20%.

As shown in Table 3, most prediction models include imaging. Medical imaging is a fast-growing field in which advanced techniques are developed to increase imaging performance. This includes radiomics, a quantitative approach for medical imaging and a form of artificial intelligence.[67] Using radiomics, a high number of features such as size, shape, intensity and texture are extracted from images (CT, PET-CT, and MRI) and compared in a database with algorithms for objective assessment. Over the past years, radiomics has been integrated into nomograms to increase their predictive value on LNM in cervical cancer patients (Table 3). Higher diagnostic performances (concordance (C)-indexes 0.75–0.99) are seen in nomograms with radiomic signatures of CT or MRI, compared to models with clinicopathological parameters and/or visual assessment only (C-indexes 0.62–0.80).[29, 30, 54]

Most nomograms on LNM in cervical cancer are developed to predict pelvic metastases, however, Shim et al. and Wang et al. developed a model to predict para-aortic LNM with a C-index of 0.89 and 0.95, respectively. These models can be useful to tailor treatment decisions for patients with LACC, such as the performance of a lymphadenectomy and adaptation of radiation fields.[58, 59] However, a major limitation of the last study is that all LNM were diagnosed by imaging (CT, MRI or [^{18}F]FDG-PET-CT) without histological confirmation. Although radiomics seems to have much potential, there are still some challenges to overcome. These include standardization of various technical factors influencing the extracted radiomic features and proper validation in study cohorts.[67]

Table 3. Prediction models with the predictive values for lymph node metastases in cervical cancer, listed by corresponding studies with first authors' name.

	Study	*n*	Stage	Prediction model	Cohort	C- index	Acc (%)
(Pelvic) LNM	Sun[12]	207	IB-IIA	Serum SCC — depth of cervical stroma invasion			76
	Kim[6]	493	IA2-IIA	Age — tumor size by MRI — LNM on [^{18}F]FDG-PET/CT	Model	0.88	
					Validate	0.83	
	Li[53]	394	IA-IIA	Tumor size (≥4 cm) — TLG — SUVmax LN — SUVmean LN		0.84	
	Wang[54]	96	IA2, IB1, IIA	Age — pathological grade — LNM on MRI	Model	0.62	
					Validate	0.80	
				Age — pathological grade — LNM on MRI — radiomics signature of MRI (T2WI & DWI)	Model	0.89	
					Validate	0.92	
	Wu[29]	187	IB-IIB	LNM on MRI — FIGO 2009 stage — maximal tumor diameter	Model	0.73	84
					Validate	0.72	86
				LNM on MRI — radiomics signature of MRI (intratumoral and peritumoral tissues on T2WI)	Model	0.90	87
					Validate	0.85	76
	Yu[28]	153	IB–IIA	Clinical stage — LNM on MRI — radiomics signature of MRI (one feature: grey level non-uniformity)	Model	0.86	
					Validate	0.87	
	Chen[55]	150	IB1-IIA2	Radiomics signature of CT (two features) — FIGO 2009 stage IB	Model	0.80	
					Validate	0.75	
	Dong[56]	226	IA-IIB	Tumor histology — grade — radiomics signature of CT (five features)	Model	0.99	97
					Validate	0.90	92
	Hou[30]	168	IB-IIA	LNM on MRI	Model	0.68	79
					Validate	0.71	
				LNM on MRI — radiomics signature of MRI (six features)	Model	0.87	76
					Validate	0.86	87
	Xiao[32]	233	IB-IIB	FIGO 2009 stage — LNM on MRI — radiomics signature of MRI (23 features of high-resolution T1WI, fat saturated T2WI, DWI, ADC maps, and contrast-enhanced T1WI)	Model	0.88	
					Validate	0.89	
	Xu[57]	95	IB-III	LNM on PET-MRI — TGL — Dmin		0.91	
Para-aortic LNM	Shim[58]	245	IB2-IVA	Tumor size on MRI — para-aortic LNM on [^{18}F]FDG-PET-CT		0.89	
	Wang[59]	1903	IA-IVA	Histology — tumor size (≥ 6 cm) — bilateral pelvic LNM — common iliac LNM — pelvic lymph nodes convergence of muscle involvement	Model	0.92	
					Validate	0.95	

Abbreviations: *C-index* concordance-index; *Acc*, accuracy; *LN* lymph node; *LNM* lymph node metastasis; *SCC* squamous cell carcinoma antigen; *MRI* magnetic resonance imaging; *PET* positron emission tomography; *CT* computed tomography; *TGL* total lesion glycolysis; *SUVmax* maximum standardized uptake value; *SUVmean* mean standardized uptake value; *T2WI* T2-weighted MRI; *DWI* diffusion-weighted imaging; *T1WI* T1-weighted imaging, *ADC* apparent diffusion coefficient; *Dmin* diffusion-related coefficient min.

SUMMARY AND CONCLUSION

In this review, we summarized the available literature on pre-treatment identification of lymph node metastasis in cervical cancer. Accurate prediction of a patient's nodal status facilitates personalized treatment adjustments, thereby preventing over- and undertreatment. Incidence rates of nodal metastases increase with 2009 FIGO stage, ranging from 2% (stage IA2) to 14–36% (IB), 38–51% (IIA) and 47% (IIB) in the pelvic region; and from 2 to 5% (stage IB), 10–20% (IIA), 9% (IIB), 13–30% (III) and 50% (IV) in the paraaortic region.

Clinicopathological parameters may contribute to the identification of patients with LNM, as various parameters are independent prognostic factors for LNM. Furthermore, biomarkers can contribute to the prediction of LNM in patients with cervical cancer, such as SCC-Ag. Yet, the diagnostic power is still insufficient. Currently, pretreatment lymph node assessment is primarily performed by imaging, of which DW-MRI has the highest sensitivity and [^{18}F]FDG-PET-CT the highest specificity. Clinicopathological parameters, biomarkers and imaging can be combined in a nomogram to gain higher predictive values on detecting LNM in cervical cancer. Several nomograms have been developed of which addition of radiomics seems to have the most potential. Currently, all these non-invasive tools can help to tailor treatment decisions, but do not reach the accuracy of surgical staging or biopsy confirmations yet. Standardization of clinical procedures and optimization of these tools and/or additional procedures may lead to improved pre-treatment diagnosis of LNM in the future.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Terms used for electronic searches.

Topic	Search term
Cervix carcinoma	Uterine Cervical Neoplasms [Mesh]
	cervi* [tiab]
Lymph node metastases	combined with "Lymph Nodes [Mesh]
	nodal disease [tiab]
	nodal involv* [tiab]
	nodal metastas* [tiab]
	nodal positiv* [tiab]
	nodal tumo* [tiab]
	node involv* [tiab]
	node-positiv* [tiab]
	positive node* [tiab]
	positive lymph node* [tiab]
	nodal status [tiab]
Incidence	Incidence [Mesh]
	Cohort Studies [Mesh]
	incidence* [tiab]
	occurence* [tiab]
Risk factors	Risk factors [Mesh]
	Risk factor* [tiab]
	Predictor* [tiab]
	Prognostic factor* [tiab]
	Risk parameter* [tiab]
	Metabolic tumor volume [tiab]
Biomarkers	Biomarkers, Tumor [Mesh]
	Biomarkers [Mesh]
	Biomarker* [tiab]
	marker* [tiab]
	Carcinoembryonic Antigen [Mesh]
	squamous cell carcinoma-related antigen [Supplementary Concept]
	CA-125 Antigen [Mesh]
Imaging	Diagnostic Imaging [Mesh]
	Image Processing, Computer-Assisted [Mesh]
	Uterine Cervical Neoplasms/diagnostic imaging [MAJR]
	Neoplasm Staging [Mesh]
	Sensitivity and Specificity [Mesh]
	Magnetic Resonance Imaging [Mesh]
	Diffusion Magnetic Resonance Imaging [Mesh]
	Positron-Emission Tomography [Mesh]
	Positron Emission Tomography Computed Tomography [Mesh]
	Ultrasonography [Mesh]
	Tomography, X-Ray Computed [Mesh]
	Imaging [tiab]
	CT [tiab]
	PET [tiab]
	MRI [tiab]
	DW* [tiab]
	Ultrasound [tiab]
Prediction models	Nomogram [MeSH Terms]
	Prediction model* [tiab]

Chapter 3

Diagnostic accuracy of MRI, CT and [18^{F}] FDG-PET/CT in detecting lymph node metastases in clinically early-stage cervical cancer – a nationwide Dutch cohort study

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ABSTRACT

Objectives: Imaging is increasingly used to assess lymph node involvement in clinically early-stage cervical cancer. This retrospective study aimed to evaluate the diagnostic accuracy of MRI, CT and [18F]FDG-PET-CT.

Methods: Women with International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IA2-IIA cervical cancer and pretreatment imaging between 2009-2017 were selected from the Netherlands Cancer Registry. Patient-based and region-based (i.e. pelvic and common iliac) nodal status was extracted from radiology reports. Pathology results were considered the reference standard for calculating accuracy indices. Multiple imputation was used for missing pathology to limit verification bias risk.

Results: Nodal assessment was performed in 1,676 patients with MRI, 926 with CT, and 379 with [18F]FDG-PET-CT, with suspicious nodes detected in 17%, 16%, and 48%, respectively. [18F]FDG-PET-CT was used to confirm MRI/CT results in 95% of patients. Pathology results were imputed for 30% of patients. [18F]FDG-PET-CT outperformed MRI and CT in detecting patient-based nodal metastases with sensitivities of 80%, 48%, and 40%, and AUCs of 0.814, 0.706, and 0.667, respectively, but not in specificity: 79%, 92% and 92%. Region-based analyses showed similar indices in the pelvic region, but worse performance in the common iliac region with AUCs of 0.575, 0.554, and 0.517, respectively.

Conclusions: [18F]FDG-PET-CT outperformed MRI and CT in detecting nodal metastases, which may be related to its use as a verification modality. However, MRI and CT had the highest specificity. As MRI is generally performed routinely to assess local and regional spread of cervical cancer, [18F]FDG-PET-CT can be used to confirm suspicious nodes.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, representing 604,000 new cases and 342,000 deaths in 2020.[1] One of the most important prognostic factors in cervical cancer is lymph node involvement, a factor included in the revised International Federation of Gynaecology and Obstetrics (FIGO) system in 2018. In this FIGO system, pelvic and para-aortic lymph nodes suspicious for metastasis on imaging are classified as stage IIIC1 and IIIC2, respectively, with the annotation 'r' (radiologic), indicating that the role of imaging in the staging and management of cervical cancer has increased.[2, 3]

Accurate assessment of the nodal status is essential when deciding on treatment options. In early-stage cervical cancer, the nodal status determines whether radical hysterectomy or (chemo)radiotherapy is recommended.[4] In (chemo)radiotherapy, suspicious nodes on imaging may influence radiotherapy settings (i.e. extended-field and nodal boosting). Imaging-based treatment modifications are observed in approximately 13% of patients with early-stage cervical cancer, with magnetic resonance imaging (MRI), computed tomography (CT) or 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography ([18F]FDG-PET/CT) being the most commonly used modalities.[4, 5] The current Dutch guidelines recommend the use of MRI for clinical staging of patients with early-stage cervical cancer, because of its accuracy in determining tumour size and local spread, while [18F]FDG-PET-CT is recommended as a verification modality for the validation of suspicious nodes.[6, 7] However, due to the lack of consensus, the use of imaging modalities in clinical practice remains variable.

The performance of these techniques has been described in several meta-analyses, reporting an overall pooled sensitivity and specificity of 41-57% and 93-98% for MRI, 51-59% and 87-92% for CT, and 52-78% and 92-95% for [18F]FDG-PET-CT.[8-10] However, these results are mainly based on outdated retrospective data, with a high risk of selection bias, as pathological verification of suspicious nodes on imaging is often partially lacking, as patients with suspicious nodes usually receive primary chemoradiotherapy. This form of selection bias, where the reference standard (i.e. pathological examination of lymph nodes) is not performed in all patients, is also known as partial verification bias and can lead to biased accuracy estimates.[11] Therefore, the accuracy of nodal imaging by MRI, CT and [18F]FDG-PET-CT is still controversial and their performance may have improved over time due to technological advances.

As imaging is increasingly used for nodal staging in cervical cancer patients, we believe it is necessary to provide diagnostic indices of pretreatment imaging based on a more recent and larger cohort of patients, while taking into account the risk of partial verification bias. Therefore, the present study aimed to evaluate the diagnostic accuracy of MRI, CT and [18F]FDG-PET-CT for lymph node metastases in clinically early-stage cervical cancer, on a patient-based and region-based (i.e. pelvic and common iliac) level.

METHODS

Study design

We performed a nationwide, retrospective, cohort study by analysing data between 2009-2017 from the Netherlands Cancer Registry, after Privacy Review Board approval (No K22.262). This registry holds

population-based data containing >95% of all cancer patients in the Netherlands since 1989. Patients with FIGO (2009) stage IA2-IIA cervical cancer and pretreatment nodal status assessment by MRI, CT and/or [18F]FDG-PET-CT, were eligible for this study. Patients were excluded if pathological examination of lymph nodes was obtained >8 weeks after imaging, as prolonged intervals might increase the risk of inaccuracy.

Trained data managers collected additional data on lymph node metastases from hospital records. Lymph node status was recorded for five nodal regions (i.e. pelvic left/right, common iliac left/right and para-aortic) as suspicious, inconclusive, negative or unknown, as reported by the radiologist. Per patient, the nodal status of all regions was combined for patient-based analyses, and the laterality was combined for region-based analyses, according to the order mentioned above. Inconclusive nodes were first considered suspicious and later negative in subgroup analyses to explore the robustness of our findings and to assess how different interpretations of inconclusive results may affect the diagnostic accuracy. If reported, the short-axis diameter was recorded for positive or inconclusive nodes. Although there are no (inter)national protocols available, lymph nodes in cervical cancer are generally considered suspicious if they have a short axis diameter ≥1.0 cm, morphological tumour features (i.e. central necrosis) and/or increased FDG uptake (more than the adjacent vessel).[12, 13] All MRI, CT and [18F]FDG-PET-CT scans were performed according to local protocols, with [18F]FDG-PET-CT scans following the Dutch (Nedpas) and international (EARL) standards.[14] As most patients (94%) were referred to specialised oncology centres, it is likely that the majority of scans were interpreted by experienced radiologists and nuclear medicine physicians.

Pathological examination of the lymph nodes was considered the reference standard. Examination could be performed by lymphadenectomy, debulking surgery, sentinel lymph node biopsy or fine-needle cytology or biopsy. The pathological lymph node status was also recorded for the five nodal regions. The sentinel lymph nodes' laterality, but not the region, was registered, though considered to be pelvic as this is the case in >93% of sentinel nodes in cervical cancer.[15] According to current guidelines, isolated tumour cells (≤0.2 mm) on pathological examination were not considered to be lymph node metastases.[4] Pathological nodal status was considered missing if patients were treated with neoadjuvant chemotherapy prior to pathological examination. Furthermore, data on patient and tumour characteristics were also collected. Direct conversion to FIGO 2018 was not possible due to missing information on horizontal spread.

Statistical analysis

Multiple imputation has been described as a reliable method to reduce partial verification bias, even when data are not missing at random, as in our case.[11] Therefore, we imputed the pathological nodal status when missing, using multivariate imputation by chained equations (MICE) with 20 imputations (Supplementary Table 1-3).[16] We repeated this procedure twice, for the patient- and region-based analyses, and established the validity by reviewing convergence plots and comparing original and imputed data. We applied Rubin's rule to combine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating curve (AUC) of all imaging modalities for detecting lymph node metastases in the imputed data.[17, 18]

The para-aortic region was excluded from region-based analyses because para-aortic lymphadenectomies are not routinely performed in the Netherlands, resulting in too few patients with

pathological verification. Subgroup analyses included patient cohorts with >1 imaging modality and recalculation of diagnostic indices after considering an inconclusive nodal status as negative. The Wilcoxon signed-rank test was used to compare paired data without a normal distribution. Confidence intervals for AUCs were calculated using the DeLong test and compared using the chi-squared test; p-values below 0.05 were considered statistically significant. South Texas Art Therapy Association SE 17 (StataCorp, College Station, TX) and R software were used for all analyses.

RESULTS

Baseline characteristics

In total, 2,236 patients with early-stage cervical cancer were included (Supplementary Figure S1), whose baseline characteristics are presented in Table 1. Nodal evaluation was performed in 1,676 (75%) patients by MRI, and in 926 (41%) and 379 (17%) patients by CT and [18F]FDG-PET-CT, respectively. The rate of MRI and [18F]FDG-PET-CT imaging increased over time from 7-8% to 16%, while the rate of CT decreased from 14% to 9%. Suspicious nodes were observed in 286 (17%) patients on MRI, 148 (16%) on CT, and 183 (48%) on [18F]FDG-PET-CT. The rate of suspicious nodes remained constant over the years, within a range of 15-21% (p=0.56). Of all patients, suspicious nodes on MRI, CT, or [18F]FDG-PET-CT were located in the pelvic, common iliac and para-aortic regions in 18% (n=393), 2% (n=54) and 3% (n=70), respectively. The median short-axis of these nodes was 11 mm (range 5-50) in the pelvic region, 9 mm (range 6-29) in the common iliac region (p=0.013) and 10 mm (5-28) in the para-aortic region. In 361/379 (95%) patients who underwent [18F]FDG-PET-CT, MRI and/or separate CT were also performed. Neoadjuvant therapy was administered to 89 patients (4%). Pathologic assessment of the nodal status was available in 1,557 (70%) patients, mainly by lymphadenectomy (97%; n=1,517), with a prevalence of nodal metastases of 19% (n=234), 24% (n=142) and 44% (n=60) in the MRI, CT, and [18F]FDG-PET-CT groups, respectively, which increased to 24% (n=402), 26% (n=241) and 46% (n=174) after imputation.

Table 1. Baseline characteristics.

Characteristics	n=2236	
	n / median	% / range
Age, years	44	19-102
BMI, kg/m^2	25	15-77
FIGO 2009 stage		
IA2	57	2.6
IB1	1554	69.5
IB2	349	15.6
IIA1	158	7.1
IIA2	118	5.3
Tumour size, mm	30	0-150
Histology		
Squamous cell carcinoma	1487	66.5
Adenocarcinoma	602	26.9
Adenosquamous cell carcinoma	100	4.5
Neuroendocrine carcinoma	35	1.6
Other	12	0.5

Table 1. (continued)

Type of imaging		
MRI	1676	75.0
CT	926	41.4
[18F]FDG-PET-CT	379	17.0
MRI and CT	384	17.2
MRI and [18F]FDG-PET-CT	314	14.0
CT and [18F]FDG-PET-CT	106	4.7
MRI, CT, and [18F]FDG-PET-CT	59	2.5
Short-axis of suspicious pelvic node, mm [a]	10	5-50
Short-axis of suspicious common iliac node, mm [a]	9	6-29
Patient-based nodal status on MRI		
Negative	1390	82.9
Inconclusive	89	5.3
Positive	197	11.8
Patient-based nodal status on CT		
Negative	778	84.0
Inconclusive	53	5.7
Positive	95	10.3
Patient-based nodal status on [18F]FDG-PET-CT		
Negative	196	51.7
Inconclusive	21	5.5
Positive	162	42.7
Region with positive nodal status on imaging [b]		
Pelvic	393	17.7
Common iliac	54	2.4
Para-aortic	70	3.1
Patient-based nodal status on pathology		
Negative	1240	55.5
Positive	317	14.2
Unknown	679	30.4
Time between imaging and pathological examination, days		
MRI	25	1-56
CT	26	1-56
[18F]FDG-PET-CT	20	0-44
Nodal examination		
Absent	679	30.4
Lymphadenectomy	1517	67.8
Nodal debulking	32	1.4
Biopsy/fine-needle aspiration	2	0.1
Intraoperative frozen section	4	0.2
Sentinel node biopsy only	2	0.1

Abbreviations*: n*, number of patients; *BMI*, body mass index; *FIGO*, International Federation of Gynaecology and Obstetrics; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET-CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

[a] for positive and inconclusive nodes only.

[b] including a positive and inconclusive nodal status at MRI, CT, or [18F]FDG-PET-CT.

Patient-based diagnostic accuracy

The accuracy of MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases on a patient-based level of original and imputed data are shown in Table 2. [18F]FDG-PET-CT outperformed MRI and CT in sensitivity (80% vs. 48% and 40%, respectively), but not in specificity (79% vs. 92% and 92%, respectively), resulting in an AUC of 0.814 vs. 0.706 and 0.667 (p=0.003, imputed data), as shown in Figure 1A. [18F]FDG-PET-CT had the highest PPV (76%), while MRI had the highest NPV (85%). All indices increased or remained stable after imputation, as did the prevalence of lymph node metastases (from 19-44% to 24-46%).

Subgroup analyses of patient cohorts with >1 imaging modality after imputation included samples ranging from 59 to 384 patients, depending on the combination of MRI, CT and/or [18F]FDG-PET-CT (Supplementary Table 4). Within these cohorts, the AUCs of all three modalities after imputation were nearly equivalent to those in the original patient-based analyses (± 0.005-0.072). As in the original analyses, the AUC of [18F]FDG-PET-CT was consistently higher than of MRI and CT in all cohorts, although not significantly (p=0.58 imputed data), while the AUC of MRI was generally higher than CT. Nodal status discordance between one of the three imaging modalities was observed in 20/59 (34%) patients.

The prevalence of metastatic nodes after imputation was determined for cohorts with different combinations of MRI, CT, and/or [18F]FDG-PET-CT results (Supplementary Table 5). The prevalence of nodal metastases in cohorts with discrepancy in the nodal status between two imaging modalities (14-73%) was substantially higher compared to the total cohort with a negative MRI, CT or [18F]FDG-PET-CT (15-18%), especially in the case of a positive [18F]FDG-PET-CT (58-73%).

Table 2. Patient-based diagnostic indices for MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases based on original and imputed data.

Modality	Prev LNM	Sensitivity	Specificity	PPV	NPV	AUC[a]
Original data						
MRI	19 (17-22)	34 (31-36)	93 (92-94)	54 (52-57)	85 (83-87)	0.639 (0.607-0.670)
CT	24 (21-28)	37 (33-41)	91 (89-93)	57 (53-61)	82 (79-85)	0.646 (0.603-0.688)
[18F]FDG-PET-CT	44 (35-52)	73 (66-81)	77 (70-84)	71 (63-79)	79 (72-86)	0.787 (0.714-0.860)
Imputed data						
MRI	24 (22-26)	48 (45-50)	92 (91-94)	66 (64-69)	85 (83-87)	0.706 (0.674-0.737)
CT	26 (23-29)	40 (37-43)	92 (91-94)	64 (61-67)	82 (79-84)	0.667 (0.630-0.704)
[18F]FDG-PET-CT	46 (41-51)	80 (76-84)	79 (75-83)	76 (72-81)	82 (78-86)	0.814 (0.752-0.876)

Abbreviations*: Prev LNM*, prevalence of lymph node metastases; *PPV*, positive predictive value; *NPV*, negative predictive value; *AUC*, area under the receiver operating curve; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET-CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

[a] AUC without dichotomizing the nodal status on imaging.

Numbers represent % with (95% confidence interval).

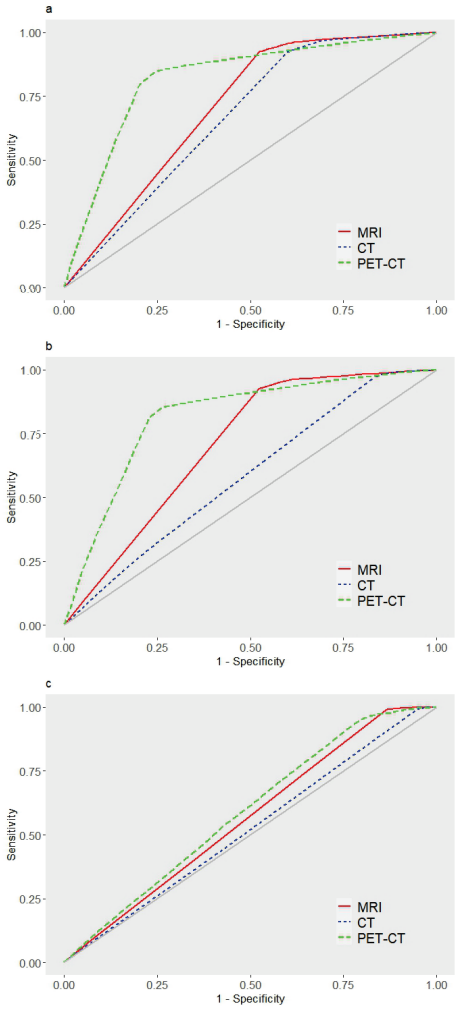

Figure 1. ROC-curves for MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases regarding (a) patient-based (b) region-based pelvic, and (c) region-based common iliac analyses.

Region-based diagnostic accuracy

Table 3 shows the performance of MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases on a region-based level for original and imputed data. The prevalence of nodal metastases and the accuracy of the different diagnostic modalities in the pelvic region were highly comparable to the patient-based results. [18F]FDG-PET-CT outperformed MRI and CT with respect to the AUC (0.803 vs. 0.705 and 0.656,; Figure 1B), the sensitivity (77% vs. 47% and 37%), and PPV (76% vs. 66% and 64%), respectively. In contrast, inferior performance was observed for specificity (80% vs. 93% and 93%,) and NPV (81% vs. 85% and 81%, respectively).

Comparing the performance of MRI, CT, and [18F]FDG-PET-CT in the common iliac region with the pelvic region, the AUCs (0.554, 0.517, and 0.575; Figure 1C), sensitivities (12%, 4%, and 20%), and PPVs (56%, 33%, and 51%), respectively, were considerably lower in the common iliac region. On the other hand, this region had equivalent or higher specificities (99%, 99%, and 95%) and NPVs (93%, 92%, and 81%) for MRI, CT, and [18F]FDG-PET-CT, respectively. Again, [18F]FDG-PET-CT outperformed MRI and CT in terms of AUC and sensitivity. The prevalence of common iliac metastases (8-22%) was substantially lower than that of pelvic metastases (23-45%) for all modalities.

Table 3. Region-based diagnostic indices for MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases based on original and imputed data.

Modality	Region	Prev. LNM	Sensitivity	Specificity	PPV	NPV	AUC[a]
Original data							
MRI	Pelvic	19 (16-21)	33 (30-36)	93 (92-95)	53 (50-56)	86 (84-88)	0.631 (0.599-0.663)
	Common iliac	4 (3-5)	10 (8-12)	99 (99-100)	44 (41-48)	96 (95-98)	0.549 (0.500-0.597)
CT	Pelvic	23 (20-27)	32 (28-36)	92 (90-94)	54 (50-58)	82 (79-85)	0.620 (0.578-0.661)
	Common iliac	4 (2-6)	0 (-)	99 (99-100)	0 (-)	96 (94-98)	0.497 (0.493-0.500)
[18F]FDG-PET-CT	Pelvic	42 (34-51)	70 (62-77)	80 (73-87)	80 (73-87)	72 (65-80)	0.750 (0.674-0.825)
	Common iliac	16 (9-23)	19 (11-26)	98 (95-100)	60 (50-69)	87 (80-93)	0.582 (0.482-0.682)
Imputed data							
MRI	Pelvic	23 (21-25)	47 (45-50)	93 (91-94)	66 (63-68)	85 (84-87)	0.705 (0.675-0.736)
	Common iliac	8 (7-9)	12 (10-13)	99 (99-100)	56 (53-58)	93 (92-94)	0.554 (0.508-0.600)
CT	Pelvic	25 (22-28)	37 (34-41)	93 (91-95)	64 (61-67)	81 (79-84)	0.656 (0.615-0.697)
	Common iliac	8 (7-10)	4 (3-5)	99 (99-100)	33 (30-36)	92 (90-94)	0.517 (0.487-0.547)
[18F]FDG-PET-CT	Pelvic	45 (40-50)	77 (73-82)	80 (76-84)	76 (72-80)	81 (77-85)	0.803 (0.725-0.881)
	Common iliac	22 (18-26)	20 (16-24)	95 (92-97)	51 (46-56)	81 (77-85)	0.575 (0.489-0.661)

Abbreviations: *Prev LNM*, prevalence of lymph node metastases; *PPV*, positive predictive value; *NPV*, negative predictive value; *AUC*, area under the receiver operating curve; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET-CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

[a]AUC without dichotomizing the nodal status on imaging.

Numbers represent % with (95% confidence interval).

Inconclusive lymph nodes regarded as negative

Patient- and region-based diagnostic indices were recalculated, and changed minimally after inconclusive lymph nodes (5-6%) were considered negative instead of suspicious (Supplementary Tables 6 and 7). The sensitivity of MRI, CT and [18F]FDG-PET-CT in detecting nodal metastases on a patient-based level decreased to 38%, 31% and 75%, the NPV to 83%, 80%, and 80%, and the AUC to 0.671, 0.636, and 0.795, respectively. Conversely, the specificity (96%, 97%, and 85%) and PPV (77%, 77%, and 81%) of all three modalities increased after inconclusive statuses were included as negative. Similar trends were observed in the pelvic and para-aortic regions.

DISCUSSION

In this study, we evaluated the diagnostic performance of pretreatment imaging for lymph node metastases in recent years in clinically early-stage cervical cancer on a patient- and region-based level, while reducing

the risk of partial verification bias by multiple imputation. [18F]FDG-PET-CT was superior in detecting nodal metastases (sensitivity/PPV) at both levels, compared to MRI and CT. Although, this is probably related to its use as a verification modality. In contrast, MRI and CT had the highest specificity. The accuracy of all three modalities was lower in the common iliac than the pelvic region, especially regarding sensitivity. In addition, there may be a significant risk of nodal involvement in the case of multiple imaging with at least one positive result, particularly a positive [18F]FDG-PET-CT. Based on our results, we believe that verification with [18F]FDG-PET-CT may be valuable in differentiating between patients at low and high risk of metastasis, particularly in cases of suspicious nodes on MRI. However, caution should be exercised when using this information to guide treatment planning because of the risk of false-positive or false-negative results, especially for FIGO 2018 stage IIIC 'r' involving the common iliac region.

Consistent with our findings, previous studies have demonstrated that [18F]FDG-PET-CT has an overall higher diagnostic performance than MRI and CT in detecting nodal metastases in patients with cervical cancer.[9, 10, 19, 20] The outperformance of [18F]FDG-PET-CT can be explained by the following. Advantages of functional imaging: [18F]FDG-PET-CT detects potential metastases due to increased glucose metabolism, whereas MRI and CT rely mainly on nodal size (≥ 1 cm) and morphology.[21] In addition, [18F]FDG-PET-CT imaging fields generally cover a more comprehensive area than MRI and CT. Therefore, more lymph node metastases can be detected, including those outside the pelvis. However, the higher accuracy of [18F]FDG-PET-CT in our study may also be explained by its use as a verification modality, as 95% of our patients with [18F]FDG-PET-CT had an MRI or CT previously. Previous MRI and/or CT findings may have influenced the interpretation of the [18F]FDG-[18F]FDG-PET-CT scan by the nuclear medicine physician. In addition, the prevalence of lymph node metastases in the [18F]FDG-PET-CT group was nearly twice the prevalence with MRI and CT. As [18F]FDG-PET-CT is recommended by the Dutch guidelines for the validation of suspicious nodes, patients receiving [18F]FDG-PET-CT will have a higher probability of suspicious nodes and nodal metastases, as reflected in our study. Verification of MRI/CT results with [18F]FDG-PET-CT seems useful to identify patients at high-risk of metastasis, particularly in cases with suspicious nodes on MRI. Our results suggest that this strategy reduces the risk of unwarranted omission of surgery or, in case of primary chemoradiotherapy, overtreatment with nodal boosting/extended-field (fewer false-positives). However, due to the low sensitivity of MRI (more false negatives), patients may require adjuvant chemoradiotherapy due to postoperative pathological detection of lymph node metastases missed by pretreatment imaging. And in the case of primary radiotherapy, the low sensitivity of MRI may result in undertreatment because of inadequate radiotherapy settings.

In the region-based analyses, all three modalities showed higher accuracy in the pelvic region than in the common iliac region, especially in terms of sensitivity. Cervical cancer generally metastasizes via the lymphatic system, where the common iliac region is considered a secondary lymphatic drainage station.[22, 23] The size of metastatic lymph nodes in this region may be smaller. Therefore, metastases may be harder to detect, as demonstrated in our study. These findings align with the literature where higher sensitivities have been demonstrated in the pelvic region than in the para-aortic region.[8, 24-26] For MRI, the resolution setting is generally lower for the common iliac than pelvic region, which may have contributed to its lower accuracy in this region. Nevertheless, the identification of metastatic nodes in secondary stations is important, because they are associated with a poor prognosis and, as a consequence, extended field radiotherapy is often recommended.[4, 27] According to our results, metastatic nodes in the common

iliac region are underdiagnosed. Therefore, patients are at risk of undertreatment when receiving primary chemoradiotherapy, due to inadequate radiotherapy-field settings. Meanwhile, patients are at risk of receiving adjuvant therapy after surgery due to lymph node metastases.

In the literature, the diagnostic accuracy of MRI, CT and [18F]FDG-PET-CT varies in detecting lymph node metastases in cervical cancer, possibly related to different study designs, definitions of suspicious nodes, imaging techniques, and heterogeneous patient cohorts. Sensitivities and specificities were reported to be 24-73% and 69-96% for MRI, 33-67% and 56-97% for CT, and 35-91% and 90-100% for [18F]FDG-PET-CT. The PPV and NPV were 48-67% and 78-98% for MRI, 20-86% and 72-93% for CT, and 47-100% and 81-96% for [18F]FDG-PET-CT. Corresponding metastatic nodal prevalence rates were 16% to 34%.[8-10, 20, 28-35] Most of our rates fall within the broad ranges described in the literature, although we found a slightly lower specificity and a higher metastatic rate for [18F]FDG-PET-CT. As mentioned before, this may be related to the use of [18F]FDG-PET-CT as a verification modality in our cohort. In addition, all metastatic rates increased after imputation, which was expected, as pathological verification is often lacking in patients with poor prognostic factors who are at risk of metastasis (e.g. suspicious nodes and larger tumour size). Consequently, these patients are often excluded from both prospective and retrospective studies, leading to biased estimates of diagnostic indices.

