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Prognostic factors in patients with primary invasive vaginal carcinoma

Czynniki prognostyczne u chorych na pierwotnego inwazyjnego raka pochwy

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Abstract

Aim of the study: *Aim of the study was the assessment of prognostic factors in the group of primary invasive vaginal carcinoma (PIVC) patients subjected to radical radiation therapy.*

Material and methods: *The analysis was performed for the group of 152 PIVC patients treated with intracavitary brachytherapy alone (16.5%), the combination of brachytherapy and external radiotherapy (78.9%), or external radiotherapy alone (4.6%). The relationship was investigated between treatment outcome and the following demographic, clinical and histopathological features: age, duration of pathological symptoms, number of births given, prior hysterectomy, haemoglobin level, Karnofsky performance status score, primary tumour location in vagina, length of vagina involved, FIGO stage, gross appearance, histological type, and tumour grade.*

Results: *Five-year disease-free survival was observed in 46.1% of the patients (70/152). Patients below 60 years of age, with Karnofsky score of 80-90, diagnosed with PIVC in stage I0 or II0, and with tumour of grade G1 or G2 had significantly higher 5-year disease-free survival. Multifactoral analysis showed that age below 60 and FIGO stage I0 and II0 are independent favourable prognostic factors.*

Conclusions: *The independent prognostic factors in PIVC patients treated with radical radiotherapy are patient age and FIGO stage.*

Key words: **vaginal cancer** / **radiotherapy** / **prognostic factors** /

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Streszczenie

Cel pracy: *Celem pracy była ocena czynników prognostycznych w grupie chorych na pierwotnego inwazyjnego raka pochwy (PIVC) poddanych radykalnej radioterapii.*

Materiał i metody: *Przedmiotem analizy była grupa 152 chorych na PIVC poddanych: samodzielnej brachyterapii dojamowej (16,5%), brachyterapii dojamowej skojarzonej z teleradioterapią (78,9%) lub samodzielnej teleradioterapii (4,6%). Przeprowadzono analizę zależności pomiędzy wynikami leczenia, a następującymi cechami populacyjnymi, klinicznymi i mikroskopowymi: wiek, czas trwania objawów chorobowych, liczba porodów, uprzednio wykonana histerektomia, poziom hemoglobiny, stopień sprawności wg skali Karnofskiego, punkt wyjścia raka w obrębie pochwy, długość pochwy zajętej przez raka, zaawansowanie raka wg FIGO, postać makroskopowa guza, postać mikroskopowa i zróżnicowanie raka.*

Wyniki: *5 lat bez objawów nowotworu przeżyło 46,1% chorych (70/152). Statystycznie znamiennie wyższe bezobjawowe przeżycie 5-letnie uzyskano u chorych poniżej 60 roku życia, w stopniu sprawności Karnofskiego 80-90, chorych na PIVC w I0 i II0 zaawansowania oraz chorych na PIVC G1 i G2. W analizie wielocechowej niezależnymi, korzystnymi czynnikami prognostycznymi były: wiek poniżej 60 lat oraz I0 i II0 zaawansowania raka wg FIGO.*

Wnioski: *Niezależnymi czynnikami prognostycznymi u chorych na PIVC poddanych radykalnej radioterapii są wiek i stopień zaawansowania raka wg FIGO.*

Słowa kluczowe: **rak pochwy** / **radioterapia** / **czynniki prognostyczne** /

Introduction

Primary invasive vaginal carcinoma (PIVC) is a disease of a rare occurrence accounting for 1-2% of gynaecologic malignancies and 0.1-0.2% of all malignant neoplasms [1-14]. In Poland in 2006, there were 87 newly diagnosed cases of PIVC notified, which comprised 0.1% of the overall incidence of malignant neoplasm (standardized rate of 0.2/100 000), and 67 deaths, being 0.2% of the total number of deaths due to malignant neoplasm [15].

The treatment of choice for most of PIVC patients is radiation therapy administered as intracavitary brachytherapy, interstitial brachytherapy and external radiotherapy [2, 1, 4, 6, -9, 12, 13, 16, -20, 47, 52].

Aim of the study

Due to PIVC rare occurrence, some aspects of radiotherapy of the patients are still the subject of controversy in the literature. Aim of the presented study was to analyze one of them, namely the issue of prognostic factors in the group of PIVC patients subjected to radical radiation therapy.

Material and methods

Between 1967 and 2005, 173 PIVC patients were treated in COOK; 13 (7.5%) received surgical treatment alone or in combination with radiotherapy; 8 (4.6%), palliative radio- or chemotherapy; and 152 (87.9%), radical radiation therapy alone.

