

Para-aortic lymph node recurrence in cervical cancer patients

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DOI: [10.31083/j.ejgo4206177](https://doi.org/10.31083/j.ejgo4206177)

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Submitted: 4 April 2021 Revised: 8 June 2021 Accepted: 18 June 2021 Published: 15 December 2021

Objective: The primary aim of the study was to analyze incidence and risk factors for para-aortic lymph node recurrence (PALNR) in IA1 to IB2 International Federation of Gynecology and Obstetrics (FIGO) 2009 stage cervical cancer patients who were initially treated with radical hysterectomy and pelvic lymph node dissection. **Methods:** We conducted a retrospective analysis of stage I cervical cancer patients who had been treated with radical hysterectomy and pelvic lymphadenectomy with or without adjuvant therapy. We identified 242 patients, of whom 58 (24%) were diagnosed with PALNR by imaging studies. **Results:** The group of patients with PALNR had higher tumor grades (G1: 2 patients (3.4%); G2: 44 (75.9%) and G3: 12 (20.7%) vs G1: 48 (26.1%), G2: 112 (60.9%) and G3: 24 (13.0%); $p = 0.001$), more advanced age (median; range 54 (29–78) vs 49 (23–76); $p = 0.02$) and fewer pelvic lymph nodes harvested during primary surgery (median; range 11 (3–27) vs 14 (2–40); $p = 0.002$) when compared to patients without PALNR. The prognosis of patients with PALNR was significantly worse when compared to patients without PALNR (5-year overall survival of 72% vs 87%, $p = 0.01$). 5-year overall survival following PALNR was 69%. We found no association between PALNR and tumor stage, tumor size, the presence of pelvic lymph node metastases or the histopathologic type of the tumor. **Conclusion:** We conclude that cervical cancer patients with high tumor grade, older age, and low number of pelvic lymph nodes harvested during initial surgery are at higher risk of PALNR.

Keywords

Cervical cancer recurrence; Para-aortic lymph node recurrence; Para-aortic lymph node metastases; Cervical cancer surgery

1. Introduction

Cervical cancer is the third most common cancer among women worldwide, and the third highest cause of death due to gynecological malignancies in the Western World [1]. The unique characteristics of cervical cancer are related to its prolonged and slow growth from precancerous lesions and human papilloma virus (HPV) infection. In recent years, mainly due to screening programs and HPV-vaccinations, cervical cancer incidence and mortality rates have decreased in Europe and the United States [2, 3]. The introduction of

screening programs which result in the detection of precancerous lesions and early stage cervical cancers (confined to the cervix), means that patients can be safely treated by surgery alone [4, 5].

Early-stage cervical cancers are mostly treated surgically. Radical hysterectomy with lymphadenectomy results in very good overall survival and a low incidence of adverse events [6, 7]. Surgical management of early-stage cervical cancer is based on adequate resection of parametria and evaluation of regional lymph nodes. Recently, a number of studies have shown the efficiency and safety of sentinel lymph node biopsy in cervical cancer [8]. However, systematic lymphadenectomy remains the recommended route for lymph node evaluation [4, 5]. Cervical cancer is spread mainly to pelvic lymph nodes. The five major groups of lymph nodes affected in the spread of cancer from the cervix are the external iliac, obturator, internal iliac, common iliac, and presacral [9]. Thereafter, the lymphatic system spreads cancer cells to the para-aortic lymph nodes. On rare occasions, when ovarian metastases are present, cancer cells may spread through the gonadal route which is a mechanism of the development of isolated para-aortic lymph node metastases (PALNM) [10].

Data on the prevalence of pelvic lymph node metastasis consistently shows that incidence rises rapidly according to the stage of the disease from 0% (range 0–1%) in stage Ia1, to 5% (range 0–5%) in stage Ia2, and then to 17% (range 5–17%) and 24.2% (range 17–24.2%) for stages Ib1 and Ib2, respectively [11–17]. However, para-aortic lymph nodes are less likely to be involved at the time of primary surgery for early-stage cervical cancer. In a study by Du *et al.* [15], PALNM were found in 3% of stage Ib1 and 7% of stage Ib2 cervical cancers respectively. Other recent studies have shown lower incidences of PALNM. In a study by Bogani *et al.* [18], the authors found PALNM in only 0.8% of the group of cervical cancer patients at stage IA–IIB. In a study by McComas *et al.* [11], in a cohort of 17,173 cervical cancer patients, presence of PALNM was associated with cancer staging, with ranges

beginning at <0.1% for T1A1 and rising to 9% for T1B3.