By means of a retrospective study design, we provided the diagnostic indices of three imaging modalities within one large, nationwide cohort. However, there are several limitations. We used multiple imputation to account for partial verification bias. Although the imputation rates were high (30-40%), the variable distributions after imputation were similar to the original data after imputation. Except for the prevalence of pathological nodal metastases, which was expected and explained above. Other potential factors influencing our results include intra- and inter-observer variability, as nodal status was recorded in different centres over an extended period of time (2009 to 2017). Differences in imaging techniques may have introduced variability into our results, but adjustment for these technical variations was unfortunately not possible, as detailed data on the technical parameters are not available. On the other hand, our results provide insight into the diagnostic performance in the daily Dutch clinical practice. Finally, our results are mostly based on conventional imaging techniques, as our data cover the years 2009-2017. For future studies, it would be interesting to include more advanced techniques such as diffusion-weighted (DW)-MRI, which may increase the sensitivity to 86-87% and reduce the need for verification by [18F]FDG-PET-CT.[9, 36]

In conclusion, [18F]FDG-PET-CT outperformed MRI and CT in detecting nodal metastases in patients with early stage cervical cancer with a sensitivity of 80%, when used as verification modality, while MRI and CT had the highest specificity (92%). In other words, MRI might be the preferred imaging modality for pretreatment staging cervical cancer patients by accurately excluding patients without nodal metastases, next to determining tumour size and local spread. [18F]FDG-PET-CT may be added in patients with suspicious nodes on MRI or in patients at high risk of nodal metastases (e.g. large tumour size and increased tumour marker). However, this hypothesis should be confirmed in prospective studies before clinical implementation. Finally, accounting for partial verification bias increased almost all diagnostic indices, suggesting that diagnostic performance in previous studies based on retrospective data may have been underestimated.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Imputation models.

Imputed model	Included variables
Patient-based	Pathologic nodal status, clinical nodal metastasis status according to TNM 8, age, lympho-vascular space invasion, FIGO 2009 stage, primary tumour size, grade, histology, depth of invasion, horizontal spread, suspicion of parametrial invasion, nodal status and short-axis at MRI, CT, [18F]FDG-PET-CT
Region-based	Pathologic nodal status of the pelvic and common iliac regions, clinical nodal metastasis status according to TNM 8, age, lympho-vascular space invasion, FIGO 2009 stage, primary tumour size, grade, histology, depth of invasion, horizontal spread, suspicion of parametrial invasion, pelvic and common iliac nodal status and short-axis at MRI, CT, [18F]FDG-PET-CT

Abbreviations*: FIGO*, International Federation of Gynaecology and Obstetrics; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET/CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

Supplementary Table 2. Distribution of variables with missing data before and after multiple imputation on patient-based level.

Imputed variables	Missing	Original data	Imputed data
Pathologic nodal metastasis	679 (30.4%)		
Positive		20.4	23.6
Negative		79.6	76.4
Tumour grade	543 (29.9%)		
1		11.6	11.7
2		47.2	47.0
3		40.8	40.8
4		0.5	0.5
cN	114 (5.1%)		
0		83.9	83.9
1		16.1	16.1
Tumour grade	720 (32.2%)		
1		11.5	11.7
2		47.2	47.2
3		40.8	40.6
4		0.5	0.5
LVSI	492 (22.0%)		
Present		42.4	41.7
Absent		57.6	58.3
Depth of invasion, mm	729 (32.6%)		
<3		16.9	14.5
3-5		22.4	20.6
>5		60.7	65.0
Nodal short-axis category, mm [a]	56 (2.5%)		
Not suspicious		83.5	81.4
<10		8.2	9.4
10-19		6.5	7.2
≥20		1.9	2.0
Suspicion of parametrial invasion	392 (17.5%)		
Absent		92.6	91.6
Presumably absent		1.7	1.9
Presumably present		5.7	6.5
Tumour size, cm	49 (2.2)		
≤2		31.0	30.6
<4		8.2	8.2

Supplementary Table 2. (continued)

>2-4	33.4	33.3
>4	27.4	27.9

Abbreviations: *cN*, clinical nodal status; *LVSI*, lympho-vascular space invasion.

Numbers represent % or number of patients.

[a] negative nodes were allocated as category '0'.

Supplementary Table 3. Distribution of variables with missing data before and after multiple imputation on region-based level.

Imputed variables	Missing	Original data	Imputed data
Pathologic nodal metastasis			
Pelvic	691 (30.9%)		
Positive		19.5	22.8
Negative		80.5	77.2
Common iliac	921 (41.2%)		
Positive		4.0	7.8
Negative		96.0	92.2
Tumour grade	720 (32.2%)		
1		11.5	11.6
2		47.2	47.1
3		40.8	40.7
4		0.5	0.6
cN	114 (5.1%)		
0		83.9	83.9
1		16.1	16.1
LVSI	492 (22.0%)		
Present		42.4	41.4
Absent		57.6	58.6
Depth of invasion, mm	729 (32.6%)		
<3		16.9	14.6
3-5		22.4	20.5
>5		60.7	64.9
Short-axis of suspicious pelvic node, mm [a]	32 (1.4%)		
Not suspicious		84.5	83.4
0-10		7.6	8.2
>10-20		6.2	6.6
>20		1.7	1.8
Suspicion of parametrial invasion	392 (17.5%)		
Absence		92.6	92.1
Presumably absent		1.7	1.8
Presumably present		5.7	6.1
Tumour size, cm	49 (2.2)		
≤2		31.0	30.7
<4		8.2	8.2
>2-4		33.4	33.3
>4		27.4	27.9

Abbreviations*: cN*, clinical nodal status; *LVSI*, lympho-vascular space invasion.

[a] The short-axis diameter of suspicious common iliac nodes was included in the model but not imputed, as it was only missing for four patients.

Numbers represent % or number of patients.

Supplementary Table 4. Patient-based diagnostic indices for MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases of patient cohorts with multiple imaging results.

Cohort	n	Modality	AUC of original data[a]	n	AUC of imputed data[a]
MRI + [18F]FDG-PET-CT	114	MRI	0.706 (0.615-0.798)	314	0.749 (0.684-0.815)
		[18F]FDG-PET-CT	0.792 (0.710-0.873)		0.814 (0.746-0.882)
MRI + CT	234	MRI	0.647 (0.580-0.713)	384	0.713 (0.656-0.771)
		CT	0.613 (0.548-0.678)		0.655 (0.599-0.710)
[18F]FDG-PET-CT + CT	40	[18F]FDG-PET-CT	0.773 (0.634-0.914)	106	0.796 (0.694-0.898)
		CT	0.685 (0.523-0.847)		0.722 (0.614-0.829)
MRI + CT + [18F]FDG-PET-CT	23	MRI	0.631 (0.410-0.851)	59	0.703 (0.559-0.847)
		CT	0.673 (0.458-0.888)		0.668 (0.522-0.814)
		[18F]FDG-PET-CT	0.769 (0.575-0.964)		0.762 (0.614-0.911)

Abbreviations*: n*, number of patients; *AUC*, area under the receiver operating curve; ; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET/CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

[a] AUC (95% confidence interval) without dichotomizing the nodal status on imaging.

Supplementary Table 5. The prevalence of lymph node metastases in patient cohorts according to (multiple) imaging results.

Cohorts	n	MRI	CT	[18F]FDG-PET-CT	Prev LNM (%)
	1,390	Negative			15
	286	Positive			66
	778		Negative		18
	148		Positive		64
	196			Negative	18
	183			Positive	76
1	283	Negative	Negative		17
2	20	Negative	Positive		38
3	31	Positive	Negative		65
4	50	Positive	Positive		74
5	40		Negative	Negative	15
6	16		Negative	Positive	73
7	11		Positive	Negative	52
8	39		Positive	Positive	78
9	126	Negative		Negative	18
10	31	Negative		Positive	58
11	21	Positive		Negative	14
12	136	Positive		Positive	79
13	17	Negative	Negative	Negative	19
14	22	Positive	Positive	Positive	71

Abbreviations*: n*, number of patients; ; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET/CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography; *Prev LNM*, prevalence of lymph node metastases.

Based on imputed data for cohorts with n>10.

Supplementary Table 6. Patient-based diagnostic indices for MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases based on original and imputed data, inconclusive nodes considered negative.

Modality	Prev LNM	Sensitivity	Specificity	PPV	NPV	AUC[a]
Original data						
MRI	19 (17-22)	24 (21-26)	98 (97-98)	70 (67-72)	84 (82-86)	0.605 (0.577-0.633)
CT	24 (21-28)	27 (24-31)	97 (96-98)	75 (71-79)	81 (77-84)	0.623 (0.585-0.660)
[18F]FDG-PET-CT	44 (35-52)	68 (61-76)	88 (83-94)	82 (76-88)	78 (71-85)	0.783 (0.714-0.853)
Imputed data						
MRI	24 (22-26)	38 (35-40)	96 (95-97)	77 (75-79)	83 (81-85)	0.671 (0.642-0.700)
CT	26 (23-29)	31 (28-33)	97 (96-98)	77 (74-79)	80 (78-83)	0.636 (0.600-0.672)
[18F]FDG-PET-CT	46 (41-51)	75 (71-79)	85 (81-89)	81 (77-85)	80 (76-84)	0.795 (0.740-0.850)

Abbreviations*: Prev LNM*, prevalence of lymph node metastases; *PPV*, positive predictive value; *NPV*, negative predictive value; *AUC*, area under the receiver operating curve; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET/CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

[a] AUC with dichotomizing the nodal status on imaging.

Numbers represent % with (95% confidence interval).

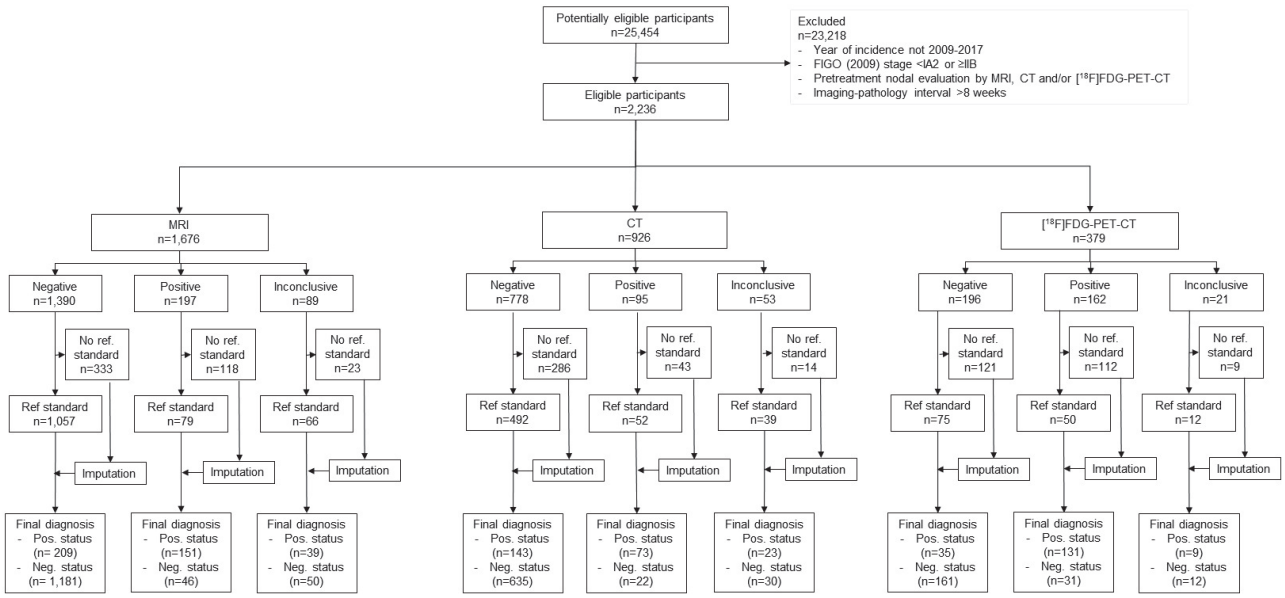
Supplementary Table 7. Region-based diagnostic indices for MRI, CT and [18F]FDG-PET-CT in detecting lymph node metastases based on original and imputed data, inconclusive nodes considered negative.

Modality	Region	Prev LNM	Sensitivity	Specificity	PPV	NPV	AUC[a]
Original data							
MRI	Pelvic	19 (16-21)	23 (21-25)	97 (97-98)	67 (64-68)	85 (83-87)	0.602 (0.574-0.630)
	Common iliac	4 (3-5)	8 (6-9)	100 (-)	100 (-)	96 (95-98)	0.539 (0.496-0.581)
CT	Pelvic	23 (20-27)	25 (22-29)	97 (96-98)	72 (69-76)	81 (78-84)	0.612 (0.574-0.650)
	Common iliac	4 (2-6)	0 (-)	100 (99-100)	0 (-)	96 (94-98)	0.499 (0.497-0.501)
[18F]FDG-PET/CT	Pelvic	42 (34-51)	68 (60-76)	89 (84-95)	83 (76-89)	79 (72-86)	0.787 (0.716-0.857)
	Common iliac	16 (9-23)	13 (6-19)	99 (97-100)	67 (58-76)	86 (79-93)	0.557 (0.472-0.641)
Imputed data							
MRI	Pelvic	23 (21-25)	38 (36-41)	96 (95-97)	75 (73-77)	84 (82-86)	0.673 (0.645-0.700)
	Common iliac	8 (7-9)	9 (8-10)	100 (99-100)	71 (70-73)	93 (91-94)	0.540 (0.512-0.578)
CT	Pelvic	25 (22-28)	29 (26-32)	97 (96-98)	76 (73-79)	80 (78-83)	0.629 (0.593-0.665)
	Common iliac	8 (7-10)	2 (1-3)	100 (99-100)	34 (31-37)	92 (90-93)	0.509 (0.487-0.543)
[18F]FDG-PET/CT	Pelvic	45 (40-50)	74 (69-78)	85 (82-89)	80 (76-84)	80 (76-84)	0.795 (0.720-0.870)
	Common iliac	22 (18-26)	17 (13-21)	96 (94-98)	53 (49-58)	80 (76-84)	0.566 (0.490-0.642)

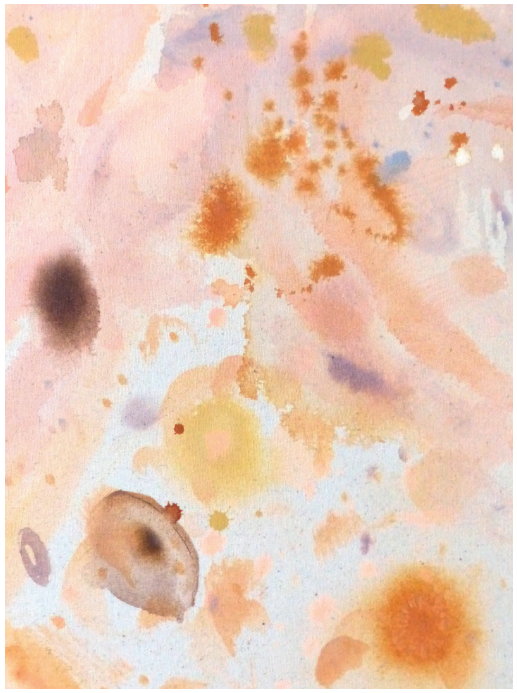
Abbreviations*: Prev LNM*, prevalence of lymph node metastases; *PPV*, positive predictive value; *NPV*, negative predictive value; *AUC*, area under the receiver operating curve; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *[18F]FDG-PET/CT*, 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography.

[a] AUC with dichotomizing the nodal status on imaging.

Numbers represent % with (95% confidence interval).



Supplementary Figure 1. Patient-flow chart of patient-based analyses according to Standards for Reporting of Diagnostic Accuracy (STARD).



Chapter 4

Treatment strategies guided by [18F]FDG-PET/CT in patients with locally advanced cervical cancer and [18^{F}]FDG-positive lymph nodes

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ABSTRACT

Background: Modern treatment guidelines for women with advanced cervical cancer recommend staging using 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography ([18F]FDG-PET/CT). However, the risk of false-positive nodes and therapy-related adverse events requires caution in treatment planning. Using data from the Netherlands Cancer Registry (NCR), we estimated the impact of [18F]FDG-PET/CT on treatment management in women with locally-advanced cervical cancer, i.e., on nodal boosting, field extension and/or debulking in case of suspected lymph nodes.

Methods: Women diagnosed between 2009–2017, who received chemo-radiotherapy for International Federation of Gynaecology and Obstetrics (2009) stage IB2, IIA2-IVB cervical cancer with an [18F]FDG-positive node, were retrospectively selected from the NCR database. Patients with pathological nodal examination before treatment were excluded. The frequency of nodal boosting, extended-field radiotherapy, and debulking procedures applied to patients with [18F]FDG-positive lymph nodes was evaluated.

Results: Among the 434 eligible patients with [18F]FDG-positive nodes, 380 (88%) received interventions targeting these lymph nodes: 84% of these 380 patients received nodal boosting, 78% extended-field radiotherapy, and 12% debulking surgery. [18F]FDG-positive nodes in patients receiving these treatments were more likely to be classified as suspicious than inconclusive (p=0.009), located in the para-aortic region (p<0.001), and larger (p<0.001), than in patients who did not receive these treatments.

Conclusion: While existing guidelines advocate [18F]FDG-PET/CT-guided treatment planning for the management of advanced cervical cancer, this study highlights that not all cases of [18F]FDG-positive nodes received an intervention, possibly due to the risk of false-positive results. Improvement of nodal staging may reduce suboptimal treatment planning.

INTRODUCTION

Cervical cancer is one of the most common cancers in women worldwide, with approximately 604,000 new cases and 342,000 deaths in 2020.[1] Around 40% of cervical cancer patients are diagnosed with locally advanced disease, defined as International Federation of Gynaecology and Obstetrics (FIGO) 2018 stage IB3, IIA2-IVA or FIGO 2009 stage IB2, IIA2-IVA.[2-5] In this group, the five-year overall survival rate after completion of standard treatment with chemoradiotherapy is ~66%.[6] Survival is worse in patients with lymph node metastases, especially in the para-aortic region.[7, 8] Based on one of the few studies with prospective data from a relatively large cohort (n=120), the prevalence of pathologically confirmed pelvic and para-aortic metastases in locally advanced cervical cancer is 51% and 24%, respectively.[9] This group of patients may benefit from nodal therapy in addition to primary chemoradiotherapy by boosting, extended-field radiotherapy or debulking.[10-18]

Guidelines recommend the use of 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography ([18F]FDG-PET/CT) to assess lymph node metastases and guide treatment planning in locally advanced cervical cancer.[19, 20] If a suspicious lymph node is detected, an additional radiation boost should be applied and debulking may be considered, whereas metastases confined to the para-aortic region should be treated with extended-field radiotherapy.[19] [18F]FDG-PET/CT detects increased glucose metabolism, a characteristic of tumour cells. Detection of FDG-uptake helps to differentiate between physiologically enlarged lymph nodes and metastatic nodes. It also facilitates identification of smaller metastases compared to conventional imaging, but at the expense of detecting false-positive reactive nodes.[21]

A recent meta-analysis reported positive-predictive values of 68%-96% for detecting pelvic and/or para-aortic metastases in locally advanced cervical cancer, depending on the prevalence of lymph node metastases (15%-65%).[22] In other words, [18F]FDG-positive nodes may be false-positive in up to one third of these patients. Therapy-related adverse events, such as surgical complications from nodal debulking and genitourinary and gastrointestinal toxicity from radiotherapy, require caution in treatment planning.[11, 23, 24] On the other hand, inadequately treated [18F]FDG-positive nodes representing true metastases could reduce the chance of survival.

Despite this daily dilemma in clinical practice, only few studies have assessed the management of [18F]FDG-positive nodes with nodal boosting, extended-field radiotherapy and nodal debulking. Therefore, this study aims to evaluate how often patients with advanced-stage cervical cancer and an [18F]FDG-positive lymph node receive nodal boosting, extended-field radiotherapy and/or debulking in addition to standard field/dose primary chemoradiotherapy.

METHODS

Study design and data collection

For this retrospective study, all cervical cancer patients diagnosed in 2009-2017, with suspected pelvic and/or para-aortic lymph node metastases on [18F]FDG-PET/CT, were selected from the population-based Netherlands Cancer Registry (NCR). Patients with: (1) an age of ≥18 years, (2) International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IB2, IIA2-IVA, and (3) primary chemoradiotherapy were

included. Patients were excluded if they had: (1) a previous malignancy or a concurrent malignancy interfering with cervical cancer therapy, (2) pathological examination of suspicious nodes before nodal debulking or primary therapy, (3) a pregnancy during cervical cancer treatment, or (4) neoadjuvant chemotherapy.

Patient, tumour, imaging and treatment characteristics were recorded retrospectively from patient records by trained data managers. Lymph node status on [18F]FDG-PET/CT was registered for five anatomic regions: pelvic left/right, common iliac left/right (including presacral nodes) and para-aortic conform Liu et al. (2016).[25] They were recorded as negative, inconclusive, suspicious, or unknown, as reported by the nuclear medicine physician. A lymph node was considered suspicious if recorded as inconclusive or suspicious, which would normally include nodes with a short-axis diameter of ≥1.0 cm and/or focally increased FDG uptake (more than the adjacent vessel), as imaging was performed according to local protocols following Dutch (Nedpas) and international (EARL) standards.[26]

The management of cervical cancer in the Netherlands is based on European treatment guidelines, with limited local variation.[19, 20] According to these guidelines, chemoradiotherapy consisted of pelvic external beam radiotherapy (i.e. 45-50 Gy) and concurrent chemotherapy (i.e. cisplatin 40 mg/m2 weekly) or hyperthermia. Additional treatment of [18F]FDG-positive lymph nodes included boosting, extended-field radiotherapy and/or debulking. Debulking, or surgical resection, addressed bulky nodes without a definitive size specification.[20] Moreover, patients could receive nodal boosting for [18F]FDG-positive nodes with a targeted higher dose of radiation. The predetermined total dose for a nodal boost, including the contribution of brachytherapy, was 55 to 60 Gy (equieffective dose to 2 Gy per fraction (EQD2) assuming an α/β of 10 Gy for tumour). In addition, in accordance with the EMBRACE protocol, radiotherapy was extended to the para-aortic region in cases with common iliac or para-aortic involvement.[27]

Outcomes and definitions

The primary outcome of the study was the overall treatment rate of [18F]FDG-positive nodes in addition to standard chemoradiotherapy and for each nodal treatment separately. Nodal treatment included: (1) boost irradiation, (2) extended-field radiotherapy for common iliac and/or para-aortic involvement, and (3) debulking ± lymphadenectomy, combined with primary chemoradiotherapy. Patients who had lymph node debulking were excluded from analysis on nodal boosting and extended field radiotherapy, but not vice versa: debulking may have been followed by nodal boosting and/or extended-field radiotherapy. For each nodal treatment strategy (i.e., boosting, extended-field radiotherapy and/or debulking), baseline characteristics were compared between patients who did and did not receive the treatment, to identify factors that may have influenced treatment decisions. Subgroup analyses were performed to assess the impact of para-aortic [18F]FDG-positive nodes on extended-field radiotherapy rates, and to assess the impact of bulky nodes (with a short-axis of ≥15 mm) on nodal debulking rates. Overall survival was defined as the interval from diagnosis to death. Patient vital status was obtained by linkage to the Municipal Personal Records Database (updated to January 31st, 2023). Patients who were still alive were censored at that time.

Statistical analysis

The rate of patients receiving nodal treatment for [18F]FDG-positive nodes was calculated by dividing the number of patients receiving nodal treatment by all patients with [18F]FDG-positive nodes. Normally and non-normally distributed variables were compared using unpaired T-test and Mann–Whitney U Test, respectively. Discrete variables were compared using Fisher's exact test. Survival analyses were performed using the Kaplan-Meier method. A p-value <0.05 was considered significant and Stata™ statistical software version 17.0 (StataCorp, College Station, TX, USA) was used for all analyses.

RESULTS

A total of 434 patients, with locally advanced cervical cancer and at least one [18F]FDG-positive lymph node on pretreatment [18F]FDG-PET/CT, were included (see Figure 1). In 88% of these patients (380/434), the [18F]FDG PET/CT lymph node information was used for additional treatment of the lymph nodes, as shown in Table 1. Baseline characteristics of patients with and without treatment with nodal boosting, extended-field radiotherapy, and/or debulking are shown in Table 2. [18F]FDG-positive nodes in patients receiving these treatments were more likely to be suspicious (95% versus 85%; p=0.009), located in the para-aortic region (23% versus 0%; p<0.001), and larger (median short-axis of 13 mm versus 10 mm; p<0.001), than in patients who did not receive these treatments.

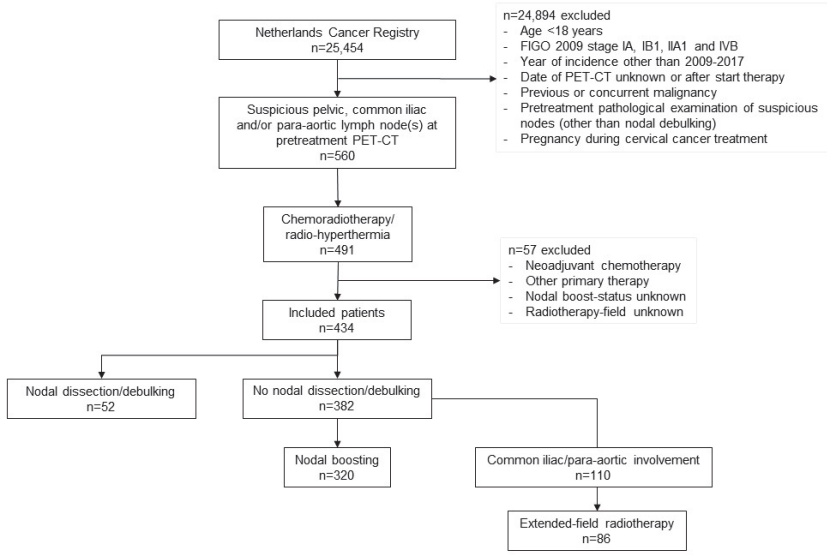

Figure 1. Flowchart of patient inclusion and exclusion in this study.

Table 1. [18F]FDG-positive nodal treatment rates.

		Overall	Nodal boosting	Extended-field [1]		Nodal debulking [2]	
[18F]FDG-positive nodal treatment	n	380/434	320/382	86/110	63/67	52/434	42/127
	%	88	84	78	94	12	33

Abbreviations: *FDG*, fluoro-D-glucose.

[1] the right row concerns patients with [18F]FDG-positive para-aortic nodes.

[2] the right row concerns patients with nodes ≥15 mm.

Data represents number of patients (n) or percentages (%).

Nodal boosting, extended-field radiotherapy, or debulking separately was observed in 84%, 78% and 12% of patients, respectively. Nodal debulking was followed by boost and/or extended-field radiotherapy in 75% (n=39). Boost with extended-field radiotherapy (without debulking) was given to 29% of patients (n=109). After debulking, 2/52 patients (4%) were pathologically negative for metastasis. The 5-year overall survival rates after boosting, extended-field radiotherapy, and debulking were 67% (95% confidence interval 61-72%), 49% (38-59%), and 53% (39-66%), respectively. Baseline characteristics stratified by treatment modality are shown in Supplementary Table S1. Notably, the boosting group had larger [18F]FDG-positive nodes than the group without boosting (12 mm vs 10 mm; p=0.02). Patients with extended-field radiotherapy were more likely to have para-aortic involvement compared with patients who received pelvic radiotherapy (74% versus 17%; p<0.001). In addition, patients treated with nodal debulking had larger tumours (55 mm versus 50 mm; p=0.017), larger [18F]FDG-positive nodes (21 mm versus 12 mm; p<0.001) and more often para-aortic involvement (37% versus 18%; p=0.003). Subgroup analyses of patients with bulky node(s) (≥15 mm) increased the rate of nodal treatment by debulking from 12% to 33%. In addition, analysis of patients with para-aortic involvement increased the rate of extended-field radiotherapy from 78% to 94%.

Table 2. Baseline characteristics of patients receiving nodal treatment and of those who did not.

Baseline characteristics	Missing	Without nodal treatment (n=54)		With nodal treatment (n=380)		p-value
Median age, years	0	50	(26-88)	49	(22-82)	0.17
Median body mass index, kg/m^2	23	26	(15-36)	24	(15-77)	0.20
Charlson Comorbidity Index	70					
0		37	82.0%	252	79.0%	0.95
1		7	15.6%	53	16.6%	
≥2		1	2.2%	14	4.4%	
FIGO 2009 stage	0					
IB2		3	5.6%	56	14.7%	0.20
IIA2		1	1.9%	16	4.2%	
IIB		27	50.0%	197	51.8%	
IIIA		3	5.5%	12	3.2%	
IIIB		16	29.6%	75	19.7%	
IVA		4	7.4%	24	6.3%	
Median tumour size, mm	21	50	(24-220)	50	(20-105)	0.70
Histological subtype	0					
Squamous cell carcinoma		46	85.2%	336	88.4%	0.61
Adeno(squamous) carcinoma		7	13.0%	37	9.7%	
Other carcinomas		1	1.9%	7	1.8%	

Table 2. (continued)

Additional imaging techniques	0					
CT		11	20.4%	109	28.7%	0.26
MRI		49	90.7%	356	93.7%	0.39
Status of [18F]FDG-positive node	0					
Suspicious		46	85.2%	362	95.3%	0.009*
Inconclusive		8	14.8%	18	4.7%	
FDG-positive nodes per region [1]						
Pelvic	1	53	98.2%	373	98.2%	1.00
Common iliac	6	4	7.4%	69	18.2%	0.51
Para-aortic	6	0	0.0%	86	22.6%	<0.001*
Median short-axis of suspicious node, mm	85	10	(6-26)	13	(6-86)	<0.001*

Abbreviations: *FIGO*, International Federation of Gynaecology and Obstetrics; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *FDG*, fluoro-D-glucose.

[1] patients may have positive lymph nodes in multiple regions,

* statistically significant.

Data represents number of patients, percentages, or median with (range).

DISCUSSION

This study showed that treatment strategies was guided by [18F]FDG-PET/CT in 88% of patients with advanced-stage cervical cancer and [18F]FDG-positive nodes. Among these strategies, nodal boosting was the predominant intervention (84%) for managing [18F]FDG-positive nodes, followed by extended-field radiotherapy (78%) and debulking (12%). Despite existing guidelines advocating [18F]FDG-PET/CT-guided treatment planning for the management of advanced cervical cancer, this study highlights that not all cases of [18F]FDG-positive nodes received an intervention. This raises the question if these patients were undertreated or were intentionally withheld additional treatment to prevent overtreatment.

Undertreatment of lymph node metastases can reduce survival and should therefore be minimised. While in 88% of the patients with [18F]FDG-positive nodes the treatment policy was according to the current guidelines, the remaining 12%, not following the guidelines, could theoretically have been undertreated. For nodal boosting and/or nodal debulking, there is no level 1 evidence that these treatment strategies result in better oncological outcomes.[19, 28-31] Furthermore, there is no proven superiority for either boosting or debulking, nor in the context of bulky nodes (short-axis ≥1.5 cm).[32] Therefore, current guidelines consider rather than recommend these treatments for suspicious nodes.[19, 20] However, several studies, including randomized controlled trials, have shown a survival benefit after extended-field radiotherapy for suspicious common iliac/para-aortic nodes.[16-18] In our study, 78% of patients received extended-field radiotherapy, resulting in potential undertreatment in 22% of patients, which is relatively high compared to other reports (0%-27%).[33-35] This may be related to the proportion of inconclusive nodes and the portion of presacral nodes who were registered as common iliac nodes in our study. This hypothesis is supported by our analysis of patients with para-aortic involvement only, of whom 94% received extended-field radiotherapy.

On the other hand, overtreatment is a serious concern because of potential therapy-related toxicity. Unacceptable high acute (27-81%) and late (17-40%) grade ≥3 toxicity rates, mostly gastrointestinal and genitourinary, have been reported for conventional radiotherapy techniques.[36, 37] Fortunately, improved

techniques (e.g. intensity-modulated radiotherapy) have reduced toxicity rates to 4-41% and 3-29%, respectively.[10, 14, 15, 17, 18, 30, 38] Overtreatment is caused by targeting false [18F]FDG-positive nodes. According to a recently published systematic review including 778 patients with locally-advanced cervical cancer, the positive predictive value of [18F]FDG-PET/CT varies from 68% to 96%, depending on the prevalence of lymph node metastases (range 15-65%).[22]

Using prevalences of pathologically confirmed pelvic (51%) and para-aortic (24%) lymph node metastases from a prospective, comparable study cohort, together with corresponding positive predictive values of 93% and 65%, respectively, for [18F]FDG-positive nodes from a meta-analysis,[10, 22] overtreatment of pelvic nodes with boosting and para-aortic nodes with extended-field (chemo)radiotherapy in respectively 7% and 35% of patients may occur. In our study population, this would have resulted in overtreatment with boosting in 22/382 (6%) patients and with extended-field radiotherapy in 30/110 (27%) patients. Therefore, caution should be exercised, especially in the group of patients where extended-field (chemo)radiotherapy is considered only on the basis of [18F]FDG-PET/CT. In these circumstances, other variables that increase the likelihood of nodal metastases, such as FIGO stage, larger tumour size, parametrial invasion, and the presence of lymphovascular space invasion should also be taken into account. In the end, fine-needle aspiration or debulking of [18F]FDG-positive nodes, is the only strategy that could potentially reduce radiotherapy-related toxicity and overtreatment, by reducing the required doses and adjusting the radiotherapy field settings. However, nodal debulking is associated with surgical complications, such as infection and intraoperative injury, with a prevalence of 10-15%.[11, 28]

Two limitations of this study need to be addressed. First, because of its retrospective nature with limited data, we do not know the reason why [18F]FDG-positive lymph nodes were not treated, which may have biased our results. In the Netherlands, most treatment recommendations are made at a multidisciplinary meeting, where patient and physician preferences, but also MRI/CT imaging results, may influence treatment decisions. In addition, [18F]FDG-positive nodes may be reassessed and sometimes reclassified as not suspicious, which may not have been reported accurately. These cases may have negatively affected our nodal treatment rates. Second, the characteristics of the [18F]FDG-positive nodes that were treated differed from those that were not treated in terms of status, location and size. The untreated nodes appeared less suspicious and may not have been treated for this reason. Despite these limitations, this study provides insight into the implementation of current guidelines with an appraisal of its consequences for the treatment of [18F]FDG-positive nodes with boosting, extended-field radiotherapy and debulking, based on a relatively large patient cohort (n=434).

Although [18F]FDG-PET/CT is currently considered the best imaging modality for assessing nodal status in patients with locally advanced cervical cancer, suboptimal negative and positive predictive values (especially for para-aortic nodes) may still lead to inadequate treatment planning. For future research, it would be relevant to improve this value (e.g. by artificial intelligence or nomograms) or to determine treatment rates after pathologic verification of [18F]FDG-positive nodes (e.g. surgical staging or imaging guided biopsy). Currently, the PARa-aOrtic LymphAdenectomy in locally advanced cervical cancer (PAROLA)-trial is open for accrual, investigating the effect of para-aortic surgical staging on treatment modification and recurrences in patients with suspicious pelvic nodes.[39] Furthermore, to improve the understanding of the overall efficacy and safety of the nodal treatment strategies explored in this study, it

may be interesting for future research to further investigate survival outcomes and complication rates beyond prevalence.

