

P R A C E O R Y G I N A L N E
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Clinical and histopathological factors in patients with cervical cancer allowing to identify candidates for less radical surgery

Analiza klinicznych i histopatologicznych czynników ryzyka u chorych z rakiem szyjki macicy pozwalających na identyfikacją pacjentek, u których można zastosować mniej radykalne leczenie

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Abstract

Objective: To determine clinical and histopathological factors in patients with cervical cancer tumors smaller than 2cm in order to identify those who could be operated less extensively with preservation of reproductive organs and lower morbidity.

Material and methods: We retrospectively reviewed the records of patients with cervical cancer and a maximum tumor of 2cm in diameter who were qualified for primary surgery in the years 2001-2007 at the Department of Gynecologic Oncology, Cancer Center in Warsaw.

Results: From the group of 110 operated patients, 96 were included into the study. Within the analyzed group the infiltration of the parametrium was found in 4 women (4.2%). All of them had squamous cell cancer; stage IB, grade G3. One patient had a tumor 1.5cm in diameter and 3 patients had tumors up to 2cm in diameter. The involvement of lymph nodes was observed in 3 patients with squamous cell carcinoma: in one case the tumor was intermediate grade (G2) and in two cases low grade (G3). The lymph nodes were involved only in patients with tumors greater than 0.5cm. The lymph vascular space invasion was found in 14 patients (14.7%): in 12 with squamous cell cancer and in 2 with adenocarcinoma. The diameter of the tumor was 0.5-1cm in 4 women, 1-1.4cm in 3 women and 1.5-2cm in the majority (7 women accounted for 29% of all patients in that group). No infiltration of the blood vessels could be seen in all 30 women with tumors smaller than 0.5cm. We found a statistically significant relationship between the size of the tumor and the incidence of lymph vascular space invasion ($p=0.024$).

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Conclusion: In selective cases fertility organ preserving surgery is possible and safe. In the group of patients with tumor less than 5 mm in diameter no parametrium involvement or lymph metastases were observed. In such situation cervical conisation can be justified. In well-differentiated (G1) tumors less than 2 cm in diameter, less radical surgical procedures can also be performed because no treatment failure has been observed.

Key words: **cervical cancer / fertility preservation / treatment**

Streszczenie

Cel pracy: Celem pracy była analiza wybranych czynników klinicznych i histopatologicznych umożliwiających mniej radykalne leczenie chorych na raka szyjki macicy z guzami do 2cm średnicy.

Materiał i metody: Grupę badaną stanowiły pacjentki ze zdiagnozowanym rakiem szyjki macicy i guzem wielkości do 2cm zakwalifikowane do pierwotnego leczenia operacyjnego w latach 2001-2007 w Klinice Nowotworów Narządów Płciowych Kobięcych Instytutu Centrum Onkologii w Warszawie.

Wyniki: Z grupy 110 operowanych chorych do retrospektywnej analizy włączono 96 osób. W analizowanej grupie pacjentek naciekanie przymacicz odnotowano u 4 pacjentek (4,2%). We wszystkich tych przypadkach były to raki płaskonabłonkowe, w stopniu zaawansowania IB i zróżnicowania G3. Naciek przymacicz zdiagnozowano u jednej chorej z guzem o średnicy 1,5cm, a u 3 kobiet guz miał średnicę 2 cm. Zajęcie węzłów chłonnych odnotowano u 3 pacjentek z rakiem płaskonabłonkowym przy czym w jednym przypadku był to rak średnioróżnicowany (G2), a w dwóch przypadkach niskoróżnicowany (G3). Zajęcie węzłów chłonnych zaobserwowano jedynie u pacjentek z guzami o średnicy większej niż 0,5cm. Zajęcie naczyń chłonnych zaobserwowano u 14 pacjentek (14,7%), u 12 z rakiem płaskonabłonkowym i 2 z rakiem gruczolowym. U 4 pacjentek rozmiar guza mieścił się w przedziale 0,5-1cm, u 3 1-1,5cm a u zdecydowanej większości (7 chorych co stanowiło 29% wszystkich pacjentek w tej grupie) 1,5-2cm. Zaobserwowano statystycznie znamiennej zależność między rozmiarem guza a zajęciem naczyń chłonnych ($p=0,024$).