In 2018, Matsuo *et al.* [10], published data on more than five thousand cervical cancer cases from the Japanese national database, and among this cohort PALNM was present in 120 patients (2.1%). Due to the low incidence of para-aortic lymph node metastases in early-stage cervical cancer patients, generally, only pelvic lymph node dissection is recommended for surgical staging in this group of patients. The European Society of Gynaecological Oncology recommends pelvic lymphadenectomy as a standard procedure in cases of T1b1/T2a1 cervical cancers [4]. Such lymphadenectomies should include lymph node dissection from the obturator fossa, external iliac, common iliac and presacral regions. Similarly, the National Comprehensive Cancer Network (NCCN) recommends pelvic lymphadenectomy as the standard management for early stage cervical cancer [5]. Para-aortic lymph node dissection for diagnostic purposes is only recommended for more advanced stages (T1b2 and T1b3) with an evidence level of 2B [5]. Furthermore, it is speculated, that locally advanced cervical cancer patient may benefit from para-aortic lymph node dissection, especially when minimal invasive surgery is used. In these patients, evaluation of para-aortic lymph nodes enables adequate radiation treatment planning [19, 20].

The recurrence risk for cervical cancer patients treated with hysterectomy prompts further treatment with adjuvant radiotherapy [4]. The irradiated area following radical hysterectomy incorporates the pelvic region, and extending the radiotherapy field to the para-aortic region is only undertaken when para-aortic lymph node metastases are presented or highly suspected [5]. Therefore, the management of early-stage cervical cancer is focused on the pelvic area, even when post-hysterectomy radiation therapy is needed. Nevertheless, para-aortic lymph node recurrence (PALNR) is a significant cause of failure in early-stage cervical cancer management. The reported incidence of PALNR ranges between 2.5% and 18% [10, 21]. However, data on PALNR is sparse. Therefore, the main aim of our study was to analyze the incidence and the risk factors for PALNR in cervical cancer patients who were initially treated surgically. Furthermore, we evaluated the prognosis of patients diagnosed with PALNR.

2. Material and methods

We performed a retrospective analysis of cervical cancer patients who had been treated in the Clinical Department of Gynecological Oncology of the Franciszek Lukaszczyk Oncological Center in Bydgoszcz, Poland between 2007 and 2014. The inclusion criteria for the study were: cervical cancer stage IA1–IB2 according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system treated surgically with radical hysterectomy, no evidence of para-aortic lymph node metastases at the beginning of the therapy, no para-aortic lymphadenectomy was performed, no external beam radiotherapy (EBRT) to the para-aortic region, and a follow-up period of at least 11 months. Before the surgery, all the patients had undergone pelvic magnetic

resonance imaging (MRI) with the extended evaluation to the level of renal vessels. The patients underwent abdominal surgery classified as a C2 radical hysterectomy according to the Querleu-Morrow Classification. During surgery, palpable and visual evaluations of the para-aortic region were performed. Any suspicion of para-aortic lymph node metastases before or during the surgery prompted us to perform para-aortic lymph node dissection, and therefore, the patient was excluded from the analysis. All the patients had undergone pelvic lymphadenectomy that included dissection of external iliac, internal iliac, obturator, common iliac and presacral lymph nodes. We did not performed frozen section of pelvic lymph nodes during surgery. Adjuvant therapy comprised either EBRT or chemoradiation in the pelvic region and was administered according to analysis of the risk factors and there were no specific criteria for the adjuvant therapy. In general, chemoradiation was used when the patient was diagnosed with lymph node metastases, positive tumor margins, parametrial infiltration, or a tumor diameter greater than 4 cm. EBRT without chemotherapy was administered for IB patients with negative prognostic factors, like: lymphovascular space invasion, deep stromal invasion (above 1/3), adenocarcinomas, and tumor with diameter greater than 2 cm. In general, we used radiation therapy composed of 1.8–2 Gy daily per fraction for a total of 50.4 to 54 Gy in 28 fractions to the pelvic region. When chemoradiation was administered, we used intravenous cisplatin (40 mg/m²) once a week during radiotherapy. EBRT and chemoradiation treatments were always followed by brachytherapy consisting of 25 to 35 Gy in 2 or 3 fractions. Brachytherapy was commenced during the 2nd or 3rd weeks following EBRT/chemoradiation. In most cases, postoperative radiation therapy included positron emission tomography with computed tomography imaging (PET-CT) for the radiotherapy planning.