CONCLUSIONS

In conclusion, treatment planning based on [18F]FDG-PET/CT was applied in 88% of patients with locally advanced cervical cancer and [18F]FDG-positive lymph nodes, mainly consisting of nodal boosting (84%) followed by extended-field radiotherapy (78%) and debulking (12%). Nodal treatment for [18F]FDG-positive lymph nodes should be weighed and discussed for each individual patient in terms of the risk of false-positivity/negativity, morbidity and survival benefit. Future research may reduce suboptimal treatment planning by improving nodal staging.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Baseline characteristics according to nodal treatment by nodal boosting, extended-field radiotherapy, and debulking separately.

	Boosting						Extended-field radiotherapy						Debulking					
Baseline characteristics	M	Without (n=62)		With (n=320)		p-value	M	Without (n=24)		With (n=86)		p-value	M	Without (n=382)		With (n=52)		p-value
Median age, years	0	50	(22-88)	49	(23-82)	0.33	0	47	(27-82)	51	(22-79)	0102	0	49	(22-88)	50	(25-77)	0.26
Median body mass index, kg/m^2	21	25	(15-36)	24	(15-77)	0.51	4	23	(19-77)	25	(16-44)	0.51	23	24	(15-77)	26	(17-39)	0.33
Charlson Comorbidity Index	58						17						70					
0		40	78.8%	216	78.8%	1.00		18	85.7%	55	76.4%	0.53		256	79.0%	33	82.5%	1.00
1		8	16.8%	46	16.8%			3	14.3%	10	13.9%			54	16.7%	6	15.0%	
≥2		2	4.0%	12	4.4%			0	0.0%	7	9.7%			14	4.3%	1	2.5%	
FIGO 2009 stage	0						0						0					
IB2		3	4.8%	46	14.4%	0.11		2	8.3%	8	9.3%	0.23		49	12.8%	10	19.2%	0.65
IIA2		1	1.6%	13	4.1%			2	8.3%	4	4.7%			14	3.7%	3	5.8%	
IIB		31	50.0%	169	52.8%			14	58.3%	39	45.4%			200	52.4%	24	46.2%	
IIIA		3	4.8%	11	3.4%			2	8.3%	2	2.3%			14	3.7%	1	1.9%	
IIIB		18	29.0%	61	19.1%			2	8.3%	23	26.7%			79	20.7%	12	23.1%	
IVA		6	9.7%	20	6.3%			2	8.3%	10	11.6%			26	6.8%	2	3.9%	
Median tumour size, mm	20	56	(24-220)	50	(20-105)	0.10	10	50	(25-85)	50	(30-105)	0.97	21	50	(20-220)	55	(38-100)	0.017*
Histological subtype	0						0						0					
Squamous cell carcinoma		54	87.1%	280	87.5%	0.93		18	75.0%	75	87.2%	0.11		334	87.4%	48	92.3%	0.65
Adeno(squamous) carcinoma		7	11.3%	33	10.3%			3	12.5%	9	10.5%			40	10.5%	4	7.7%	
Other carcinomas		1	1.6%	7	2.2%			3	12.5%	2	2.3%			8	2.1%	0	0.0%	
Additional imaging techniques	0						0						0					
CT		16	26.0%	82	25.6%	1.00		7	29.2%	34	39.5%	0.48		98	25.7%	22	42.3%	0.020*
MRI		57	91.9%	304	95.0%	0.36		23	95.8%	77	89.5%	0.69		361	94.5%	44	84.6%	0.014*
Status of [18F]FDG-positive node	0						0						0					
Suspicious		54	87.1%	302	94.4%	0.051		22	91.7%	79	91.9%	1.00		356	93.2%	52	100.0%	0.058
Inconclusive		8	12.9%	18	5.6%			2	8.3%	7	8.1%			26	6.8%	0	0.0%	
FDG-positive nodes per region [1]																		
Pelvic	1	61	98.4%	314	98.4%	1.00	1	21	87.5%	82	96.5%	0.12	1	375	98.2%	51	98.1%	0.59
Common iliac	6	6	9.7%	53	16.9%	0.18	3	21	87.5%	38	45.8%	<0.001*	6	59	15.7%	14	26.9%	0.050

Supplementary Table 1. (continued)

Para-aortic	6	7	11.5%	60	19.1%	0.20	1	4	16.7%	63	74.1%	<0.001*	6	69	17.8%	19	36.5%	0.003*
Median short-axis of suspicious node, mm [2]	83	10	(6-26)	12	(6-86)	0.02*	48	8	(6-16)	10	(4-33)	0.31	85	12	(6-86)	21	(9-50)	<0.001*

Abbreviations: *M*, missing; *FIGO*, International Federation of Gynaecology and Obstetrics; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *FDG*, fluoro-D-glucose.

[1] patients may have positive lymph nodes in multiple regions,

[2] concerns common iliac and para-aortic nodes for extended-field radiotherapy analysis,

* statistically significant.

Part 2

Treatment of lymph node metastases

Chapter 5

The prognostic value of the number of positive lymph nodes and the lymph node ratio in early-stage cervical cancer

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ABSTRACT

Introduction: To establish the impact of the number of lymph node metastases (nLNM) and the lymph node ratio (LNR) on survival in patients with early-stage cervical cancer after surgery.

Material and methods: In this nationwide historical cohort study, all women diagnosed between 1995 and 2020 with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA2–IIA1 cervical cancer and nodal metastases after radical hysterectomy and pelvic lymphadenectomy from the Netherlands Cancer Registry were selected. Optimal cut-offs for prognostic stratification by nLNM and LNR were calculated to categorize patients into low-risk or high-risk groups. Kaplan–Meier overall survival analysis and flexible parametric relative survival analysis were used to determine the impact of nLNM and LNR on survival. Missing data were imputed.

Results: The optimal cut-off point was ≥4 for nLNM and ≥0.177 for LNR. Of the 593 women included, 500 and 501 (both 84%) were categorized into the low-risk and 93 and 92 (both 16%) into the high-risk groups for nLNM and LNR, respectively. Both high-risk groups had a worse 5-year overall survival ($p < 0.001$) compared with the low-risk groups. Being classified into the high-risk groups is an independent risk factor for relative survival, with excess hazard ratios of 2.4 (95% confidence interval 1.6–3.5) for nLNM and 2.5 (95% confidence interval 1.7–3.8) for LNR.

Conclusions: Presenting a patient's nodal status postoperatively by the number of positive nodes, or by the nodal ratio, can support further risk stratification regarding survival in the case of node-positive early-stage cervical cancer.

INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed type of cancer and the fourth leading cause of cancer deaths among women worldwide.[1] In high-income countries, about half of all cervical cancers are diagnosed at an early stage.[2, 3] The presence of lymph node metastases is one of the most important prognostic factors. The 5-year overall survival rate for patients diagnosed with early-stage cervical cancer and negative nodes is 87%–95%, compared with 65%–80% in patients with positive lymph nodes.[4] The risk of pelvic lymph node metastases increases per International Federation of Gynecology and Obstetrics (FIGO) (2009) stage with reported incidence rates of 1%, 12%–22%, and 10%–27% for stages IA2, IB, and IIA, respectively.[4-6] Furthermore, lymph node metastases are now considered as stage IIIC in the FIGO 2018 classification.[7]

The prognostic impact on survival of various characteristics of lymph node metastases has been assessed in several ways, of which the most widely used is the number of lymph node metastases (nLNM).[8-11] A relatively new prognostic factor is lymph node ratio (LNR), the ratio between the number of positive and retrieved nodes after surgery. The value of this ratio has already been demonstrated in various other malignancies.[12, 13] However, conflicting results about the importance of LNR and the therapeutic effect of lymphadenectomy in cervical cancer make it necessary to critically reassess the prognostic value of LNR and to identify the best cut-offs for risk stratification with regard to survival.[8, 14]

To make these reassessments, this study was conducted to establish the impact of nLNM and LNR on the survival of patients with early-stage cervical cancer who were treated with radical hysterectomy and lymphadenectomy, and to determine if these parameters can be useful for further risk stratification with respect to survival.

MATERIAL AND METHODS

Study design

A nationwide historical cohort study was performed by analyzing data between 1995 and 2020 from the Netherlands Cancer Registry, containing population-based data of more than 95% of all cancer patients in the Netherlands since 1989. The date of death was obtained by annual linkage with the Personal Records Database. Women with the following inclusion criteria were enrolled in this study: (a) clinical stage IA2–IIA1 cervical cancer (FIGO 2009), (b) treated by completed radical hysterectomy and pelvic lymph node dissection, and (c) one or more pathologically confirmed lymph node metastases (>0.2 mm). Patients who received neoadjuvant therapy were excluded. Data on patient, tumor, and treatment characteristics were included, as well as follow up from diagnosis and vital status. Information on location of the metastatic node (either pelvic or para-aortic) was not available in the registry. Data on body mass index, tumor diameter (clinical, or pathological when missing), invasion depth, lymphovascular space invasion, and resection margin distance were available from 2010. LNR was defined as the ratio of positive nodes to the total number of retrieved nodes.

Statistical analyses

An optimal cut-off point was determined for nLNM and LNR to classify patients into low-risk and high-risk groups for survival analysis by using the Evaluate Cut points application.[15] The program uses “maxstat” function from the survival package in R to calculate maximally selected rank statistics on survival outcome and continuous covariates, after which a cut-off point is computed. Both values were manually confirmed by means of the log rank and Cox proportional hazards test. Discrete variables were compared using Fisher's exact test and the Kaplan–Meier method was used to construct overall survival curves. The relative survival is the ratio of overall survival in a patient cohort to the expected survival of a comparable group in the general population, using national life tables matched by age, sex, and period. To calculate the relative survival and excess hazard ratios (EHR) with corresponding 95% confidence intervals (CI) and p values, a proportional hazards model was used, according to the flexible parametric approach with the stpm2 command in Stata.[16] This flexible parametric survival model can fit relative survival models by incorporating expected mortality. Complete case analysis was not feasible for 234 women because of missing data of covariates (see Table 1), which were regarded as missing at random. To account for this, multiple imputation changed equations model and Nelson–Aalen estimate of the cumulative hazard were used to impute 30 data sets by using the same variables as the multivariable analysis.[17] To establish the validity of the imputed data, observed values of complete cases with imputed values were compared (see Table S1). Values of p less than 0.05 were considered statistically significant. South Texas Art Therapy Association SE 16 (StataCorp) and R 4.0.2 (Rstudio 1.3.1073.0) software were used for analyses.

Ethical approval

This study was approved by the by the Privacy Review Board of the NCR (#210015) on July 20, 2021.

RESULTS

Patient characteristics

The optimal cut-off point calculated for nLNM was four and for LNR was 0.177. A total of 593 women were included in the analysis, of whom 500 and 501 (both 84%) were categorized into the low-risk and 93 and 92 (both 16%) into the high-risk groups for nLNM and LNR, respectively. Clinical and pathological data of the total cohort are listed in Table 1. Most patients had stage IB1 disease (77%) and were treated by laparotomy (88%). The surgical approach did not differ between the low-risk and high-risk groups according to nLNM (p = 0.16) or LNR (p = 0.71). A sentinel lymph node (SLN) procedure, followed by a pelvic lymphadenectomy, was performed in 4% of patients. In total, five patients were diagnosed with micrometastases (>0.2 to ≤2 mm). The median numbers of positive and retrieved nodes were 2 (range 1–34 nodes) and 23 (range 2–60 nodes), respectively. Adjuvant therapy was administered to 95% of the patients and did not differ between the low-risk and high-risk groups. Administration of adjuvant therapy was equally distributed over the risk groups, before and after a guideline adjustment implemented in 2001. The median follow-up time was 88 months (range 3–270 months).

Table 1. Clinicopathological characteristics of all patients.

Patient characteristics (n = 593)	n[c]	%
Age median, years [range]	43 [21-86]	
BMI median, kg/m^2 [range][a]	24 [16-47]	
FIGO 2009 stage		
IA2	8	1
IB1	455	77
IB2	76	13
IIA1	54	9
Tumor diameter (cm)[a]		
≤2	78	13
>2-4	177	30
>4	112	19
Unknown	226	38
Histological subtype		
Squamous	414	70
Non-squamous	179	30
Differentiation grade		
1	21	4
2	196	33
3	262	44
Unknown	114	19
Invasion depth (mm)[a]		
<3	12	2
3-5	36	6
>5	228	38
Unknown	317	54
Parametrial invasion		
Absent	486	82
Present	103	17
Unknown	4	1
LVSI[†]		
Absent	58	10
Present	258	43
Unknown	277	47
Close resection margins[a]		
Absent	275	46
Present	26	5
Unknown	292	49
Surgical approach		
Laparotomic	524	88
Laparoscopic	46	8
Unknown	23	4
Sentinel node procedure[b]	24	4
Median nLNM [range]	2 [1-34]	
Median retrieved lymph nodes [range]	23 [2-60]	
nLNM risk-groups		
<4	500	84
≥4	93	16
LNR risk-groups		
<0.177	501	84
≥0.177	92	16

Table 1. (continued)

Adjuvant therapy		
None	30	5
Radiotherapy	222	38
Chemoradiation	336	56
Chemotherapy	5	1
Median follow-up, months [range]	88 [3-270]	

Abbreviations: *BMI*, body mass index; *FIGO*, International Federation of Gynecology and Obstetrics; *LNR*, lymph node ratio; *LVSI*, lymphovascular space invasion; *nLNM*, number of lymph node metastases.

[a]Data available from 2010

[b]in combination with full pelvic lymphadenectomy

[c]data represents number of patients and (%) or median with [range].

Prognostic impact of nLNM

In univariable survival analysis for nLNM, the EHR for patients in the high-risk group was 2.7 (95% CI 1.8–3.8; p < 0.001) compared with patients in the low-risk group (Table 2). After correcting for stage, histological subtype, grade, parametrial invasion, invasion depth, and lymphovascular space invasion, the high-risk group remained associated with a poor relative survival (EHR 2.4; 95% CI 1.6–3.5; p < 0.001). In addition, non-squamous histological subtype was associated with poor relative survival after correcting for confounders (EHR 1.9; 95% CI 1.3–2.8; p < 0.001). The 5-year overall survival for high-risk patients was 58% (47%–67%) compared with 80% (76%–83%) for the low-risk patients (p < 0.001) (Figure 1).

Prognostic impact of LNR

In univariable survival analysis for LNR, an EHR of 2.6 (95% CI 1.8–3.8; p < 0.001) was found in case of a high ratio (Table 2). After correction for confounders, the high-risk group remained associated with poor relative survival (EHR 2.5; 95% CI 1.7–3.8; p < 0.001), similar to non-squamous histological subtypes (EHR 1.7; 95% CI 1.2–2.5; p = 0.007). Patients in the high-risk group had a worse 5-year survival than those in the low-risk group (p < 0.001), with 5-year overall survival rates of 58% (48%–68%) vs. 79% (75%–83%) (Figure 2). As the potential benefit of LNR over nLNM results from the incorporation of retrieved nodes, we also conducted analysis of the number of retrieved nodes as a surrogate for the extent of the lymphadenectomy. However, it was not associated with survival in univariable analysis (EHR 1.0; 95% CI 0.98–1.02; p = 0.83).

Figure 1. Kaplan–Meier survival curves for women with FIGO-stage IA2–IIA1 cervical cancer and nodal metastasis, stratified by low- and high-risk groups for number of lymph node metastases.

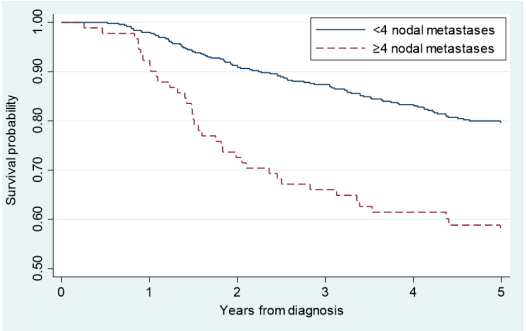

Figure 2. Kaplan–Meier survival curves, stratified by low- and high-risk groups for lymph node ratio.

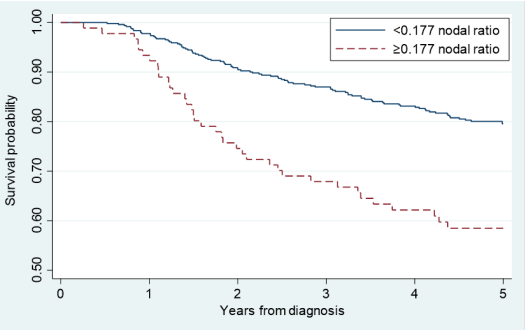

Table 2. Univariable and multivariable analysis of prognostic factors influencing the five-year relative survival.

	Univariable analysis			Multivariable analysis					
				nLNM			LNR		
Characteristics	**EHR**	**95% CI**	**P-value**	**EHR**	**95% CI**	**P-value**	**EHR**	**95% CI**	**P-value**
nLNM									
<4	100	reference		1.00	reference				
≥4	2.65	1.83-3.84	<0.001*	2.38	1.61-3.53	<0.001*			
LNR									
<0.177	1.00	reference					1.00	reference	
≥0.177	2.62	1.80-3.80	<0.001*				2.52	1.67-3.80	<0.001*
FIGO 2009 stage									
IA2	0.92	0.17-5.11	0.92	1.26	0.19-8.20	0.81	1.25	0.19-8.31	0.98
IB1	1.00	reference		1.00	reference		1.00	(reference)	
IB2	1.49	0.93-2.40	0.10	1.49	0.92-2.42	0.11	1.48	0.92-2.40	0.09
IIA1	1.45	0.85-2.48	0.17	1.27	0.73-2.21	0.40	1.35	0.77-2.36	0.40
Histological subtype									
Squamous	1.00	reference		1.00	reference		1.00	reference	
Non-squamous	1.69	1.19-2.39	0.004*	1.94	1.34-2.80	<0.001*	1.73	1.19-2.51	0.007*
Differentiation grade									
1	1.00	reference		1.00	reference		1.00	reference	
2	1.17	0.31-4.50	0.82	1.45	0.41-5.13	0.56	1.31	0.35-4.82	0.69
3	2.18	0.59-8.13	0.25	2.65	0.77-9.08	0.12	2.71	0.77-9.57	0.12

Table 2. (continued)

Parametrial invasion									
Absent	1.00	reference		1.00	reference		1.00	reference	
Present	1.55	1.04-2.31	0.032*	1.35	0.87-2.09	0.18	1.34	0.87-2.06	0.18
Invasion depth (mm)									
<3	1.00	reference		1.00	reference		1.00	reference	
3-5	2.36	0.18-30.26	0.51	1.09	0.15-7.93	0.93	1.03	0.19-5.50	0.98
>5	2.56	0.23-28.79	0.45	0.99	0.13-7.60	0.99	0.96	0.19-4.90	0.97
LVSI									
Absent	1.00	reference		1.00	reference		1.00	reference	
Present	2.06	0.86-4.95	0.11	1.97	0.77-4.36	0.11	1.69	0.79-3.63	0.17

Abbreviations: *nLNM*, number of lymph node metastases; *LNR*, lymph node ratio; *HER*, excess hazard ratio; *LVSI*, lymphovascular space invasion.

* statistically significant.

nLNM vs. LNR

Classification according to nLNM or LNR seems to have a similar prognostic performance (EHR of 2.4 and 2.5, respectively). Even though the number of patients in the low-risk and high-risk groups was almost the same for the classification based on nLNM and LNR, 51 patients were categorized differently (Table 3). Patients categorized as low-risk according to nLNM, but as high-risk according to LNR (n = 26; 4 %) and vice versa (n = 27; 5%), had a poor relative survival (EHR of 1.7 and 1.8, respectively) compared with patients who were categorized in both low-risk groups (n = 474; 80%). Categorization in both high-risk groups (n = 66; 11%) indicated the worst relative survival (EHR 3.2; 95% CI 2.1–4.8).

Table 3. Univariable subgroup analysis for the low- and high-risk groups on five-year relative survival.

nLNM	LNR	N	EHR	95% CI	P-value
< 4	< 0.177	474	1.00	reference	-
≥ 4	< 0.177	27	1.78	0.87-3.63	0.12
< 4	≥ 0.177	26	1.71	0.83-3.53	0.15
≥ 4	≥ 0.177	66	3.21	2.14-4.83	<0.001*

Abbreviations: *nLNM*, number of lymph node metastases; *LNR*, lymph node ratio; *EHR*, excess hazard ratio.

* statistically significant.

DISCUSSION

This study establishes the impact of nLNM and LNR on survival in patients with node-positive early-stage cervical cancer after radical hysterectomy and pelvic lymphadenectomy. We demonstrate that both parameters are independently associated with impaired survival, using ≥4 nodal metastases and a ratio of ≥0.177 as optimal cut-offs. Despite the potential benefit of LNR, by taking into account not only the number of positive nodes, but also the extent of lymphadenectomy, both parameters had similar prognostic performances. Translated into clinical practice, this means that patients with ≥4 positive nodes and/or a ratio of ≥0.177 are expected to have worse prognosis. Therefore, both parameters may contribute to further risk stratification regarding survival, which could be useful in decision-making for adjuvant therapy.

One of the largest studies on this topic compared multiple prognostic classification systems for nodal metastases in cervical cancer of the squamous subtype (n = 928).[18] LNR (>0.16), nLNM (>5), FIGO 2018 stage (IIIC1/IIIC2), and the log odds of positive nodes (>−0.61), were reported as prognostic factors for survival. nLNM was the most predictive parameter of survival. The negative association between nLNM and prognosis was also demonstrated in studies including both squamous and non-squamous cervical cancer.[9, 10, 13, 19] One of these studies was an analysis of 2222 node-positive cervical cancer patients, demonstrating 5-year overall survival rates of 77% vs. 63%, for patients with ≤2 vs. >2 nodal metastases, respectively (p < 0.001).[19]

Regarding LNR, multiple studies were published on prognostic performance with respect to survival in node-positive early-stage cervical cancer.[20-24] Li et al evaluated the association of nLNM and LNR with survival in 273 patients with 2018 stage pIIIC1 cervical cancer, after radical hysterectomy.[24] Similar to our study, the number of retrieved nodes was not associated with survival, but the number of positive nodes (<2 vs. ≥2) and the ratio (<0.08 vs. ≥0.08) were. In multivariable analysis, LNR (but not nLNM) was identified as an independent prognostic factor for overall survival (p = 0.001). In a study by Aslan et al, a high LNR (≥0.05) was an independent adverse prognostic factor for overall survival as well.[21] Furthermore, in a study by Joo et al, 397 patients with nodal metastases were categorized into three groups according to LNR: <0.1, 0.1–0.4, and >0.4.[23] This study showed that survival decreases when LNR increases, with 5-year overall survival rates of 83%, 66%, and 17%, respectively. In summary, the prognostic values of nLNM and LNR have been demonstrated before. Some studies (including the largest) are in favor of nLNM,[9-11, 25] whereas others are in favor of LNR.[20-23] Our study contributes to the current literature, as this is the largest study, to our knowledge, on all histological subtypes of cervical cancer, while correcting for the most relevant confounders for both nLNM and LNR. Additionally, whereas most studies on nLNM and LNR are of Asian origin, our cohort is European based.

In literature, cut-off values for LNR range from 0.05 to 0.40 and there are several studies with comparable cut-offs to our cut-off of 0.177.[8, 18, 20, 21, 23] The two most recent papers showed similar survival outcomes as our study. For nLNM, various cut-offs (range ≥2 to ≥4) are reported in literature as well.[10, 11, 19, 24, 26] The diversity in cut-offs is probably due to a variety of inclusion criteria, divergent sample sizes, and/or treatment strategies, leading to dissimilar survival rates. Use of cut-offs for risk stratification should be interpreted with caution, as illustrated in Table 3. Patients who were categorized as low risk by one parameter, but as high-risk by the other, still tend to be at higher risk for death; therefore, it might be valuable to use both parameters when possible. Furthermore, nLNM and LNR are useful prognostic parameters after lymphadenectomy but not after only an SLN procedure, as this latter procedure will not provide full insight of the nodal status and might lead to mispresenting the number of positive and removed nodes. Although the SLN procedure is not yet standard of care globally, it might become so for selected subgroups of patients in the near future. As a consequence, the benefit of powerful prognostic parameters by performing a complete pelvic lymphadenectomy must be weighed against the benefits of less invasive surgery in terms of morbidity. In our study, we expect low-risk of bias because the SLN was always followed by a lymphadenectomy.

Due to the retrospective design of this study, it was impossible to differentiate between a nodal debulking or a dissection in the case of few retrieved nodes. Nevertheless, the numbers of retrieved nodes (range 2–60) matches earlier studies on lymphadenectomy (range 4–85).[8, 24] Moreover, it has been

common policy in the Netherlands not to perform a radical hysterectomy if only bulky nodes are removed. To bypass this problem, some studies use a lower limit of 10 or more retrieved nodes. In our study we chose not to, because this would exclude patients with few nodes present. Besides, we were unable to demonstrate better survival after more retrieved nodes. This was in contrast to non-squamous histological subtype, which was independently associated with poor prognosis, which has also been demonstrated in previous studies.[9, 19, 21, 23, 27]

The strengths of this study were its large sample size and nationwide data coverage. Additionally, we were able to compare nLNM and LNR, by multivariable analysis. Our study has several limitations, all related to its retrospective design. First, historical cohort studies may be inherently biased toward heterogeneous patient populations. Second, details regarding adjuvant therapy, like dosage and type of chemotherapy or radiotherapy, and on the extent of the radical hysterectomy and lymphadenectomy, were missing. These details could impact survival and therefore affect our results. Fourth, invasion depth, lymphovascular space invasion, differentiation grade, and parametrial invasion contained missing data. To deal with these missing data and reduce the risk of bias, we performed multiple imputation: a statistical technique for dealing with missing data.[28] Finally, a guideline adjustment regarding the role of postoperative chemoradiation was implemented during our study period in 2001.[29] Although this potentially could have affected survival outcomes, we expect no bias because the administration of various adjuvant therapies did not differ between the low-risk and high-risk groups before and after 2001.

Monk et al suggested that a subgroup of patients with more than one positive lymph node would benefit more from the addition of chemotherapy to adjuvant radiotherapy after radical hysterectomy.[30] This study illustrates that not all node-positive patients benefit equally from adjuvant therapy, and that it is crucial to identify those who might benefit. In line with these findings, we would suggest more research on the addition of chemotherapy, either concomitantly or consequently, for high-risk patients. Identification of a high-risk group of lymph-node- positive patients may aid in selection of patients that benefit most from additional chemotherapy. Both LNR and nLNM may potentially play a role in this selection. Furthermore, external validation of nLNM and LNR in multiple, disparate data sets should be obtained first, before implementation in clinical practice is possible, especially regarding both cut-off values for low-risk and high-risk groups.

CONCLUSION

Both nLNM and LNR are independently associated with relative and overall survival in node-positive early-stage cervical cancer patients after radical hysterectomy. Representation of a patient's nodal status by both parameters might therefore be of additional value compared with only indicating the presence or absence of lymph node metastases.

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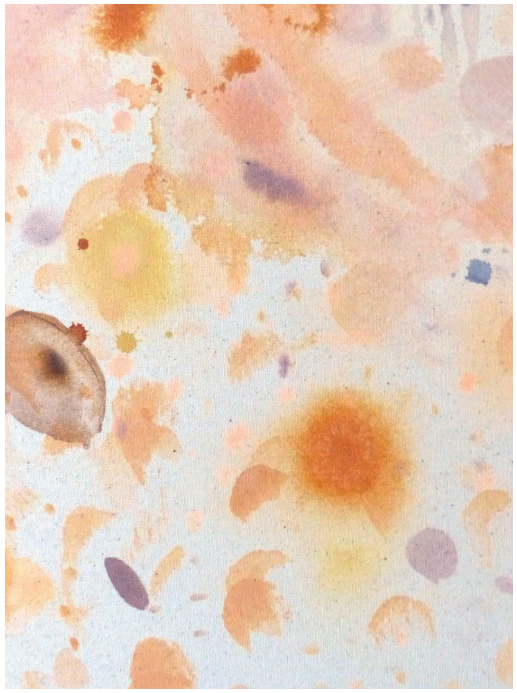
SUPPLEMENTARY MATERIALS

Table S1. Distribution of variables with missing data before and after multiple imputation.

		After imputation for	
Characteristics, %	Original data	Number of nodal metastases	Lymph node ratio
Differentiation grade			
1	4	4	4
2	41	41	41
3	55	55	55
Invasion depth (mm)			
<3	4	5	5
3-5	13	12	12
>5	83	83	83
Parametrial invasion			
Present	17	18	18
Lymphovascular space invasion			
Present	82	80	81



Chapter 6

Radical hysterectomy or chemoradiotherapy for clinically early-stage cervical cancer with suspicious lymph nodes on imaging

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ABSTRACT

Objective: The optimal treatment of clinically early-stage cervical cancer with suspicious lymph nodes on pretreatment imaging is unclear. Therefore, we aimed to compare surgery (i.e., radical hysterectomy and pelvic lymphadenectomy ± adjuvant therapy) with primary chemoradiotherapy as treatment strategies in this patient group regarding recurrence-free, overall survival and toxicity.

Methods: Women diagnosed between 2009-2017 with the International Federation of Gynecology and Obstetrics (2009) stage IA-IIA and suspicious nodes based on radiologic assessment of pretreatment imaging were retrospectively selected from the Netherlands Cancer Registry. Cox proportional hazard was used to estimate survival and logistic regression for toxicity. Inverse probability weighting was used to correct for confounding. Grade ≥2 surgery-related (≤30 days) and grade ≥3 chemotherapy or radiotherapy-related (≤6 months) toxicity were collected. Missing data were imputed.

Results: Of 330 patients included, 131 (40%) received surgery (followed by adjuvant therapy in 54%) and 199 (60%) chemoradiotherapy. Pathological nodal status was known in 100% of the surgery group and 32% (n=63) of the chemoradiotherapy group, of whom 43% (56/131) and 89% (56/63), respectively, had metastases. After adjustment for confounders, the recurrence-free survival (HR 0.67; 95% CI 0.34-1.31) and overall survival (HR 0.75; 95% CI 0.38-1.47) were not significantly different between the surgery and chemoradiotherapy groups, while surgery was associated with more toxicity (OR 2.82; 95% CI 1.42-5.60), mainly surgery-related.

Conclusion: In patients with clinically early-stage cervical cancer and suspicious nodes on imaging, surgery and primary chemoradiotherapy yielded comparable results in terms of survival, whereas surgery might be associated with more (surgery-related) short-term toxicity.

INTRODUCTION

Women with clinically early-stage cervical cancer have a 5-year survival rate of ~92%.[1, 2] This rate is negatively affected by the presence of lymph node metastasis, one of the most important prognostic factors in cervical cancer.[3] There are differences in treatment strategies for patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA2-IIA2 disease and suspicious nodes on imaging. Current guidelines recommend primary chemoradiotherapy over treatment by radical hysterectomy with lymphadenectomy, followed by tailored adjuvant therapy in the presence of postoperative risk factors.[4] Research on this subject has suggested that both strategies can achieve similar survival rates.[5-9] However, these studies are mainly retrospective, with limited confounding adjustment, and rarely included only patients with suspicious nodes. Additionally, toxicity was often not evaluated in these studies, although both strategies have different toxicity profiles.[10, 11] Moreover, adjuvant therapy after surgery, known as multimodality treatment, may be associated with more toxicity, such as genitourinary morbidity.[8, 10, 11]

Today, treatment strategies are usually guided by pretreatment imaging: computed tomography (CT), magnetic resonance imaging (MRI), and/or 2-deoxy-2-[18F]fluoro-D-glucose positron emission computed tomography ([18F]FDG-PET/CT), of which the latter is generally considered superior in detecting metastatic nodes.[12, 13] However, it is important to consider the risk of false-positive findings when deciding treatment strategies, as studies of pretreatment imaging (CT, MRI, and/or PET-CT) in early-stage cervical cancer have reported positive predictive values of only 47-60%.[5, 14, 15] This means that approximately half of the patients with suspicious nodes on imaging are node-negative and, therefore, could have been treated with surgery without adjuvant therapy.

Despite the increasing role of imaging in cervical cancer staging and the negative prognostic impact of nodal metastases, there remains a paucity of evidence regarding the best therapeutic approach for women with radiologic suspicious nodes. In this retrospective cohort study, we compare surgery (i.e., radical hysterectomy with lymphadenectomy ± adjuvant therapy) with primary chemoradiotherapy regarding recurrence-free, overall survival and therapy-related toxicities in patients with FIGO stage IA2-IIA2 cervical cancer and radiologic suspicious nodes. Additionally, we will evaluate preoperative clinicopathologic characteristics associated with multimodality treatment.

MATERIALS AND METHODS

Study design and data collection

This retrospective cohort study was approved by the Privacy Review Board (#22263) of the Netherlands Cancer Registry. Data on patient-, tumor- and treatment-related characteristics were obtained from the population-based Netherlands Cancer Registry, which covers all malignancies in the Netherlands since 1989. Trained data managers collected additional data on lymph node metastases from hospital records. Eligible cervical cancer patients were (1) diagnosed between January 2009 and December 2017 because of sufficient follow-up, (2) ≥18 years at diagnosis, (3) received pretreatment imaging (CT, MRI, PET-CT, or PET-MRI), (4) had FIGO 2009 stage IA2-IIA2, (5) either squamous cell, adeno-, or

adenosquamous carcinoma and (6) ≥1 suspicious lymph node(s). All patients were categorized by treatment strategy: surgery (i.e., radical hysterectomy with lymphadenectomy) or primary chemoradiotherapy. Patients treated with neoadjuvant therapy were excluded. Adjuvant (chemo)radiotherapy was administered according to local protocols and indicated in case of postoperative intermediate/high-risk factors.[4, 16] Chemoradiotherapy consisted of pelvic external beam radiotherapy (i.e., 45-50 Gy) and concurrent chemotherapy (i.e., cisplatin 40 mg/m^2 weekly) or hyperthermia according to European treatment guidelines.[4]

Lymph node status was registered for five anatomic regions (i.e., left/right pelvic, left/right common iliac, and para-aortic) as negative, inconclusive, suspicious or unknown, as reported by the radiologist. The short-axis diameter was recorded for inconclusive or suspicious nodes. Generally, a lymph node was considered suspicious if the short-axis diameter was ≥1.0 cm, and morphologic tumor features (e.g., central necrosis) and/or focally increased FDG-uptake were present. Imaging was performed according to local protocols, following the Dutch (Nedpas) and international (EARL) standards.[17] FIGO stage IA2 (n=3) was pooled with stage IB. Furthermore, direct conversion to FIGO 2018 was not possible due to missing information on horizontal spread.

Outcomes and definitions

Recurrence-free and overall survival were the primary outcomes and defined as the interval from start of primary therapy until recurrence and from diagnosis to death, respectively. Patient vital status was obtained by linkage to the Municipal Personal Records Database (updated to January 31st, 2022). Patients who were still alive were censored at that time. Recurrence status was obtained from hospital records. Patients without recurrence, or who were lost to follow-up, were censored at the last date of clinical contact. Secondary outcomes were therapy-related toxicity and differences in clinicopathological characteristics, stratified by presence of adjuvant treatment. Surgery-related toxicity was defined as grade ≥2 Clavien-Dindo complication ≤30 days after surgery.[18] Radiotherapy and chemotherapy related toxicities were defined as grade ≥3 Common Terminology Criteria for Adverse Events (version 4.03) complications ≤6 months after the start of treatment.[19] To identify factors that might help predict patients at risk for multimodality treatment, preoperative characteristics were compared between the surgery group with and without adjuvant therapy.

