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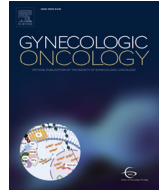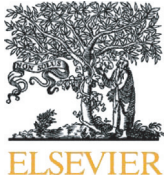
The prognostic value of the presence of pelvic and/or para-aortic lymph node metastases in cervical cancer patients; the influence of the new FIGO classification (stage IIIC)

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HIGHLIGHTS

- Survival rates of FIGO 2009 stage IB–IIB are significantly affected by lymph node metastases
- Survival rates of FIGO 2009 stage IIIA–IVA are not affected by lymph node metastases
- Survival rates of IIICr are significantly more impaired compared to stage IIICp.

ARTICLE INFO

ABSTRACT

Introduction. One of the major changes in the revised (2018) FIGO-staging system is the addition of stage IIIC to the previously used 2009 system. We evaluated the prognostic value of positive pelvic and/or para-aortic lymph nodes in patients with cervical cancer.

Methods. A nationwide retrospective cohort study was performed by analyzing data from the Netherlands Cancer Registry. All patients newly diagnosed with stage IB-IVA between 2005 and 2018 were identified. Three-year, 5-year and 15-year overall survival (OS) rates were estimated with the Kaplan-Meier method.

Results. Of the included 6082 patients, 1740 patients (29%) had pelvic and/or para-aortic lymph node metastases. For patients with FIGO 2009 stage IB-IB1-IIA-IIA1 and stage IB2-IIA2-IIB with pelvic and/or para-aortic lymph node metastases the OS was significantly different ($p < 0.001$ and $p = 0.009$), with a 5-year OS of 77% and 67%, compared with 92% and 74% for women without lymph node metastases. For FIGO 2009 stage IIIA-IIIB-IVA with and without lymph node metastases, survival rates are not significantly different ($p = 0.064$). For FIGO 2018 stage IIIC the 3y-OS, 5y-OS and 15-year OS are 72%, 65% and 59% respectively. Survival rates of IIIC diagnosed based on imaging (IIICr) are significantly impaired compared to stage IIIC diagnosed based on pathology (IIICp) ($p < 0.001$).

Conclusion. Patients with FIGO 2009 stage IB–IIB cervical cancer with pelvic and/or para-aortic lymph node metastases have significantly impaired survival compared to patients without metastases. Survival rates of patients with FIGO 2009 stage IIIA–IVA are not affected by lymph node metastases.

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1. Introduction

In 2018, the International Federation of Gynecology and Obstetrics (FIGO) staging system for patients with cervical cancer has been revised. One of the major changes in the revised staging system is the addition of stage IIIC to the previously used 2009 version. Stage IIIC includes patients with pelvic (IIIC1) and/or para-aortic lymph node (IIIC2) metastases, without distant metastases, regardless of tumor size and extent. Thereby, an addition to stage IIIC has been made to indicate if lymph node involvement is diagnosed based on pathology (p) or imaging (r) (1).

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One of the consequences of the addition of stage IIIC, is that the presence of pelvic and/or para-aortic lymph node metastases might affect the treatment plan. Patients diagnosed with stage IB-IIA are commonly categorized as early-stage cervical cancer and are generally treated with primary radical surgery (1). Lymph node metastases are found in approximately 8–32% of the women with early-stage cervical cancer, and in case of postoperatively confirmed positive lymph nodes, adjuvant therapy is indicated (2) (3). Patients diagnosed with stage IIB-IVA are classified as locally advanced cervical cancer and are generally treated with chemoradiotherapy including brachytherapy (1). The addition of stage IIIC enables us to identify women with pelvic and/or para-aortic lymph nodes, mostly resulting in upstaging and improving treatment plans.

Five-year overall survival (OS) rates range from 83% for stage IB to 32% for stage IVA (4). However, patients with lymph node metastases are more likely to relapse, and the presence of lymph node metastases is an important adverse prognostic factor (5). A recent study showed that upstaging to IIIC is associated with a strongly impaired prognosis (6). A single-center study by Yang et al. showed a comparable OS for patients with stage IIICr to stage IA, IB, IIA, IIB and a worse survival for patients with IIICp (7). Data on the survival rate of stage IIIC cervical cancer, as well as data on the new stages without lymph node metastases, are limitedly available.

