Effectiveness of radiotherapy in patients with primary invasive vaginal carcinoma

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Summary

Introduction: The aim of the study was to present an institutional experience in radiation therapy of primary invasive vaginal carcinoma (PIVC) patients treated in the Krakow Branch of Centre of Oncology, with special regard to treatment effectiveness and failure causes. *Materials and Methods:* Between February 1967 and January 2007, 162 PIVC patients were treated with radical radiotherapy in the Krakow Branch of Centre of Oncology, Maria Sklodowska-Curie Memorial Institute. Twenty-seven (16.7%) patients in Stage I^0 were treated with intracavitary brachytherapy alone; for 127 (78.4%) patients in Stage I^0 - IV^0 intracavitary brachytherapy was combined with external radiation therapy; and eight (4.9%) patients in Stage IVA^0 were given only external radiotherapy. *Results:* In the investigated group of 162 patients, five-year disease-free survival was observed in 46.3% of the cases. Patient age and FIGO Stage of neoplastic disease were independent prognostic factors. Five-year disease-free survival was observed in 64.9% of the patients < 60 years of age and only in 30.7% ≥ 60 years of age; and in 62.3% of PIVC patients in Stages I and II^0 as compared to 19.7% of Stages III^0 and IV^0 cases. Among 78 patients who died of PIVC, in 60 (76.9%) cases the cause of death was locoregional failure; in six (7.7%), locoregional failure and distant metastasis; and in 12 (15.4%), distant metastasis. *Conclusions:* Radiotherapy is effective treatment for PIVC patients. Age below 60 years and non-advanced neoplastic disease were independent favourable prognostic factors in the investigated group of patients. The primary cause of treatment failure was failure to achieve locoregional disease control.

Key words: PIVC; Radiotherapy; Effectiveness; Failure.

Introduction

Primary invasive vaginal carcinoma (PIVC) accounts for 0.1%-0.2% of all malignant neoplasms, hence it is a carcinoma of rare occurrence [1-6]. The treatment of choice for most PIVC patients is radiation therapy administered as intracavitary brachytherapy, interstitial brachytherapy, and external radiotherapy [1-5, 7-13]. The results of radiotherapy of PIVC patients are slow, however its prognosis has consistently improved; in the 1950s, five-year survival was running at around 25%, nowadays it amounts to 50%-60% for all Stages altogether [1, 3, 4, 12, 14-17]. However, treatment effectiveness reported in the literature varies significantly from one radiotherapy centre to another, which is mainly the result of rare occurrence of PIVC, and hence small number of patients in presented groups; differences in clinical profile of the groups; changes and development of therapeutic approaches, which were introduced to clinical practice of individual centres at different time, and finally, differences in evaluation criteria of treatment effectiveness and its presentation [3, 4, 8, 11-13, 16-24]. The literature also presents different views the researchers maintain regarding the causes of radiotherapy failures in PIVC patients. While all generally agree that the primary cause of treatment failures is locoregional failure of disease control, there is much dispute over the percentage of vaginal and/or pelvic failures, as well as incidence and location of distant metastases [3, 4, 8, 11, 13, 17-20, 25-27].

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The purpose of this work is to present the 40-year experience of Centre of Oncology in Krakow (COOK) in radiation therapy of PIVC patients, with special regard to its effectiveness and failure causes.

Materials and Methods

Between January/February 1967 and January 31st, 2007, 162 PIVC patients in Stage I^0 – IVA^0 were given radical radiotherapy in COOK. The very group of patients was the subject of further detailed analysis. The youngest patient was 26- years-old, the oldest 78-years-old; the median age of patients was 62 years. More than half (54.3%) of the patients in the investigated group was 60 years or older. Thirty (18.5%) patients were nulliparous, 58 (35.8%) had one or two children, and 74 (45.7%) had three or more children.

The most common histopathology type of PIVC in the investigated group was squamous cell carcinoma found in 137 (84.6%) cases; 22 (13.6%) patients had adenocarcinoma; and three (1.8%), undifferentiated cell carcinoma. Thirty-four (21.0%) patients had tumour of grade G1; 54 (33.3%) G2; and 74 (45.7%) G3.

In 85 (52.5%) cases, primary site of PIVC was the upper third of vagina; in 30 (18.5%), the middle third, and in 47 (29.0%), the lower third. In 98 (60.5%) patients, site of the original lesion was the posterior wall of vagina; in 40 (24.7%) the anterior wall; and in 24 (14.8%) the lateral walls. In total, in 79 (48.8%) cases, the site of primary tumour was the posterior wall of upper third of vagina.