Statistical analysis

The Mann–Whitney U, Kruskal–Wallis, and Fisher's exact test were used for descriptive statistics. Unadjusted survival analyses were performed using the Kaplan-Meier method and the log-rank test. Missing data were considered missing at random and imputed using chained equations multiple imputation.[20] We repeated the imputation 20 times, followed by application of Rubin's rule to combine parameter estimates from multivariable Cox regression analysis.[21] We examined convergence plots and compared distributions of original and imputed data to establish validity. The proportional hazards assumption was tested by plotting scaled Schoenfeld residuals. No violations were found with an exit time of 5-years. Therefore, all survival-analyses were restricted to 5-years.

Propensity score analysis was used to control for measured heterogeneity between treatment groups, using logistic regression models to estimate the probability of treatment. These models included variables related only to the outcome of interest or to both outcome and treatment, see Supplementary Table S1. We used different propensity score methods to determine which method achieved the best balance of covariates. An absolute standardized difference of ≤0.25 was considered to be balanced.[22] Inverse-probability-treatment-weighting was used to balance the treatment groups and control for confounding in the analyses of survival and toxicity risk using Cox and logistic regression, respectively. A subgroup analysis of toxicity was performed for patients treated with surgery, either with or without adjuvant therapy. Logistic regression analysis was used to demonstrate an association with multimodality treatment. A p-value <0.05 was considered significant, and Stata statistical software version 17.0 (StataCorp, College Station, TX, USA) was used for all analyses.

RESULTS

Baseline characteristics

Of 330 eligible patients, 131 (40%) received surgery (of which 85% by open approach and 15% by minimally invasive surgery) and 199 (60%) received primary chemoradiotherapy. All baseline characteristics are shown in Table 1. The nodal status was assessed by MRI, PET-CT, CT and/or PET-MRI in 82%, 52%, 44% and 7%, respectively. PET-CT imaging was more common in the chemoradiotherapy group than in the surgery group (69% versus 26%; p<0.001). Poor prognostic characteristics (i.e., higher FIGO stage, larger tumor size and nodal short-axis diameter, suspicious nodal status, higher squamous cell carcinoma antigen level, and involvement of the common iliac and para-aortic regions) were more common in the chemoradiotherapy than surgery group (p<0.001). Of all propensity score methods tested, inverse-probability-treatment-weighting achieved the best balance: all characteristics were balanced except for para-aortic region involvement, which remained more common in the chemoradiotherapy group (Supplementary Figure S1 and Table S1). The distributions of the original and imputed data were consistent (Supplementary Table S2). Pathological characteristics were more frequently missing in the chemoradiotherapy group. Including the nodal status, which was known in 100% of the surgery and 32% of the chemoradiotherapy group, of whom 43% (56/131) and 89% (56/63), respectively, had metastases. (p<0.001). This corresponded to an overall positive predictive value of 58%. As shown in Table 1, the chemoradiotherapy group received the most extensive treatment, with more nodal boosting (p<0.001), extended-field radiotherapy (p<0.003), and brachytherapy (p<0.001). After surgery, 54% received adjuvant therapy, with 62% receiving chemoradiotherapy.

Table 1. Baseline characteristics of original cohort.

Patient and tumor characteristics	Surgery N=131	Chemoradiotherapy N=199	p-value
Median age, years	43 (22-77)	43 (25-81)	0.59
Charlson comorbidity index			0.48
0	102 (78%)	139 (70%)	
1	10 (8%)	21 (11%)	
≥2	3 (2%)	6 (3%)	
Unknown	16 (12%)	33 (17%)	
Smoking, yes	45 (34%)	65 (33%)	0.81
Median Body Mass Index, kg/m^2	24 (16-40)	24 (18-55)	0.37
Median pretreatment squamous cell carcinoma antigen, ng/ml†	2.5 (0.2-28.9)	5.3 (0.3-93.0)	<0.001*
FIGO 2009 stage			0.041*
IA/B	162 (81%)	118 (90%)	
IIA	37 (19%)	13 (10%)	
Median clinical tumor diameter, mm	35 (2-80)	50 (12-80)	<0.001*
Status of suspicious node			<0.001*
Suspicious	54 (41%)	182 (91%)	
Inconclusive	77 (59%)	17 (9%)	
Location of suspicious node(s)‡			<0.001*
Pelvic	115 (88%)	138 (69%)	
Common iliac	5 (4%)	22 (11%)	
Para-aortic	11 (8%)	39 (20%)	
Median short-axis of largest suspicious node, mm	9 (5-50)	12 (6-43)	<0.001*
Histologic subtype			0.12
Squamous cell carcinoma	92 (70%)	158 (79%)	
Adeno carcinoma	33 (25%)	32 (16%)	
Adenosquamous cell carcinoma	6 (5%)	9 (5%)	
Lymphovascular space invasion			<0.001*
Absent	48 (37%)	70 (35%)	
Present	73 (56%)	27 (14%)	
Unknown	10 (8%)	102 (51%)	
Tumor grade			<0.001*
1	6 (5%)	4 (2%)	
2	59 (45%)	52 (26%)	
3	42 (32%)	76 (38%)	
Unknown	24 (18%)	67 (34%)	
Pathologic node status			<0.001*
Negative	75 (57%)	7 (4%)	
Positive	56 (43%)	56 (28%)	
Unknown	-	136 (68%)	

Table 1. (continued)

Treatment characteristics			
Median removed nodes§	25 (5-57)	9 (1-44)	<0.001*
Median positive nodes¶	2 (1-33)	2 (1-20)	0.85
Nodal examination			<0.001*
Lymphadenectomy	131 (100%)	36 (18%)	
Debulking	-	23 (12%)	
Fresh frozen section only	-	1 (1%)	
Fine needle aspiration/biopsy	-	3 (2%)	
No	-	136 (68%)	
Surgical approach			<0.001*
Open	111 (85%)	26 (42%)	
Laparoscopic	20 (15%)	8 (13%)	
Unknown	-	28 (45%)	
Nodal boosting, yes	5 (7%)	140 (70%)	<0.001*
Radiotherapy volume			0.003*
Pelvic	63 (90%)	152 (76%)	
Pelvic + para-aortic	4 (6%)	43 (22%)	
Unknown	3 (4%)	4 (2%)	
Brachytherapy, yes	17 (13%)	195 (78%)	<0.001*
Adjuvant treatment			
Chemoradiotherapy	44 (34%)	-	
Radiotherapy	26 (20%)	-	
Chemotherapy	1 (1%)	2 (1%)	
Salvage hysterectomy	-	2 (1%)	
No	60 (46%)	195 (98%)	

Abbreviations: *FIGO*, International Federation of Gynecology and Obstetrics.

† For squamous-cell carcinoma's only.

‡ Most cranial location was decisive; § Patients with nodal examination only.

¶ Patients with pathologically metastatic nodes only.

* Statistically significant.

Data are expressed as number of patients and (percentage) or median with (range).

Survival

Median follow-up for recurrence-free and overall survival was 49 (range 1-134) and 90 (1-157) months after surgery and 46 (2-138) and 69 (5-156) months after chemoradiotherapy, respectively. Recurrence was observed in 26 patients (20%) after surgery and 63 patients (32%) after chemoradiotherapy (p=0.22), with pelvic metastasis (62%) and distant metastasis (42%) as most common patterns of failure (Figure 1). Without adjustment for confounding, the 5-year recurrence-free and overall survival were superior for surgery (80% and 83%) compared to chemoradiotherapy (67% and 69%; p=0.003 and p=0.004). However, inverse-probability-treatment-weighting analyses showed that treatment strategy was not associated with survival, with a 5-year recurrence-free and overall survival of 81% and 82% for surgery and 75% and 76% for chemoradiotherapy (p=0.38 and p=0.39; Figure 2), respectively. Multivariable analyses of original and imputed data showed similar results (Table 2; see Supplementary Table S3 for the complete analyses). Consistently, sensitivity analysis for patients with suspicious nodes only showed no association between treatment strategy and recurrence-free (HR 0.90; 95% CI 0.47-1.74; p=0.48) or overall survival (HR 1.04; 95% CI 0.54-2.01; p=0.91).

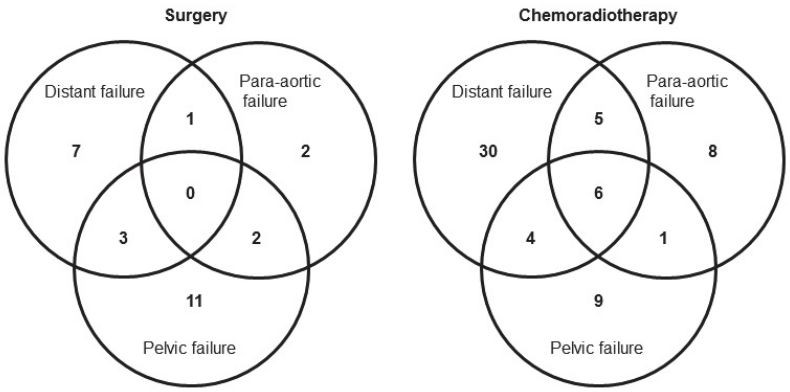

Figure 1. Patterns of failure in patients with a recurrence after surgery (n=26) and primary chemoradiation (n=63).

Table 2. Cox regression 5-year survival analyses.

Analysis type	Therapy group	Recurrence-free survival			Overall survival		
		HR	95% CI	p-value	HR	95% CI	p-value
Univariable	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.49	0.30-0.80	0.004*	0.54	0.35-0.84	0.006*
Multivariable original data	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.92	0.48-1.76	0.79	0.87	0.45-1.69	0.68
Multivariable imputed data	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.82	0.45-1.49	0.51	0.77	0.42-1.42	0.40
Inverse-probability-treatment-weighting Imputed data	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.73	0.36-1.48	0.38	0.73	0.35-1.50	0.39

Abbreviations*: HR*, hazard ratio; *CI*, confidence interval.

* Statistically significant.

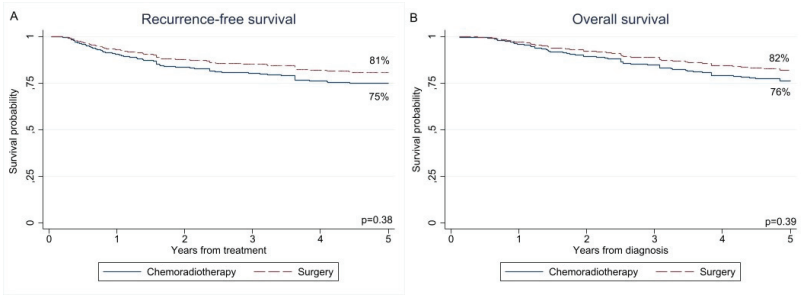

Figure 2. Predicted survival curves from Cox proportional hazards models using inverse-probability-of treatment weighting for (A) recurrence-free survival and (B) overall-survival.

Toxicity

As shown in Table 3, more patients experienced treatment-related toxicity after surgery (34%) than after chemoradiotherapy (20%; p=0.007). This was primarily due to the post-operative complications (26%) in the surgery group, with bladder dysfunction (11%; i.e., urinary retention requiring catheterization) and infection (8%) being the most common. After chemoradiotherapy, more chemo- and radiotherapy-related toxicities were observed than after surgery (11% versus 3%; p=0.011 and 13% versus 6%; p=0.044, respectively). Moreover, surgery remained associated with an increased risk of toxicity after inverse-probability-treatment-weighting covariate adjustment (OR 2.82; 95% CI 1.42-5.60; p=0.003). Subgroup analysis of surgery without adjuvant therapy versus primary chemoradiotherapy showed a comparable prevalence of therapy-related toxicity (28% and 20%; p=0.21), while surgery with adjuvant therapy was associated with a higher prevalence (38%; p=0.011).

Table 3. Therapy-related toxicities.

Toxicities	Surgery N=131	Chemoradiotherapy N=199	p-value
Surgery-related			
Intra-operative injury	3 (2%)	2 (1%)	0.39
Infection	11 (8%)	-	<0.001*
Thromboembolism	2 (2%)	-	0.16
Intensive-care admission	1 (1%)	1 (1%)	1.00
Bladder dysfunction	15 (11%)	-	<0.001*
Blood transfusion	7 (5%)	1 (1%)	0.007*
Other	5 (4%)	-	0.009*
Total patients	34 (26%)	2 (1%)	<0.001*
Radiotherapy-related			
Urological	1 (1%)	3 (2%)	1.00
Gastro-intestinal	2 (2%)	12 (6%)	0.053
Genital	-	2 (1%)	0.52
Other	2 (2%)	5 (3%)	0.71
Total patients	4 (3%)	21 (11%)	0.011*
Chemotherapy-related			
Nausea/vomiting	1 (1%)	10 (5%)	0.55
Nephrotoxicity	2 (2%)	1 (1%)	0.57
Mucositis/stomatitis	2 (2%)	-	0.16
Bone marrow depression	-	4 (2%)	0.16
Malaise/fatigue	-	2 (1%)	0.52
Neurotoxicity	-	2 (1%)	0.52
Other	5 (4%)	11 (6%)	0.60
Total patients	8 (6%)	26 (13%)	0.044*
Total patients with therapy-related toxicity	44 (34%)	40 (20%)	0.007*

* statistically significant.

Multimodality treatment

The surgery group (n=131) was subdivided into two groups: with (n=71) and without (n=60) adjuvant treatment. Among preoperative characteristics, lymphovascular space invasion and depth of invasion differed significantly between both groups (Supplementary Table S4). Adjuvant treatment was associated with: lymphovascular space invasion (OR 6.0; 95% CI 2.7-13.4), depth of invasion ≥15 mm (OR 2.5; 95% CI 1.1-5.8), tumors >4 cm on MRI (OR 6.0; 95% CI 1.4-26.4), and a suspicious nodal status (OR 2.1; 95% CI 1.0-4.3).

DISCUSSION

This study compared surgery with primary chemoradiotherapy as a treatment strategy for women with FIGO stage IA-IIA2 cervical cancer and suspicious lymph nodes on pretreatment imaging. The chemoradiotherapy group included more patients with poor prognostic characteristics than the surgery group and therefore had worse survival outcomes. However, after adjustment for confounders, recurrence-free and overall survival were not significantly different between the two strategies. Additionally, surgery was associated with more short-term toxicity due to postoperative complications and multimodality treatment. Of note, only half (54%) of patients received adjuvant therapy after surgery, supporting the low predictive value of suspicious nodes on pretreatment imaging (58%). Preoperative characteristics (i.e., lymphovascular space invasion, depth of invasion, tumor size on MRI, and radiologic nodal status) may help guide treatment decisions by predicting patients at risk for multimodality treatment.

Surgery and primary chemoradiotherapy seem equally effective regarding survival outcomes, supporting evidence from previous observations.[5, 7-9, 23] The only randomized controlled trial comparing both strategies included only a few patients with suspicious nodes on imaging (13%), and radiotherapy was not combined with chemotherapy, as this study dates from 1997.[9] Therefore, this study does not provide evidence of treatment strategies for our study cohort. More recently, Park et al. (2021) retrospectively compared radical hysterectomy (n=195) with chemoradiotherapy (n=67) in a cohort with suspicious nodes, using propensity score matching (n=33) for age, histology, and vaginal invasion, and found no differences in 5-year disease-free (81-83%) and overall survival (~89%) between the two treatments.[5] These survival rates are comparable to ours, including the overall recurrence rate (24-26% versus 27%). However, we found more distant relapses after chemoradiotherapy, possibly explained by the poorer prognostic characteristics of our group. Survival comparability of both treatment strategies in early-stage cervical cancer has been suggested previously, although cohorts varied with respect to prognostic factors (e.g., tumor size, suspicion of parametrial invasion or nodal metastases) across studies.[7, 8] Unlike previous analyses, we adjusted for more relevant confounders and included a larger cohort of patients with suspicious nodes only. Additionally, we assessed therapy-related toxicity since both strategies were expected to have different toxicity profiles.

The prevalence of toxicity in our two treatment groups lies within the range reported by others: 10-30% grade ≥3 toxicities after surgery and 15-59% after chemoradiotherapy.[7, 11, 24, 25] These broad ranges possibly result from varying toxicity-scoring systems across studies. Our results suggest that surgery is associated with more short-term toxicity. However, most of these toxicities consist of postoperative complications, including blood transfusion, infection, and bladder dysfunction, which are often (partially) reversible.[26, 27] Chemoradiotherapy was associated with more radiotherapy-related toxicity, which is often characterized by its late and long-term occurrence (e.g., gastrointestinal, genitourinary, and fistula).[28] Moreover, the risk of short-term toxicity after surgery without adjuvant therapy was comparable to primary chemoradiotherapy. The detrimental effect of multimodality treatment on toxicity has been described previously and may be related to inaccurate staging.[24, 25, 29] Potential strategies to reduce the risk of multimodality treatment include pretreatment pathologic

evaluation of suspicious nodes (e.g., image-guided fine-needle cytology/biopsy or debulking) or treatment guidance based on clinicopathologic characteristics. Patients with lymphovascular space invasion, depth of invasion ≥15 mm, tumors >4 cm on MRI, and suspicious nodes on pretreatment imaging are likely to require multimodality treatment and could therefore be referred for primary chemoradiotherapy. Previous studies have shown that lymphovascular space invasion, depth of invasion, and tumor size are associated with nodal involvement, poor prognosis, and the need for adjuvant treatment.[16, 30]

Another point worth discussing is the approach of the radical hysterectomy, which can be performed by open or minimally invasive surgery. During the tie period of our study, minimally invasive surgery gained popularity and 15% of our surgical cohort had surgery using this approach. In 2018, the prospective, randomized LACC trial showed that minimally invasive radical hysterectomy is associated with worse survival for tumors >2 cm [31]. As a result, an open approach has become the standard of care, whereas a minimally invasive approach may be considered in low-risk tumors, preferably in a research setting [4, 32]. Since 2018, several retrospective studies have reported conflicting results, including similar survival rates for both approaches [33, 34]. In addition, two trials comparing robotic-assisted radical hysterectomy with open radical hysterectomy are currently open for enrolment to provide further evidence on the safety of minimally invasive surgery [35, 36].

A major limitation of this study is confounding by disease severity, reflected by heterogeneity in baseline characteristics between treatment groups. This bias was expected, as larger tumors and lymph node metastases are indications for primary chemoradiotherapy.[4] Adjustment by inverse-probability-treatment-weighting resulted in a more balanced analysis of covariates. However, unmeasured variables (e.g., deep invasion and multiple suspicious nodes) may still be unbalanced. Additionally, our analyses contained up to 38% missing data, which could be considered a limitation. However, we used multiple imputation, which has been described as a reliable approach to handling missing data, even for large proportions.[20] In fact, the estimates after imputation were more accurate than those of complete case analysis. Another limitation concerns our toxicity outcome, which was dependent on hospital record reporting and limited to the first six months after treatment due to time-consuming retrospective recording. Consequently, our radiotherapy-related toxicity may be underestimated by missing late-term events (e.g., fistula, stricture, and chronic enteritis), which may have biased our toxicity results. Finally, whether and how therapy-related toxicity affects the quality of life in both treatment groups remains unanswered and should be addressed in future research.

Despite its limitations, this study provides more insight into the outcome of treatment strategies for patients with FIGO 2009 stage IA-IIA cervical cancer and suspicious nodes on imaging. First, poor prognostic factors (e.g., higher FIGO stage and squamous cell carcinoma antigen level, larger tumor and node size, and para-aortic node involvement) may guide treatment choice toward chemoradiotherapy. Second, if radical surgery is feasible, it seems to be an equally effective treatment strategy in terms of survival. Third, surgery and chemoradiotherapy have different toxicity profiles, highlighting the need for counselling with shared decision-making. In addition, avoiding multimodality treatment by better predicting the need for adjuvant therapy based on clinicopathologic characteristics, may reduce the risk of toxicity. These results must be interpreted with caution, because they are based

on retrospective data and are subject to bias due to unmeasured confounding. However, prospective randomization may not be feasible because large sample sizes will be required, as retrospective studies have failed to demonstrate superiority of either strategy. Additionally, possible patient and physician preferences for one of the two treatment strategies may further complicate enrollment. Future studies could focus on improving pretreatment detection of metastatic nodes and thereby tailoring treatment decisions (e.g., pathologic evaluation of suspicious nodes, advanced imaging techniques, radiomics, or nomograms).

CONCLUSIONS

In conclusion, in patients with clinically early-stage cervical cancer and suspicious nodes on imaging, both surgery and primary chemoradiotherapy yielded comparable results in terms of recurrence-free and overall survival. As both strategies are associated with different short-term toxicity profiles, shared decision-making seems to be the best approach for patients with suspicious nodes. Furthermore, preoperative clinicopathologic characteristics may help to select patients at risk for multimodality treatment.

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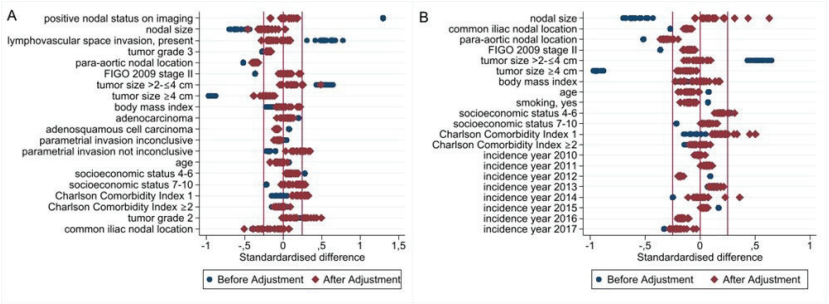
SUPPLEMENTARY MATERIALS



Supplementary Figure 1. Standardized difference of propensity score model covariates before and after adjustment for: (A) survival and (B) toxicity.

Abbreviations*: FIGO*, International Federation of Gynecology and Obstetrics.

Supplementary Table 1. Baseline characteristics before and after inverse-probability-treatment-weighting analysis regarding survival and toxicity.

Characteristics	Original cohort			Survival weighted cohort			Toxicity weighted cohort		
	Surgery N=131	CRT N=199	Sd	Surgery N=131	CRT N=199	Sd	Surgery N=131	CRT N=199	Sd
Median age, years	46	45	0.078	43	44	0.055	43	44	0.097
Charlson comorbidity index									
0	84%	83%		79%	87%		79%	87%	
1	11%	12%	0.038	18%	10%	0.237	18%	10%	0.230
≥2	5%	5%	0.017	3%	3%	0.026	3%	3%	0.006
Socioeconomic status									
1-3	32%	33%		27%	40%		24%	36%	
4-6	36%	24%	**0.282**	27%	22%	0.109	35%	26%	0.205
7-10	32%	43%	0.215	46%	38%	0.166	41%	38%	0.074
Mean body mass index, kg/m^2	25	26	0.162	26	26	0.043	26	26	0.019
Smoking									
No	65%	68%					72%	68%	
Yes	35%	32%	0.073				28%	32%	0.092
FIGO 2009 stage									
IA/B	93%	81%		84%	86%		88%	85%	
IIA	7%	19%	**0.361**	16%	14%	0.061	12%	15%	0.098
Tumor diameter, cm									
≤20	22%	4%		12%	8%		13%	7%	
>20-≤40	55%	30%	**0.536**	50%	44%	0.124	43%	44%	0.017
≥40	23%	66%	**0.939**	38%	48%	0.230	44%	49%	0.112
Parametrium invasion clinically									
Absent	89%	86%		87%	90%				
Inconclusive/ absent	8%	8%	0.001	4%	6%	0.059			
Inconclusive/ present	3%	6%	0.166	9%	4%	0.220			

Supplementary Table 1. (continued)

Status of suspicious node									
Suspicious	42%	93%		70%	72%				
Inconclusive	58%	7%	**1.301**	30%	28%	0.040			
Location of suspicious node(s)†									
Pelvic	92%	79%		95%	78%		90%	77%	
Common iliac	4%	11%	**0.270**	3%	8%	0.186	4%	8%	0.118
Para-aortic	4%	20%	**0.516**	2%	14%	**0.363**	6%	15%	**0.303**
Mean short-axis of largest suspicious node, mm	11	15	**0.516**	12	13	0.211	14	13	0.144
Histological subtype									
Squamous cell	71%	80%		79%	80%				
Adeno	24%	16%	0.203	18%	16%	0.166			
Adenosquamous cell	5%	4%	0.080	3%	4%	0.053			
Lymphovascular space invasion									
Absent	39%	66%		55%	52%				
Present	61%	34%	**0.585**	45%	48%	0.078			
Tumor grade									
1	7%	5%		5%	7%				
2	48%	37%	0.219	46%	36%	0.200			
3	45%	58%	**0.269**	49%	57%	0.176			
Year of incidence									
2009	19%	8%					20%	12%	
2010	11%	12%	0.050				10%	10%	0.010
2011	11%	9%	0..071				11%	9%	0.066
2012	11%	8%	0.093				7%	13%	0.181
2013	11%	9%	0.071				14%	10%	0.143
2014	7%	14%	0.246				12%	11%	0.030
2015	15%	9%	0.170				11%	9%	0.038
2016	11%	18%	0.205				9%	15%	0.163
2017	4%	13%	**0.324**				6%	11%	0.194

Abbreviations: *CRT*, chemoradiotherapy; Sd, standardized difference; *FIGO*, International Federation of Gynecology and Obstetrics.

† most cranial location was decisive.

Data represent the percentage of patients or mean. Bold standardized differences indicate unbalance variables between the treatment groups.

Supplementary Table 2. Data distribution before and after multiple imputation.

Variables	Missing	Original data	Imputed data
Charlson comorbidity index	15%		
0		86%	84%
1		11%	12%
≥2		3%	4%
Median weight, kg	4%	70 (40-132)	72 (40-132)
Median length, m	3%	1.68 (1.28-1.87)	1.68 (1.28-1.87)
Pretreatment squamous cell carcinoma antigen†	38%		
0.0-2.3 ng/ml		36%	36%
2.4-10.0 ng/ml		44%	41%
10.1-20.0 ng/ml		11%	12%
>20.0 ng/ml		9%	11%
Median tumor diameter, mm	7%	41 (2-80)	41 (2-80)
Median short-axis of largest suspicious, mm	14%	11 (5-50)	13 (5-50)
Lymphovascular space invasion	34%		
Absent		54%	56%
Present		46%	45%
Tumor grade	28%		
1		4%	6%
2		46%	44%
3		49%	50%
Parametrium invasion clinically	2%		
Absent		86%	86%
Inconclusive absent		10%	10%
Inconclusive present		4%	4%

† For squamous cell carcinoma only.

Supplementary Table 3. Multivariable Cox-regression and inverse-probability-treatment-weighting analysis regarding recurrence-free and overall survival of original and imputed data.

	Original data						Imputed data						inverse-probability-treatment-weighting imputed data					
	Recurrence-free survival			Overall survival			Recurrence-free survival			Overall survival			Recurrence-free survival			Overall survival		
Variables	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Therapy group																		
CRT	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
Surgery	0.92	0.48-1.76	0.79	0.87	0.45-1.69	0.68	0.82	0.45-1.49	0.51	0.77	0.42-1.42	0.40	0.73	0.36-1.48	0.38	0.73	0.35-1.50	0.39
Nodal location																		
Pelvic	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
Common iliac	2.13	1.06-4.28	0.035*	1.88	0.87-4.05	0.11	1.79	0.91-3.51	0.09	1.57	0.77-3.19	0.22	1.45	0.64-3.32	0.37	1.33	0.58-3.06	0.50
Para-aortic	1.40	0.75-2.61	0.29	1.67	0.89-3.11	0.11	1.65	0.96-2.83	0.07	1.81	1.07-3.07	0.028*	2.14	1.11-4.12	0.022*	2.33	1.21-4.52	0.012*
Age				1.03	1.01-1.05	0.002				1.02	1.01-1.04	0.003*						
FIGO stage																		
I	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.							
II	1.32	0.74-2.35	0.35	1.41	0.80-2.50	0.23	1.13	0.65-1.99	0.66	1.37	0.81-2.31	0.24						
Tumor size	1.02	1.00-1.03	0.028*	1.02	1.00-1.04	0.020*	1.02	1.00-1.03	0.011*	1.02	1.00-1.04	0.009*						
Histotype																		
Squamous	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.							
Adeno	2.01	1.16-3.50	0.013*	1.79	1.00-3.21	0.051	2.38	1.45-3.90	0.001*	2.20	1.33-3.64	0.002*						
Adenosqua-mous	3.20	1.32-7.76	0.010*	3.23	1.33-7.81	0.009*	2.75	1.25-6.04	0.012*	2.39	1.10-5.20	0.028*						
Nodal status																		
Suspicious	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.							
Inconclusive	0.68	0.27-1.15	0.12	0.93	0.43-2.01	0.85	0.56	0.32-1.24	0.18	0.69	0.33-1.41	0.30						
Nodal size	1.02	0.98-1.05	0.37	1.02	0.98-1.05	0.37	1.00	0.97-1.04	0.81	1.01	0.97-1.04	0.76						
Propensity score													0.44	0.15-1.26	0.13	0.53	0.18-1.59	0.26

Abbreviations: *CRT*, chemoradiotherapy; *HR*, hazard ratio; *CI*, confidence interval.
* statistically significant.

Supplementary Table 4. Preoperative clinicopathological characteristics of patients with or without adjuvant treatment after surgery.

Preoperative characteristics	Without adjuvant therapy N=60	With adjuvant therapy N=71	p-value
Median age, years	44 (23-74)	43 (22-77)	0.43
Charlson comorbidity index			0.60
0	46 (77%)	56 (79%)	
1	5 (8%)	6 (8%)	
≥2	-	2 (3%)	
Unknown	9 (15%)	7 (10%)	
Median Body Mass Index, kg/m^2	24 (16-40)	24 (16-37)	0.99
Median pretreatment squamous cell carcinoma antigen, ng/ml†	1.5 (0.3-28.9)	3.2 (0.3-17.0)	0.08
Histological subtype			0.77
Squamous cell carcinoma	44 (73%)	48 (68%)	
Adeno carcinoma	14 (23%)	19 (27%)	
Adenosquamous cell carcinoma	2 (3%)	4 (6%)	
Lymphovascular space invasion			<0.001*
Absent	34 (57%)	14 (20%)	
Present	21 (35%)	52 (73%)	
Unknown	5 (8%)	5 (7%)	
Tumor grade			0.058
1	5 (8%)	1 (1%)	
2	23 (38%)	36 (51%)	
3	17 (15%)	25 (35%)	
Unknown	15 (25%)	9 (13%)	
Depth of invasion			0.013*
<15 mm	45 (75%)	36 (51%)	
≥15 mm	11 (18%)	22 (31%)	
Unknown	4 (7%)	13 (18%)	
FIGO 2009 stage			0.52
IB1	47 (78%)	48 (68%)	
IB2	9 (15%)	14 (20%)	
IIA1	1 (2%)	4 (6%)	
IIA2	3 (5%)	5 (7%)	
Median clinical tumor diameter, mm	33 (2-80)	35 (10-70)	0.18
Clinical tumor diameter			0.19
≤2 cm	13 (22%)	9 (13%)	
>2-4 cm	27 (45%)	39 (55%)	
>4 cm	12 (20%)	19 (27%)	
Unknown	8 (13%)	4 (6%)	
Median tumor diameter on MRI, mm	37 (0-50)	51 (30-54)	0.40
Tumor diameter on MRI			0.056
≤2 cm	11 (18%)	3 (4%)	
>2-4 cm	19 (32%)	21 (30%)	
>4 cm	11 (18%)	18 (25%)	
Unknown	19 (32%)	29 (41%)	
Status of suspicious node			0.051
Suspicious	19 (32%)	35 (49%)	
Inconclusive	41 (68%)	36 (51%)	

Supplementary Table 4. (continued)

Location of suspicious node(s)‡			0.92
Pelvic	52 (87 %)	63 (89%)	
Common iliac	2 (3%)	3 (4%)	
Para-aortic	6 (10%)	5 (7%)	
Median short-axis of largest suspicious node, mm	9 (5-50)	10 (5-29)	0.09

Abbreviations: *FIGO*, International Federation of Gynecology and Obstetrics; *MRI*, magnetic resonance imaging.

† for squamous-cell carcinoma's only.

‡ most cranial location was decisive.

* statistically significant.

Data represent the number of patients and (percentage) or median with (range).

Chapter 7

Treatment of bulky lymph nodes in locally advanced cervical cancer: boosting versus

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ABSTRACT

Objective: Treatment strategies for bulky lymph nodes in patients with locally advanced cervical cancer scheduled for definitive chemoradiation include nodal boosting with radiotherapy, surgical debulking, or both. The aim of this retrospective cohort study was to compare survival and toxicity in patients receiving these treatments and to compare them with a group that received neither form of treatment.

Methods: Women diagnosed between January 2009 and January 2017 with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB2, IIA2–IVA cervical cancer with lymph nodes ≥1.5 cm without upper limit on pretreatment imaging and treated with definitive chemoradiation were selected from the Netherlands Cancer Registry. Patients were categorized by intention-to-treat strategy: boosting, debulking, or neither treatment, with subgroup analysis for patients receiving both treatments, that is, debulking with boosting. Overall and relapse-free survival outcomes were compared by Kaplan-Meier and Cox regression analyses and toxicity by logistic regression analysis.

Results: Of 190 patients, 101 (53%) received only nodal boosting, 31 (16%) debulking alone, 29 (15%) debulking combined with boosting, and 29 (15%) received neither treatment. The 5-year overall and relapse-free survival for the treatment groups were 58%, 45% and 45% (p=0.19), and 47%, 44% and 46% (p=0.87), respectively. Multivariable Cox regression analyses demonstrated no differences in overall and relapse-free survival. Combination of debulking with boosting was associated with decreased overall and relapse-free survival compared with debulking alone (HR 2.47, 95% CI 1.22 to 5.00; and HR 2.37, 95% CI 1.14 to 4.93). Nodal boosting was independently associated with a decreased toxicity risk compared with debulking strategy (OR 0.37, 95% CI 0.16 to 0.83).

Conclusions: This study showed no survival benefit from either nodal boosting or debulking strategy in patients with suspicious bulky nodes. Nodal boosting might, however, be associated with less toxicity. Dual treatment with debulking and boosting showed a worse survival outcome because this group probably represents patients with poor prognostic factors.