This study aims to evaluate the prognostic value of the presence of positive pelvic and/or para-aortic lymph nodes in patients with cervical cancer. Thereby, we created reference survival data for patients with stage IIIC cervical cancer, and for patients with different stages of cervical cancer without suspected pelvic and/or para-aortic lymph node metastases.

2. Method

2.1. Study design and patient selection

A nationwide retrospective cohort study was performed, by analyzing data from the Netherlands Cancer Registry (NCR), a registry of all newly diagnosed malignancies in the Netherlands. Data managers from the NCR extract patient information from medical records within hospitals, and the registry has nationwide coverage since 1989. Data on vital status was obtained by annual linkage with the nationwide

Personal Records Database (BRP, last linkage: January 31, 2021). The study was approved by the NCR Privacy Review Board (K20.322) and was exempt from institutional review board approval because data were gathered retrospectively and analyzed anonymously. All patients newly diagnosed with stage IB-IVA between 2005 and 2018 were identified from the NCR. The extent of disease of all patients in this study was classified using the FIGO 2009 staging system. Inclusion criteria: squamous cell carcinoma, adenocarcinoma or adenosquamous; primary treatment with radiation therapy, chemotherapy, chemoradiation therapy or surgery. Patients with other histological subtypes or distant metastases (stage IVB) were excluded. Data on age, FIGO stage, histological subtype, the clinical and pathological Tumor-Node-Metastasis (TNM) classification, primary treatment, adjuvant treatment, recurrence and survival status, were collected. FIGO 2009 and 2018 stages were derived from the TNM classification. The survival rates were subdivided into three categories (1) FIGO 2009, (2) conversion to 2018 without suspected pelvic and/or para-aortic lymph node metastases, and (3) positive pelvic and/or para-aortic lymph node metastases clinically and/or pathologically confirmed. Survival rates were shown for each stage separately and in groups; Group 1: early-stage cervical cancer, including stage IB-IB1-IIA-IIA1, generally treated with surgery. Group 2: locally advanced cervical cancer without extension to pelvic wall, stage IB2-IIA2-IIB, generally treated with chemoradiation. Group 3: locally advanced cervical cancer with involvement of lower third of the vagina and/or extension to the pelvic wall, stage IIIA-IIIB, generally treated with chemoradiation. Group 4: locally advanced cervical cancer with invasion of the mucosa of the bladder/rectum, stage IVA, generally treated with chemoradiation. At last, survival rates were shown for patients treated with surgery followed by adjuvant treatment for which the same three categories were used.

2.2. Statistical analysis

Descriptive statistics were used to describe characteristics and the presence of pelvic and/or para-aortic lymph node metastases. Survival was calculated as the interval from date of diagnosis until date of death due to any cause (i.e. event) or censoring (i.e. emigration, loss to follow-up or January 31, 2021), whichever came first. The Kaplan–Meier method was applied to calculate the 3-year, 5-year, and 15-year OS rates and the log-rank test was used for statistically comparing
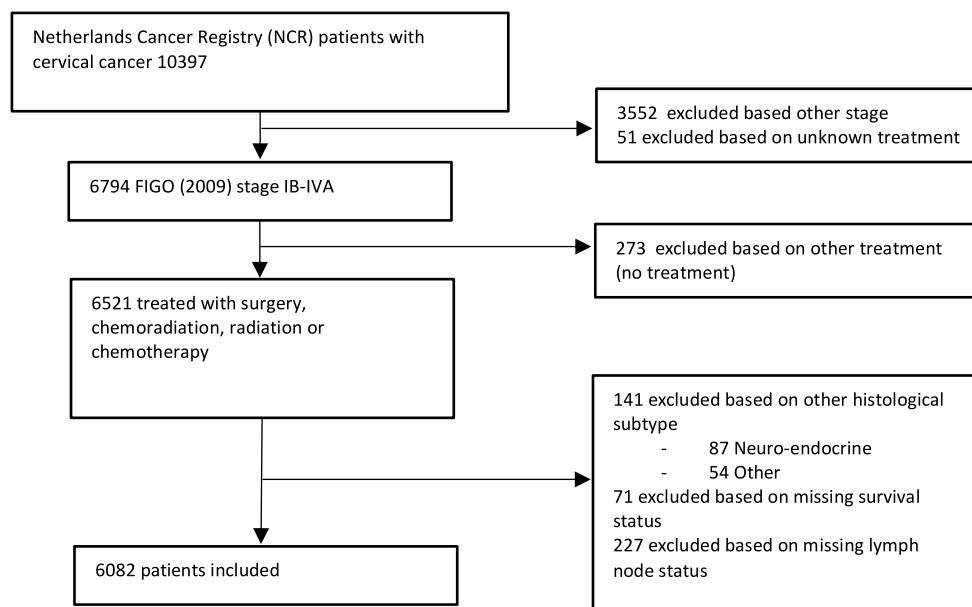