Wnioski: W wybranej grupie pacjentek z rakiem szyjki macicy leczenie chirurgiczne pozwalające na zachowanie płodności jest bezpieczne i możliwe do wykonania. W grupie chorych z guzem nieprzekraczającym średnicy 5mm nie obserwowano naciekania przymacicz ani zajęcia węzłów chłonnych. W tych sytuacjach leczeniem z wyboru może być konizacja szyjki macicy. Ze względu na brak niepowodzeń w badanym materiale, mniej radykalne leczenie może być również rozważone w grupie pacjentek z dobrze zróżnicowanym guzem (G1) o średnicy nieprzekraczającej 2cm.

Słowa kluczowe: **nowotwory szyjki macicy / zachowanie płodności / leczenie /**

Introduction

Cervical cancer is the second most common cancer among women. The incidence in Poland in 2008 was 11,2 while mortality reached 5.3 in 100000 women [1]. Surgery is the treatment of choice in the early stages of the disease [2]. Commonly accepted risk factors of disease recurrence include: clinical stage, histological type, pathological grade, size of the tumor, depth of infiltration, involvement of regional lymph nodes, involvement of the adnexa, vascular space invasion and radicality of the primary surgery [3]. Extensive radical hysterectomy according to Wertheim method is associated with significant morbidity: urinary bladder and bowel dysfunction, fistulas, hematomas and abscesses [4, 5]. Risk of complications can be minimized by limiting the extent of the operation. Due to the effective use of screening, an increasing number of women are being diagnosed with cervical cancer at a younger age.

Many of these women are of childbearing age and wish to preserve their fertility. Concurrently, women decide to have their first and second child significantly later in life. Both, young age of cervical cancer patients and delayed motherhood justify the search for less invasive treatment methods of that disease.

Over the past years the extent of the operations has been greatly reduced, resulting in smaller number of complications and preserved fertility, but not affecting treatment effectiveness [6-9]. The present research identifies a group of 'low risk' patients who could be operated using less extensive techniques.

Aim

We analyzed selected clinical and histopathological factors in patients with cervical cancer tumors smaller than 2cm in order to identify those who could be operated less extensively.

Materials and methods

A retrospective study was performed using the database of patients with diagnosed cervical carcinoma and tumor not exceeding 2 cm in diameter, who were qualified for primary surgery in the years 2001-2007 at the Gynecologic Oncology Department, Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland. Tumor diameter was defined on the basis of histopathological examination. From the group of 110 operated patients, 96 were included into the study. These patients had a post-treatment follow-up period of no less than 12 months.

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The mean follow-up was 5 years long (12-105 months). The mean patient age was 51.3 years (25-78 years). The statistical analysis was performed using the Statistical Package for Social Science software, version 17.0 (SPSS Inc., IL, USA). Descriptive statistical methods, univariate ANOVA test, U Mann-Whitney test and Spearman correlation test were applied, if appropriate. The level of statistical significance was defined as $p < 0.05$. Clinicohistopathological data are presented in table 1.

Results

Within the analyzed group the infiltration of the parametrium was found in 4 women (4.2%). All of them had squamous cell cancer; stage IB, grade G3. One patient (1.5%) had a tumor of 1.5cm and 3 (3.15%) patients had tumors of 2cm.

The involvement of lymph nodes was observed in 3.15% patients with squamous cell carcinoma: in one case the tumor was intermediate grade (G2) and in two cases low grade (G3). The lymph nodes were involved only in patients with tumors greater than 0.5cm.

The lymphatic space invasion was observed in 14 patients (14.7%): in 12 (12.6%) with squamous cell cancer and in 2 (2.1%) with adenocarcinoma. The diameter of the tumor was 0.5-1cm in 4 women, 1-1.4cm in 3 women and 1.5-2cm in 7 women, what accounted for 29% of all patients in that group. We found a statistically significant relationship between the size of the tumor and the incidence of lymphatic space invasion ($p=0.024$).