INTRODUCTION

The age-standardized incidence rate of cervical cancer was 5.2 per 100,000 women for developed countries in 2020.[1] Of these women, approximately 40% were diagnosed with locally advanced disease, defined as International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB2, IIA2–IVA, with a 5 year relative survival rate of ~58%.[2, 3] Survival is worse in patients with lymph node metastases and depends on the number, size, and affected region of nodal metastases.[4, 5] Macroscopically enlarged nodes are also known as 'bulky' nodes and can be defined as nodes with a short axis of ≥1.5 or ≥2.0 cm on imaging, but an unambiguous definition is lacking.[6-10] For bulky nodes, standard dose of conventional external beam radiation (50–60 Gray (Gy)) may be insufficient for sterilization, and additional treatment may be warranted.[4, 7-9, 11-13]

Currently, two main strategies are used to treat bulky nodes: high-dose boost irradiation as part of standard chemoradiation and nodal debulking prior to definitive chemoradiation.[14] Debulking nodal tumor load might increase the chance of complete sterilization by chemoradiation and decrease the risk of toxicity by avoiding a boost. To date, there has been little agreement on the most effective and safe strategy, with only a few studies evaluating the impact on survival. Some studies demonstrated effective nodal control by boosting in patients with suspicious nodes on imaging,[10, 13, 15-17] while others showed improved survival after nodal debulking.[6, 18-20] Furthermore, both strategies are associated with different toxicities: surgical complications versus genitourinary and gastrointestinal toxicity.[6, 13, 21] Unfortunately, direct comparative studies on survival or toxicity are missing.

This retrospective study aims to compare intention-to-treat strategies for bulky node(s) - boosting, debulking, or neither treatment - as part of a chemoradiation treatment plan in patients with locally advanced cervical cancer and suspicious bulky nodes on imaging. Relapse-free survival, overall survival, and toxicity were compared among groups.

METHODS

Study Design

With Privacy Review Board approval (No 210029) of the Netherlands Cancer Registry, we performed a nationwide retrospective cohort study analyzing data between January 2009 and January 2017 from the Registry, which contains data of >95% of all patients with cancer in the Netherlands. The following inclusion criteria were used: (1) FIGO 2009 stage IB2, IIA2–IVA, (2) suspicious or inconclusive pelvic and/or para-aortic bulky nodes on imaging (CT, positron emission tomography (PET)-CT, MRI, or PET-MRI), and (3) treatment with curative intent (radiotherapy alone, combined with chemo- therapy, or hyperthermia). Patients with neuroendocrine carcinoma or treatment with neoadjuvant chemotherapy were excluded. Details of chemoradiation at a patient level are not available, but we assumed that patients were treated according to the Dutch guidelines: external beam radiation (total dose 45–50 Gy) with concurrent single-agent chemotherapy (cisplatin weekly 40 mg/m²), and brachytherapy until a minimal dose equivalent of 80 Gy.[22] Extended-field radiotherapy was indicated if common iliac or para-aortic regions were involved, following the EMBRACE protocol.[23] Although there is no clear definition, based on previous studies, we defined bulky nodes as ≥1.5 cm short axis without upper limit, with subgroup analysis for those ≥2.0 cm.[6,

[7, 10] All patients were categorized according to intention-to-treat strategy for bulky nodes: a 'boosting' only, 'debulking', or 'neither' group, the latter for patients without additional nodal treatment. Patients who were treated with debulking but also received boosting were allocated to the debulking group, as allocation was based on an intention-to-treat strategy.

Nodal characteristics (including short-axis diameter and radiological judgment) were registered for five regions: pelvic left/right, common iliac left/right, and para-aortic. Data on patient, tumor, and treatment characteristics were collected. Postoperative complications were noted for those who had surgery and defined as any complication ≤30 days from surgery, scored as grade ≥2 on the Clavien-Dindo scale.[24] Radiotherapy and chemotherapy related toxicities were defined as any complication ≤6 months after starting treatment, classified as grade ≥3 of the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.[25] In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if requested.

Statistical Analysis

Continuous variables were compared by the Mann-Whitney U test or Kruskal-Wallis test, while discrete variables were assessed using the Fisher exact test. The primary outcomes, relapse-free and overall survival, were defined as the interval from the start of primary therapy to the date of recurrence and from diagnosis to death, respectively. The date of death was obtained by annual linkage with the Personal Records Database. Survival analyses were performed using the Kaplan-Meier method and the log-rank test. Furthermore, Cox regression analyses were used for calculating HRs, with 95% CIs. Subgroup analyses were performed for patients who underwent surgical debulking with and without additional boosting to account for heterogenicity within this treatment group. The multivariable models for the subgroup analyses included fewer confounders to avoid model overfitting in the case of fewer observations. Logistic regression analysis was used to calculate ORs with 95% CIs for toxicity. A p-value <0.05 was considered significant, and South Texas Art Therapy Association SE 17 (StataCorp, College Station, TX) software was used for all analyses.

RESULTS

Patient and Treatment Characteristics

In this study, 190 patients with bulky nodes were included (Online supplemental figure 1), of which 53% received nodal boosting (n=101), 32% surgical debulking (n=60), and 15% neither treatment (n=29). The suspicious bulky nodes in patients who received debulking were larger (median 22 mm) than the nodes of patients treated by boosting (18 mm) or without additional nodal treatment (17 mm; p<0.001), and most (≥79%) were located in the pelvic region (Table 1). Compared with the boosting group, the median interval between diagnosis and chemoradiation was 14 and 7 days longer in the debulking and neither group, respectively. Primary treatment differed between the groups. The group without debulking or boosting received the least comprehensive treatment, with less chemotherapy and/or hyperthermia (p<0.001), brachytherapy (p<0.001), and extended field radiotherapy (p=0.002). Out of the debulking procedures, 47% were performed with a combination of pelvic and/or para-aortic lymphadenectomy, and the majority (67%) were performed by open surgery. Histological examination of bulky nodes was negative in four

patients (7%) after surgical resection and was only performed in the debulking group. The median number of retrieved nodes was nine (range 1–33), with a median of three positive nodes (range 0–22).

Table 1. Patient characteristics, categorized per treatment group for patients with bulky nodes ≥1.5 cm.

Characteristics	Overall (n=190)	Boosting (n=101)	Debulking (n=60)	Neither (n=29)	p-value
Age (years)	51 (25–92)	51 (27–92)	50 (25–77)	55 (31–83)	0.005*
Charlson morbidity index					0.56
0	121 (64%)	63 (62%)	40 (67%)	18 (62%)	
1	23 (12%)	14 (14%)	5 (8%)	4 (14%)	
≥2	13 (7%)	9 (9%)	4 (7%)	–	
Unknown	33 (17%)	15 (15%)	11 (18%)	7 (24%)	
Smoking (yes)	62 (33%)	33 (33%)	18 (30%)	11 (38%)	0.75
Pretreatment SCC-Ag† (ng/mL)	10.9 (0.1–278.0)	8.0 (0.1–224.3)	16.4 (1.0–176.0)	11.9 (0.3–278.0)	0.14
FIGO 2009 stage					0.16
IB2	30 (16%)	15 (15%)	14 (23%)	1 (3%)	
II	105 (55%)	54 (53%)	33 (55%)	18 (62%)	
III	46 (24%)	28 (28%)	11 (18%)	7 (24%)	
IVA	9 (5%)	4 (4%)	2 (3%)	3 (10%)	
Primary tumor size					0.08
≤4	31 (16%)	13 (13%)	11 (18%)	7 (24%)	
>4	156 (82%)	87 (86%)	49 (82%)	20 (69%)	
Unknown	3 (2%)	1 (1%)	0 (0%)	2 (7%)	
Histological type					0.92
Squamous	165 (87%)	87 (86%)	53 (88%)	25 (86%)	
Non-squamous	25 (13%)	14 (14%)	7 (12%)	4 (14%)	
Bulky node size (mm)	19 (15–86)	18 (15–86)	22 (15–83)	17 (15–60)	<0.001*
Region of bulky node‡					0.21
Pelvic	158 (83%)	84 (83%)	51 (85%)	23 (79%)	
Common iliac	12 (6%)	7 (7%)	5 (8%)	–	
Para-aortic	20 (11%)	10 (10%)	4 (7%)	6 (21%)	
Diagnosis to primary treatment interval (days)	53 (11–128)	48 (11–96)	62 (28–128)	55 (30–125)	<0.001*
Primary treatment					<0.001*
CRT	149 (78%)	75 (74%)	57 (95%)	17 (59%)	
(C)HRT	25 (13%)	17 (17%)	1 (2%)	7 (24%)	
RT only	16 (8%)	9 (9%)	2 (3%)	5 (17%)	
Brachytherapy (yes)	178 (94%)	98 (97%)	58 (97%)	22 (76%)	<0.001*
Nodal boost (yes)	130 (68%)	101 (100%)	29 (48%)	–	<0.001*
Radiotherapy field					0.002*
Pelvic	114 (60%)	64 (63%)	28 (47%)	22 (76%)	
Pelvic +para-aortic	71 (37%)	37 (37%)	27 (48%)	5 (17%)	
Unknown	5 (3%)	–	3 (5%)	2 (7%)	
Follow-up (months)	45 (3–144)	49 (3–143)	42 (5–144)	40 (8–134)	0.85
Recurrence	93 (49%)	49 (49%)	31 (52%)	13 (45%)	0.83

Table 1. (continued)

Recurrence location§					0.31
Central pelvic	14 (15%)	7 (14%)	4 (13%)	3 (23%)	0.62
Lateral pelvic	24 (26%)	11 (22%)	10 (32%)	3 (23%)	0.64
Para-aortic	30 (32%)	16 (33%)	11 (35%)	3 (23%)	0.75
Distant	70 (75%)	36 (73%)	24 (77%)	10 (77%)	0.94
Unknown	1 (1%)	1 (2%)	–	–	–
Vital status					0.26
Alive	86 (45%)	51 (51%)	25 (42%)	10 (34%)	
Deaths	104 (55%)	50 (49%)	35 (58%)	19 (66%)	

Abbreviations: *SCC-Ag*, squamous cell antigen; *FIGO*, International Federation of Gynecology and Obstetrics; *CRT*, chemoradiation; *(C)HRT*, (chemotherapy with) hyperthermia and radiotherapy; *RT*, radiotherapy.

Data are the number of patients (percentage) or median (range).

* Statistically significant.

† For squamous cell type only.

‡ Most cranial lymph node region was decisive.

§ Some patients had multiple recurrence locations.

Oncological Outcome

With a median follow-up of 45 months (range 3–144), 93 recurrences (49%) and 104 deaths (55%) were observed (Table 1). Infield recurrences were observed in 34 (36.5%) of 93 patients with a relapse, and distant relapse was the most common cause of recurrence and death (≥73%). The 5 year overall survival was 58% (95% CI 48% to 67%) in the boosting, 45% (32%–57%) in the debulking, and 45% (26%–61%) in the neither treatment group (p=0.19; Figure 1A). Additionally, there were no differences observed in the 5 year relapse-free survival (Figure 1B) among the treatment groups, which was 47% (36%–57%) after boosting, 44% (30%–57%) after debulking, and 46% (26%–65%) after no treatment (p=0.87). Results of multivariable analyses are presented in Table 2. Overall and relapse-free survival were not affected by the different treatment strategies.

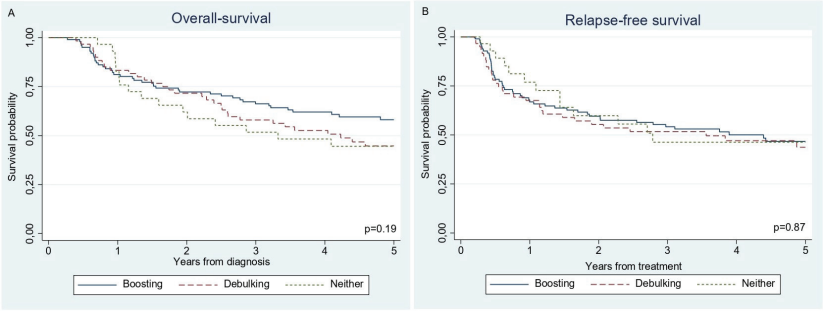

Figure 1. Kaplan-Meier estimates after treatment of women with locally advanced cervical cancer plus bulky nodes (≥1.5 cm). (A) Overall survival; (B) relapse-free survival.

Table 2. Multivariable analysis regarding overall and relapse-free survival.

Variables	HR	95% CI	p-value	HR	95% CI	p-value
Treatment group						
Debulking	1.00	Reference		1.00	Reference	
Boosting	0.65	0.51 to 1.03	0.07	0.85	0.53 to 1.37	0.51
Neither	0.85	0.45 to 1.59	0.61	0.78	0.38 to 1.61	0.51
Age†	1.02	1.01 to 1.03	0.007*	1.01	0.99 to 1.02	0.42
Bulky node location						
Pelvic	1.00	Reference		1.00	Reference	
Common iliac	1.20	0.57 to 2.51	0.64	1.00	0.44 to 2.29	1.00
Para-aortic	1.42	0.79 to 2.57	0.25	1.37	0.70 to 2.70	0.36
Bulky node size†	1.00	0.98 to 1.02	0.97	1.01	0.99 to 1.03	0.36
FIGO 2009 stage						
IB2	1.00	Reference		1.00	Reference	
II	1.03	0.54 to 1.97	0.94	1.00	0.53 to 1.90	1.00
III	1.50	0.73 to 3.08	0.27	1.36	0.66 to 2.80	0.40
IVA	2.82	1.04 to 7.66	0.042*	2.07	0.69 to 6.25	0.20
Primary tumor size (cm)						
≤4	1.00	Reference		1.00	Reference	
>4	1.60	0.90 to 2.86	0.11	1.44	0.77 to 2.70	0.25

Abbreviations: *FIGO*, International Federation of Gynecology and Obstetrics.

† Continuous scale.

* Statistically significant.

Toxicity

Toxicities related to surgery, radiotherapy, and chemotherapy are presented in Table 3. By definition, postoperative complications only occurred in the debulking group (10%), and infection was most common (7%; n=4). The number of patients experiencing radiotherapy-related (p=0.29), chemotherapy-related (p=0.16), or any toxicity (p=0.06) did not differ between treatment groups. Additionally, toxicity in the debulking group did not differ between patients with and without a lymphadenectomy (29% and 41%; p=0.42). After adjusting for age, primary treatment, extended-field radiotherapy, and bulky node size, nodal boosting was associated with less toxicity (OR 0.37; 95% CI 0.16 to 0.83) compared with debulking (Online supplemental table 1).

Table 3. Toxicities related to surgery (grade ≥2), radiotherapy, and chemotherapy (grade ≥3) per treatment group.

	Boosting (n=101)	Debulking (n=60)	Neither (n=29)	p-value
Surgery				
Intraoperative injury	–	2 (3%)	–	
Infection	–	4 (7%)	–	
IC-admission	–	1 (2%)	–	
Blood transfusion	–	1 (2%)	–	
Total†	–	8	–	
Total patients	–	6 (10%)	–	
Radiotherapy				
Urological	3 (3%)	–	2 (7%)	0.10
Gastrointestinal	9 (9%)	5 (8%)	6 (21%)	0.19

Table 3. (continued)

Genital	1 (1%)	–	1 (4%)	0.38
Other	2 (2%)	2 (3%)	2 (7%)	0.30
Total†	15	5	2	
Total patients	15 (15%)	7 (12%)	7 (24%)	0.29
Chemotherapy				
Nausea/vomiting	3 (3%)	3 (5%)	–	0.62
Nephrotoxicity	4 (4%)	1 (2%)	–	0.57
Ototoxicity	1 (1%)	–	–	
Bone marrow depression	–	4 (7%)	1 (3%)	0.022*
Malaise/fatigue	–	2 (3%)	1 (3%)	0.14
Neurotoxicity	1 (1%)	–	–	
Other	3 (3%)	3 (5%)	3 (10%)	0.19
Total†	12	4	9	
Total patients	9 (9%)	11 (18%)	5 (17%)	0.16
Total adverse events				
Total†	27	17	11	
Total patients	21 (21%)	21 (35%)	11 (38%)	0.06

Abbreviations: *IC*, intensive care.

† Some patients experienced multiple toxicities.

* Statistically significant.

Subgroup Analyses

Subgroup analysis of patients who received debulking with (n=29) or without (n=31) boosting demonstrated a worse 5 year relapse-free and overall survival for those who had boosting (33%, 95% CI 15% to 53%; and 38%, 95% CI 21% to 55%), while the survival of those without boosting was comparable to boosting alone (54%, 95% CI 34% to 70%; and 53%, 95% CI 34% to 69%) (Figure 2A,B).

In multivariable analysis, nodal debulking with boost was negatively associated with overall (HR 2.47, 95% CI 1.22 to 5.00) and relapse-free survival (HR 2.37, 95% CI 1.14 to 4.93), compared with debulking alone (Online supplemental table 2). Toxicity did not differ between the boosted and non-boosted groups (n=10, 48% vs n=11, 52%).

Subgroup analysis for bulky nodes ≥2 cm included 35, 48, and 9 patients in the boosting, debulking, and neither treatment groups, respectively. Although patients and treatment characteristics were more balanced among the treatment groups (Online supplemental table 3), the 5 year overall (53%, 46%, 53%; p=0.83) and relapse-free survival (43%, 43%, 36%; p=0.91) did not differ between the boosting, debulking, and neither treatment groups. Furthermore, overall and relapse-free survival were not affected by the different treatment strategies in multivariable analysis (Online supplemental table 2). No differences were observed regarding toxicities (data not shown).

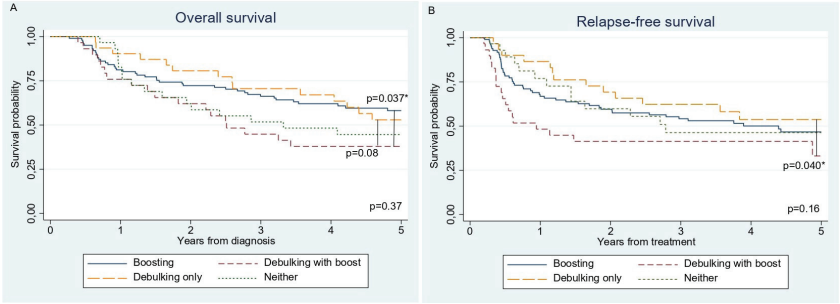

Figure 2. Kaplan-Meier estimates after treatment of women with locally advanced cervical cancer plus bulky nodes (≥1.5 cm), with subgroup analyses for nodal debulking with and without boost. (A) Overall survival; (B) relapse-free survival.

DISCUSSION

Summary of Main Results

In this study, we were unable to demonstrate superiority of any one of three treatment strategies on overall or relapse-free survival. However, boosting alone might be associated with less toxicity compared with the debulking strategy, with or without boosting. Subgroup analysis for bulky nodes ≥2 cm demonstrated similar survival results among the treatment groups, although the sample size is too small to draw firm conclusions. Subgroup analysis for debulking with or without boosting demonstrated that dual treatment by debulking with boosting was independently associated with a worse survival outcome compared with debulking alone. This is most likely related to the selection of eligible patients for dual treatment, a subgroup with poor prognostic factors.

Results in the Context of Published Literature

This study directly compared different treatment strategies in one patient cohort with cervical cancer and suspicious bulky nodes. In literature, the few studies on this topic focus either on nodal debulking or boosting. Three studies on debulking demonstrated survival benefits, but were performed before concurrent chemoradiation was standard care for locally advanced cervical cancer.[18-20] These studies showed that patients in whom microscopic and macroscopic nodal metastases were removed during surgical staging had comparable 5 year relapse-free survival rates (50%–57% versus 43%–57%, respectively), while patients with unresectable nodes had a survival of 0%. Vascular and nervous adherence or invasion was the main cause of unsuccessful resections, and none of the nodes were boosted. More recently, another study on nodal debulking demonstrated no survival benefits in patients with locally advanced cervical cancer.[26] Laparoscopic para-aortic staging was combined with or without debulking suspicious pelvic nodes on imaging. Patients with suspicious or histologically confirmed pelvic metastases received nodal boosting in addition to chemoradiation. The 5-year disease-free (both ~55%) and overall survival did not differ between the debulked (~65%; n=164) and non-debulked groups (63%; n=111). Notably, the suspicious nodes on MRI or PET-CT were relatively small (range 1.0–1.8 cm), and only 43% of the debulked nodes were positive on pathological examination.

Most recent studies on strategies for bulky nodes focus on boosting in relatively small patient cohorts.[11, 13, 15-17] Bulky nodes on imaging are associated with lower loco-regional control rates, which could be increased by radiotherapy dose escalation (>55.8 Gy) in patients with stage IB–IVA cervical cancer treated with definitive chemoradiation.[13, 17] Some studies achieve local control in 83%–92% of patients after nodal boosting of suspicious pelvic and/or para-aortic nodes, with disease-free and overall survival rates of 73%–76% and 58%–71%, respectively.[15, 16] In a study on patients with locally advanced cervical cancer and suspicious pelvic nodes treated by definitive chemoradiation with (n=36) and without (n=31) nodal boosting, the 5 year recurrence-free (49% vs 65%; p=0.17) and overall survival (74% vs 81%; p=0.14) did not differ between groups, which is in line with our results.[27] Notably, the survival rates of these studies on boosting are considerably higher than ours, which might be related to varying definitions of bulky nodes (≥1.0 to ≥2.4) and boost administration (50.4–63.0 Gy). Remarkably, none of the suspicious nodes in the above-listed studies were histologically confirmed. Therefore, it is difficult to compare separate studies on nodal boosting or debulking.

Pelvic and para-aortic nodes are adjacent to high-risk organs for radiotherapy. Dose escalation could therefore lead to increased toxicity. The potential benefit from debulking nodal tumor load in terms of toxicity could not be demonstrated in our study because nodal boosting was associated with less toxicity. This can be explained by the contribution of surgery-related toxicities, which naturally can only occur after debulking. Even though open surgery was the most common approach in our study, the 10% of surgery-related complications is in concordance with toxicity described in the literature on surgical staging in locally advanced cervical cancer, including two studies with a laparoscopic approach.[20, 28, 29] Studies on nodal boosting report higher acute (4%–41%) and late (4%–29%) radiotherapy-related toxicity (grade ≥2) compared with our cohort (15%–17%).[10, 15, 16, 27] This could be attributed to the shorter follow-up (≤6 months), unreported toxicity in patient records, or potentially other doses of boost irradiation in our study.

Overall, studies on treatment strategies for bulky nodes in cervical cancer are scarce, and direct comparisons of nodal boosting with debulking are lacking. It is important to keep in mind that the nodes in most studies were generally <1.5 cm and that the studies on nodal boosting might have included false positives, which could positively affect survival rates.[10, 13, 15-17] Therefore, there is a need to directly compare both strategies within one cohort.

Strengths and Weaknesses

Our study is based on national data of a relatively large retrospective study cohort, allowing correction for several confounders. It provides data from real-world clinical practice but is unfortunately also inherently associated with the risk of bias. First, histological confirmation of suspicious bulky nodes was only performed after debulking, while the positive predictive value for nodal imaging is only 55%–96%.[30] Therefore, both 'boosting' and 'neither' groups probably contain false-positive bulky nodes. We have analyzed a subgroup with nodes ≥2.0 cm, in which positive predictive values were likely higher. However, this has led to small cohort sizes limiting statistical power. Second, the 'neither' group probably represents a poor prognostic group with higher age and lower performance scores, as primary treatment in this group was less comprehensive. Also, extended-field radiotherapy was more commonly applied after debulking than in the boosting group, which might reflect those with a poorer prognosis. However, extended-field radiotherapy was equally common in the treatment groups with bulky nodes ≥2 cm, with similar survival

outcomes as in the whole patient group. Another limitation is the lack of details on chemoradiation modalities and boost irradiation, including dose and location. This is especially important in the debulking with boosting group because the boost might also have targeted other suspicious nodes and not only the location of the (possibly incompletely) resected node. Lastly, the debulking procedures in our study were extensive, with nine median retrieved nodes (range 1–33) and a combination with lymphadenectomy in 47%. More extensive procedures are associated with higher toxicity, which might be reflected by our results on toxicity after debulking. Despite these limitations, this study represents the largest cohort of patients comparing different treatment strategies of bulky nodes in locally advanced cervical cancer and adds valuable information to existing literature.

Implications for Practice and Future Research

A randomized clinical trial on strategies for bulky nodes might overcome bias related to retrospective study designs. However, the feasibility might be poor due to insufficient eligible patients, and international collaboration would be necessary. However, as ≥73% of the recurrences included distant metastases, strategies that may reduce distant relapse rather than achieving local control by boosting or debulking may be more urgently warranted for this patient group.

CONCLUSION

In conclusion, we were unable to demonstrate superiority of the addition of nodal boosting or debulking over chemoradiation on overall and relapse-free survival in patients with locally advanced cervical cancer and suspicious bulky nodes of ≥1.5 cm on imaging. Furthermore, reducing tumor load by nodal debulking might increase the risk of toxicity compared with nodal boosting. However, these results must be interpreted cautiously because of our retrospective study design. Finally, the combination of debulking with boosting was associated with decreased survival outcomes, but this group probably represents patients with poor prognostic factors. As none of the strategies were superior to survival, shared decision-making and individualized treatment seem to be the best approach for patients with bulky nodes.

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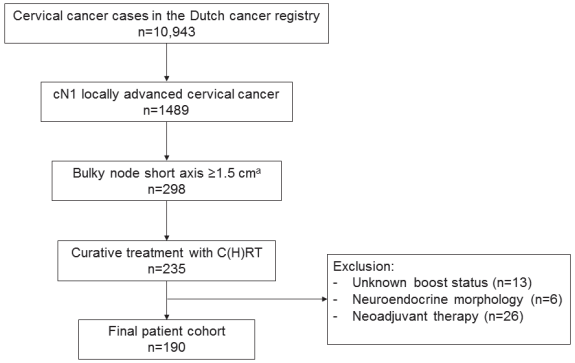
SUPPLEMENTAL MATERIAL



Supplementary Figure 1. Flow chart of patient inclusion with locally advanced cervical cancer and suspicious bulky nodes ≥1.5 cm.

Abbreviations*:* cN1, presence of regional lymph node metastasis bases on clinical examination and imaging; C(H)RT, radiotherapy with or without chemotherapy and/or hyperthermia.

* Data were collected on project basis for cervical cancer patients diagnosed between 2009 and 2017.

Supplementary Table 1. Logistic regression analysis for total patients experiencing surgery, radiotherapy or chemotherapy related adverse events.

Variables	OR	95% CI	p-value
Therapy group			
Debulking	1.00	Reference	
Boosting	0.37	0.16-0.83	0.017*
Neither	0.89	0.30-2.70	0.84
Age†	1.04	1.01-1.07	0.003*
Primary treatment			
CRT	1.00	Reference	
(C)HRT	1.17	0.42-3.24	0.23
RT only	0.06	0.01-0.59	0.015*
Radiotherapy field			
Pelvic	1.00	Reference	
Pelvic + para-aortic	1.20	0.58-2.47	0.62
Bulky node size†	1.03	0.99-1.07	0.18
Constant	0.04	0.01-0.23	<0.001*

Abbreviations*: RT*, radiotherapy; *CRT*, chemoradiation; *(C)HRT*, (chemotherapy with) hyperthermia and radiotherapy; *OR*, odds ratio; *CI*, confidence interval.

† Continues scale.

* statistically significant.

Supplementary Table 2. Multivariable subgroup analysis for nodal debulking with and without boost, and for bulky nodes ≥2 cm regarding overall and relapse-free survival.

	Debulking with/without boost (n=60)						Bulky nodes ≥2 cm (n=92)					
	Overall survival			Relapse-free survival			Overall survival			Relapse-free survival		
Variables	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Therapy group												
Debulking only	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Debulking with boost	2.47	1.22-5.00	0.012*	1.24	1.07-4.72	0.033*						
Boosting							0.67	0.35-1.28	0.23	0.91	0.48-1.72	0.76
Neither							0.61	0.23-1.65	0.33	0.55	0.16-1.86	0.34
Age†	1.03	1.00-1.06	0.07	1.03	1.00-1.06	0.10	1.02	1.00-1.04	0.023*	1.02	1.00-1.04	0.046*
Bulky node location												
Pelvic	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Common iliac	0.80	0.24-2.69	0.72	0.60	0.14-2.56	0.49	1.08	0.33-3.54	0.90	0.38	0.05-2.79	0.34
Para-aortic	3.10	1.04-9.23	0.042*	2.28	0.67-7.72	0.19	1.70	0.69-4.18	0.25	1.98	0.76-5.16	0.16
Bulky nodes size†	1.01	0.98-1.04	0.49	1.02	0.99-1.05	0.29	1.01	0.98-1.03	0.57	1.00	0.98-1.03	0.93

Abbreviations: *HR*, hazard ratio; *CI*, confidence interval.

† Continues scale.

* statistically significant.

Supplementary Table 3. Patients and treatment characteristics categorized per treatment group for patients with bulky nodes ≥2 cm.

Characteristics	**Overall** (n=92)	**Boosting** (n=35)	**Debulking** (n=48)	**Neither** (n=9)	**P-value**
Age (years)	53 (27-86)	50 (25-77)	54 (31-82)	52 (25-77)	0.07
Charlson comorbidity index					0.19
0	55 (60%)	20 (57%)	21 (67%)	16 (62%)	
1	14 (15%)	7 (20%)	5 (10%)	2 (8%)	
≥2	7 (8%)	4 (11%)	3 (6%)	3 (12%)	
Unknown	16 (17%	4 (11%)	8 (17%)	5 (19%)	
Squamous cell antigen† (ng/mL)	11.4 (0.3-224.3)	7.5 (0.5-224.3)	14.8 (1.0-176.0)	5.0 (0.3-79.5)	0.24
FIGO 2009 stage					0.21
IB2	17 (18%)	4 (11%)	13 (27%)	-	
II	48 (52%)	18 (51%)	22 (46%)	8 (89%)	
III	23 (25%)	11 (31%)	11 (23%)	1 (11%)	
IVA	4 (4%)	2 (6%)	2 (4%)	-	
Primary tumor size (cm)					0.42
≤4	16 (18%)	4 (11%)	11 (23%)	1 (13%)	
>4	75 (82%)	31 (89%)	37 (77%)	7 (88%)	
Histology					>0.99
Squamous	82 (89%)	31 (89%)	43 (90%)	8 (89%)	
Non-squamous	10 (11%)	4 (11%)	5 (10%)	1 (11%)	
Bulky node size (mm)	25 (20-86)	24 (20-86)	24 (20-83)	26 (20-60)	0.64
Bulky node location‡					0.64
Pelvic	81 (88%)	29 (83%)	44 (92%)	8 (89%)	
Common iliac	4 (4%)	2 (6%)	2 (4%)	-	
Para-aortic	7 (8%)	4 (11%)	2 (4%)	1 (11%)	
Primary treatment					0.005*
CRT	75 (82%)	24 (69%)	45 (94%)	6 (67%)	
(C)HRT	10 (11%)	8 (23%)	1 (2%)	1 (11%)	
RT only	7 (8%)	3 (9%)	2 (4%)	2 (22%)	
Brachytherapy (yes)	85 (92%)	33 (94%)	46 (96%)	6 (67%)	0.023*
Nodal boost (yes)	57 (62%)	35 (100%)	22 (46%)	-	<0.001*
Radiotherapy field					0.09
Pelvic	48 (52%)	19 (54%)	22 (46%)	7 (78%)	
Pelvic + para-aortic	40 (43%)	16 (46%)	23 (48%)	1 (11%)	
Other/unknown	4 (4%)	-	3 (6%)	1 (11%)	
Recurrence	45 (49%)	18 (51%)	24 (50%)	3 (33%)	0.68
Recurrence location§					0.91
Central pelvic	6 (13%)	3 (17%)	3 (13%)	-	>0.99
Lateral pelvic	10 (22%)	4 (22%)	6 (25%)	-	>0.99
Para-aortic	15 (33%)	5 (28%)	10 (42%)	-	0.34
Distant	36 (80%)	14 (78%)	19 (79%)	3 (100%)	>0.99

Supplementary Table 3 (continued)

Vital status					0.83
Alive	43 (47%)	18 (51%)	21 (44%)	4 (44%)	
Deaths	49 (53%)	17 (49%)	27 (56%)	5 (56%)	

Abbreviations*: FIGO*, International Federation of Gynecology and Obstetrics; *CRT*, chemoradiation; *(C)HRT*, (chemotherapy with) hyperthermia and radiotherapy; *RT*, radiotherapy.

† Pretreatment level for squamous cell type only.

‡ most cranial lymph node region was decisive.

§ some patients had multiple recurrence locations.

* statistically significant.

Chapter 8

The impact of surgery and chemoradiotherapy on toxicity and long-term health-related quality of life in cervical cancer survivors: results from the population-based PROFILES registry

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ABSTRACT

Objective: This study evaluated long-term health-related quality of life (HRQoL) and short-term toxicity after radical hysterectomy and primary chemoradiotherapy in stage I-II cervical cancer survivors.

Methods: Patients selected from the Netherlands Cancer Registry were invited to participate in a cross-sectional questionnaire study 2-11 years post-treatment. Clinical stage I-II (TNM classification 8th edition) cervical cancer patients treated with radical hysterectomy or chemoradiotherapy between 2011 and 2017 were included. HRQoL was evaluated using EORTC QLQ-C30 and QLQ-CX24 questionnaires. Grade ≥2 surgery-related (≤30 days) and grade ≥3 chemotherapy or radiotherapy-related (≤6 months) toxicities were collected from patient records. Differences in HRQoL between treatment groups and associations between HRQoL and toxicities were analysed using multivariable linear regression, controlling for age, comorbidities, and diagnosis to questionnaire interval. Subgroup analyses were performed for surgery with adjuvant therapy.

Results: Of 288 women included, 63% (n=181) had a radical hysterectomy, of whom 27% received adjuvant (chemo)radiotherapy, and 37% (n=107) had primary chemoradiotherapy. The median diagnosis-questionnaire interval was 6 years (interquartile range 4-8). Women who had chemoradiotherapy reported worse functioning (role (mean surgery 83 vs chemoradiotherapy 76), cognitive (83 vs 75), and social (85 vs 77), all differences were considered as small clinically important) and more symptoms (fatigue (33 vs 42), financial problems (8 vs 13), symptom experience (12 vs 15), neuropathy (13 vs 25), sexual activity (37 vs 30), and sexual functioning (30 vs 41), with a small clinically important difference for fatigue and financial problems) than those receiving surgery. Lymphoedema (29 vs 13) was more common after surgery, which was considered as a clinically important difference. Women with adjuvant therapy reported more sexual activity (mean surgery with adjuvant therapy 37 vs primary chemoradiotherapy 30), but also more lymphoedema (31 vs 13) than those with primary chemoradiotherapy, while other HRQoL scales were comparable. Toxicity profiles differed between treatment groups, with bladder dysfunction most common after surgery and gastro-intestinal toxicity after primary chemoradiotherapy.

Conclusions: Primary chemoradiotherapy may affect more long-term HRQoL domains than surgery. However, when adjuvant therapy was administered, results seemed to be more comparable. These insights may support treatment counselling.