Fig. 1. Flowchart of the inclusion procedure.

Table 1
patient characteristcs.

		N
Total		6082
Age in years, median (range)	47 (19–96)	
Histology	Squamous cell carcinoma	4571 (75%)
	Adenocarcinoma	1287 (21%)
	Adenosquamous cell carcinoma	224 (4%)
FIGO 2009	IB	138 (2%)
	IB1	2744 (45%)
	IB2	528 (9%)
	IIA	214 (4%)
	IIA1	109 (2%)
	IIA2	106 (2%)
	IIB	1480 (24%)
	IIIA	149 (2%)
	IIIB	427 (7%)
	IVA	187 (3%)
FIGO 2018	IB	114 (2%)
	IB1	2252 (37%)
	IB2	309 (5%)
	IIA	167 (3%)
	IIA1	82 (1%)
	IIA2	74 (1%)
	IIB	930 (15%)
	IIIA	98 (2%)
	IIIB	229 (4%)
	IIIC	1640 (27%)
	IVA	87 (1%)
	IVA (with positive nodes)	100 (2%)
Positive nodes	Positive nodes	1740
	IIIC Based on cN	1242 (71%)
	IIIC Based on pN	376 (22%)
	IIIC Based on cN and pN	122 (7%)
Treatment	Chemoradiation	2103 (35%)
	Radiation therapy	843 (14%)
	Chemotherapy	24 (0%)
	Surgery	3112 (51%)
Surgery specification	Conization	56 (2%)
	Simple trachelectomy	6 (0%)
	Radical trachelectomy	233 (7%)
	Trachelectomy	42 (1%)
	Simple hysterectomy	163 (5%)
	Radical hysterectomy	2592 (83%)
	Exenteration	13 (0%)
	Surgery unknown	7 (0%)
Adjuvant treatment after surgery	Total	813
	Radiation therapy	438 (54%)
	Chemotherapy	6 (1%)
	Chemoradiation	369 (54%)
Patients with surgery and adjuvant treatment	IB	37 (5%)
	IB1	528 (65%)
	IB2	104 (13%)
	IIA	43 (5%)
	IIA1	31 (4%)
	IIA2	8 (1%)
	IIB	50 (6%)
	IIIA	1 (0%)
	IIIB	7 (1%)
	IVA	4 (0%)
Survival	Alive	4301
	Death	1781
Survival months	Median 70 months (range 1–196 months)	

survival curves. If 15-year OS was unknown, the 10-year OS was shown. *P*-values were calculated based on the OS. All analyses were performed with the software IBM SPSS 22 (Statistical Package for Social Science). Differences were considered significant if $p < 0.05$.

3. Results

In total 10,397 patients with cervical cancer were registered in the NCR between 2005 and 2018, of which 6794 patients were diagnosed with 2009 stage IB-IVA cervical cancer. Of these patients, 273 patients were excluded because they did not receive treatment for cervical cancer. Furthermore, patients were excluded because of other histological subtypes ($n = 141$, missing lymph node status ($n = 227$) and missing survival status ($n = 71$) (Fig. 1).