The subject of further detailed analysis is the group of 152 patients treated with radical irradiation. The youngest patient was 26, the oldest 76; mean age of patients was 62 with median of 65. Duration of pathological symptoms varied from 3 to 14 months; it amounted to 7 months on average with median of 8 months. Twenty eight (18.4%) patients were nulliparous, 54 (35.5%) had one or two children, and 70 (46.1%) had three or more children. Nineteen (12.5%) patients had prior hysterectomy indicated for uterine myomas (16 patients) or preinvasive cancer (3 patients); the latter, more than 10 years before PIVC was diagnosed. Pretreatment haemoglobin (Hg) level was equal or lower than 12g/dl (10.1-12.0g/dl) in 48 (31.6%) patients; the remaining 79 (52.0%) patients had higher Hg level (12.1-15.6g/dl). Karnofsky performance status was rated 80-90 in 73 (48.0%) patients and 60-70 in 79 (52.0%) patients. In 80 (52.6%) cases, primary site of PIVC was the upper third of vagina; in 28 (18.4%), the middle third; and in 44 (29.0%), the lower third. In 92 (60.5%) patients, primary focus of the tumour was located on the posterior wall of vagina; in 38 (25.0%), on the anterior wall; and in 22 (14.5%), on the lateral wall. In total in 74 (48.7%) cases, the site of primary tumour was the posterior wall of the upper third of vagina. Exophytic tumour was definitely the most often macroscopic type observed, found in 95 (62.5%) patients; next most often was infiltrating tumour – 52 (34.2%) cases; and the least frequently recorded was multifocal growth – 5 (3.3%) cases. In 68 (44.8%) cases, 1/3 of vagina length was involved; in 49 (32.2%), 2/3; and in 35 (23.0%), more than 2/3.

Ninety five (62.5%) patients were in FIGO stage I° or II°; 35 (23%), in stage III°; and 22 (14.5%), in stage IV^0A. Using available diagnostic methods, distant metastases were found in none of the patients of the investigated group at the time their treatment started. In 4 cases, metastases in inguinal lymph nodes were cytologically confirmed; and in 13 cases, based on ultrasound or CT scans, metastases in regional lymph nodes of pelvis minor were suspected.

Definitely the most frequent histological type of PIVC in the investigated group was squamous cell carcinoma, found in 129 (84.9%) cases; 21 (13.8%) patients had adenocarcinoma; and 2 (1.3%), undifferentiated cell carcinoma. There were 4 cases of clear cell adenocarcinoma in the investigated group, but none of them was diethyl-stilbestrol-related. Well-differentiated tumour (G1) was found in 29 (19.1%) patients; moderately differentiated (G2), in 54 (35.5%); and poorly differentiated (G3), in 69 (45.4%).

All patients of the group were treated with radiation only. Hundred forty five (95.4%) patients received intracavitary LDR brachyterapy with Ra-226 (manual loading) or Cs-137 sources (Selectron LDR/MDR afterloader). Hundred twenty seven (83.5%) patients underwent external radiation therapy, including 58 (45.7%) treated with Co-60 teletherapy unit; the remaining 69 (54.3%), with 10MV or 6MV linear accelerator. Four-field box technique (anterior, posterior and two opposite lateral fields) was applied with the total dose to the pelvis minor area of 50 Gy in 25 fractions in 5 weeks.

For 25 (16.5%) patients, intracavitary brachytherapy was the only treatment advised; all of them were in FIGO stage I° and the primary tumour did not exceed 0.5 cm in thickness and 2 cm in its largest dimension. Total radiation dose to primary tumour calculated at the depth of 0.5 cm from vaginal mucosa surface was 65-70 Gy. Fourteen (9.2%) patients in stage I° with primary tumour of the thickness larger than 0.5cm, all the patients in stage II° and III° (91 = 59.8%), as well as 15 (9.9%) patients in stage IVa° received intracavitary brachytherapy in combination with external radiation therapy. Brachytherapy dose to the infiltration base was 65-70Gy; external radiotherapy dose to the pelvis minor was 50Gy given in 25 fractions during 5-week period. Seven (4.6%) PIVC patients in stage IVa°, for whom it was technically not possible to perform intracavitary brachytherapy due to the local extent of neoplastic disease in vagina, were treated with external radiation therapy alone. Patients irradiated with four-field box technique to the dose of 50Gy received additional 20-25Gy boost using "shrinking-field technique" up to total dose of 70-75Gy.