INTRODUCTION

Cervical cancer is the fourth most common type of malignancy in women worldwide, affecting young women with a peak incidence between the ages of 35 and 45 years.[1, 2] In high-income countries, approximately half of all cervical cancers are diagnosed at an early (FIGO 2009 stage <IIB), usually curable, stage with a 5-year relative survival up to 91%.[2] Consequently, a substantial group of cervical cancer survivors has a relatively long life expectancy, with potential long-term effects of the disease and its treatment on health-related quality of life (HRQoL). This highlights the importance of assessing HRQoL as an outcome in cervical cancer survivors. As patients who are well-informed about treatment-related morbidity have shown to cope better with the disease and its consequences, it is valuable to provide accurate information to optimise counselling.[3]

Current guidelines recommend radical hysterectomy and pelvic lymphadenectomy, followed by adjuvant (chemo)radiotherapy in the presence of pathological risk factors, as standard treatment for early-stage cervical cancer.[4-6] Chemoradiotherapy is recommended for locally advanced stages. Both treatment modalities have different short-term and long-term toxicity profiles and affect HRQoL and sexual function in different ways.[7-9] Previous studies reported that primary chemoradiotherapy is typically associated with bowel dysfunction, genitourinary morbidity, and dyspareunia due to vaginal fibrosis.[7, 10-12] In contrast, radical hysterectomy is mainly associated with postoperative complications, lymphoedema, urinary dysfunction, and dyspareunia due to vaginal shortening.[7, 10-12] In addition, radical hysterectomy is generally combined with a pelvic lymphadenectomy for staging purposes. Obstruction of lymphatic vessels due to lymphadenectomy or changes in connective tissue by radiotherapy can lead to lymphoedema in approximately 12-14% of patients.[13]

Despite the disparities observed in HRQoL and toxicity between the two primary therapeutic modalities for cervical cancer, there is a paucity of published research investigating these aspects within a single cohort. Therefore, this cross-sectional study aimed to evaluate (1) long-term HRQoL and (2) short-term toxicity rates in cervical cancer survivors after radical hysterectomy with pelvic lymphadenectomy and primary chemoradiotherapy, and (3) to examine the association between HRQoL and therapy-related toxicities. We also performed an explorative analysis of these outcomes in patients who underwent radical hysterectomy with adjuvant therapy vs those who had primary chemoradiotherapy.

METHODS

Study design and participants

For this study, we combined data from the Netherlands Cancer Registry together with data from two patient-reported outcomes studies. The Netherlands Cancer Registry, including all newly diagnosed malignancies in the Netherlands since 1989, was used to obtain patient, tumour and treatment characteristics. This information was supplemented on record level with patient-reported outcome data from two studies: the Dutch nation-wide FOllow-up among Cervical cancer sUrvivorS (FOCUS) study and the International Collaboration of the Healthcare professionals And Researchers for Gynecologic cancer survivors' Empowerment (InCHARGE) study. Both studies were conducted using the Patient Reported

Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry.[14] The FOCUS study included patients diagnosed with cervical cancer between 2011 and 2017 in eight (out of nine) gynaecological oncology centres in the Netherlands. They were invited to participate between April 2019 and September 2021. The InCHARGE study included patients diagnosed with cervical cancer between 2011 and 2016 in four Dutch hospitals in the South of the Netherlands. These patients were invited to participate from October 2018 to June 2019.[15]

We included patients with International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage I and II cervical cancer, who were treated with radical hysterectomy or primary chemoradiotherapy. Patients treated with neoadjuvant therapy or a salvage hysterectomy were excluded. Chemoradiotherapy was administered according to European guidelines: pelvic external beam radiation (total dose 45–50 Gy) with concurrent single-agent chemotherapy (cisplatin weekly 40 mg/m²), and/or brachytherapy, preferably 3D MRI guided, until a minimal dose equivalent of 80 Gy in Manchester point A by low, high, or pulsed dose rate.[4] Adjuvant (chemo)radiotherapy was administered according to local protocols and was indicated in case of pathologically proven intermediate/high-risk factors.[4, 16]

Data collection

In both studies, survivors were informed and invited to participate by a letter from their (former) attending gynaecologist 2-11 years posttreatment. The invitation included a secured link to a web-based informed consent form and online questionnaire. A paper version with a stamped addressed envelope was also included and could be returned by post if the patient preferred to complete the paper-and-pencil questionnaire. Non-responders received a reminder letter and paper questionnaire within 2 months after the first invitation. For each participant, consent was obtained by returning the online or paper informed consent form.

Baseline clinical characteristics, recurrence status, and toxicity were collected from hospital records by trained data managers from the Netherlands Cancer Registry. The definition of socio-economic status (i.e., low, middle, high) has been described previously.[17] Therapy-related toxicity data were retrospectively graded and registered from patient files as part of a Dutch Cancer Society project on lymph node metastasis [IKNL2019-12398]. As this project concerned a specific cohort of cervical cancer patients, toxicity data were not available for all patients. This project included patients with a diagnosis between 2009-2017 and: (1) clinical tumour stage (cT) <2B and pathologically verified lymph nodes, (2) cT <2B and pretreatment imaging, or (3) cT ≥2B and a suspicious lymph node on imaging (cN1).

Outcome measures

HRQoL was defined as the primary outcome and was assessed using validated questionnaires: the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ) C30 (version 3.0) and the disease-specific cervical cancer module CX24.[18, 19] The 30-item EORTC QLQ-C30 questionnaire contains functional scales (physical, role, cognitive, emotional, and social), a global health and general QoL domain, and symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). The EORTC QLQ-CX24 module is a 24-item questionnaire which contains: multi-item scales (symptom experience, body image, and sexual/vaginal functioning) and single-item scales (lymphoedema, peripheral neuropathy, menopausal symptoms, sexual

worry, sexual activity, and sexual enjoyment). Answers are reported on a 4-point Likert scale including: 'Not at all', 'A bit', 'Quite a bit', and 'Very much', except for sexuality-related questions, which include an extra answer 'Don't know/don't want to share' and the global health status/QoL, which ranges on a 7-point Likert scale from 'Very poor' to 'Excellent'. All scales were converted to a score between 0 and 100 according to the manual.[18, 20] For the functional scales and for global health status/QoL, higher scores indicate better functioning/global health/QoL, whereas for the symptom scales higher scores indicate higher symptom burden.

Secondary outcomes concerned therapy-related toxicity. Surgery-related toxicity was defined as a grade ≥2 complication on the Clavien-Dindo scale ≤30 days after surgery.[21] Radiotherapy- and chemotherapy-related toxicity were defined as a grade ≥3 Common Terminology Criteria for Adverse Events (CTCAE version 4.03) complication, ≤6 months after the start of treatment.[22] Toxicity profiles included a number of commonly observed adverse reactions including: anorexia/nausea, vomiting, nephrotoxicity, ototoxicity, stomatitis, mucositis, bone marrow depression, general malaise/fatigue, neurotoxicity, anaphylactic shock, arthralgia/muscle pain, hypertension, proteinuria, headache and dyspnoea associated with chemotherapy. Urological, gastrointestinal, genital or other complaints were included for radiotherapy. In addition, age, marital status, education level, body mass index, number of comorbidities and working status were also derived from a self-reported questionnaire. The diagnosis-to-questionnaire interval was calculated as the time between the date of diagnosis in the registry and the self-reported date of the questionnaire completion form.

Statistical analyses

Patients were categorized by treatment strategy: radical hysterectomy with pelvic lymphadenectomy or primary chemoradiotherapy. Descriptive statistics were used to describe the baseline characteristics: continuous variables were compared between treatment groups using the Mann-Whitney U (non-normally distributed) or unpaired T-test (normally distributed), and discrete variables with Fisher's exact test. Clinically important differences were identified using guidelines for the EORTC QLQ-C30, a methodology based on high-quality QoL studies, expert opinions, and meta-analytic techniques to score trivial to large QLQ-C30 QoL differences.[23] Differences in the EORTC QLQ-C30 subscales are classified as large (representing unequivocal clinical relevance), medium (likely to be clinically relevant but to a lesser extent), small (subtle but nevertheless clinically relevant), and trivial (unlikely to have any clinical relevance) effects. For the EORTC QLQ-CX24, no guideline is available and, therefore, Norman's rule of thumb was used, which states that differences between groups of ≥0.5 SD can be considered as clinically significant.[24]

Multivariable linear regression analyses were used to assess the associations between the dependent variables (HRQoL and number of toxicities) and independent variable (treatment group/number of toxicities), controlled for potential confounders (i.e., age, comorbidity and diagnosis to questionnaire interval, determined using Directed Acyclic Graphs (DAG) via the web application 'DAGitty').[25] A DAG is a graphical model that helps to identify causal and biasing paths to find a set of variables of interest. The presence of multicollinearity was tested by the variance inflation factor, which was <10 for all factors. In addition, similar analyses were performed to compare the radical hysterectomy with adjuvant therapy and primary chemoradiotherapy treatment groups. A p-value <0.05 was considered significant. Stata statistical software version 17.0 (StataCorp, College Station, TX, USA) was used for all analyses.

RESULTS

Study participants

Of the 1,866 cervical cancer survivors contacted, 325 women (17%) responded to the questionnaire and 288 (89%) met the inclusion criteria for the current study. Baseline and treatment characteristics were comparable to the non-responders who met the inclusion criteria (Supplementary Table S1). Of the 288 patients, 181 (63%) were treated with a radical hysterectomy and 107 patients (37%) with primary chemoradiotherapy. Women treated with a radical hysterectomy were more likely to be premenopausal (64% vs 41%; p=0.024), to have stage I disease (97% vs 28%; p<0.001), and to have a smaller tumour (21 mm vs 42 mm; p<0.001) compared to women treated with chemoradiotherapy, as shown in Table 1. Radical hysterectomy was combined with lymphadenectomy in 99% of cases and was mainly performed using an open approach (66%). Of 181 patients treated with radical hysterectomy, 27% (n=48) received adjuvant therapy consisting of chemoradiotherapy (n=25; 14%), radiotherapy (n=22; 12%), or chemotherapy alone (n=1; 1%). Primary chemoradiotherapy was preceded by nodal resections in 12% of women and included brachytherapy in 94%.

Table 1. Baseline characteristics for patients per treatment group.

Patient and tumour characteristics	Missing	Radical hysterectomy (n=181)	Chemoradiotherapy (n=107)	p-value
Median age at diagnosis, years (IQR)	0 (0%)	45 (39-53)	47 (38-59)	0.08
Median age at questionnaire, years (IQR)	9 (3%)	50 (43-58)	52 (44-61)	0.37
Marital status, n (%) [a]	59 (20%)			0.12
Partner		95 (65%)	45 (54%)	
No partner		51 (35%)	38 (46%)	
Highest education level, n (%) [b]	3 (1%)			0.07
Low		17 (9%)	20 (19%)	
Medium		83 (46%)	44 (42%)	
High		80 (44%)	41 (39%)	
Number of comorbidities, n (%)	21 (7%)			0.21
0		68 (40%)	34 (34%)	
1		45 (27%)	37 (37%)	
≥2		55 (33%)	28 (28%)	
Menopausal status, n (%)	165 (57%)			0.024*
Pre		47 (64%)	20 (41%)	
Peri		2 (3%)	1 (2%)	
Post		25 (34%)	28 (57%)	
Working status, n (%)	14 (5%)			0.89
Yes		122 (70%)	68 (69%)	
No		53 (30%)	31 (31%)	
Diagnosis to questionnaire interval, years (IRQ)	0 (0%)	6 (4-8)	6 (4-8)	0.63
Socio-economic status, n (%)	1 (0%)			0.23
Low		59 (33%)	25 (23%)	
Middle		47 (26%)	33 (31%)	
High		74 (41%)	49 (46%)	
FIGO 2009 stage, n (%)	0 (0%)			<0.001*
IA2		3 (2%)	0 (0%)	

Table 1. (continued)

IB1		161 (89%)	17 (16%)	
IB2		11 (6%)	13 (12%)	
IIA1		4 (2%)	2 (2%)	
IIA2		0 (0%)	9 (8%)	
IIB		2 (1%)	66 (62%)	
Median tumour diameter, mm	64 (22%)	21 (15-35)	42 (30-50)	<0.001*
Treatment characteristics				
Nodal examination, n (%)	0 (0%)			<0.001*
Lymphadenectomy		180 (99%)	11 (10%)	
Debulking		0 (0%)	2 (2%)	
No examination		1 (1%)	94 (88%)	
Surgical approach, n (%) [c]	10 (5%)			0.55
Open		119 (66%)	3 (100%)	
Laparoscopic		62 (34%)	-	
Brachytherapy, yes, n (%)	0 (0%)	11 (6%)	101 (94%)	<0.001*
Adjuvant treatment, n (%)	0 (0%)			<0.001*
Chemoradiotherapy		25 (14%)	-	
Radiotherapy		22 (12%)	-	
Chemotherapy		1 (1%)	1 (1%)	
No		133 (73%)	106 (99%)	
Type of chemotherapy, n (%) [d]	0 (0%)			0.41
Platinum based		21 (92%)	102 (95%)	
With paclitaxel		-	2 (2%)	
With etoposide		1 (4%)	2 (2%)	
Other		1 (4%)	1 (1%)	
Cycles of chemotherapy, number (range) [d]	27 (20%)	6 (5-6)	6 (6-6)	0.008*

Abbreviations: *FIGO*, International Federation of Gynecology and Obstetrics; *IQR*, interquartile range.

[a] Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.

[b] Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.

[c] patients with surgery only.

[d] patients with chemo(radio)therapy only.

P-value based on Mann-Whitney U or Fisher's exact test.

* statistically significant.

Health-related quality of life

Descriptive analyses of the HRQoL scales are shown in Table 2. The EORTC QLQ-C30 and CX24 questionnaires were completed by 285 (99%) and 287 (100%) survivors, respectively. The radical hysterectomy group reported higher functioning scores than the chemoradiotherapy group on role (p=0.016), cognitive (p=0.001) and social functioning (p=0.001) scales. The clinical importance of these differences was considered small. Women who underwent primary surgical treatment reported more symptoms of lymphoedema (p<0.001), a difference that was considered clinically important. In contrast, fatigue (p=0.018), financial problems (p=0.006), symptom experience (p=0.025), and peripheral neuropathy (p=0.002) were all reported more frequently after chemoradiotherapy. Individual scores on the symptom experience items are shown in Supplementary Table S2. The differences in scores for fatigue and financial problems were considered to be of small clinical importance, while others were considered trivial.

In total, 168 out of 230 women (73%) reported being 'A bit' to 'Very much' sexually active, whereas 62 women (27%) reported being 'Not at all' sexually active. Up to 27% of the women did not answer the sexual-related questions. Better sexual activity (p=0.020) and sexual/vaginal functioning (p=0.029) were reported by patients who had received radical hysterectomy compared with chemoradiotherapy. Differences in the sexuality-related scales were not considered clinically important.

Table 2. HRQoL related scores according to EORTC QLQ-C30 and QLQ-CX24 questionnaires per treatment group with multivariable linear regression analysis and clinically important difference.

	Missing	Radical hysterectomy N=181		Chemoradiotherapy N=107						
Functioning scales	N	Mean (SD)		Mean (SD)	Mean difference	0.5 x sample SD	Clinically important difference	Coefficient	95% CI	p-value
Physical functioning	5 (2%)	89 (16)		85 (18)	4		Trivial [a]	-3.7	-7.6 ; 0.3	0.07
Role functioning	5 (2%)	83 (25)		76 (27)	7		Small [a]	-7.9	-14.3 ; -1.5	0.016*
Emotional functioning	4 (1%)	79 (24)		76 (24)	3		-	-4.5	-10.4 ; 1.5	0.14
Cognitive functioning	4 (1%)	83 (24)		75 (25)	8		Small [a]	-9.9	-15.6 ; -4.2	0.001*
Social functioning	5 (2%)	85 (22)		77 (28)	8		Small [a]	-9.5	-15.3 ; -3.7	0.001*
Global health status/QoL	5 (2%)	76 (19)		74 (20)	2		Trivial [a]	-2.6	-7.0 ; 1.8	0.24
Sexual activity	58 (20%)	37 (26)		30 (27)	7	13	No [b]	-8.3	-15.4 ; -1.3	0.020*
Sexual enjoyment	76 (26%)	52 (33)		46 (34)	6	17	No [b]	-6.0	-16.0 ; 4.0	0.24
Symptom scales										
Fatigue	5 (2%)	33 (32)		42 (32)	9		Small [a]	9.7	1.7 ; 17.7	0.018*
Nausea / vomiting	5 (2%)	4 (13)		7 (19)	3		Small [a]	2.1	-1.5 ; 5.8	0.26
Pain	4 (1%)	19 (28)		22 (27)	3		Trivial [a]	2.5	-4.0 ; 9.1	0.45
Dyspnoea	5 (2%)	8 (19)		9 (20)	1		Trivial [a]	1.0	-3.4 ; 5.5	0.65
Insomnia	5 (2%)	28 (31)		30 (32)	2		Trivial [a]	5.1	-2.3 ; 12.6	0.18
Appetite loss	5 (2%)	7 (19)		10 (22)	3		Trivial [a]	1.9	-3.2 ; 6.9	0.47
Constipation	4 (1%)	12 (24)		12 (23)	0		Trivial [a]	0.4	-5.6 ; 6.5	0.89
Diarrhoea	4 (1%)	10 (24)		15 (26)	5		Small [a]	3.4	-2.9 ; 9.6	0.29
Financial problems	5 (2%)	8 (21)		13 (26)	5		Small [a]	7.5	-2.2 ; 12.8	0.006*
Symptom experience	1 (0%)	12 (11)		15 (12)	3	6	No [b]	3.0	0.4 ; 5.7	0.025*
Lymphedema	2 (1%)	29 (32)		13 (24)	16	15	Yes [b]	-15.1	-22.6 ; -7.7	<0.001*
Peripheral neuropathy	3 (1%)	13 (24)		25 (32)	12	14	No [b]	10.5	4.0 ; 17.0	0.002*
Menopausal symptoms	1 (0%)	25 (31)		27 (31)	2	16	No [b]	4.2	-3.7 ; 12.1	0.29
Body image	1 (0%)	22 (26)		24 (26)	2	13	No [b]	4.1	-2.2 ; 10.4	0.20
Sexual worry	74 (26%)	34 (34)		42 (33)	8	17	No [b]	9.0	-0.78 ; 18.7	0.07
Sexual/vaginal functioning	77 (27%)	30 (30)		41 (30)	11	15	No [b]	10.1	-1.1 ; 19.2	0.029*

Abbreviations: *SD*, standard deviation; *CI*, confidence interval. Clinically important differences between the QLQ-C30 scales were based on [a] Cocks et al. and between the CX24 scales on [b] Norman's rule of thumb. For the functional scales and global health status/QoL higher scores imply better functioning/ global health status/QoL, for the symptoms scales a higher score implies more symptoms/impairment. Scales range from 0-100. P-value based on multivariable linear regression analysis, adjusted for age, comorbidity and diagnosis to questionnaire interval.

* statistically significant

Toxicity

Information on therapy-related toxicity was available for 173 (96%) and 58 (54%) patients in the radical hysterectomy and chemoradiotherapy groups, respectively (Table 3). The total number of patients with any therapy-related toxicity did not differ between the two groups (21% vs 27%; p=0.39). Surgery-related adverse events occurred in 25% of patients who underwent radical hysterectomy, with bladder dysfunction being the most common event (11%). One patient (2%) in the chemoradiotherapy group experienced a surgery-related adverse event as a result of intraoperative injury during nodal examination. Radiotherapy- and chemotherapy-related toxicities were reported in 9% and 14% in the chemoradiotherapy group and 2% and 14% in the radical hysterectomy group. Gastrointestinal toxicity was the most common radiotherapy-related event (7%) and nausea/vomiting was the most common toxicity related to chemotherapy (3%).

Table 3. Therapy-related toxicity per treatment group. N (%)

Toxicities	Radical hysterectomy (n=173)	Chemoradiotherapy (n=58)
Surgery-related		
Intra-operative injury	6 (3%)	1 (2%)
Infection	9 (5%)	0 (0%)
Thromboembolism	1 (1%)	0 (0%)
Intensive-care admission	1 (1%)	0 (0%)
Bladder dysfunction	19 (11%)	0 (0%)
Blood transfusion	5 (3%)	0 (0%)
Other	5 (3%)	0 (0%)
Total patients [a]	43 (25%)	1 (2%)
Radiotherapy-related		
Urological	1 (1%)	0 (0%)
Gastro-intestinal	3 (2%)	4 (7%)
Other	0 (0%)	1 (2%)
Total patients [a]	4 (2%)	5 (9%)
Chemotherapy-related		
Nausea/vomiting	2 (1%)	2 (3%)
Ototoxicity	1 (1%)	0 (0%)
Bone marrow depression	1 (1%)	0 (0%)
Malaise/fatigue	0 (0%)	1 (2%)
Neurotoxicity	1 (1%)	0 (0%)
Dyspnoea	0 (0%)	1 (2%)
Other	1 (1%)	5 (9%)
Total patients [a]	3 (2%)	8 (14%)
Total patients with therapy-related toxicity [a]	47 (27%)	12 (21%)

[a] some patients experienced multiple therapy-related toxicities

Health-related quality of life and toxicity

Women who experienced more therapy-related toxicity reported worse physical functioning (coefficient [95% CI]: -5.7 [-10.2 to -1.2]; p=0.014), role functioning (-8.7 [-16.5 to 0.9]; p=0.029) and social functioning (-8.5 [-15.5 to -1.5]; p=0.018), as shown in Table 4. In addition, therapy-related toxicity was positively associated with pain symptoms (12.6 [4.7 to 20.5]; p=0.002), financial problems (9.3 [3.0 to 15.5]; p=0.004) and symptom experience (3.3 [-0.2 to 6.3]; p=0.036). Sensitivity analysis with adjustment for treatment

group, in addition to age and comorbidity, did not affect the association between therapy-related toxicity and any of the functioning or symptom scales (data not presented).

Table 4. Multivariable linear regression analysis for association HRQoL and the number of toxicities, adjusted for age, comorbidity and diagnosis to questionnaire interval.

Functioning scales	Missing, n	Coefficient	95% CI	p-value
Physical functioning	5 (2%)	-5.7	-10.2 ; -1.2	0.014*
Role functioning	5 (2%)	-8.7	-16.5 ; -0.9	0.029*
Emotional functioning	4 (1%)	1.2	-6.1 ; 8.4	0.75
Cognitive functioning	4 (1%)	-4.3	-11.2 ; 2.6	0.22
Social functioning	5 (2%)	-8.5	-15.5 ; -1.5	0.018*
Global health status/QoL	5 (2%)	-2.5	-7.8 ; 2.8	0.35
Sexual activity	58 (20%)	-1.1	-10.0 ; 7.7	0.80
Sexual enjoyment	76 (26%)	-0.53	-13.1 ; 12.0	0.93
Symptom scales				
Fatigue	5 (2%)	6.5	-3.3 ; 16.3	0.19
Nausea / vomiting	5 (2%)	3.9	-0.2 ; 7.9	0.06
Pain	4 (1%)	12.6	4.7 ; 20.5	0.002*
Dyspnoea	5 (2%)	-0.0	-5.0 ; 5.1	0.99
Insomnia	5 (2%)	3.0	-5.9 ; 11.8	0.51
Appetite loss	5 (2%)	2.6	-3.4 ; 8.6	0.40
Constipation	4 (1%)	5.3	-2.0 ; 12.5	0.15
Diarrhoea	4 (1%)	-0.3	-7.4 ; 8.0	0.93
Financial problems	5 (2%)	9.3	3.0 ; 15.5	0.004*
Symptom experience	1 (0%)	3.3	-0.2 ; 6.3	0.036*
Lymphedema	2 (1%)	-3.2	-12.9 ; 6.4	0.51
Peripheral neuropathy	3 (1%)	-5.1	-12.9 ; 2.7	0.20
Menopausal symptoms	1 (0%)	4.5	-5.2 ; 14.2	0.36
Body image	1 (0%)	3.9	-3.7 ; 11.5	0.32
Sexual worry	74 (26%)	2.6	-9.4 ; 14.6	0.67
Sexual/vaginal functioning	77 (27%)	6.2	-5.0 ; 17.3	0.28

Abbreviations: *CI*, confidence interval. For the functional scales higher scores imply better functioning, for the symptoms scales a higher score implies more symptoms, and for global health status/QoL, higher scores denote a better global health/QoL.

* statistically significant.

Radical hysterectomy with adjuvant therapy

Baseline characteristics of patients treated with radical hysterectomy and adjuvant therapy (n=48) were compared to those treated with primary chemoradiotherapy (n=107), as shown in Supplementary Table S3. Patients receiving adjuvant therapy were more likely to have multiple comorbidities (49% vs 28%; p=0.032, respectively) than patients receiving primary chemoradiotherapy, whereas patients with primary chemoradiotherapy had larger tumours (42 mm vs 32 mm; p<0.001) and more often had stage II disease (72% vs 8%; p<0.001).

Regarding HRQoL, the adjuvant therapy group scored better than the primary chemoradiotherapy group on sexual activity (p=0.011). However, this was not regarded a clinically relevant difference (Table 5). Women who underwent radical hysterectomy and adjuvant therapy reported more symptoms of lymphoedema compared to women with primary chemoradiotherapy (p=0.007), a difference that was considered clinically important.

Therapy-related toxicity rates after adjuvant therapy and primary chemoradiotherapy were available for 48 and 58 patients, respectively (Table 6). The surgery-related toxicity rate was higher after surgery followed by adjuvant therapy (27%) than after primary chemoradiotherapy (2%; p<0.001), especially due to bladder dysfunction. Radiotherapy- and chemotherapy-related toxicities occurred in 9% and 7% of patients treated with adjuvant therapy, and in 9% and 14% of patients with primary chemoradiotherapy, respectively, without a significant difference. The overall toxicity rate was 36% after adjuvant therapy and 21% after primary chemoradiotherapy (p=0.12).

Table 5. HRQoL related scores according to EORTC QLQ-C30 and QLQ-CX24 questionnaires for the subgroup analysis, with multivariable linear regression analysis and clinically important difference.

	Missing	Radical hysterectomy with adjuvant therapy N=48	Primary chemoradiotherapy n=107							
Functioning scales	N	Mean (SD)	Mean (SD)	Mean difference	0.5 x sample SD	Clinically important difference	Coefficient	95% CI	p-value
Physical functioning	1 (1%)	86 (19)	85 (18)	1		Trivial [a]	-2.1	-8.5 ; 4.3	0.53
Role functioning	1 (1%)	81 (27)	76 (27)	5		Trivial [a]	-8.5	-18.7 ; 1.7	0.10
Emotional functioning	1 (1%)	77 (24)	76 (24)	1		-	-4.3	-13.2 ; 4.7	0.35
Cognitive functioning	1 (1%)	78 (29)	75 (25)	3		Small [a]	-7.1	-16.5 ; 2.3	0.14
Social functioning	2 (1%)	81 (26)	77 (28)	4		Trivial [a]	-8.2	-18.0 ; 1.6	0.10
Global health status/QoL	2 (1%)	73 (19)	74 (20)	1		Trivial [a]	-1.2	-8.0 ; 5.6	0.74
Sexual activity	31 (17%)	37 (26)	30 (27)	7	13	No [b]	-13.3	-23.5 ; -3.2	0.011*
Sexual enjoyment	41 (23%)	48 (30)	46 (34)	2	17	No [b]	-4.7	-19.4 ; 10.0	0.53
Symptom scales									
Fatigue	1 (1%)	34 (32)	42 (32)	8		Small [a]	8.6	-3.3 ; 20.5	0.15
Nausea / vomiting	1 (1%)	5 (16)	7 (19)	2		Trivial [a]	0.5	-5.8 ; 6.8	0.89
Pain	1 (1%)	20 (32)	22 (27)	2		Trivial [a]	4.5	-5.8 ; 14.8	0.39
Dyspnoea	1 (1%)	11 (23)	9 (20)	2		Small [a]	-0.5	-7.7 ; 6.7	0.89
Insomnia	1 (1%)	34 (35)	30 (32)	4		Small [a]	1.7	-10.2 ; 13.7	0.77
Appetite loss	1 (1%)	11 (22)	10 (22)	1		Trivial [a]	-0.7	-8.8 ; 7.3	0.86
Constipation	1 (1%)	13 (28)	12 (23)	1		Trivial [a]	0.9	-8.3 ; 10.1	0.84
Diarrhoea	1 (1%)	18 (30)	15 (26)	3		Small [a]	-4.4	-14.4 ; 5.6	0.39
Financial problems	3 (2%)	13 (27)	13 (26)	0		Trivial [a]	6.7	-2.5 ; 15.9	0.15
Symptom experience	1 (1%)	16 (12)	15 (12)	1	6	No [b]	1.8	-2.4 ; 6.0	0.40
Lymphedema	1 (1%)	31 (34)	13 (24)	18	16	Yes [b]	-14.2	-24.5 ; -3.9	0.007*
Peripheral neuropathy	3 (2%)	18 (28)	25 (32)	7	12	No [b]	9.3	-1.4 ; 19.9	0.09
Menopausal symptoms	1 (1%)	24 (31)	27 (31)	3	16	No [b]	7.0	-4.4 ; 18.4	0.23
Body image	1 (1%)	28 (30)	24 (26)	4	13	No [b]	-0.1	-9.9 ; 10.1	0.99
Sexual worry	40 (22%)	42 (39)	42 (33)	0	17	No [b]	-2.1	-17.1 ; 12.9	0.79
Sexual/vaginal functioning	44 (24%)	38 (32)	41 (30)	4	15	No [b]	1.8	-11.8 ; 15.4	0.80

Abbreviations: *SD*, standard deviation; *CI*, confidence interval. Clinically important differences between the QLQ-C30 scales were based on [a] Cocks et al. and between the CX24 scales on [b] Norman's rule of thumb. For the functional scales and global health status/QoL higher scores imply better functioning/ global health status/QoL, for the symptoms scales a higher score implies more symptoms/impairment. P-value based on multivariable linear regression analysis, adjusted for age, comorbidity and diagnosis to questionnaire interval. * statistically significant.

Table 6. Therapy-related toxicity for patients who received radical hysterectomy with adjuvant therapy or primary chemoradiotherapy. N (%)

Treatment group	Radical hysterectomy with adjuvant therapy (n=48)	Primary chemoradiotherapy (n=58)	p-value
Surgery-related			
Intra-operative injury	0 (0%)	1 (2%)	1.00
Infection	3 (7%)	0 (0%)	0.08
Thromboembolism	0 (0%)	0 (0%)	1.00
Intensive-care admission	0 (0%)	0 (0%)	1.00
Bladder dysfunction	7 (16%)	0 (0%)	0.002*
Blood transfusion	2 (4%)	0 (0%)	0.19
Other	1 (2%)	0 (0%)	0.44
Total patients [a]	12 (27%)	1 (2%)	<0.001*
Radiotherapy-related			
Urological	1 (2%)	0 (0%)	0.44
Gastro-intestinal	3 (7%)	4 (7%)	1.00
Other	0 (0%)	1 (2%)	0.56
Total patients [a]	4 (9%)	5 (9%)	1.00
Chemotherapy-related			
Nausea/vomiting	2 (4%)	2 (3%)	1.00
Ototoxicity	1 (2%)	0 (0%)	0.44
Bone marrow depression	1 (2%)	0 (0%)	0.44
Malaise/fatigue	0 (0%)	1 (2%)	1.00
Neurotoxicity	1 (2%)	0 (0%)	0.44
Dyspnoea	0 (0%)	1 (2%)	0.45
Other	1 (2%)	5 (9%)	0.23
Total patients [a]	3 (7%)	8 (14%)	0.34
Total patients with therapy-related toxicity [a]	16 (36%)	12 (21%)	0.12

[a] some patients experienced multiple therapy-related toxicities.

* statistically significant by univariate analysis.

DISCUSSION

This study evaluated the long-term HRQoL and short-term toxicity in cervical cancer survivors who underwent a radical hysterectomy with pelvic lymphadenectomy and those who received primary chemoradiotherapy. Overall, patients who received primary chemoradiotherapy may report worse functioning (role, cognitive, and social) and more symptoms (fatigue, financial problems, symptom experience, neuropathy, sexual activity, and sexual functioning) than those who had a radical hysterectomy. However, lymphoedema appears to be more common after radical hysterectomy. Both treatment strategies had different toxicity profiles, although the overall toxicity rate appeared to be similar. Experiencing short-term toxicity was negatively associated with several long-term HRQoL outcomes (i.e., physical, role and social functioning, pain symptoms, financial problems and symptom experience), irrespective of the type of treatment. Exploration of HRQoL and toxicity after radical hysterectomy with adjuvant therapy vs primary chemoradiotherapy suggests more sexual activity but worse lymphoedema symptoms after surgery.

The higher reporting of symptoms after primary chemoradiotherapy than surgery may explain the functioning observed in this group. Peripheral neuropathy is a well-known long-term side effect of cisplatin, the most widely used radiosensitiser in cervical cancer.[4, 26] In addition, fatigue has been described as another common long-term treatment-related symptom of chemoradiotherapy.[27] In line with previous research, we found more symptoms of lymphoedema after radical hysterectomy than after (chemo)radiotherapy.[11, 13, 28] Symptoms of lymphoedema include heaviness, discomfort, swelling and tightness of the skin, which can have a negative impact on HRQoL.[10] The prevalence of lymphoedema after radical hysterectomy in our study, with 26% of patients reporting 'Quite a bit' to 'Very much' of lymphoedema symptoms, is consistent with the rates of 24-29% reported in the review by Pfaendler et al. (2015).[10]

Another important aspect of HRQoL that is negatively affected by cervical cancer and its treatment is sexuality, regardless of treatment modality.[12] In addition to previous findings, sexual functioning may be worse after primary chemoradiotherapy than after radical hysterectomy in terms of sexual activity and sexual/vaginal functioning, even when surgery was followed by adjuvant therapy. These results are consistent with several reviews on this topic, showing that cervical cancer survivors treated with surgery have less sexual dysfunction than those treated with radiotherapy.[10, 12, 29] In addition, the effect of radiotherapy on sexual function appears to be more pronounced when combined with chemotherapy, possibly because of chemotherapy-induced ovarian failure or depression.[30] The effect of surgery alone on long-term sexual functioning in cervical cancer survivors remains controversial. Some studies suggest a long persistency of sexual dysfunction, whereas others suggest a return to baseline after 6-12 months.[10, 12, 29, 31] The effect of surgery on sexual functioning seems to be negatively influenced by the radicality of the surgery.[12]

The short-term toxicity rates in our two treatment groups are within the range reported by others: 17-30% grade ≥3 toxicity after surgery and 12-31% after chemoradiotherapy.[32-35] Most postoperative complications, including bladder dysfunction and infection, are often (partially) reversible, whereas radiotherapy-related toxicity is more often characterised by its late onset and chronic character (e.g., late gastrointestinal and genitourinary symptoms, and fistula).[36] Nevertheless, we did not find more constipation and diarrhoea after primary chemoradiotherapy than after radical hysterectomy. However, the symptom experience scale, which also included items such as abdominal cramps, control of bowels, blood in stool, but also incontinence and vaginal symptoms, was worse after primary chemoradiotherapy. This lack of difference in gastrointestinal symptoms between the two treatment strategies may be related to the proportion of patients who received adjuvant (chemo)radiotherapy (27%).