3.1. Patient characteristics

In total 6082 patients were included in this study with a median age at diagnosis 47 years (range 19–96 years). A total of 4571 patients (75%) were diagnosed with squamous cell carcinoma, 1287 (21%) with adenocarcinoma and 224 (4%) with adenosquamous cell carcinoma. Other patient characteristics are stated in Table 1. Primary treatment of the included patients consisted of chemoradiation ($n = 2103$), radiation therapy ($n = 843$), chemotherapy ($n = 24$) and surgery ($n = 3112$). After surgery, 813 patients (26%) received adjuvant treatment, in the form of radiation therapy ($n = 438$; 54%), chemotherapy ($n = 6$; 1%) or chemoradiation therapy ($n = 369$; 45%). From the total group of patients, 1740 (28%) were diagnosed with pelvic and/or para-aortic lymph node metastases of which 1242 (71%) were diagnosed on imaging, while 376 (22%) had pathology-proven positive lymph nodes. One hundred twenty-two patients (7%) had radiologically suspect and pathology-proven pelvic and/or para-aortic lymph node metastases (Table 1).

3.2. Survival rates

The survival rates for patients with and without pelvic and/or para-aortic lymph node metastases are stated in Table 2 and Fig. 2. After a median follow-up 70 months (range 1–196 months) a total of 1781 patients had died. The 3-year, 5-year, and 15-year OS rate for patients with FIGO 2009 stage IB-IB1-IIA-IIA1 cervical cancer with pelvic and/or para-aortic lymph node metastases are 84%, 77% and 70% respectively. For patients without pelvic and/or para-aortic lymph node metastases the 3-year, 5 year, and 15-year OS are significantly higher, with 95%, 92% and 87% respectively, $p < 0.001$.

The 3-year, 5-year, and 15-year OS for patients with FIGO 2009 stage IB2-IIA2-IIB cervical cancer with pelvic and/or para-aortic lymph node metastases are 74%, 67% and 62% respectively. This is significantly lower compared to these patients without pelvic and/or para-aortic lymph node metastases, with 3-year, 5 year, and 15-year OS of 81%, 74% and 65% respectively, $p = 0.009$.

The 3-year, 5-year, and 15-year OS for patients with FIGO 2009 stage IIIA-IIIB and stage IVA cervical cancer with pelvic and/or para-aortic lymph node metastases are not significantly different from those of patients without pelvic and/or para-aortic lymph node metastases $p = 0.064$ and $p = 0.939$ respectively.

The 3-year, 5-year, and 15-year OS for all patients with pelvic and/or para-aortic lymph node metastases (FIGO 2018 stage IIIC) are 72%, 65%, and 59% respectively. The 3-year, 5-year and 15-year OS for patients with pathological stage IIICp are 86%, 78%, 71% and the survival rates for patients with radiological stage IIICr 67%, 61%, 55% respectively $p < 0.001$. The 3-year, 5-year, and 15-year survival rates for patients with, compared to without lymph node metastases are significantly worse for each histological subtype (Table 3). The survival rates for stage IIIC with per treatment are stated in Table 3. The survival rates per stage are stated in de supplemental information (S1).

4. Discussion

Patients with FIGO 2009 stage IB–IIB cervical cancer with the presence of positive pelvic and/or para-aortic lymph nodes have a significantly worse survival compared to those without pelvic and/or para-aortic lymph node metastases. With the introduction of stage IIIC in the 2018 FIGO classification, estimated survival are different for patients compared with the 2009 FIGO classification. Patients diagnosed

Table 2

Survival rates per group for patients with cervical cancer.