Forty-two (26.0%) patients were in FIGO Stage I^0, 59 (36.4%) in Stage II^0, 37 (22.8%) in Stage III^0, and 24 (14.8%) in Stage IV^0A. Nineteen (11.7%) patients of the investigated group

underwent earlier hysterectomy indicated for uterine myomas (16 patients) or preinvasive cervix carcinoma (three patients); the latter, more than ten years before PIVC was diagnosed.

All patients in the investigated group were given radiation therapy. Radiotherapy treatment plans were customized according to tumour stage, its location in the vagina, patient age and condition, accompanying diseases, and performed earlier hysterectomy. One hundred fifty-five (95.7%) patients were given intracavitary low-dose-rate (LDR) brachytherapy performed with Ra-226 or Cs-137 sources. One hundred thirty-five (83.3%) patients underwent external radiotherapy, including 58 (43.0%) treated with Co-60 teletherapy unit, and the remaining 77 (57.0%) with ten MV or six MV linear accelerator. Patients were treated with four external beams: anterior field, posterior field, and two opposite lateral fields (so called box technique). Entry field sizes were as following: 15 x 15 cm to 15 x 18 cm for AP-PA fields, and 15 x 8 cm to 15 x 10 cm for lateral fields. Pelvis minor area determined this way was irradiated with a daily dose of two Gy to total dose of 50 Gy in 25 fractions within five-week-period. Patients with primary tumour in the lower third of vagina were advised elective inguinal irradiation. Four patients with confirmed PIVC metastasis in inguinal lymph nodes were given additional 15-20 Gy dose ("boost") to that area using smaller fields of 15 MeV electron beams.

For 27 (16.7%) patients in the investigated group, intracavitary brachytherapy was the only treatment advised; all of them had Stage I^0 PIVC and the primary tumour did not exceed 0.5 cm in thickness and two cm in its largest dimension. The treatment was performed using vaginal colpostat (two applicators along vagina axis with two additional dome applicators in cases of upper vagina involvement). Total radiation dose to primary tumour calculated at 0.5 cm distance from vaginal mucosa was 65-70 Gy; vaginal mucosa received dose of 90-100 Gy. The remaining 15 (9.3%) patients in Stage I^0 PIVC with primary tumour exceeding 0.5 cm thickness were additionally given external radiation therapy and received 50 Gy in 25 fractions within five-week-period.

All of the 96 patients (59.2%) with Stages II^0 and III^0, PIVC were treated with the combination of intracavitary brachytherapy and external radiotherapy. Brachytherapy dose to infiltration base was 65-70 Gy. Dose to Manchester A points varied from 44 to 62 Gy (median dose of 52 Gy) with the overall irradiation time from 72 to 132 hours, most commonly within 96-120 hour range. If the primary tumour was located in the upper third of vagina, vaginal colpostat was used together with intrauterine applicator.

Sixteen (9.9%) of 22 IVA^0 Stage PIVC patients were advised intracavitary brachytherapy (as in the case of Stage II^0 and III^0 patients) in combination with external radiotherapy; eight (4.9%) patients, for whom it was technically not possible to perform intracavitary brachytherapy due to the extent of neoplastic disease in vagina, were treated with external radiation therapy alone. The eight patients irradiated using four-field box technique to the total dose of 50 Gy received additional 15-20 Gy boost using "shrinking-field technique" up to total dose of 65-70 Gy.

Radiotherapy tolerance was good in the investigated group; 156 (96.3%) patients completed full-planned radiation therapy treatment. Six (3.7%) patients completed planned brachytherapy, but were not given full-planned external radiotherapy dose due to condition deterioration (two patients), exacerbation of accompanying disease symptoms (three patients), and further radiotherapy refusal (one patient).

Severe late radiotherapy complications of grade 3^0 according to the glossary by Chassagne *et al.* published in 1993 [28] were observed in six (3.7%) patients, and included five cases of recto-vaginal fistula (G3a) and one case of vesico-vaginal fistula (G3d). Four of these patients died of locoregional failure, and one patient of simultaneous distant metastasis. One patient survived five years with no evidence of disease after surgical closure of fistula.

The criterion to assess radiotherapy effectiveness was five-year disease-free survival, counting from the day irradiation was begun. Survival probability was estimated using the Kaplan-Meier method [29]. Log-rank test by Peto *et al.* [30] was used to evaluate significance of the differences found in the research material. Influence of selected factors on patient survival times was assessed using Cox's proportional hazard model [31].