Some therapy-related toxicities may recover or improve over time, while others persist. Therefore, our short-term toxicity rates may not be consistent with the long-term self-reported symptom scales (e.g., fatigue and peripheral neuropathy), even when adjusted for time since diagnosis. Moreover, experiencing toxicities was negatively associated with multiple HRQoL outcomes (e.g., physical, role and social functioning, pain, and financial problems) regardless of the treatment strategy. The negative impact of toxicity on HRQoL has been demonstrated before, in prospective cohorts treated with radiotherapy for gynaecological cancer with longitudinal follow-up up to 5 years after treatment.[37, 38] Patients with high therapy-related toxicity scores had lower global QoL scores. Accordingly, reducing toxicity, for example by

using more advanced radiotherapy techniques (i.e., imaging-guided and intensity-modulated radiotherapy), may improve HRQoL.[39]

This study evaluated and compared the two main treatment strategies for cervical cancer to provide more accurate information about treatment-related morbidity to support counselling. Although the majority of treatment decisions in clinical practice are primarily influenced by clinical factors, it is worth noting that certain patient groups who are eligible for both treatment strategies may benefit from considering HRQoL outcomes as an additional factor in shared decision-making. For example, patients with clinically early-stage cervical cancer and a high likelihood of adjuvant therapy after surgery due to pathological risk factors (e.g., larger tumours, suspected parametrial invasion or lymph node metastases on pretreatment imaging). Current guidelines recommend primary chemoradiotherapy over radical hysterectomy because the combination of surgery and (chemo)radiotherapy may be associated with more toxicity and worse HRQoL. However, the literature is conflicting, with no evidence that either treatment strategy is superior in maintaining HRQoL.[9, 11, 30, 32, 33, 40] Our results suggests that there is no superiority for either strategy on HRQoL and toxicity, with better sexual activity but worse lymphoedema after surgery followed by adjuvant therapy. Therefore, shared decision-making may be the best approach for these patients. Currently, if all patients with a high likelihood of pathological risk factors are treated with primary chemoradiotherapy as suggested in the guidelines, this may lead to overtreatment with impaired HRQoL over time, as some of these patients may have been treated with radical hysterectomy without the need for adjuvant therapy. Of note, these findings should be confirmed in larger studies, as this subgroup analysis was probably underpowered.

This study has several limitations that need to be discussed. First, the response rate to the questionnaires was low (17%), which may be attributed to the relatively young age and lower socio-economic status of cervical cancer patients; characteristics that have been associated with non-participation in observational patient-reported outcome studies.[2, 41, 42] However, reassuringly, baseline characteristics from the Netherlands Cancer Registry indicated that the responders could be considered representative of the wider population in terms of patient, tumour and treatment characteristics. Second, our treatment groups were unbalanced with respect to some baseline characteristics, including menopausal status, FIGO stage, and tumour size. This discrepancy is the result from following guideline recommendations with an age limit for surgery and the administration of chemoradiotherapy for the treatment of locally advanced cervical cancer, which typically include larger tumours and stage II disease. Higher dose/volume radiotherapy is associated with increased toxicity, and thereby worse HRQoL, suggesting that adverse effects may be less pronounced in patients with stage IB compared to IIB cervical cancer.[43-45] Yet, the impact of this imbalance on our results is unclear. Third, our toxicity results may have been biased, because toxicity data were available for only 54% of the chemoradiotherapy group, which is related to the project-based inclusion criteria for additional data collection. Therefore, this group was likely to have more FIGO <IIB stages and patients with suspicious lymph nodes than the overall population treated with primary chemoradiotherapy. In addition, toxicity data were limited to the first 30 days after surgery and six months after (chemo)radiotherapy, at any time during the first six months of follow-up. Although a longer toxicity follow-up may have been informative, the long-term effects of treatment were covered by the symptom scales of the HRQoL questionnaires. Furthermore, under-reporting of toxicity by clinicians in patient records may have introduced a potential bias into our toxicity rates. Fourth,

unfortunately, detailed information on the radiotherapy technique (e.g., imaging-guided, radiotherapy-field, and nodal boosting) at a patient-level was not available. Consequently, we were unable to evaluate and adjust for the potential influence of varying radiotherapy techniques on our HRQoL outcomes. Another important aspect to consider is the interpretation of the clinical significance of a treatment effect. Despite our use of standardised methods described previously, in addition to statistically significant differences, it remains difficult to identify important patient-perceived changes on HRQoL scales, and therefore caution is required in the clinical interpretation of our HRQoL results. Despite these limitations, this study contributes to the existing literature on HRQoL and toxicity in cervical cancer, by analysing two main treatment strategies for cervical cancer: radical hysterectomy vs primary chemoradiotherapy, within one study cohort using validated questionnaires and grading systems.

Future research with a non-randomized, longitudinal design would be a realistic strategy to confirm current findings, as HRQoL questionnaires are increasingly used and embedded in the clinical practice. These studies could focus on (A) patients undergoing a sentinel lymph node procedure instead of lymphadenectomy, as this may reduce the risk of lymphoedema and improve HRQoL, and (B) patients with tumours ≤2 cm, as they are likely to be treated with simple instead of radical hysterectomy in the future, according to the preliminary results from the SHAPE trial.[46, 47] Survival outcomes were comparable in this trial, but all HRQoL scales with significant differences over time were in favour of the simple over the radical hysterectomy.

CONCLUSION

In conclusion, our data appear to support the assumption that primary chemoradiotherapy may have a greater impact on various domains of long-term HRQoL (i.e., role, cognitive, and social functioning, fatigue, financial problems, symptom experience, neuropathy, sexual activity, and sexual functioning) than radical hysterectomy, except for lymphoedema which was more common after radical hysterectomy. However, if adjuvant therapy is required, HRQoL outcomes appear to align more closely with those of patients receiving primary chemoradiotherapy. In addition, both strategies may be associated with distinct short-term toxicity profiles, with bladder dysfunction most common after surgery and gastro-intestinal toxicity after primary chemoradiotherapy. This information may support treatment counselling and raising awareness of HRQoL domains that are affected after cervical cancer treatment. However, it is important to be aware of the potential bias in this study. Therefore, larger-scale studies with balanced groups, including details of radiotherapy techniques, are needed to confirm these findings and establish valid comparisons between different subgroups.

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SUPPLEMENTARY

Supplementary Table 1. Baseline characteristics of respondents versus non-respondents.

Patient and tumour characteristics	Missing	Respondents (n=288)	Non-respondents (n=1,001)	p-value
Median age at diagnosis, years (IQR)	0 (0%)	45 (38-52)	45 (3-55)	0.14
Menopausal status, N (%)	784 (61%)			0.06
Pre		67 (54%)	246 (64%)	
Peri		3 (2%)	15 (4%)	
Post		53 (43%)	121 (32%)	
Socio-economic status	8 (1%)			0.37
Low		84 (29%)	335 (34%)	
Middle		80 (28%)	257 (26%)	
High		123 (43%)	402 (40%)	
FIGO 2009 stage	0 (0%)			0.78
IA1		0 (0%)	8 (1%)	
IA2		3 (1%)	14 (1%)	
IB1		178 (62%)	593 (59%)	
IB2		24 (8%)	90 (9%)	
IIA1		6 (2%)	32 (3%)	
IIA2		9 (3%)	28 (3%)	
IIB		68 (24%)	236 (24%)	
Median tumour diameter, mm	294 (23%)	26 (18-40)	26 (15-40)	0.27
Treatment characteristics				
Treatment strategy	0 (0%)			0.73
Radial hysterectomy		181 (63%)	642 (64%)	
Chemoradiotherapy		107 (37%)	359 (36%)	
Nodal examination	0 (0%)			0.84
Lymphadenectomy		95 (33%)	320 (32%)	
Debulking		191 (66%)	669 (67%)	
No examination		2 (1%)	12 (1%)	
Surgical approach [a]	38 (4%)			0.47
Open		122 (66%)	456 (69%)	
Laparoscopic		62 (34%)	204 (31%)	
Brachytherapy, yes	0 (0%)	112 (39%)	362 (36%)	0.41
Adjuvant treatment	0 (0%)			0.21
Chemoradiotherapy		2 (8%)	70 (7%)	
Radiotherapy		22 (8%)	75 (7%)	
Chemotherapy		2 (1%)	1 (0%)	
No		239 (83%)	855 (85%)	
Type of chemotherapy [b]	571 (57%)			0.09
Platinum based		126 (95%)	419 (42%)	
With paclitaxel		2 (2%)	5 (1%)	
With etoposide		3 (2%)	1 (0%)	
Other		2 (2%)	5 (1%)	
Cycles of chemotherapy [b]	704 (62%)	6 (6-6)	6 (6-6)	0.86

Abbreviations: *FIGO*, International Federation of Gynecology and Obstetrics; *IQR*, interquartile range.

[a] patients with surgery only.

[b] patients with chemo(radio)therapy only.

P-value based on Mann-Whitney U or Fisher's exact test. * statistically significant.

Supplementary Table 2. Raw scores of individual items for "symptom experience" of the EORTC QLQ-CX24 questionnaire per treatment group with multivariable linear regression analysis.

Items of the symptom scales	Missing	Radical hysterectomy n=181	Chemo-radiotherapy n=107				
	n	Mean (SD)	Mean (SD)	Mean difference	Coefficient	95% CI	p-value
Symptom experience	1 (0%)	1.4 (0.3)	1.4 (0.4)	0.1	0.1	0.0 ; 0.2	0.025*
Abdominal cramps	1 (0%)	1.6 (0.9)	1.7 (0.8)	0.1	0.2	0.0 ; 0.4	0.12
Bowel control	4 (1%)	1.2 (0.6)	1.5 (0.8)	0.2	0.2	0.1 ; 0.4	0.004*
Blood in stools	2 (1%)	1.1 (0.4)	1.1 (0.4)	0.1	0.1	0.0 ; 0.2	0.28
Frequent urinating	4 (1%)	1.8 (0.9)	2.0 (1.0)	0.2	0.2	0.0 ; 0.4	0.12
Pain/burning feeling when urinating	1 (0%)	1.1 (0.3)	1.1 (0.4)	0.0	0.0	-0.1 ; 0.1	0.54
Leaking of urine	1 (0%)	1.5 (0.8)	1.6 (0.8)	0.1	0.0	-0.1 ; 0.2	0.64
Bladder emptying difficulty	2 (1%)	1.5 (0.8)	1.3 (0.6)	0.1	-0.1	-0.3 ; 0.0	0.14
Lower back pain	3 (1%)	1.7 (0.9)	1.8 (0.9)	0.1	0.1	-0.1 ; 0.3	0.21
Vaginal/vulvar irritation/soreness	1 (0%)	1.3 (0.6)	1.4 (0.7)	0.1	0.1	-0.1 ; 0.3	0.24
Vaginal discharge	1 (0%)	1.2 (0.4)	1.3 (0.4)	0.1	0.1	0.0 ; 0.2	0.12
Abnormal vaginal bleeding	1 (0%)	1.0 (0.0)	1.1 (0.0)	0.1	0.1	0.0 ; 0.2	0.005*

Abbreviations: *SD*, standard deviation; *CI*, confidence interval. A higher score implies more symptoms/impairment. P-value based on multivariable linear regression analysis, adjusted for age, comorbidity and diagnosis to questionnaire interval.

* statistically significant.

Supplementary Table 3. Baseline characteristics for patients who received radical hysterectomy with adjuvant therapy or primary chemoradiotherapy.

Patient and tumour characteristics	Missing	Radical hysterectomy with adjuvant therapy (n=48)	Primary chemoradiotherapy (n=107)	p-value
Median age at diagnosis, years (IQR)	0 (0%)	45 (37-57)	47 (38-59)	0.52
Median age at questionnaire, years (IQR)	7 (5%)	49 (41-63)	52 (44-61)	0.58
Marital status, n (%) [a]	34 (22%)			0.43
Partner		24 (63%)	45 (54%)	
No partner		14 (37%)	38 (46%)	
Highest education level, n (%) [b]	2 (1%)			0.24
Low		4 (8%)	20 (19%)	
Medium		22 (46%)	44 (42%)	
High		22 (46%)	41 (39%)	
Number of comorbidities, n (%)	13 (8%)			0.032*
0		14 (33%)	34 (34%)	
1		8 (19%)	37 (37%)	
≥2		21 (49%)	28 (28%)	
Menopausal status, n (%)	84 (54%)			0.33
Pre		13 (59%)	20 (41%)	
Peri		0 (0%)	1 (2%)	
Post		9 (41%)	28 (57%)	
Working status, n (%)	8 (5%)			0.46
Yes		30 (63%)	68 (69%)	
No		18 (38%)	31 (31%)	
Diagnosis to questionnaire interval, years (IRQ)	0 (0%)	6 (4-8)	6 (4-8)	0.24

Socio-economic status	0 (0%)			0.60
Low		14 (29%)	25 (23%)	
Middle		16 (33%)	33 (31%)	
High		18 (38%)	49 (46%)	
FIGO 2009 stage	0 (0%)			<0.001*
IA2		0 (0%)	0 (0%)	
IB1		40 (83%)	17 (16%)	
IB2		4 (8%)	13 (12%)	
IIA1		3 (6%)	2 (2%)	
IIA2		0 (0%)	9 (8%)	
IIB		1 (2%)	66 (62%)	
Median tumour diameter, mm	53 (34%)	32 (21-40)	42 (30-50)	<0.001*
Treatment characteristics				
Nodal examination	0 (0%)			<0.001*
Lymphadenectomy		48 (100%)	11 (10%)	
Debulking		0 (0%)	2 (2%)	
No examination		0 (0%)	94 (88%)	
Surgical approach [c]	10 (16%)			1.00
Open		36 (75%)	3 (100%)	
Laparoscopic		12 (25%)	0 (0%)	

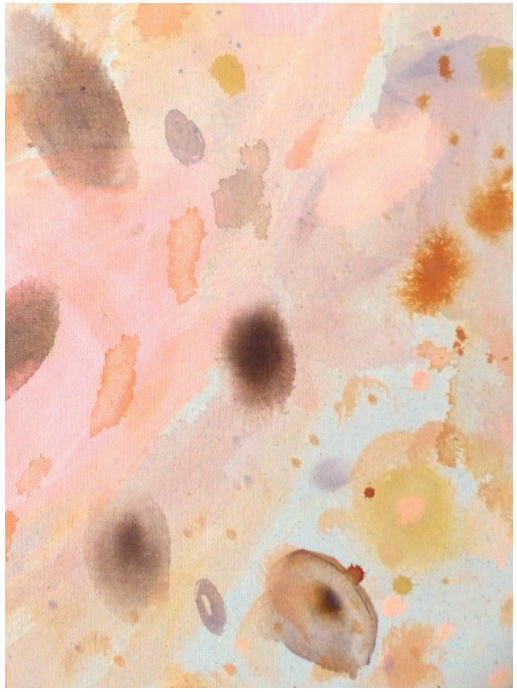
Abbreviations*: FIGO*, International Federation of Gynecology and Obstetrics; *IQR*, interquartile range.

[a] Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.

[b] Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.

[c] patients with surgery only.

P-value based on Mann-Whitney U or Fisher's exact test. * statistically significant.



Chapter 9

General discussion

The overall objective of this thesis is to contribute to improving the survival and quality of life of women with cervical cancer and lymph node metastases. Part I (**Chapters 2-4)** focuses on the detection of lymph node metastases and Part II (**Chapters 5-8)** on the treatment.

Box 1. Main findings of this thesis.

I.	Despite all the progress regarding pre-treatment prediction of lymph node metastases in cervical cancer in recent years, prediction models are not yet sufficiently robust to accurately assess the nodal status and safely abandon surgical staging for early stages.
II.	In clinically early-stage cervical cancer, pre-treatment imaging with MRI and the addition of [^{18}F]FDG-PET/CT to verify high-risk cases seems to be a good approach for lymph node staging.
III.	In the Dutch clinical practice, treatment planning based on [^{18}F]FDG-PET/CT is applied in 88% of patients with locally advanced cervical cancer and [^{18}F]FDG-positive lymph nodes, mainly consisting of nodal boosting (84%).
IV.	Presenting a patient's nodal status postoperatively by the number of positive nodes, or by the nodal ratio, can support further risk stratification regarding survival in the case of stage IIIC1p, which could be useful in decision making for adjuvant therapy.
V.	Radical hysterectomy with tailored adjuvant therapy and primary chemoradiotherapy seem equally effective in terms of survival, for patients with clinically early-stage cervical cancer and suspicious nodes on imaging, but have different toxicity profiles.
VI.	In patients with clinically early-stage cervical cancer and suspicious nodes on imaging, certain risk factors (i.e., lymphovascular space, depth of invasion ≥15 mm, tumours >4 cm on MRI, and a suspicious nodal status) may help to guide treatment decisions by identifying patients with a high likelihood of needing adjuvant therapy.
VII.	Primary chemoradiotherapy affects more domains of long-term health-related quality of life (HRQoL) than radical hysterectomy. In addition, primary chemoradiotherapy may not have a long-term HRQoL benefit compared with surgery followed by adjuvant (chemo)radiotherapy.
VIII.	In patients with locally advanced cervical cancer with suspicious bulky nodes, there is currently no evidence of a survival benefit for either nodal boosting or debulking strategies. However, nodal boosting may be associated with less toxicity than debulking.

Part I - Identification of lymph node metastases

The presence of lymph node metastases is a poor prognostic factor in cervical cancer.[1] It is associated with decreased survival and is therefore included as stage IIIC in the most recent FIGO 2018 classification system.[2, 3] Because of the prognostic significance, correct identification and appropriate treatment of lymph node metastases is crucial. In addition, patients can be spared unnecessary surgery or (chemo)radiotherapy if the nodal status can be correctly assessed prior to treatment.

Currently, nodal staging is primarily performed using computed tomography (CT) imaging, magnetic resonance imaging (MRI), and/or positron emission tomography plus computed tomography (PET-CT) using 2-deoxy-2-[^{18}F]fluoro-D-glucose as a tracer ([^{18}F]FDG-PET/CT).[4] Of these imaging techniques, diffusion-weighted (DW) MRI has the highest sensitivity (87%) and PET-CT the highest specificity (97%), according to the literature reviewed in **Chapter 2**.[5] However, most of these diagnostic indices are based on retrospective data that are limited to early-stage cervical cancer cases, as pathological results, which are considered the reference standard, are generally only available in this subset of patients. Pathological confirmation of lymph node metastases is often not available for advanced stages, as surgical staging is not standard practice in Europe.[6] In addition, patients eligible for radical surgery, but with a high likelihood of lymph node metastases based on imaging, are generally treated with primary chemoradiotherapy.[6]

Consequently, these patients are excluded from diagnostic accuracy studies, resulting in an unrepresentative study population with a lower prevalence of metastases. This is also known as partial verification bias and can lead to biased accuracy estimates.[7]

In **Chapter** 3, we studied the diagnostic accuracy of MRI, CT and PET-CT in clinically early-stage cervical cancer. We adjusted for verification bias by imputing missing pathological lymph node status for up to 30% of patients. As expected, this resulted in higher prevalences than the original rates. PET-CT outperformed MRI and CT with the highest area under the receiver operating characteristic curve, sensitivity and positive-predictive value (PPV). However, MRI was superior in terms of specificity and negative-predictive value. These results are applicable only in a setting where PET-CT is used as a verification modality, because 95% of the patients had MRI/CT and PET-CT.

Translated into clinical practice, PET-CT appears to be the appropriate modality to verify suspicious nodes on MRI or in the presence of other high-risk factors for lymph node metastases (e.g., large tumour size and elevated tumour markers). In cases with conflicting imaging results, there is still an increased risk of lymph node metastases if one of the modalities is positive (prevalence of nodal metastases 14-73%), especially if it concerns the PET-CT (58-73%). In clinically early-stage patients with double-negative results, the risk of lymph node metastases is much lower (15-19%), but not low enough to safely abandon surgical staging. Unfortunately, we do not have data to address the issue of inconclusive nodes. As this group was very small in our study, we do not know how diagnostic accuracy is affected by inconclusive results.

For all three imaging modalities, we found a lower accuracy in the common iliac region than in the pelvic region, which is consistent with previous findings.[8, 9] This is of concern because nodal involvement in the common iliac and para-aortic regions is associated with a poor prognosis and require extended-field radiotherapy.[6, 10, 11] However, whether patients without suspicious lymph nodes benefit from prophylactic extended-field (chemo)radiotherapy is still controversial and has mainly been studied in advanced-stage cervical cancer.[12, 13] Since inclusion of the para-aortic region as a radiotherapy target volume will also increase the volume of healthy organs at risk, field-extension may lead to increased toxicity and should be applied with caution. Current guidelines recommend extended-field radiotherapy for cases with ≥3 pelvic lymph node metastases, common iliac and/or para-aortic involvement, according to current guidelines following the EMBRACE protocol.[6, 14, 15]

In locally advanced cervical cancer, the diagnostic accuracy of imaging for nodal staging is higher than in early-stages, particularly the sensitivity, with superiority for PET-CT.[5, 16] Therefore, current guidelines recommend the use of PET-CT to guide treatment planning in locally advanced cervical cancer, especially for radiotherapy field settings.[6, 15] However, in **Chapter 4**, we estimated that in daily clinical practice in the Netherlands, almost one-third of patients may be at risk of toxicity from extended-field radiotherapy for no benefit. For this reason, extending the volume of radiotherapy based on PET-CT alone should be done very cautiously. Especially for those with a low likelihood of metastasis (e.g., lower stage, smaller tumour size, no lymphovascular space invasion), as the PPV will be lower and therefore the risk of overtreatment by targeting false-positive nodes will be higher.[9]

Pathological confirmation of suspicious nodes may improve tailored treatment and thereby reduce toxicity. Currently, the PARa-aOrtic LymphAdenectomy (PAROLA) trial is open for accrual, comparing the effect of para-aortic surgical staging with staging by PET-CT, on recurrence in patients with locally advanced cervical cancer and suspicious pelvic lymph nodes, but without suspicious common iliac or para-aortic nodes.[17] Possible disadvantages of surgical staging are delayed radiotherapy, increased morbidity due to the accumulation of surgical and radiotherapy-related toxicity, and increased radiotherapy toxicity due to organ adhesion. To date, there is no unequivocal evidence in favour of surgical para-aortic staging in terms of survival or toxicity.[18] The UTERUS-11 randomized controlled trial showed no difference in disease-free survival between surgical and clinical (MRI/CT) staging in patients with locally-advanced cervical cancer, despite upstaging in 33% of patients.[19] However, developments in recent years, such as the use of minimally invasive surgery and more advanced radiotherapy and imaging techniques, both of which result in less morbidity, warrant updated research on this topic.

Our study of nodal treatment for [^{18}F]FDG-positive nodes was restricted to nodal boosting, extended-field radiotherapy and nodal debulking, as these strategies are recommended by the guidelines.[6, 15] However, other strategies may be considered, including neoadjuvant or adjuvant chemotherapy combined with primary chemoradiotherapy or radiotherapy combined with deep hyperthermia.[20-22] The results of these approaches do not provide compelling evidence of a survival benefit and suggest an increased risk of therapy-related toxicity. Furthermore, it would have been interesting to conduct a comparative analysis of survival and toxicity rates among patients who underwent nodal treatment versus those who did not, in addition to our analysis on treatment rates. However, conducting such an analysis posed challenges, as our study would have been underpowered. Moreover, adjustment for baseline characteristics would have been necessary, due to notable differences between the two groups in terms of nodal size, tumour size and para-aortic region involvement.

Part II - Treatment of lymph node metastases

The group of patients with FIGO 2018 stage IIIC is very heterogeneous in terms of prognosis. Five-year survival rates vary from 39% to 75% within the group of patients with stage IIIC1 disease, due to local tumour factors such as size and extension and histological type.[23] This argues for a more tailored approach in the management of FIGO stage IIIC cervical cancer, rather than a one-size-fits-all strategy. In addition to tailoring treatment decisions, the integration of health-related quality of life (HRQoL) outcomes alongside survival considerations is becoming increasingly important in shared decision making.

In **Chapter 5**, we explored the use of two prognostic parameters, “the number of positive nodes” and “the lymph node ratio”, for further risk stratification of FIGO stage IIIC1 patients after radical hysterectomy with lymphadenectomy. Adjuvant therapy may be less intensive (radiotherapy or chemotherapy only) in patients with a good prognosis, to reduce toxicity, or more intensive (chemoradiotherapy followed by chemotherapy) in patients with a poor prognosis (e.g., ≥4 nodal metastases and a ratio of ≥0.177) to improve survival. These considerations are consistent with some of the ideas put forward by Monk et al. (2005). They suggested that radiotherapy alone may be sufficient for women with one positive node.[24] However, before both parameters can be used for risk stratification in clinical practice, external validation is warranted.

Looking forward, an important question is whether these prognostic parameters remain relevant with the advent of sentinel lymph node staging. Nevertheless, the eligibility criteria for sentinel lymph node mapping apply to smaller tumours, <4 cm and preferably <2 cm, with no suspicion of lymph node involvement on pretreatment imaging.[6, 25] Consequently, patients with larger tumours or those with inconclusive/suspicious nodes will still require staging by lymphadenectomy, even if sentinel lymph node mapping becomes part of standard practice in the future. In addition, the prevalence of lymph node metastases is higher in patients with larger tumours.[26-28] Therefore, the number of metastases and its ratio may be particularly useful for certain high-risk patient groups.

For patients with clinically early-stage cervical cancer and suspicious lymph nodes on imaging, one may proceed with surgical treatment because of the risk of false-positive lymph nodes, or switch to primary chemoradiotherapy.[6, 15, 25] Offering primary chemoradiotherapy to all patients with suspicious nodes may be too simplistic, as this strategy may unnecessarily deny surgical treatment to some patients, because of the risk of false-positive suspicious nodes. We demonstrated this in Chapter 3, with PPV’s of 66% for MRI and of 76% after validation with PET-CT. Moreover, in **Chapter 6**, we found that only 43% of the surgically treated patients with suspicious nodes on pretreatment imaging had metastases and that only 54% required adjuvant therapy. In line with previous studies, we concluded that shared decision making is the best approach, as radical hysterectomy (± adjuvant therapy) and primary chemoradiotherapy were equally effective in terms of survival, but had different toxicity profiles: short-term surgery-related versus long-term chemoradiotherapy-related toxicities.[29]

However, if patients require adjuvant therapy, they may suffer more toxicity due to the accumulation of surgical and (chemo)radiotherapy-related toxicities, as we have demonstrated in our research. One strategy to reduce the risk of multimodality treatment is to improve patient selection for radical surgery based on preoperative clinicopathological characteristics. Patients with suspicious nodes and lymphovascular space invasion, depth of invasion ≥15 mm or tumours >4 cm on MRI are more likely to require multimodality treatment and could therefore be used to guide treatment decisions towards primary chemoradiotherapy. Unfortunately, we were not able to assess whether and how these different toxicity-profiles affect the HRQoL after both treatment strategies.

In **Chapter 8** we addressed the impact of radical hysterectomy and primary chemoradiotherapy on long-term HRQoL and sexual functioning and short-term toxicity in patients with FIGO (2009) stage I-II. In this study, HRQoL outcomes were generally more favourable after surgery, except for lymphedema, which was more common after surgery. With the advent of sentinel lymph node staging, the prevalence of lymphedema after surgery will hopefully decrease. This has been demonstrated by the multicentre randomised trial (SENTICOL-2).[30] In contrast, another prospective study (SENTIX), although observational and without a control group, found no evidence of reduced lymphedema after sentinel lymph node staging.[31]

Our findings in Chapter 8 are particularly relevant for certain patient groups who are candidates for both treatment strategies. For example, those with clinically early disease and suspicious nodes, as reviewed in chapter 6, or those with a high likelihood of pathological risk factors or with intraoperative evidence of lymph node metastases. Patients who are likely to be adequately treated with surgery alone

may be advised to have surgery, rather than primary chemoradiotherapy, on the basis of HRQoL outcomes. For those with a high likelihood of needing adjuvant therapy, counselling seems to be the best approach. Our exploratory analysis of HRQoL and toxicity after surgery with adjuvant therapy and after primary chemoradiotherapy showed no superiority for either strategy, with better sexual activity, but worse lymphedema after adjuvant therapy. These findings challenge the recommendation in the European guideline, which advocates primary chemoradiotherapy for these patients. To the best of our knowledge, this recommendation is not based on solid evidence, from a small number of studies only, with heterogeneous patient and treatment characteristics.[32-34]

Because the majority of cervical cancer patients are relatively young and have a good prognosis, a substantial group of survivors will potentially experience long-term treatment-related morbidity. This highlights the importance of addressing HRQoL in counselling, even though most patients prioritise survival.[35] Still, providing accurate information can improve HRQoL, since well-informed patients tend to cope better with the disease and its consequences.[36] Therefore, this study may contribute to improve HRQoL.

The literature on bulky nodes is scarce, with low levels of evidence. Patients with locally advanced cervical cancer and bulky nodes (short-axis ≥1.5 cm) may be offered boosting, debulking, or neither form of nodal treatment, in addition to standard primary chemoradiotherapy. We found no superiority of any of the three strategies in terms of survival (**Chapter 7**). However, caution is needed in interpreting these results. For example, because of the absence of pathological confirmation of lymph node metastasis in the boosting group and in those without additional nodal treatment. Unfortunately, there are no other studies that, directly compared survival or toxicity after boosting or debulking. Some studies have shown effective nodal control by boosting in patients with suspicious nodes on imaging,[37-41] while others have shown improved survival after nodal debulking.[42-45]

In addition, we found that boosting may be associated with less toxicity than nodal debulking. This is an unexpected finding that challenges the concept that debulking nodal tumour load (1) increases the chance of complete sterilisation by chemoradiation, and (2) reduces toxicity by avoiding or minimising boosting doses. However, half of the debulked patients still received a nodal boost. In addition, the extensive nature of most of our debulking procedures should be taken into account, as half were combined with lymphadenectomy and the majority were performed through an open approach. This may also have contributed to the relatively high toxicity rates observed after debulking.

This thesis is mainly based on data from the Netherlands Cancer Registry (NCR), a nationwide population-based registry of all newly diagnosed malignancies in the Netherlands. Our studies with real-world data provide insights into daily clinical practice and a more comprehensive view of characteristics, treatment strategies and realistic survival outcomes. These findings complement randomised controlled trials and help to fill knowledge gaps. While randomised controlled trials provide the highest level of evidence, they have limitations, including their time-consuming nature, limited generalisability and focus on the intervention itself, often not addressing real-world implementation challenges. However, it is important to recognise that our studies are retrospective in design and therefore prone to bias due to confounding

factors. To reduce this bias, we used methods such as multivariable analysis and inverse probability treatment weighting.

Our results are applicable to modern clinical practice, assuming the availability of advanced imaging and radiotherapy techniques. Therefore, our results are not always generalisable, especially not to low- and middle-income countries that do not have access to these advanced facilities. Unfortunately, these countries have the highest incidence of cervical cancer.[46] Nevertheless, in line with the aims of this thesis, our findings may contribute to improving survival and HRQoL of patients with lymph node metastases when treated according to standards in high-income countries.

Box 2. Future perspectives: seven steps towards a tailored approach for lymph node metastases in cervical cancer.

I.	More accurate identification of lymph node metastases prior to treatment may potentially be achieved by using more advanced imaging techniques with radiomics, complemented by multiple clinicopathological risk factors and biomarkers for nodal metastases, all combined in nomograms.
II.	The use of more advanced imaging techniques such as diffusion-weighted (DW)-MRI, may hold the potential to increase the sensitivity of nodal staging and reduce the need for verification by [^{18}F]FDG-PET-CT.
III.	Reduction of inappropriate treatment planning can be achieved by improving the suboptimal negative and positive predictive values of [^{18}F]FDG-PET-CT for nodal staging, for example by using artificial intelligence, nomograms, or by pathological confirmation of [^{18}F]FDG-positive nodes.
IV.	The number of positive nodes (≥4) and the nodal ratio (≥0.177) holds potential as prognostic parameters for FIGO stage IIIC1p after radical hysterectomy with pelvic lymphadenectomy to better inform patients and tailor treatment strategies and follow-up.
V.	Accurate counselling on toxicity profiles and HRQoL with shared decision making seems to be the best approach for some patients eligible for radical hysterectomy and primary chemoradiotherapy.
VI.	Future treatment options with more advanced (radio)therapy techniques and less extensive surgery may reduce therapy-related toxicity and improve HRQoL for cervical cancer survivors.
VII.	Improving survival in patients with locally-advanced cervical cancer and bulky nodes may be achieved by strategies that reduce distant recurrence, such as targeted therapy, in addition to achieving local control by boosting or debulking, as most recurrences involve distant metastases.

Future perspectives

It is widely assumed that global human papillomavirus (HPV) vaccination will reduce HPV-related cervical cancer incidence and mortality in the future.[47] However, despite the introduction of nationwide HPV vaccination, the cervical cancer incidence in the Netherlands has increased over the past decade, as described in Chapter 1. This unexpected development is not yet fully understood, but underlines the continuing need for better diagnosis and treatment of cervical cancer. The accuracy of the diagnosis of lymph node involvement in cervical cancer can, for example, be achieved by developing validated nomograms that combine clinicopathological risk factors, biomarkers and radiomics. In addition, investigating the impact of advanced imaging techniques such as DW-MRI, AI-enhanced imaging, and cancer-specific imaging agents, along with supporting staging through pathological verification strategies like fine-needle biopsy or surgical staging, could yield valuable insights.[5, 17, 48, 49] For now, treatment decisions should be weighted based on survival benefit versus morbidity, taking into account the risk of false-positive and false-negative results regarding the lymph node status.

Regarding future perspectives in therapy for early-stage cervical cancer, where mortality is generally low, research is focussing on reducing treatment-related morbidity without compromising

survival. This includes efforts to reduce the radicality of surgical treatment (SHAPE-trial)[50], exploring minimally invasive robotic surgery (RACC-trial)[51], and investigating sentinel lymph node mapping (SENTIX/SENTICOL III).[52, 53] One-step nucleic acid amplification (OSNA) appears to be a promising tool to improve intraoperative metastasis detection, as only half of nodal metastases are currently detected by frozen section.[54, 55] In addition, it may be interesting to explore the possibilities of sentinel lymph node mapping in patients with suspicious nodes on imaging.[25] Notably, although the sentinel lymph node procedure is more accurate than MRI (pooled sensitivity 91% and specificity 100%), it is still an invasive procedure.[16].

Significant progress has been made in improving survival and reducing morbidity in women with locally advanced cervical cancer, for example with the transition from two-dimensional to image-guided three-dimensional radiotherapy. Ongoing advances aim to further enhance precision and minimise damage to surrounding tissues.[56] Furthermore, immunotherapy is emerging and offers potential benefits, as evidenced by the preliminary results of the phase 3 KEYNOTE-A18 trial, where pembrolizumab in combination with chemoradiotherapy improved progression-free survival.[57] This trial enrolled high-risk, locally advanced cervical cancer patients, including those with lymph node involvement. Another ongoing trial is investigating the effectiveness of chemotherapy prior to chemoradiotherapy in patients with locally advanced cervical cancer, offering hope for those with lymph node metastases.[58]

To conclude, the chase on lymph node metastases in cervical cancer is challenged by the current limitations in accurate pre-treatment non-invasive nodal staging. Although the chase is not over, we are making progress and ongoing developments hold promise for improvement. By integrating a more tailored treatment approach, reduced toxicity and improved HRQoL without compromising survival may be achieved for future patients with lymph node metastases.