Stage FIGO 2009	2009 total	2018 without pelvic and/or para-aortic lymph node metastases*	2018 IIIC with pelvic and/or para-aortic lymph node metastases*	P-value
Group: 1 IB-IB1-IIA-IIA1 ($n = 3205$)	3y OS: 93% 5y OS: 89% 10y OS: 85% 15y OS: 84%	3y OS: 95% 5y OS: 92% 10y OS: 88% 15y OS: 87%	3y OS: 84% 5y OS: 77% 10y OS: 72% 15y OS: 70%	<0.001
Group 2: IB2-IIA2-IIB ($n = 2114$)	3y OS: 78% 5y OS: 72% 10y OS: 66% 15y OS: 64%	3y OS: 81% 5y OS: 74% 10y OS: 67% 15y OS: 65%	3y OS: 74% 5y OS: 67% 10y OS: 63% 15y OS: 62%	0.009
Group 3: IIIA-IIIB ($n = 576$)	3y OS: 51% 5y OS: 44% 10y OS: 37% 15y OS: 36%	3y OS: 54% 5y OS: 46% 10y OS: 38% 15y OS: 36%	3y OS: 48% 5y OS: 42% 10y OS: 36% 15y OS: 35%	0.640
Group 4: IVA ($n = 187$)	3y OS: 43% 5y OS: 36% 10y OS: 33% 15y OS: 32%	3y OS: 44% 5y OS: 44% 10y OS: 31% 15y OS: 29%	3y OS: 43% 5y OS: 38% 10y OS: 34% 15y OS: 34%	0.939
Treated with surgery and adjuvant RT or surgery and adjuvant CRT	3y OS: 86% 5y OS: 80% 10y OS: 76% 15y OS: 74%	3y OS: 87% 5y OS: 82% 10y OS: 78% 15y OS: 77%	3y OS: 85% 5y OS: 78% 10y OS: 74% 15y OS: 71%	0.255

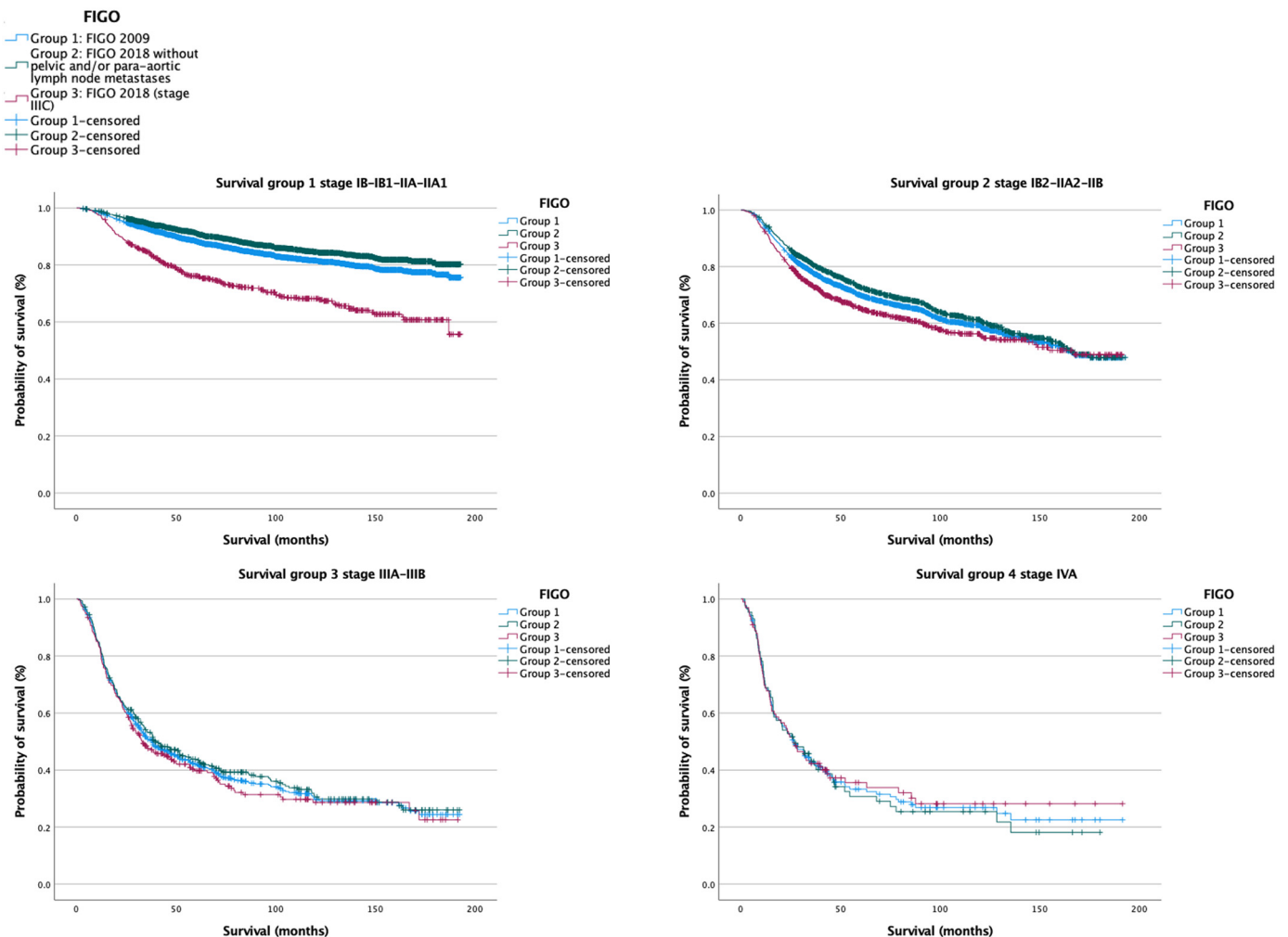* FIGO 2018 stages were derived from the TNM classification (FIGO 2009).