Results

Of the 162 patients in the investigated group, 75 (46.3%) were disease-free for five years. The relationship between treatment outcome and demographic, clinical, and histopathological characteristics is presented in Table 1.

Single factor as well as multifactoral Cox analysis showed that age and FIGO Stage of PIVC were independent prognostic factors for five-year disease-free survival in the investigated group of patients; age 60 years or over, and Stages III^0 and IVA^0 were of statistically significant unfavourable impact on therapy results. The fate of the patients in the investigated group is presented in Table 2.

Three (1.9%) patients died of second neoplasm - malignant glioma, and non-small cell lung cancer. Six (3.7%) patients died during five-year follow-up with no evidence of PIVC; three died of myocardial infarction, two of cerebral haemorrhage, and one of pulmonary infection combined with circulatory failure.

Causes of treatment failure in the group of 78 patients not cured of PIVC are shown in Table 3. Due to interpretation difficulty of the failure analysis, local and regional failures were taken as a whole and considered as locoregional failures.

In the investigated group of patients, the primary cause of radical radiotherapy failure was locoregional failure, which amounted to 84.6% of treatment failures; in six (7.7%) cases local recurrence was accompanied by distant metastasis. Distant metastasis was observed in 18 (23.1%) patients not cured of PIVC, and in 12 (15.4%) cases it was the only cause of radiotherapy treatment failure. Distant metastases were found in lungs (nine patients), liver (six patients), and bones (three patients). Average time to PIVC recurrence was nine months (one to 47-month range) with the median of eight months; 82.1% of treatment failures manifested within two years.

Of 78 patients not cured of PIVC, 22 (28.2%) died during the first year after the treatment; 48 (61.5%), during the second year; and 71 (91.0%), during the third year; none of the patients survived five years.

Discussion

Detailed analysis was performed for the group of 162 PIVC patients treated with radical radiotherapy. Comparison of the investigated group profile in terms of FIGO clin-

Table 1. — *Relationship between treatment outcome and demographics, clinical, and histopathological characteristics in the group of 162 PIVC patients.*

Demographics, histopathological, and clinical characteristics	N. of patients treated	Five-year disease-free survival N. of patients	%
* *Age:*			
< 60-years-old	74	48	64.9
≥ 60-years-old	88	27	30.7
N. of births given:			
none	30	14	46.7
1 or 2	58	27	46.6
3 or more	74	34	45.9
Histopathology:			
squamous cell carcinoma	137	64	46.7
adenocarcinoma	22	11	50.0
undifferentiated cell carcinoma	3	–	–
Tumour grade:			
G1	34	17	50.0
G2	54	28	51.9
G3	74	30	40.5
Primary site of tumour in vagina:			
posterior wall of upper third of vagina	79	38	48.1
other locations	83	37	44.6
* *FIGO Stage:*			
I^0	42	32	76.2
II^0	59	31	52.5
III^0	37	10	27.0
IVA^0	24	2	8.3
Earlier hysterectomy:			
yes	19	8	42.1
no	143	67	46.8
Total	162	75	46.3

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

Table 2. — *Fate of 162 patients of the investigated group.*

Fate of patients	N. of patients	%
Survived five-years disease-free	75	46.3
Died during five-year follow-up of other neoplasm	3	1.9
Died during five-year follow-up of other causes	6	3.7
Died during five-year follow-up of PIVC	78	48.1
Total	*162*	*100.0*

Table 3. — *Fate of 162 patients of the investigated group.*

Causes of radiotherapy treatment failure	N. of patients	%
Local failure	60	76.9
Local failure + distant metastasis	6	7.7
Distant metastasis	12	15.4
Total	*78*	*100.0*

ical Stage of PIVC with other groups presented in the literature is shown in Table 4.

The analysis of data in Table 4 shows great diversity of clinical profile in terms of FIGO stage of PIVC in patient groups presented in the literature. Stage I^0 constitutes 6.7% to 52.4% of the cases; Stage II^0, 10.7% to 69.3%; Stage III^0, 6.3% to 60.0%; and Stage IV^0, 2.3% to 20.1%. In 2004, Hacker [32] presented compilation of selected 13 reports on PIVC published in 1982 to 2001, and describing 1,501 patients in total; 395 (26.3%) were diagnosed Stage I^0 PIVC; 562 (37.4%), Stage II^0; 352 (23.5%), Stage III^0; and 192 (12.8%), Stage IV^0. The group of 162 patients discussed in this paper has a clinical profile similar to that presented by Hacker; Stage I^0 – 26.0%, Stage II^0- 36.4%, Stage III^0 – 22.8%, and Stage IVA^0 – 14.8%.