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Chapter 10

Summary

Summary

Uterine cervical cancer is one of the most common cancers in women worldwide, affecting women at a relatively young age. Focusing on lymph node metastasis can be a good strategy, as lymph node involvement is one of the most important prognostic factors in cervical cancer. Accurate identification and management of lymph node metastases may improve survival and health-related quality of life (HRQoL), raising the question: chasing nodes, saving lives? This thesis aimed to answer that question by evaluating the accuracy of diagnosis and tailoring of treatment in patients with suspicious or proven lymph node metastases.

In **Chapter 2** we summarised the available literature on the pre-treatment identification of lymph node metastases in cervical cancer. The incidence of nodal metastases in the pelvic region increases from 2% (stage IA2) to 14–36% (IB), 38–51% (IIA) and 47% (IIB) per International Federation of Gynaecology and Obstetrics (FIGO) stage 2009. In the para-aortic region, metastases were reported in 2–5% (stage IB), 10–20% (IIA), 9% (IIB), 13–30% (III) and 50% (IV) of patients. These percentages should be interpreted with caution, as most of the studies were retrospective and involved a small number of patients. The most common sites of nodal metastases in stage IA–IIB cervical cancer were the obturator region (45%) and the internal and external iliac regions (32%).

Age, tumour size, FIGO stage, tumour grade, lymphovascular space invasion, stromal invasion and parametrial invasion were reported to be independent prognostic risk factors of nodal metastases. In addition, elevated levels of the biomarker 'squamous cell carcinoma antigen (SCC)' were found to be associated with a higher likelihood of positive lymph nodes, although this was not sufficient enough to make a reliable diagnosis. Currently, pre-treatment lymph node assessment is mainly performed by imaging, of which diffusion-weighted magnetic resonance imaging (DW-MRI) has the highest sensitivity (87%) and 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission computed tomography ([^{18}F]FDG-PET/CT) the highest specificity (97%). Potentially, all these parameters can be combined in statistical models to predict the risk of lymph node metastasis in cervical cancer, also known as nomograms or prediction models. Several nomograms have been developed, of which the addition of radiomics seems to have the most potential. Currently, all of these non-invasive tools can help to tailor treatment decisions, but they do not reach the accuracy of surgical staging or biopsy confirmations yet.

Most of the literature reviewed in Chapter 2 on the diagnostic performance of imaging modalities in the detection of lymph node metastases was based on outdated retrospective data, with a high risk of verification bias. Therefore, in **Chapter 3**, we presented the diagnostic indices of MRI, CT and [^{18}F]FDG-PET/CT for lymph node metastases in clinical early-stage cervical cancer based on a more recent and larger cohort of patients (n=2,236), while taking into account the risk of partial verification bias by imputing the missing pathological nodal status in 30% of patients. PET-CT outperformed MRI and CT in terms of area under the receiver operating curve (0.803 vs. 0.705 and 0.656), sensitivity (77% vs. 47% and 37%), and positive-predictive value (76% vs. 66% and 64%), respectively. This may be related to its use as a verification modality, as PET-CT was used to confirm MRI/CT results in 95% of patients. However, MRI

and CT had the highest specificity (both 92% vs. 79%). The accuracy of all three modalities was lower in the common iliac than the pelvic region, especially regarding sensitivity.

In addition, there may be a significant risk of nodal involvement in the case of multiple imaging with at least one positive result, particularly a positive PET-CT. Based on our results, we believe that MRI may be the preferred imaging modality for pretreatment of staging cervical cancer patients by accurately excluding patients without nodal metastases, next to determining tumour size and local spread. PET-CT may be added in patients with suspicious nodes on MRI or in patients at high risk of nodal metastases (e.g., large tumour size and elevated tumour markers). Finally, accounting for partial verification bias increased almost all diagnostic indices, suggesting that diagnostic performance may have been underestimated in previous studies based on retrospective data.

[^{18}F]FDG-PET/CT is recommended by modern treatment guidelines for women with advanced cervical cancer. However, the risk of false-positive nodes and therapy-related adverse events requires caution in treatment planning. In **Chapter 4**, we reviewed 434 patients with advanced-stage cervical cancer and [^{18}F]FDG-positive nodes and showed that treatment strategies were guided by PET-CT in 88% of patients. Among these strategies, nodal boosting was the predominant intervention (84%) for managing FDG-positive nodes, followed by extended-field radiotherapy (78%) and debulking (12%).

Despite existing guidelines advocating PET-CT-guided treatment planning for the management of advanced cervical cancer, this study shows that not all cases of FDG-positive nodes received an intervention. This raises the question whether these patients were undertreated, which may reduce survival, or whether nodal treatment was withheld to avoid overtreatment. We concluded that nodal treatment for FDG-positive lymph nodes should be weighed and discussed for each individual patient in terms of the risk of false-positivity/negativity, morbidity and survival benefit.

The postoperative lymph node status is currently presented as FIGO (2018) stage IIIC1p, which represents a prognostic heterogenous group with a 5-year overall survival rate ranging from 47% to 83%. Therefore, representation of a patient's nodal status by the number of lymph node metastases (nLNM) and the lymph node ratio (LNR) might be of additional value compared with only indicating the presence or absence of lymph node metastases. In **Chapter 5**, we showed that both parameters are independently associated with impaired survival, using ≥4 nodal metastases and a ratio of ≥0.177 as optimal cut-offs. Despite the potential benefit of LNR, by taking into account not only the number of positive nodes, but also the extent of lymphadenectomy, both parameters had similar prognostic performances. Nevertheless, external validation of nLNM and LNR in multiple, disparate data sets should be obtained first, before implementation in clinical practice is possible, especially regarding the cut-off values for low-risk and high-risk groups.

Because of the negative prognostic impact of lymph node metastasis and the increasing role of imaging in staging, we studied cervical cancer patients with inconclusive/suspicious lymph nodes on pretreatment imaging in **Chapter 6**. In this study, we compared the oncological outcome and therapy-related morbidity after radical hysterectomy (n=131; 40%) and chemoradiotherapy (n=199; 60%) for FIGO (2009) stage IA-IIA cervical cancer. After surgery, only 43% of patients had metastases and 54% of patients received adjuvant therapy.

The chemoradiotherapy patients more often had poor prognostic characteristics and, therefore, a worse survival outcome. However, after adjustment for confounders by inverse probability treatment weighting, the recurrence-free survival (HR 0.67; 95% CI 0.34-1.31) and overall survival (HR 0.75; 95% CI 0.38-1.47) were not significantly different between the surgery and chemoradiotherapy groups. Radical hysterectomy was associated with more toxicity as a result of postoperative complications and the addition of adjuvant treatment (OR 2.82; 95% CI 1.42-5.60). Therefore, we identified several preoperative clinicopathologic characteristics to select patients at risk for multimodality treatment. Taken together, as both strategies yielded comparable survival rates and were associated with different toxicity profiles, shared decision-making should be the approach for patients with suspicious nodes.

In **Chapter 7**, we directly compared treatment strategies for bulky lymph nodes in patients with locally advanced cervical cancer scheduled for definitive (chemo)radiotherapy. This study included 190 patients with locally advanced cervical cancer and lymph nodes ≥1.5 cm on pretreatment imaging. All patients were treated with definitive (chemo)radiotherapy and categorised according to intention-to-treat strategy: 101 (53%) patients received only nodal boosting, 31 (16%) only debulking, 29 (15%) debulking combined with boosting, and 29 (15%) received neither treatment. We were unable to demonstrate superiority of any of these treatment strategies in terms of overall or relapse-free survival. In addition, reducing tumour load by nodal debulking may increase the risk of toxicity compared with nodal boosting. As there is no clear definition of bulky nodes, we performed a subgroup analysis for bulky nodes ≥2 cm. This analysis showed similar survival results, although the sample size is too small to draw firm conclusions.

The subgroup analysis for debulking with or without boosting showed that dual treatment with debulking and boosting was independently associated with a worse survival outcome compared with only debulking. This is most likely related to the selection of eligible patients for dual therapy, a subgroup with poor prognostic factors. As neither of both strategies is superior to survival, shared decision-making and individualised treatment seem to be the best approach for patients with bulky nodes. However, our results must be interpreted with caution due to our retrospective study design. Despite its limitations, this study represents the largest cohort of patients comparing different treatment strategies for bulky nodes in locally advanced cervical cancer and therefore adds valuable information to the existing literature.

Patients who are well informed about treatment-related morbidity have been shown to cope better with the disease and its consequences. Therefore, it is valuable to be able to provide accurate information during counselling and thereby improve HRQoL. In **Chapter 8** we evaluated and compared the long-term HRQoL and short-term toxicity in cervical cancer survivors after the two main treatment strategies: radical hysterectomy and pelvic lymphadenectomy versus primary chemoradiotherapy, using results from the population-based PROFILES registry. Women who received chemoradiotherapy (n=107; 37%) reported significantly worse functioning (role, cognitive and social) and more symptoms (fatigue, financial problems, symptom experience, neuropathy, sexual activity, and sexual functioning) than those receiving surgery (n=181; 63%). On the other hand, lymphedema was more common after surgery.

Adjuvant therapy was administered in 27% of patients; these women reported more sexual activity but also more lymphedema than those with primary chemoradiotherapy, while other HRQoL scales were comparable. Although toxicity profiles differed between treatment groups, overall toxicity rates did not. In

addition, experiencing short-term toxicity was negatively associated with several long-term HRQoL outcomes, irrespective of treatment. This information may support treatment counselling and increase awareness of HRQoL domains impaired after cervical cancer treatment. However, prospective studies are needed to confirm these findings.

In conclusion, chasing nodes can save lives! However, improvements in the accuracy of nodal staging should continue in order to tailor treatment strategies and ultimately increase survival and health-related quality of life.

Samenvatting

Baarmoederhalskanker is wereldwijd een van de meest voorkomende vormen van kanker bij vrouwen en treft hen meestal op relatief jonge leeftijd. Een van de belangrijkste prognostische factoren bij baarmoederhalskanker is de aanwezigheid van lymfekliermetastasen. Het zo goed mogelijk opsporen van lymfekliermetastasen is belangrijk voor het bepalen van de beste behandelstrategie van patiënten met baarmoederhalskanker. De centrale vraag van dit proefschrift is dan ook “chasing nodes, saving lives?” Dit proefschrift beoogde die vraag te beantwoorden door de diagnostiek en de behandeling van patiënten met (verdenking op) lymfekliermetastasen te evalueren.

In **Hoofdstuk 2** hebben we de beschikbare literatuur samengevat over de opsporing van lymfekliermetastasen bij baarmoederhalskanker voorafgaand aan de behandeling. Dit hoofdstuk laat zien dat de incidentie van pathologisch bevestigde lymfekliermetastasen in het bekken toeneemt met het stadium volgens de Fédération internationale de Gynécologie et d'Obstétrique (FIGO 2009), van 2% (stadium IA2) naar 14-36% (IB), 38-51% (IIA) en 47% (IIB). Eenzelfde beeld wordt gezien in de para-aortale regio, waarbij metastasen gerapporteerd werden in 2-5% (stadium IB), 10-20% (IIA), 9% (IIB), 13-30% (III) en 50% (IV) van de patiënten. Deze percentages dienen met enige voorzichtigheid te worden geïnterpreteerd, omdat de meeste studies retrospectief en relatief klein waren. De meest voorkomende locaties van lymfekliermetastasen bij baarmoederhalskanker in stadium IA-IIB blijken de obturatorius regio (45%) en de interne en externe iliacale regio’s (beiden 32%).

Factoren zoals leeftijd, tumorgrootte, FIGO-stadium, tumorgraad, lymfangio-invasie, stromale invasie en parametriuminvasie zijn beschreven als onafhankelijke prognostische risicofactoren voor de aanwezigheid van lymfekliermetastasen. Ook lijken verhoogde waardes van de biomarker 'squameus cel carcinoom antigeen (SCC)' geassocieerd met een verhoogde kans op positieve lymfeklieren, alhoewel deze associatie onvoldoende sterk was voor een betrouwbare diagnose. Voor aanvang van de behandeling worden lymfekliermetastasen momenteel opgespoord middels radiologische beeldvorming, waarbij diffusie-gewogen magnetische resonantiebeeldvorming (DW-MRI) de hoogste sensitiviteit heeft (87%) en 2-deoxy-2-[^{18}F]fluoro-D-glucose-positronemissietomografie ([^{18}F]FDG-PET/CT) de hoogste specificiteit (97%). Potentieel zijn alle hierboven beschreven parameters te combineren in statistische modellen, zoals nomogrammen of predictiemodellen, om het risico op lymfekliermetastasering bij baarmoederhalskanker te voorspellen. De nomogrammen en modellen met radiomics lijken de meeste potentie te hebben. Deze niet-invasieve tools kunnen helpen bij het individualiseren van behandelplannen, maar bereiken momenteel nog niet de nauwkeurigheid van chirurgische stadiëring of bevestiging van metastasen middels histologische biopten.

Het merendeel van de literatuur besproken in Hoofdstuk 2, over de diagnostische nauwkeurigheid van beeldvorming bij de detectie van lymfekliermetastasen, is gebaseerd op verouderde, retrospectieve data met een hoog risico op verificatiebias. Daarom zijn in **Hoofdstuk 3** de diagnostische indices onderzocht van MRI, CT en [^{18}F]FDG-PET/CT voor lymfekliermetastasen bij een klinisch vroeg stadium baarmoederhalskanker op basis van een recenter en groter patiënten cohort (n=2.236). Hierbij is geprobeerd om het risico op partiële verificatiebias te verminderen door het imputeren van ontbrekende

pathologische lymfeklierstatus bij 30% van de patiënten. PET-CT presteerde beter dan MRI en CT uitgedrukt in de oppervlakte onder de ‘receiver operating characteristic (ROC) curve’ (respectievelijk 0,803 vs. 0,705 en 0,656), de sensitiviteit (77% vs. 47% en 37%) en de positief voorspellende waarde (PPV; 76% vs. 66% en 64%). Dit gunstige resultaat van PET-CT is mogelijk toe te schrijven aan het gebruik van PET-CT als verificatiemodaliteit, omdat PET-CT bij 95% van de patiënten is gebruikt om de door MRI/CT verkregen resultaten te bevestigen. Echter, MRI en CT hadden de hoogste specificiteit (beide 92% vs. 79%). De nauwkeurigheid van alle drie de vormen van beeldvorming was lager in de iliaca communis regio dan in het bekken, vooral met betrekking tot de sensitiviteit.

Indien er meerdere vormen van beeldvorming zijn verricht, lijkt het risico op lymfekliermetastasen significant hoger te zijn als ten minste een van de modaliteiten positief is, met name een positieve PET-CT. Onze aanbeveling is om baarmoederhalskankerpatiënten voorafgaand aan de behandeling te stadiëren met behulp van (bij voorkeur) MRI. MRI wordt toegepast voor het initieel beoordelen van tumorgrootte en lokale uitbreiding en kan daarbij ook gebruikt worden om lymfekliermetastasen uit te sluiten. PET-CT kan dan worden toegevoegd bij patiënten met verdachte klieren op MRI of bij patiënten met een hoog risico op lymfekliermetastasen, zoals bij een grote tumor en verhoogde tumormarkers. Ten slotte leidde de correctie voor partiële verificatiebias dankzij imputeren tot lichte verbeteringen van enkele diagnostische indexen, wat suggereert dat de diagnostische prestaties van bovenstaande beeldvormingsmethoden op basis van retrospectieve gegevens in eerdere studies mogelijk zijn onderschat.

Het gebruik van [^{18}F]FDG-PET/CT wordt in de huidige behandelrichtlijnen aanbevolen voor vrouwen met gevorderde baarmoederhalskanker voor het plannen van de behandeling. Voorzichtigheid is echter geboden bij de therapieplanning, gezien de risico's van fout-positieve lymfeklieren en van therapie-gerelateerde bijwerkingen. In **Hoofdstuk 4** zijn 434 patiënten met lokaal-gevorderde baarmoederhalskanker en [^{18}F]FDG-positieve lymfeklieren onderzocht. Hierbij is geconstateerd dat PET-CT uitslagen in 88% de doorslag gaven bij het vaststellen van de behandelingsstrategie. Van deze strategieën was boost-bestraling de meest voorkomende interventie (84%) voor de behandeling van FDG-positieve klieren, gevolgd door bestraling met een uitgebreid veld richting de para-aortale regio (78%) en klierdebulking (12%).

Ondanks dat bestaande richtlijnen gebruik van de PET-CT aanbevelen voor de planning van de behandeling voor lokaal-gevorderde baarmoederhalskanker, lijkt dit niet altijd te worden toegepast. Dit roept de vraag op of deze patiënten mogelijk zijn onderbehandeld met misschien een slechtere overleving. Een andere mogelijkheid is dat de behandeling van FDG-positieve klieren met opzet uitbleef om overbehandeling en/of therapie-gerelateerde toxiciteit te voorkomen, gezien het risico op fout-positieve resultaten. We concludeerden dat de behandeling van FDG-positieve lymfeklieren voor elke individuele patiënt moet worden afgewogen en besproken op basis van het risico op fout-positieve of fout-negatieve resultaten, de te verwachten morbiditeit en de potentiële overlevingswinst.

De postoperatieve lymfeklierstatus wordt, sinds de invoering van de meest recente FIGO-classificatie in 2018, beschouwd als stadium IIIC1p. Dit is een prognostisch heterogene groep met een 5-jaarsoverleving variërend van 47% tot 83%. Het weergeven van de lymfklierstatus kan op verschillende manieren. Alleen

de af- of aanwezigheid van lymfekliermetastasen kan worden vastgelegd, maar daarnaast kunnen ook het aantal lymfekliermetastasen (nLKM) of de lymfklierratio (rLKM), de verhouding tussen het aantal positieve klieren en het totaal aantal klieren, worden vastgesteld. Het vastleggen van de nLKM en rLKM kan van prognostisch toegevoegde waarde zijn naast het bepalen van alleen de aan- of afwezigheid van lymfekliermetastasen.

In **Hoofdstuk 5** toonden we aan dat zowel nLKM als rLKM, naast het histologisch subtype, onafhankelijk geassocieerd zijn met verminderde overleving, met ≥4 lymfekliermetastasen en een ratio van ≥0.177 als optimale afkapwaardes. Ondanks het potentiële voordeel van de rLKM, waarbij niet alleen rekening wordt gehouden met het aantal positieve lymfeklieren, maar ook met de omvang van de lymfadenectomie, hadden beide parameters vergelijkbare prognostische prestaties. Toch is het nodig om eerst externe validatie in diverse, onafhankelijke datasets uit te voeren voor nLKM en rLKM standaard in de klinische praktijk te gebruiken, vooral om de optimale afkapwaarde tussen laag- en hoog-risicogroepen beter vast te stellen.

Vanwege de negatieve prognostische impact van lymfekliermetastasen en de toenemende rol van beeldvorming in de stadiëring, zijn in **Hoofdstuk 6** patiënten met baarmoederhalskanker en inconclusieve of verdachte lymfeklieren op beeldvorming voorafgaand aan de behandeling onderzocht. Deze studie vergeleek de oncologische uitkomst en therapie-gerelateerde morbiditeit na radicale hysterectomie (n=131; 40%) en primair chemoradiotherapie (n=199; 60%) voor FIGO (2009) stadium IA-IIA baarmoederhalskanker. Na de operatie had slechts 43% van de patiënten metastasen en 54% van de patiënten kreeg adjuvante behandeling. De chemoradiotherapie-groep had vaker slechte prognostische kenmerken en daardoor een slechtere overleving. Echter, na correctie voor confounders middels *inverse probability treatment weighting* waren de ziektevrije overleving (HR 0,67; 95% CI 0,34-1,31) en de algehele overleving (HR 0,75; 95% CI 0,38-1,47) niet verschillend tussen de chirurgie- en chemoradiotherapie-groepen. Radicale hysterectomie was geassocieerd met meer kortetermijn-toxiciteit door postoperatieve complicaties en de toevoeging van adjuvante behandeling (OR 2,82; 95% CI 1,42-5,60). Kortom, aangezien beide strategieën vergelijkbare overlevingskansen geven en geassocieerd zijn met verschillende toxiciteitsprofielen, lijkt gedeelde besluitvorming de benadering te zijn voor patiënten met op beeldvorming verdachte lymfeklieren.

In **Hoofdstuk 7** zijn behandelingsstrategieën vergeleken voor bulky lymfeklieren bij patiënten met lokaal gevorderde baarmoederhalskanker die werden behandeld met definitieve (chemo)radiotherapie. In deze studie includeerden we 190 patiënten met lymfeklieren ≥1,5 cm op beeldvorming voorafgaand aan de behandeling. Alle met definitieve (chemo)radiotherapie behandelde patiënten werden gecategoriseerd op basis van de beoogde behandelstrategie: 101 (53%) patiënten kregen lymfeklier boost-bestraling, 31 (16%) lymfklierdebulking, 29 (15%) debulking gecombineerd met boost-bestraling, en 29 (15%) kregen geen van deze behandelingen. We vonden niet dat één behandelingsstrategie superieur was aan een ander wat betreft de algehele of ziektevrije overleving. Bovendien kan lymfklierdebulking het risico op toxiciteit juist verhogen in vergelijking met boost-bestraling. Omdat er geen duidelijke definitie is van bulky lymfeklieren, voerden we een subgroepanalyse uit voor lymfeklieren ≥2 cm. Ook deze analyse toonde een

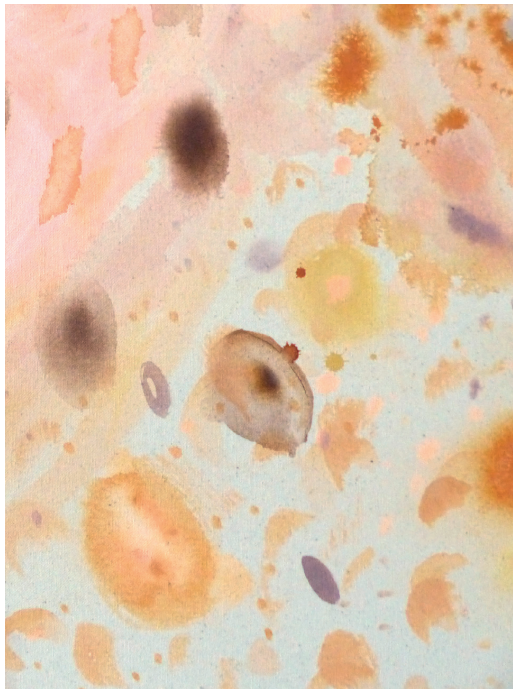
vergelijkbare overleving van de verschillende behandelingen, hoewel de steekproefgrootte te klein is om harde conclusies te trekken.

De subgroepanalyse voor debulking, al dan niet gecombineerd met boost-bestraling, toonde aan dat ‘dubbele’ behandeling met debulking en boost-bestraling geassocieerd was met een slechtere overleving vergeleken met alleen debulking. Dit is hoogstwaarschijnlijk gerelateerd aan de selectie van patiënten die in aanmerking komen voor dubbele therapie, een subgroep met ongunstige prognostische factoren. Omdat geen van beide strategieën een betere overleving laat zien, lijkt gedeelde besluitvorming en geïndividualiseerde behandeling de beste aanpak te zijn voor patiënten met bulky lymfeklieren. Onze resultaten moeten echter met voorzichtigheid worden geïnterpreteerd vanwege de retrospectieve onderzoeksopzet. Ondanks deze beperkingen beschrijft deze studie resultaten van het grootste cohort van patiënten met verschillende behandelingsstrategieën voor bulky lymfeklieren bij lokaal gevorderde baarmoederhalskanker. Deze studie voegt daarom waardevolle informatie toe aan de bestaande literatuur.

Patiënten die goed geïnformeerd zijn over de morbiditeit van hun behandeling, blijken beter om te kunnen gaan met hun ziekte en de gevolgen ervan. Daarom is het waardevol om tijdens counseling nauwkeurige informatie te kunnen geven en daarmee de kwaliteit van leven (KvL) te verbeteren. In **Hoofdstuk 8** evalueerden en vergeleken we de KvL op lange termijn en toxiciteit op korte termijn bij overlevenden van baarmoederhalskanker na de twee belangrijkste behandelstrategieën: radicale hysterectomie en bekkenklierdissectie versus primaire chemoradiotherapie, met behulp van resultaten van het PROFILES-register. Vrouwen die chemoradiotherapie kregen (n=107; 37%) rapporteerden aanzienlijk slechter functioneren (rol, cognitie en sociaal) en meer symptomen (vermoeidheid, financiële problemen, symptoombeleving, neuropathie, seksuele activiteit en seksueel functioneren) dan degenen die een operatie ondergingen (n=181; 63%). Daarentegen kwam lymfoedeem vaker voor na een chirurgische behandeling.

Adjuvante therapie werd toegediend bij 27% van de patiënten; deze vrouwen rapporteerden meer seksuele activiteit, maar ook meer lymfoedeem dan na primaire chemoradiotherapie, terwijl andere KvL-schalen vergelijkbaar waren. Hoewel toxiciteitsprofielen verschilden tussen de behandelingsgroepen, waren de totale toxiciteitspercentages vergelijkbaar. Bovendien bleek het ervaren van toxiciteit op korte termijn negatief geassocieerd te zijn met verschillende langetermijn-KvL-resultaten, ongeacht de behandeling. Deze informatie kan ondersteuning bieden bij het adviseren over behandelingen en het vergroten van het bewustzijn met betrekking tot de KvL-domeinen die beïnvloed worden na de behandeling van baarmoederhalskanker. Er zijn echter grotere prospectieve studies nodig om deze bevindingen te bevestigen.

Samengevat, de jacht op lymfeklieren kan levens redden! De identificatie van lymfekliermetastasen voorafgaand aan de behandeling moet echter eerst verder worden verbeterd om de behandeling te individualiseren en uiteindelijk de overleving en de gezondheidsgerelateerde KvL te verhogen.



Appendices

Author contributions and funding

Chapter 2

CM, MA and JV are responsible for the conceptualization of the manuscript. EO performed the literature search, data analysis and wrote the first draft. MA, JA, LS, JV, HW and CM critically revised the manuscript and contributed to the final draft.

Chapter 3

EO contributed to the conceptualisation, methodology, data analysis, interpretation and writing of this study. HW, JM, JV, LS, CM, MA contributed to the conceptualisation, methodology, writing, reviewing and editing of this manuscript. BV contributed to the methodology and data analysis and revised and edited this manuscript. AS and JA contributed to the methodology, conceptualisation, review and editing. RB, JB, BS, HN, RS, NT, PZ, RZ: contributed to the conceptualisation, review and editing.

Chapter 4

EO: conceptualization, methodology, software, formal analysis, investigation, data curation, writing, original draft preparation. HW, JV, LS, MA, CM: methodology, writing, review and editing. JV, LS, MA, CM: supervision, funding acquisition.

Chapter 5

EO: conceptualization, methodology, formal analysis, data curation, visualization and writing. CH: conceptualization, methodology, writing, reviewing and editing. HW: formal analysis, data curation, writing, reviewing and editing. MS: writing, review and editing. JV: conceptualization, methodology, writing, reviewing and editing. MA: conceptualization, methodology, supervision, writing, reviewing and editing.

Chapter 6

EO: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft. HW: conceptualization, formal analysis, methodology, writing - review & editing. MM: formal analysis, methodology, software, writing, review & editing. JV, MA, CM: conceptualization, data curation, funding acquisition, investigation, methodology, supervision, writing – review & editing. LA: conceptualization, methodology, supervision, writing – review & editing. RB, JB, BS, HN, RS, NT, PZ, RZ, AS: methodology, writing - review & editing.

Chapter 7

EO: conceptualization, methodology, data analysis, interpretation and writing. HW, JV, LS, MA, CH: conceptualization, methodology, writing, reviewing and editing. AS: methodology, conceptualization, review and editing. RB, JB, HN, BS, RS, NT, PZ, RZ: conceptualization, review and editing.

Chapter 8

EO: conceptualization, methodology, software, formal analysis, investigation, data curation, writing – original draft, visualization. HW: conceptualization, methodology, writing – review & editing. BR: data curation, methodology, writing – review & editing. JV, MA, CM: funding acquisition, conceptualization, methodology, writing – review & editing, supervision. LS: conceptualization, methodology, writing – review & editing, supervision. NE: data curation, conceptualization, methodology, writing – review & editing, supervision.

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List of publications

Publications included in this thesis

E.P. Olthof, M.A. van der Aa, J.A. Adam, L.J.A. Stalpers, H.H.B. Wenzel, J. Van der Velden, C.H. Mom. The role of lymph nodes in cervical cancer: incidence and identification of lymph node metastases-a literature review. International Journal of Clinical Oncology. 2021 Sep;26(9):1600-1610.

Ester P. Olthof, Brenda J. Bergink-Voorthuis, Hans H.B. Wenzel, Jordy Mongula, Jacobus van der Velden, Anje M. Spijkerboer, Judit A. Adam, Ruud L.M. Bekkers, Jogchum J. Beltman, Brigitte F.M. Slangen, Hans W. Nijman, Ramon G.V. Smolders, Nienke E. van Trommel, Petra L.M. Zusterzeel, Ronald P. Zweemer, Lukas J.A. Stalpers, Constantijne H. Mom, Maaike A. van der Aa. Diagnostic accuracy of MRI, CT and [^{18}F]FDG-PET-CT in detecting lymph node metastases in clinically early-stage cervical cancer – a nationwide Dutch cohort study. Insights into Imaging. 2023 *accepted*.

Ester P. Olthof, Hans H.B. Wenzel, Jacobus van der Velden, Lukas J.A. Stalpers, Constantijne H. Mom, Maaike A. van der Aa. Treatment strategies guided by [^{18}F]FDG-PET/CT in patients with locally advanced cervical cancer and [^{18}F]FDG-positive lymph nodes. Cancers. 2024 Feb;8;16(4):717.

E.P. Olthof, C.H. Mom, M.L.H. Snijders, H.H.B. Wenzel, J. van der Velden, M.A. van der Aa. The prognostic value of the number of positive lymph nodes and the lymph node ratio in early-stage cervical cancer. Acta Obstetricia et Gynecologica Scandinavica. 2022 May;101(5):550-557.

Ester P. Olthof, Hans H.B. Wenzel, Marissa C. van Maaren, Jacobus van der Velden, Anje M. Spijkerboer, Ruud L.M. Bekkers, Jogchum J. Beltman, Brigitte F.M. Slangen, Hans W. Nijman, Ramon G.V. Smolders, Nienke E. van Trommel, Petra L.M. Zusterzeel, Ronald P. Zweemer, Lukas J.A. Stalpers, Maaike A. van der Aa, Constantijne H. Mom. Radical hysterectomy or chemoradiotherapy for clinically early-stage cervical cancer with suspicious lymph nodes on imaging – a retrospective cohort study. Journal of Gynecologic Oncology. 2025 Mar;36(2):e16.

E.P. Olthof, H.H.B. Wenzel, J. van der Velden, A.M. Spijkerboer, R.L.M. Bekkers, J.J. Beltman, H.W. Nijman, B.F.M. Slangen, R.G.V. Smolders, N.E. van Trommel, P.L.M. Zusterzeel, R.P. Zweemer, L.J.A. Stalpers, M.A. van der Aa, C.H. Mom. Treatment of bulky lymph nodes in locally advanced cervical cancer: boosting versus debulking – a Dutch nationwide cohort study. International Journal of Gynecological Cancer. 2022 Jul 4;32(7):861-868.

Ester P. Olthof, Hans H.B. Wenzel, Belle H. de Rooij, Jacobus van der Velden, Lukas J.A. Stalpers, Maaike A. van der Aa, Constantijne H. Mom, Nicole P.M. Ezendam. The impact of surgery and chemoradiotherapy on toxicity and long-term health-related quality of life in cervical cancer survivors:

results from the population-based PROFILES registry. Acta Obstetricia et Gynecologica Scandinavica. 2023 *accepted with revisions*.

Other publications

Ester P. Olthof, Martijn R. van de Scheur, Annemarie E. Weis-Potters. Vulvair angio-oedeem tijdens de zwangerschap. Nederlands Tijdschrift Geneeskunde. 2018:162:D1548.

Ester P. Olthof, Jacobus Van Der Velden, Rebecca C. Painter, Constantijne H. Mom. Morbidity of radical hysterectomy combined with caesarean section in pregnant patients with cervical cancer. European Journal of Gynaecological Oncology. 2021 Apr 14;42(2);300-306.

H.H.B. Wenzel, **E.P. Olthof**, R.L.M. Bekkers, I.A. Boere, V.E.P.P. Lemmens, H.W. Nijman, L.J.A. Stalpers, M.A. van der Aa, J. van der Velden, C.H. Mom. Primary or adjuvant chemoradiotherapy for cervical cancer with intraoperative lymph node metastasis – a review. Cancer Treatment Reviews 2021 Nov 2;102:102311.

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PhD portfolio

Name PhD student:	Ester P. Olthof
PhD period:	January 2020 – March 2024
Name PhD supervisor:	Prof. L.J.A. Stalpers

	Year	Hours/ECTS
Courses		
Practical Biostatistics	2020	40/1.4
Scientific Writing in English	2021	42/1.5
Presenting in English	2022	22.4/0.8
B2+ Business English	2022	42/1.5
Clinical Epidemiology: Evaluation of Medical Tests	2020	26/0.9
Advanced Topics in Biostatistics	2021	58.8/2.1
Observational Epidemiology	2022	16.8/0.6
Seminars, workshops and master classes		
Oncologisch Spectrum IKNL	2021	8/0.3
Presentations		
Gynaecongres NVOG	2020	14/0.5
CCA conference	2023	14/0.5
European Society of Gynaecological Oncology (ESGO) congress	2023	14/0.5
(Inter)national conferences		
Webinar BRCAdemy, virtual Meeting	2020	4/0.1
Gynaecongres NVOG, virtual Meeting	2020	8/0.3
ESGO congress, virtual Meeting	2021	16/0.6
International Gynecologic Cancer Society (IGCS) congress New York	2022	32/1.1
ESGO congress, virtual Meeting	2022	16/0.6
Lecturing		
Roadshows IKNL	2020	8/0.3
Tutoring, Mentoring		
Journal club, intervision, methodology meeting PhD-IKNL	2020-2023	156/5.6
Team meeting gynaecology IKNL	2020-2023	48/3.4
Supervising		
Internship biomedical sciences bachelor student, 12 weeks	2022	84/3.0
Internship medical master student, 18 weeks	2023	84/3.0
Other		
Peer reviewing for journals (two articles)	2022	16/0.6
Trusted advisor trajectory	2023	28/1.0
Research meeting gynaecologic oncology AmsterdamUMC	2020-2023	48/3.4

Lymph node metastases
Lena Rossi, 2024

Chasing nodes, saving lives?
Lymph node metastases in cervical cancer