Fig. 2. survival rates per group for patients with cervical cancer.

Table 3
patients diagnosed with stage IIIC (FIGO 2018).

	Survival	p-value
IIIC	3y OS: 72% 5y OS: 65% 10yOS:61% 15y OS: 59%	
IIICr	3y OS: 67% 5y OS: 61% 10y OS: 56% 15y OS: 55%	<0.001
IIICp	3y OS: 86% 5y OS: 78% 10y OS: 74% 15y OS: 71%	
IIIC surgery	3y OS: 79% 5y OS: 74% 10y OS: 69% 15y OS 68%	<0.001
IIIC surgery with adjuvant treatment	3y OS: 85% 5y OS: 78% 10y OS: 74% 15 y OS: 72%	
IIIC chemoradiation	3y OS: 74% 5y OS: 67% 10y OS: 63% 15y OS: 62%	
IIIC other (chemotherapy or radiation therapy)	3y OS: 39% 5y OS: 32% 10y OS: 25% 15y OS: 24%	
SCC without LNM	3y OS 85% 5y OS 80% 15y OS 73%	<0.001
SCC with LNM	3y OS 72% 5y OS 66% 15y OS 60%	
AC without LNM	3y OS 90% 5y OS 86% 15y OS 80%	<0.001
AC with LNM	3y OS 69% 5y OS 60% 15y OS 55%	
ASC without LNM	3y OS 91% 5y OS 87% 15y OS 83%	<0.001
ASC with LNM	3y OS 73% 5y OS 63% 15y OS 58%	

radiologically with IIICr have significantly worse survival rates compared to pathological stage IIICp. Survival rates of patients with FIGO 2009 stage IIIA, IIIB and IVA cervical cancer are not significantly affected by the presence of pelvic and/or para-aortic lymph node metastases.

The addition of stage IIIC provides an overall improved discrimination in the survival rates of women with cervical cancer, and the ability to differentiate between the presence and absence of pelvic and/or para-aortic lymph node metastases. Thereby, the new survival curves provide support in discussions regarding treatment choices. Recently, a study of *Mohamud* et al. compared the survival rates of FIGO 2009 and FIGO 2018 of all patients with cervical cancer, in which 371/4461 (8.3%) patients were allocated to stage IIIC1 and IIIC2. They showed that the revision led to a higher survival for all stages except stage IA2, IIA2, IIIA and IIIB [8]. In contrast, our study showed the effects of pelvic and/or para-aortic lymph node metastases on survival for patients with FIGO 2009 cervical cancer stage IB–IIB are substantial, with a significantly worse survival compared to patients without pelvic and/or para-aortic lymph node metastases. In our group analysis stage IB and IIB were the most prevalent disease stages in group 1 and 2, respectively. Automatically, they had the largest impact on survival rates in these groups. Moreover, these were the only stages in which lymph node metastasis had a significant impact on survival. Patients with lymph node metastases are generally an unfavorable group, with a suspected poor prognosis, especially for those with early stage cervical cancer [9]. In contrast to the study of *Mohamud* et al., in the present study, the presence or absence of positive pelvic and/or para-aortic lymph nodes has not significantly affected survival of patients with FIGO 2009 stage IIIA–IVA cervical cancer. One of the explanations, that there is not a significant difference between positive pelvic and/or para-aortic lymph nodes, is that the tumor size and/or growth pattern primarily affect the survival rate [10].