Vascular space invasion was found in 8 patients. Although in 30 women with tumors smaller than 0.5cm there was no vascular space invasion, invasion was confirmed in single cases from 20 patients with tumors 0.5-1cm in diameter and from 20 patients with tumors 1-1.5cm in diameter. In the group of 24 women with tumor of 1.5-2cm, the final histopathological examination revealed vascular space invasion in 25% of the cases (6 patients). A trend towards statistical significance was observed ($p=0.09$). The authors found the body of the uterus to be involved in 3 patients with various tumor diameters: 0.5-1cm, 1-1.5cm and 1.5-2cm. These cases included 2 low grade (G3) and one intermediate grade (G2) carcinoma. Histology included two cases of squamous cell carcinomas and one of adenocarcinoma.

The table II shows the relation between tumor diameter and selected prognostic factors.

In 9 patients (9.3%) in the age group of 38 to 69 years (mean 52 years) recurrence was noted. 3 patients had local recurrence and 6 were diagnosed with distant metastases. Out of the latter, one had a single focus in the liver, one in the lungs and the remainder had multiple metastases in the liver, lungs, intestines, retroperitoneal lymph nodes, spine and the peritoneum. The mean time to recurrence was 25 months (9 to 73 months). Tumor size in this group was 0.5-1cm in 3, 1-1.5cm in 2 and 1.5-2cm in 4 patients. Seven women had a G3 and 2 had a G2 tumor. Among the patients diagnosed with recurrence 8 patients had stage IB disease and 1 patient stage IIA disease.

None of the patients with recurrence had infiltration of either the adnexa or the body of the uterus. 8 out of 9 women with recurrence underwent total Wertheim-Meigs hysterectomy and 1 had a total laparoscopic radical hysterectomy. In our observation the time to recurrence significantly depended on the fact whether vascular space was invaded ($p=0.016$).

Table 1. Clinicohistopathological characteristics of patients.

Disease stage	Number of patients	
IA	8	8,3%
IB	82	85,4%
IIA	6	6,2%
	96	
Histopathological diagnosis	Number of patients	
Squamous cell carcinoma	83	86,5%
Adenocarcinoma	11	11,5%
Clear-cell carcinoma	2	2,1%
	96	
Grade	Number of patients	
High grade (G1)	8	12,1%
Intermediate grade (G2)	27	40,9%
Low grade (G3)	31	47,0%
	66	
Final histopathological diagnosis	Number of patients	
Invasive cancer	66	68,8%
Pre-invasive cancer	22	22,9%
Micro-invasive cancer	6	6,3%
Cervix inflammation	2	2,1%
	96	
Accomplished procedures	Number of patients	
Conization	1	1,0%
Wertheim-Meigs hysterectomy	78	81,30%
Laparoscopically assisted vaginal hysterectomy (LAVH)	2	2,1%
Total abdominal hysterectomy (TAH/BSO)	4	4,2%
Total laparoscopic hysterectomy (TLRH)	11	11,5%
	96	
Adjunctive treatment	Number of patients	
Brachytherapy	34	73,9%
Radiotherapy	2	4,3%
Radiotherapy and brachytherapy	2	4,3%
Radiochemotherapy and brachytherapy	7	15,2%
Chemotherapy	1	2,2%
	46	

In the case of low grade cancers (G3) ($p=0.071$) and in the case of infiltrated lymph nodes ($p=0.079$) the authors noted a trend towards statistical significance.

In the analyzed group of 96 patients 7 died (7.3%). In the group of 66 women with confirmed invasive carcinoma 3 died due to disease progression.

Table II. Relation between tumor diameter and selected prognostic factors.