Disease stage classifications were determined using the 2009 FIGO staging system. For the purposes of our study, because all our patients were treated surgically, the stage of the cancer was reevaluated after histopathological examination of the tumor, therefore we were able to provide pathological staging for the primary tumor. The presence of lymph node metastases had no impact on the stage of the disease.

All patients were followed-up in a specialized out-patient clinic for gynecologic oncology. During the first three years following treatment, the patients underwent follow-up every 3 months, and after that, every 6 months for two years, and then subsequently, once a year. Follow-up routinely involved physical examination and pelvic transvaginal or transrectal ultrasonography. Pelvic magnetic resonance (MR) imaging and/or pelvic and abdominal CT scan were performed based on clinical findings, however, most patients had an MR or CT scan every one or two years. The diagnosis of PALNR was made on the basis of the imaging studies (MR, CT and PET-CT scan). The main aim of our study was to evaluate isolated PALNR. Therefore, when PALNR was accompanied with other type of recurrence (for example: pelvic recurrence), the patient was excluded from the study.

The nonparametric Mann-Whitney test was used to compare study group (patient with PALNR) and control group (patients without PALNR) participants with respect to age and the number of harvested pelvic lymph nodes. The analysis of the FIGO stage distribution was performed using the Chi-square test. The analysis of para-aortic lymph node recurrence in respect to the histological type of the cancer, tumor size (within the group of IB stage cancers), tumor grade and the number of pelvic lymph node metastases during initial surgery were studied using Fisher's exact test. Information on any patients who died was retrieved from the database of the National Health System of Poland. Survival analyses were conducted using Kaplan-Meier survival curves and the differences in patient survival were compared using the log-rank test. We performed univariate survival analysis. The comparison of the 5-year survival rates was conducted using Fisher-exact test. The post hoc power analysis of the study was conducted when insignificant results were obtained. The power analysis was performed using online calculator <https://clincalc.com/stats/Power.aspx>. Statistical analysis was carried out using MedCalc 11.4.2.0 (MedCalc Software Ltd, Ostend, Belgium) and GraphPad InStat 3.06 (GraphPad Software San Diego, CA, USA).

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and was conducted in accordance with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Centre of Postgraduate Medical Education Ethical Committee (7/PB/2020).

3. Results

Patients' characteristics

We identified 242 patients meeting the inclusion criteria of the study. Of these patients 58 (24%) were diagnosed with PALNR and they were included in our study group. The control group was composed of those 184 patients who were assessed but not diagnosed with PALNR. The median follow-up period was 60 months (range 11–119, standard deviation =33). The median patient age in the study group was significantly higher than in the control group (Table 1).

We found no difference in the distribution of the FIGO stages of the cancers between the study and control groups (Table 1). Similarly, in the sub-group of IB tumours, we found that differences in the PALNR rate between tumours less than and greater than 4 cm were not statistically significant ($p = 0.07$). We found significantly higher proportion moderately (G2) and poorly (G3) differentiated tumours within the group of patients with PALNR when compared to the control group (Table 1). There was no difference between the groups regarding histopathological type of the tumour (Table 1). Patients with lymph node recurrence in the para-aortic area had a significantly lower number of lymph nodes harvested during pelvic lymphadenectomy (Table 1). Patients with para-aortic lymph node recurrence had a higher rate of lymph node metastases in the pelvic area during initial

surgery, however, this difference was not statistically significant (Table 1).