It should be noted that in case of PIVC patients with primary tumour in the lower third of vagina, area irradiated with external beams was "prophylactically" extended to include inguinal nodes. Four patients with cytologically confirmed PIVC metastases in inguinal lymph nodes were given additional 15-20Gy dose ("boost") to that area using smaller fields of 15MeV electron beams. Detailed description of external radiation therapy as well as intracavitary brachytherapy techniques employed in COOK has been presented in previous works [13, 21].

The criterion to assess radiotherapy effectiveness was 5-year disease-free survival, counting from the day irradiation was started. All the patients were followed up for at least 5 years, unless patient died within that period. The mean follow-up period was 8.7 years (6.0-26.1). Log-rank test by Peto *et all.* [22] was used to evaluate significance of the differences found in the research material. Survival probability was estimated using the Kaplan-Meier method [23]. Statistical significance level was set at $p \leq 0.05$. Influence of selected factors on patient survival times was assessed using Cox's proportional hazard model [24].

Results

Of the 152 patients in the investigated group, 70, i.e., 46.1% were disease-free for 5 years. Six (3.9%) patients died during the 5-year follow-up with no evidence of PIVC: 3, of myocardial infarction; 2, of cerebral haemorrhage; 1, of acute pulmonary infection; and 2, (1.3%), of secondary cancer (malignant brain glioma and non-small cell lung cancer). The remaining 74 (48.7%) patients died of PIVC.

Table I presents the relationship between treatment outcome and demographic, clinical and histopathological features.

Results of single factor analysis presented in Table I show that the following features were of none significant impact on the therapy results, hence were not prognostic factors for 5-year disease-free survival: duration of pathological symptoms, number of births given, prior hysterectomy, pre-treatment haemoglobin level, primary tumour location in vagina, length of vagina involved, tumour gross appearance, and histological type.

Significantly higher 5-year disease-free survival was observed in patients below 60 years old, with Karnofsky performance status score of 80-90, diagnosed with PIVC in FIGO stage I° or II°, and with well or moderately differentiated tumour (G1, G2).

Cox multifactoral analysis showed that independent favourable prognostic factors for 5-year disease-free survival in the investigated group of 152 PIVC patients treated with radical irradiation were age below 60 and FIGO stage I° or II°.

Discussion

Profile of the investigated group in terms of demographic, clinical and histopathological features is clearly similar to majority of presented in the literature groups treated with radical irradiation. It particularly applies to the following features: patient age, duration of pathological symptoms, number of births given [1, 14, 20, 25-27]; tumour location in vagina [1, 6, 7, 9, 19, 28]; length of vagina involved [1, 2, 8, 13, 27]; histological type [1, 3, 6, 7, 9, 19, 26, 29]; and tumour grade [1, 2, 4-6, 12, 17, 18, 26, 27, 30]. In 2004, Hacker presented his compilation of selected 13 reports on PIVC published between 1982 and 2001, describing 1501 patients in total; 26.3% of them were diagnosed with PIVC in FIGO stage I°; 37.4%, in stage II°; 23.5%, in stage III°; and 12.8%, in stage IV^0 [31]. The group of 152 PIVC patients discussed in this paper has a clinical profile similar to that presented by Hacker: stage I° – 25.7%, stage II^0 – 36.8%, stage III° – 23.0%, stage IVa° – 14.5%.

In the investigated group of 152 radically irradiated PIVC patients, 5-year disease-free survival was observed in 70, i.e., 46.1% of patients. In the comprehensive reports by Kosary (1994), Creasman *et all.* (1998), and Hacker (2004), 5-year survival for the whole group of PIVC patients were 51.0%, 52.2%, and 45.5%, respectively [3, 31, 32]. Hence, the results achieved in the investigated group are in line with the reported in the literature.

Multifactoral analysis of prognostic factors in the investigated group of 152 PIVC patients treated with radical radiotherapy showed that patient age and FIGO stage of carcinoma were of independent and statistically significant impact on treatment results.