Tumor size (cm)	Histological type	Number of pts	Lymph node infiltration	Vascular space invasion	Lymphatic vascular space invasion	Uterus body infiltration	Adnexa infiltration	Parametrium infiltration
0-0,5	P	30 31,3%	0	0	0	0	0	0
	G	1 1,0%	0	0	0	0	0	0
	J	0	0	0	0	0	0	0
0,6-1,0	P	17 17,7%	1 1,0%	1 1,0%	4 4,2%	0	0	0
	G	2 2,1%	0	0	0	1 1,0%	0	0
	J	1 1,0%	0	0	0	0	0	0
1,1-1,5	P	17 17,7%	1 1,0%	1 1,0%	3 3,1%	1 1,0%	0	1 1,0%
	G	4 4,2%	0	0	0	0	0	0
	J	0	0	0	0	0	0	0
1,6-2,0	P	19 19,8%	1 1,0%	4 4,2%	5 5,2%	1 1,0%	0	3 3,1%
	G	4 4,2%	0	2	2	0	0	4
	J	1 1,0%	0	0	0	0	0	0

abbreviations: P-squamous cell carcinoma, G-adenocarcinoma, J-clear-cell carcinoma

The mean time to death was 24.3 months (12-42 months). Two patients died due to other reasons (leukemia – after 41 months and lung cancer – after 97 months). In the group of 30 patients with pre-invasive or minimally invasive cancer 2 died – 1 due to kidney cancer and 1 due to massive pulmonary embolism following cholecystectomy. In that group the authors did not observed deaths secondary to cervical cancer progression.

Discussion

Despite advances in diagnosis and management of cervical cancer, as well as the introduction of prophylactic human papillomavirus vaccines, the disease remains a major cause of cancer related mortality. The number of deaths caused by cervical cancer in 2008 reached 1745, which constituted 4.3% of all cancer-related deaths (seventh position among deaths) [1]. Most incidence and death cases concern middle aged woman (45-65 years). However, young women (18-44 years) account for 18% of all cases. In 2007 over 340 new cases were diagnosed in women under 40 years of age [10].

Treatment options for women with disease confined to the cervix and upper vagina (stages IA-IIA) include either radical surgery or radiotherapy. A prospective study conducted on 343

women randomized to either radical hysterectomy or pelvis irradiation revealed that survival rates were similar. Neither of the two treatment strategies proved to be superior [11]. Choice of a particular treatment method is often dictated by patient related factors, side effect profiles, and physician preference. The traditional Wertheim hysterectomy (type III) includes removal of the uterus, upper vagina, uterosacral ligaments with ligation of the uterine artery at its origin and resection of the parametrium. Although such operation often results in excellent local tumor control, it is associated with significant morbidity [4, 5, 12, 13, 14]. Late complications occur in 40% of operated patients. One of the most frequent, seen in almost one third of cases, is urinary bladder dysfunction [12, 15]. Most of the complications may be due to the resection of the parametrium because that tissue contains autonomic fibres which play a significant role in bladder and bowel innervation, as well as sexual performance. The rationale for the resection of the parametrium is to remove potential neoplastic foci. This benefit, however, is debatable in cases of early stage of the disease [16, 17].

Within the analyzed group, only 3 out of 73 patients (4.1%) who underwent radical Wertheim-Meigs hysterectomy and 4 in the whole study group had infiltrated parametrium.

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Table III. Data on patients with recurrence

Patient	Disease stage (FIGO)	Grade	Tumor size (cm)	Parametrium infiltration	Lymph node infiltration	Vascular space invasion	Lymphatic vascular space invasion	Parametrium infiltration	Adjunctive treatment	Death
1	IB	G3	1.5-2	n	n	t	t	n	rth+brth	n
2	IB	G3	1.5-2	n	n	n	n	n	rth	y
3	IB	G3	1.5-2	t	n	t	t	t	rthchth	y
4	IB	G3	1-1.5	n	n	n	n	n	brth	n
5	IIA	G3	0.5-1	n	n	n	n	n	brth	n
6	IB	G2	0.5-1	n	n	n	n	n	brth	y
7	IB	G3	0.5-1	n	n	n	n	n	brth	n
8	IB	G3	1.5-2	n	n	n	n	n	rthchth	n
9	IB	G2	1-1.5	n	T	n	n	n	brth	n

abbreviations: n – no, y – yes

All patients were in stage 1B disease and in 75% cases (3 patients) the tumor diameter was 2cm (1.5-2cm). The authors found no evidence of parametrium infiltration, either in case of G1 and G2 neoplasms or in patients with no lymphatic vascular space invasion (LVSI). Our data support already published findings where parametrium is reported to be infiltrated in 4% to 39% of cases with disease stage IA-IIA [18-24].