The median time from the date of initial surgery to para-aortic lymph node recurrence was 4.4 months (range 1.7–78.1). Patients diagnosed with PALNR had significantly lower median overall survival (mOS) when compared to the control group (87% vs 72%; $p = 0.01$; Table 1, Fig. 1). Para-aortic lymph node recurrence was associated with a hazard ratio of 2.25 (95% CI 1.21–4.16). Median patient survival after para-aortic lymph node recurrence was not reached (range 1.6–162 months) and 5-year overall survival following PALNR was 69%.

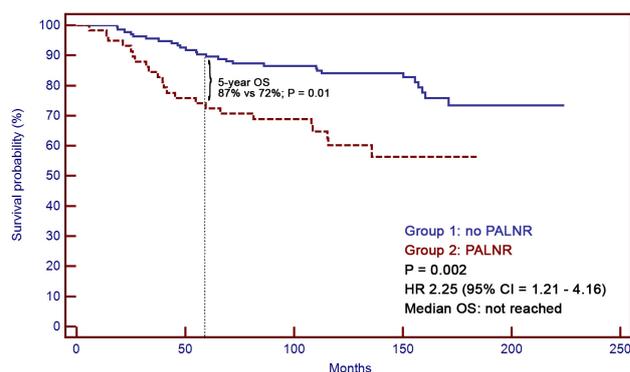


Fig. 1. Cervical cancer patients' median overall survival according to para-aortic lymph node recurrence (PALNR). Group 1: PALNR absent ($n = 184$), median overall survival (mOS) = not reached (range, 3.5–224 months); Group 2: PALNR present ($n = 58$), mOS = not reached (range, 5.6–183 months), $p = 0.002$; HR 2.25 (95% CI = 1.21–4.16).

4. Discussion

We found that nearly one third of early-stage cervical cancer patients treated with radical hysterectomy with or without adjuvant radiation were diagnosed with a PALNR. The rate of PALNR observed in our study was higher than that reported in the literature. In a study by Matsuo *et al.* [10], PALNR was observed in 4.2% of cervical cancer patients who were treated surgically. This lower rate of PALNR in the Matsuo *et al.* [10], study may be partially explained by the fact that nearly 15% of the study's women had para-aortic lymph node dissection; and it is known that such patients have PALNR less frequently. Matsuo *et al.* [10] also proposed a model for PALNR prediction based on the presence of parametrial involvement, lymphovascular space invasion (LVSI), ovarian metastases, and single or multiple lymph node metastases. In another study, Chen *et al.* [22] evaluated cervical cancer patients primarily treated with chemoradiotherapy. Of 1521 patients, PALNR was diagnosed in 65 (4.3%) [22]. In a study by Niibe *et al.* [23], the reported rate of PALNR was 2.1%. Similar to Niibe *et al.* [23], a study by Chou *et al.* [24] reported a 2.9% rate for isolated PALNR. However, some authors have reported higher rates of PALNR. For instance, Huang *et al.* [25], predicted crude PALNR in more

Table 1. Clinicopathological characteristics of cervical cancer patients with and without para-aortic lymph node recurrence.

	Study group: Cervical cancer patients diagnosed with para-aortic lymph node recurrence	Control group: Cervical cancer patients without para-aortic lymph node recurrence	<i>p</i> -value
	N = 58	N = 184	
Patient age, years median (range)	54 (29–78)	49 (23–76)	0.02
FIGO stages of the disease ¹			
IA1	2 (3.4%)	9 (4.9%)	0.21 ²
IA2	3 (5.2%)	14 (7.6%)	
IB1	32 (55.2%)	116 (63.0%)	
IB2	21 (36.2%)	45 (24.5%)	
Tumour grade			
G1	2 (3.4%)	48 (26.1%)	0.001
G2	44 (75.9%)	112 (60.9%)	
G3	12 (20.7%)	24 (13.0%)	
Histopathological type of the tumour			
Squamous cell carcinoma of the cervix	55 (94.8)	176 (95.6%)	0.73
Cervical adenocarcinoma	3 (5.2%)	8 (4.3%)	
Number of dissected lymph nodes during pelvic lymphadenectomy median (range)	11 (3–27)	14 (2–40)	0.002
Pelvic lymph node metastases (PLNM) during primary surgery			
PLNM present	12 (20.1%)	21 (11.4%)	0.08 ³
PLNM absent	46 (79.9%)	163 (88.6%)	
Adjuvant therapy			
No treatment	12 (20.7%)	59 (32.1%)	<i>p</i> = 0.1
Radiotherapy	22 (37.9%)	71 (38.6%)	
Chemoradiation	24 (41.4%)	54 (29.3%)	
Median overall survival	Not reached	Not reached	
Months (range)	(5.6–183)	(3.5–224)	<i>p</i> = 0.002
5-year overall survival	72%	87%	<i>p</i> = 0.01