In the investigated group, 5-year disease-free survival was observed in 64.3% of patients younger than 60, and 30.5% of patients aged 60 or older. Straight majority of the authors agree that age is an independent prognostic factor in the group of PIVC patients treated with radiotherapy; the younger age, the better is the prognosis [5, 6, 13, 14, 28-30, 32-34]. In the group presented by Gesta *et all.*, 65% of women <70 and only 40% of older patients were cured of cancer [35]. Vavry *et all.* reported 5-year survival for 50% and 34% of patients younger and older than 60, respectively [36]. In the study by Kojs *et all.*, 5-year disease-free survival was observed in 63.2% of patients <60 and only in 25% of older patients [34]; Frank *et all.* reported 50% and 63.2% survival, respectively [28]. In the research by Hellman *et all.*, multifactoral analysis showed that – apart from carcinoma

Table. I. Relationship between treatment outcome and demographic, clinical, and histopathological features in the group of 152 PIVC patients.

Demographic, clinical and histopathological features	Number of patients treated	5-year disease-free survival	
		Number of patients	%
** **Age:**			
< 60 years old	70	45	64.3
≥ 60 years old	82	25	30.5
Duration of pathological symptoms:			
< 7 months	79	37	46.8
≥ 7 months	73	33	45.2
Number of births given:			
none	28	13	46.4
1 or 2	54	25	46.3
3 or more	70	32	45.7
Prior hysterectomy:			
no	133	62	46.6
yes	19	8	42.1
Haemoglobin level (g/dl):			
≤ 12g/dl	48	21	43.8
> 12 g/dl	104	49	47.1
* **Karnofsky performance status score:**			
80-90	73	40	54.8
60-70	79	30	38.0
Primary site of tumour in vagina (longitudal location):			
upper third	80	39	48.8
middle third	28	12	47.9
lower third	44	19	43.2
Primary site of tumour in vagina (wall involved):			
posterior wall	92	44	47.8
anterior wall	38	16	42.1
lateral wall	22	10	45.5
Primary site of tumour in vagina:			
upper third, posterior wall	74	39	52.7
other locations	78	31	39.7
Length of vagina involved:			
1/3	68	32	47.1
2/3	49	23	46.9
> 2/3	35	15	42.9
** **FIGO stage:**			
I^0	39	30	76.9
II^0	56	29	51.8
III^0	35	9	25.7
IVa^0	22	2	9.1
Primary tumour gross appearance:			
exophytic	95	44	46.3
infiltrating	52	24	46.2
multifocal	5	2	40.0
Histopathology:			
squamous cell carcinoma	129	61	47.3
adenocarcinoma	21	9	42.9
undifferentiated cell carcinoma	2	-	-
* **Tumour grade:**			
G1	29	17	58.6
G2	54	28	51.9
G3	69	25	36.2
Total	**152**	**70**	**46.1**

* difference statistically significant, log-rank test, p<0.05
** difference statistically significant, log-rank test, p<0.01

stage and primary tumour size – age was the third independent prognostic factor [5]. Worse survival of patients >65 was also observed by Wu *et all.* in their American population research [14]. Malmstrőma *et all.* recorded 5-year survival amounting to 43% in the group of patients younger than 70, and 21% for patients older than 70 [30]. The results of the de Crevoisier *et all.* research show that age was of prognostic significance for the overall survival, but had no impact on the 5-year disease-free survival in their investigated group of patients [4]. Similar observations were made by Perez *et all.* as well as Dixit *et all.* [12, 37]. Some of the authors question independent prognostic significance of age and emphasize that its impact on treatment results is revealed mainly in single factor analyses [3, 8, 12, 17, 18, 38].

In the group of PIVC patients managed with radiotherapy, FIGO stage of carcinoma is the primary prognostic factor, never raising doubts in the literature [2-6, 8, 13, 16-20, 27, 28, 30, 33-41]. Five-year survival is observed in 60-95% of stage I^0 patients; 35-80%, of stage II^0; 29-60%, of stage III^0; and 0-25%, of stage IV^0 [2-4, 6, 8, 12, 19, 26, 28, 34]. In 1994 in his comprehensive analysis of 1973-87 SEER cases including 669 PIVC patients, Kosary reported 5-year survival for 64% of patients in stage I^0; 53.5%, in stage II^0; 36%, in stage III^0; and 18%, in stage IV^0 [32]. In the NCDB (National Cancer Data Base) report by Creasman *et all.*, 5-year survival in the group of 729 patients treated between 1984 and 1994 was observed in 73% of patients in stage I^0; 59%, in stage II^0; and 36%, in stage III^0 and IV^0 [3]. In 2004 Hacker *et all.* summarized treatment results of 934 patients presented in 8 studies conducted between 1979 and 2001, and found that 5-year survival in stage I^0, II^0, III^0, and IV^0 was 70.3%, 50.8%, 33.0%, and 17.3%, respectively [31]. Indisputable differences exist between stage IVa and IVb. While there are generally no reports in the literature on 5-year survival in stage IVb, the survival rate in stage IVa amounts from 0% to around 20% [4, 5, 12, 19], and even to 30-40%, as recorded by few authors [2, 6]. In the investigated group, 5-year survival was observed in 76.9% of PIVC patients in stage I^0; 51.8%, in stage II^0; 25.7%, in stage III^0; and 9.1%, in stage IVA^0.