Many investigators studied the possibility of preserving fertility through less radical surgery in selected low-risk patients. Kinney et al., evaluated 83 patients with stage IB1 squamous cell cervical cancer, tumor size not greater than 2cm and no involvement lymphatic vascular space invasion. None of these patients had evidence of parametrium infiltration [25]. Another group of 842 women with stage IA1 to IB1 cancer, treated with hysterectomy, was studied by Covens et al. The parametrium was infiltrated in 33 patients (4%), and the risk of infiltration was related to the large tumor size, LVSI, deep infiltration and invaded pelvic lymph nodes. Additional analyses of 536 patients with tumor diameter not exceeding 2cm, negative histological examination of pelvic lymph nodes revealed parametrium involvement only in 0.6% of cases [18].

Wright et al., studied risk factors of parametrium infiltration in 498 patients. The parametrium involvement was observed only in 6% of women with negative pelvic lymph nodes, and in 47,9% of patients with infiltrated lymph nodes. Moreover, in the first group the risk was only 0.4% if the tumor was smaller than 2cm and no LVSI could be observed. The risk factors for parametrium involvement were: LVSI, tumor size >2cm, and infiltration of pelvic and paraaortic lymph nodes ($p<0.001$) [26]. These data are similar to ours. However, we observed infiltrated parametrium also in one case where the tumor diameter was 1.5cm. No infiltration was found in patients with no LVSI. No vascular space invasion was found in any patient with tumor

diameter smaller than 0.5cm. The risk of vascular and lymphatic vascular space invasion was statistically related to the tumor size ($p=0.024$ and $p=0.09$).

The size of the tumor is an independent prognostic factor. Women with tumors not exceeding 2cm survive in about 90%, while those with larger lesions – in 60% [27]. In our group we have noted recurrence in 9 cases. All of them had low grade (G3) neoplasm and tumor larger than 0.5cm. Deaths related to progression occurred in 3 cases. In all patients the tumor diameter was at least 1.5cm, and none of them had a high grade disease (G1). We observed no disease related deaths in patients with high grade (G1) neoplasms and tumor diameter not exceeding 1cm. It seems therefore that this group of patients might include candidates for less extensive treatment.

The tumor size is an important risk factor in patients planned for less extensive surgery [8, 28, 29]. In our study the tumor size was determined during histopathological examination. Nevertheless, it seems possible that colposcopy along with magnetic resonance imaging (MRI) and ultrasonography could accurately determine the tumor size. The results of treatment in such patients are very good. In cases where tumors smaller than 2cm do not infiltrate beyond one half of the wall thickness of the cervix, 5-year survival reaches 95% [8, 29-31].

The involvement of the lymph nodes was seen only in cases of intermediate and low grade cancers (G2 and G3). One of these cases presented with a tumor of only 0.9cm. It seems that in the group of patients with tumors no greater than 1cm it is not necessary to perform radical hysterectomy with parametrium excision. Cervical conisation or simple hysterectomy may be just as sufficient. Nevertheless, the examination of lymph nodes remains necessary as also in such pre-selected groups node infiltration was documented.

Conclusions

In selective cases fertility organ preserving surgery is possible and safe. In the group of patients with tumor less than 5 mm in diameter no parametrium involvement or lymph metastases were observed. In such situations cervical conisation can be justified. In well-differentiated (G1) tumors, less than 2 cm in diameter, less radical surgical procedures can also be performed because no treatment failure has been observed.

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