¹Disease stage was assessed using the 2009 FIGO staging system. The distribution of FIGO stages was compared using the Fisher exact test with Freeman-Halton extension for a 3 × 2 table where stage 1A1 and 1A2 were analysed as one subgroup; ²post-hoc power analysis –43.9% (for the proportion of IB2 patients); ³ post-hoc power analysis = 40.5%.

than 10% of cervical cancer patients. Furthermore, in selected groups of patients, authors reported PALNR rates as high as 57% for patients with a high (Squamous Cell Carcinoma Antigen) SCC-Ag level, 34% with extensive parametrial involvement, and 37% with pelvic lymphadenopathy [25].

The incidence of PALNR observed is strictly related to the method of patient follow-up used. In the study by Huang *et al.* [25], where 758 cervical cancer patients treated with initial radiotherapy were analyzed, the overall rate of PALNR was 5% and 6% for isolated and non-isolated recurrence. However, in the study's subgroup of patients who had follow-up with regular abdominal CT scans, PALNR was diagnosed in 80 of 450 patients (18%), a much higher rate than in the overall group where follow-up was by routine clinical examination, with CT performed only when deemed necessary [25]. In comparison, our study used regular CT or MR imaging for follow-up; and therefore, the routine use of imaging examinations may be partially responsible for the high rate of PALNR reported in our study.

In the study by Matsuo *et al.* [10], the median time to develop PALNR was 16.1 months. Similarly, in the study

by Niibe *et al.* [23], the mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months. In contrast, in our study, the median interval time between primary surgery and PALNR was 4.4 months. The high rate of PALNR and short period to recurrence in our study may be partially explained by the high rates of adjuvant radiation after hysterectomy. Therefore, a significant proportion of our patients underwent imaging studies following hysterectomy for the planning of their radiation therapy. All our patients were evaluated with MR imaging before surgery and underwent palpation and visual evaluation of the para-aortic lymph nodes during the surgery. Therefore, it is less likely that we missed PLNM during the initial surgery, however, we cannot exclude the possibility of missing PLNM in the pre-operative workup. Furthermore, the planning of radiotherapy in most cases included a PET-CT scan; thus, it is also likely that changing the imaging from a preoperative MR scan to a postoperative PET scan was responsible for the higher rate of PALNR that we reported. Also, the high rate of PALNR may be related to false-positive results encountered with PET-CT imaging [26].

We found significantly shortened survival rates for cervical cancer patients with PALNR when compared to controls without PALNR. However, the prognosis after PALNR was favorable, since more than half of the patients were alive during the median follow-up period of 105 months. However, other studies of survival rates have indicated less favorable prognoses following PALNR in cervical cancer. For instance, in a study by Grigsby *et al.* [27], none of the patients with PALNR survived more than two years following recurrence. In a more recent study, Niibe *et al.* [28], reported 5 years survival for 38% of the cervical cancer patients they studied with PALNR. Similarly, Chen *et al.* [22], analyzed the survival rates of 65 patients with isolated PALNR, and reported that 33.9% survived 5 years, while the median OS was 27.7 months. In our study which observed a higher rate of PALNR, we reported better survival of our patients when compared with the aforementioned studies. Our results may be related to the high sensitivity of detection of a small burden of PALNR or a higher rate of false positive diagnoses of PALNR.