Apart from age and FIGO stage, there were not found any other independent prognostic factors in the investigated group; the literature, however, presents at least several other potential factors.

Many authors underline prognostic significance of PIVC histological type; prognosis for squamous cell carcinoma patients is supposed to be significantly better than in case of adenocarcinoma [2, 26, 28, 32, 36]. Comparing treatment results for the both most frequent histological types of PIVC, Chyle *et all.* observed local recurrence during 10-year follow-up in 52% of adenocarcinomas vs. 20% of squamous cell carcinomas; distant metastases, in 48% vs. 10%; and 10-year survival, in 20% vs. 50% of patients, respectively [2]. Stryker *et all.* observed 5-year survival in 50% of adenocarcinoma patients and in 68% of squamous cell carcinoma patients; Otton *et all.* reported 22% and 69%, respectively [26, 42]. Finally in 2005, Frank *et all.* observed higher percentage of both local control (81% vs. 39%) and overall survival (58% vs. 34%) in the group of squamous cell carcinoma patients [28]. It should be noted, however, that equally many researchers, including also authors of this work, found no significant independent correlations between radiotherapy outcome and histological type of PIVC [5, 6, 13, 18, 27, 29, 30].

Prognostic significance of tumour grade gives rise to much controversy. Some authors strongly suggest better curability in the group of PIVC patients with well differentiated (G1, G2) tumour [2, 6, 12, 13, 26, 34, 36, 37, 42, 43]. In the group presented by Malmström *et all.*, 5-year survival was observed in 57%, 32%, and 17% of PIVC patients in grade G1, G2, and G3, respectively [30]. In the material analyzed by Vavry *et all.*, 62.5% of G1 and G2 patients, 41.5% of G3 patients, and 34.9% of G4 patients were reported as disease-free; in the paper by Dixita *et all.*, 62.5%, of G1 and G2; and 38.5%, of G3 and G4 [36, 37]. Multifactoral analysis by Perez *et all.* showed that tumour histologic grade was a prognostic factor for distant metastasis [12]. Kojs *et all.* recorded 5-year disease-free survival in 57.9% of grade G1 and G2 patients, and only in 18.4% of grade G3 and G4 patients; Otton *et all.* reported 69% and 40% in G1-G2 and G3 patients, respectively [34, 42]. Many authors, including authors of this work, did not show PIVC tumour grade to be independent prognostic factor [4-6, 17, 18, 27, 38].

Some researchers emphasize that PIVC site in the proximal part of vagina provides better prognosis than distant tumour location [2, 13, 16]. Ali *et all.* observed 5-year overall survival in 81% of patients diagnosed with primary tumour in proximal part of vagina and only in 41% in case of distal location [16]. More detailed analysis of clinical material shows that the best prognosis is related with tumour location in upper third of vagina; the worst, with tumour in the lower third [2, 16, 18, 27-29, 36, 37]. Kucera and Vavra observed 5-year survival rates of 60%, 37.5%, and 37% for PIVC location in upper, middle and, lower third of vagina, respectively; Chyle *et all*. – 60%, 51%, and 29%; and Pingley *et all*. – 100%, 85%, and 45% [2, 27, 44]. Vavra *et all.* cured 61% of patients with tumour in the upper third of vagina and only 33.3% with tumour in the lower third [36]. However, considerable number of authors, including authors of this study, believes that primary tumour location within vagina is not an independent prognostic factor [4-6, 12, 13, 26, 28, 38, 41, 42].

In the literature, there are also other prognostic factors mentioned resulting, however, from single factor analyses only, e.g. primary tumour size [2, 5, 6, 8, 19, 20, 30, 33, 39]; extent of vaginal involvement [2, 8, 13, 19, 27, 36, 37, 44]; primary tumour gross appearance (exophytic vs. infiltrating ulcerating) [12, 45]; pre-treatment haemoglobin level [8, 41]; prior hysterectomy [2, 41]; accidental diagnosis of PIVC in patients with no symptoms [36, 44]; etc.

Conclusions

Independent favourable prognostic factors in PIVC patients are age below 60 and FIGO stage I° and II°.

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