Recent studies showed that the addition of stage IIIC alone is not enough to determine prognosis. The study of Yang et al. reported on OS for patients with stage I and II converted to IIICp. They showed a 5-year OS survival rate of 79% for stage IIICp based on 68 patients [7]. We showed a 5-year OS of 78% for patients with IIICp. Thereby, we reported a 5-year OS of 61% for patients with IIICr. One of the hypotheses of a worse prognosis for stage IIICr is that lymph node metastases need to be of significant extent to be detected by imaging, whereas pathological investigation can detect smaller metastases, such as micro-metastases. Thereby, lymph node metastases are not the only

factor affecting prognosis. A recent study of Bai et al. showed that nodal involvement alone is an inadequate factor to predict survival in early-stage cervical cancer. They describe that a combination of T-stage (tumor size) and the number of positive lymph nodes provides a better estimated survival [11].

Current guidelines advise surgical treatment for patients with early-stage cervical cancer, namely simple hysterectomy (for stage IA without lymphovascular space invasion), or radical hysterectomy with pelvic lymph node dissection [12]. Patients with locally advanced disease are preferably treated with chemoradiation therapy. In our study 531 patients converted to stage IIIC FIGO 2018 were primarily treated with surgery. Of these patients, 458 patients (86%) were also treated with adjuvant therapy. A recent study of *Park* et al. showed no significant difference in survival rates for patients with early-stage cervical cancer with pelvic nodal metastases treated with chemoradiation, or surgery followed by adjuvant treatment (radiotherapy/chemotherapy). The authors suggest that patients with early-stage cervical cancer and pelvic lymph node metastases should be treated with primary chemoradiation therapy to avoid unnecessary complications when treated with surgery and adjuvant treatment [13]. In contrast, our study showed a significant difference ($p < 0.001$) in the survival rates between patients with stage IIIC treated with primary chemoradiation and patients treated with surgery followed by adjuvant treatment, with worse survival rates for patients treated with chemoradiation. However, our study not only included patients with early-stage cervical cancer in the new IIIC stage but also women who were previously staged in the more advanced stages. Patients with more advanced or extended tumors have an impaired survival, not only affected by the presence of lymph node metastases, which could explain the significantly worse survival for patients treated with primary chemoradiation therapy. A clear message on optimization of therapeutic approaches are needed, but this requires further study. Our results show a better survival in patients with stage IIIC receiving surgery followed by chemoradiation. However, selection bias may have contributed to this difference and needs further study.

In conclusion, patients with FIGO 2009 stage group 1(IB-IB1-IIA-IIA1) and group 2(IB2-IIA2-IIB) cervical cancer and positive pelvic and/or para-aortic lymph node metastases have a significantly impaired survival compared to patients without lymphatic metastases. Patients with stage IIICr cervical cancer have impaired survival rates compared to patients with stage IIICp. Survival rates of patients with FIGO 2009 stage IIIA–IVA cervical cancer are not affected by the presence of lymph node metastases. This information, based on the new 2018 FIGO classification system, provides patients and medical professionals more insight in survival chances for patients with cervical cancer with or without positive pelvic and/or para-aortic lymph node metastases. It can be used to inform patients on their expected survival chances, and treatment plans may be adjusted accordingly.

CRediT authorship contribution statement

K.G.G. van Kol: Data curation, Formal analysis, Writing – original draft. **R.M.F. Ebisch:** Formal analysis, Writing – review & editing. **M. van der Aa:** Data curation, Writing – review & editing. **H.B. Wenzel:** Data curation, Writing – review & editing. **J.M.J. Piek:** Writing – review & editing. **R.L.M. Bekkers:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.01.023.

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