We observed significantly lower number of harvested lymph nodes among the patients with PALNR when compared with the controls. Although we did not observe the same difference in PALNR when comparing patients with and without pelvic lymph node metastases, the higher rate of PALNR in the group of patients with a lower number of harvested pelvic lymph nodes may be related to overlooked pelvic lymph node metastases. Takahashi *et al.* [21] underlines the higher risk of PALNR among patients with pelvic lymph nodes metastases, and reported 16% of PALNR in those cases. According to Matsuo [10], the rate of PALNR depends on the presence of pelvis lymph nodes metastasis at primary surgery. The authors have found an increased risk of PALNR in cervical cancer patients who had single or multiple pelvic lymph node metastases during initial treatment.

We observed a significantly higher age of patients with PALNR when compared to the control group without PALNR. Though higher age is associated with a worse prognosis for cervical cancer patients, previous studies have evaluated the association between patient age and PALNR and have found this factor of no significance [10, 25]. Similarly, tumor grade is another risk factor for a poor outcome in cervical cancer [29]. We found a significant association between high tumor grade and PALNR in cervical cancer patients. This observation seems to be new in the literature, since previously cited studies did not evaluate the association between PALNR and tumor grade [10, 22, 23]. On the other hand, in our study, we did not observe any relationship between histopathological type of the tumor and the risk of PALNR. However, our study included a small number of cervical adenocarcinomas. Similarly, Matsuo *et al.* [10], did not find the histological type of the tumor to be an independent risk factor of PALNR. We have found no association between FIGO stages of the disease and PALNR. Furthermore, when we focused on the IB stage, there were no differences between tumors less than and greater than 4 cm. In the study

by Niibe *et al.* [23], the authors observed a progressive increase of PALNR through the stages of the disease, with the rates of PALNR ranging from 1.4% to 5% for stages IB to IVA respectively. Chou *et al.* [24] found 26 patients with isolated PALNR among 876 with primary irradiation and in that study the FIGO staging distribution was similar, with 1.4% for stage IB and progressing up to 6.6% for stage IIIB [22, 24] the study by Huang *et al.* [25], multivariate analysis showed no significant association between staging and PALNR. In the study by Matsuo *et al.* [10], the probability of recurrence increased with FIGO stage and tumor size but was only shown in the univariate analysis. In the multivariate analysis, the associations between tumor size were not significant.

5. Conclusions

We conclude that cervical cancer patients with high tumor grade, older age, and low number of pelvic lymph nodes harvested during initial surgery are at higher risk of PALNR. Additionally, although the incidences of PALNM in stage I cervical cancer is low, the frequency of PALNR as detected by post-surgery surveillance imaging studies is high. The high rate and the early post-surgical detection of PALNR in our study, suggest that more attention should be paid to the pre-operative evaluation of PALNM. Further studies are needed to determine what patients could benefit from para-aortic lymph node dissection at the time of primary surgery for cervical cancer.

Abbreviations

PALNR, para-aortic lymph node recurrence; HPV, human papilloma virus; PALNM, para-aortic lymph node metastases; NCCN, National Comprehensive Cancer Network; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; MRI, magnetic resonance imaging; PET-CT, positron emission tomography with computed tomography imaging; MR, magnetic resonance; LVSI, lymphovascular space invasion; SCC-Ag, squamous cell carcinoma antigen; CT, computed tomography.

Author contributions

Conceptualization, SS, GZ, LW and AK; methodology, GZ, MC, BN, GC and MW-S; software, GZ and SS; validation, JT and MW-S; formal analysis, SS, GZ, BN and MC; investigation, GZ, MC, JT; resources, JT, MS and MW-S; data curation, AK, JT and MW-S; writing—original draft preparation, SS, GZ and AK; writing—review and editing, MC, MW-S, MS, BN, LW and JT; visualization, MC, MS; supervision, SS, MW-S, JT; project administration, SS, and LW; funding acquisition—no funding. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and was

conducted in accordance with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Centre of Postgraduate Medical Education Ethical Committee (7/PB/2020). Informed consent was obtained from all subjects involved in the study.

Acknowledgment

We would like to thank Robert Garret for his assistance with the manuscript.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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