Table 4. — *Clinical profile of patient groups presented in the literature in terms of FIGO Stage of PIVC.*

Authors and reference entry n.	Publication date	FIGO Stage of carcinoma (%) I^0	II^0	III^0	IV^0
Spirtos *et al*. [44]	1989	47.3%	13.2%	26.3%	13.2%
Malmström *et al*. [31]	1989	22.4%	41.4%	20.7%	15.5%
Eddy *et al*. [14]	1991	27.5%	42.8%	16.5%	13.2%
Reddy *et al*. [40]	1991	34.1%	50.0%	13.6%	2.3%
Stock *et al*. [45]	1992	12.2%	55.1%	20.4%	12.3%
Leung and Sexton [29]	1993	52.4%	10.7%	25.0%	11.9%
Dixit *et al*. [13]	1993	19.4%	14.3%	60.0%	14.3%
Lee *et al*. [27]	1994	28.8%	27.1%	33.9%	10.2%
Bouma *et al*. [4]	1994	43.7%	34.4%	6.3%	15.6%
Leminen *et al*. [28]	1995	48.8%	23.3%	9.3%	18.6%
Chyle *et al*. [7]	1996	24.6%	46.2%	22.7%	6.5%
Ali *et al*. [1]	1996	33.0%	52.0%	10.0%	5.0%
Schäfer *et al*. [42]	1997	43.0%	24.0%	22.0%	11.0%
Perez *et al*. [36]	1999	30.7%	51.0%	10.5%	7.8%
Pingley *et al*. [38]	2000	6.7%	69.3%	18.7%	5.3%
Stryker [47]	2000	26.5%	47.1%	20.5%	5.9%
Tawari *et al*. [49]	2001	14.1%	54.9%	21.1%	9.9%
Tabata *et al*. [48]	2002	23.9%	50.0%	10.9%	15.2%
Mock *et al*. [32]	2003	21.2%	47.5%	25.0%	6.3%
Frank *et al*. [17]	2005	26.0%	50.0%	20.0%	4.0%
Samant *et al*. [41]	2007	14.3%	60.7%	17.8%	7.2%
Hellman *et al*. [21]	2006	33.4%	19.7%	26.8%	20.1%
de Crevoisier *et al*. [10]	2007	29.0%	38.0%	29.0%	4.0%
Tran *et al*. [51]	2007	42.0%	29.0%	17.0%	11.0%
Lian *et al*. [30]	2008	25.4%	50.9%	16.4%	7.3%
Hegeman *et al*. [20]	2009	17.1%	31.7%	31.7%	19.5%
Sinha *et al*. [43]	2009	29.5%	45.5%	22.7%	2.3%
Blecharz *et al*. - Present paper	2012	26.0%	36.4%	22.8%	14.8%

Five-year PIVC-free survival was observed in 75 (46.3%) of the 162 patients in the investigated group. Table 5 presents comparison of treatment results achieved in COOK with literature data from the last 20 years.

According to data in Table 5 and many other literature data published during the last 20 years, five-year survival for the whole investigated group amounted to 38%-66% with 40%-100% survival for Stage I^0, 34%-90% for Stage II^0, 0%-60% for Stage III^0, and 0%-41% for Stage IV^0. Five-year survival for Stage IVA^0 ranges from 0 to even 41%, and is usually 0% for Stage IVB^0. In comprehensive reports by Kosary (1994), Creasman *et al.* (1998), and Hacker (2004), five-year survival for the whole group of PIVC patients were 51.0%, 52.2%, and 45.5%, respectively [2, 32, 33]. Treatment results achieved in the group of 152 patients given radiotherapy in COOK are comparable with data presented in the literature.

Multifactoral analysis of prognostic factors in the investigated group of 162 PIVC patients treated with radical radiotherapy showed that patient age and FIGO Stage of

Table 5. — *Radiotherapy treatment results in PIVC patients reported in the literature.*

Authors and reference entry n.	Publication date	N. of patients	Five-year survival (%)				
			For the group in total	FIGO Stage			
				I^0	II^0	III^0	IV^0
Malmström *et al*. (31)	1989	58	30.0	50.0	30.0	17.0	10.0
Spirtos *et al*. (44)	1989	38	68.4	94.0	80.0	50.0	0
Reddy *et al*. (40)	1991	45	61.4	78.0	71.0	0	0
Davis *et al*. (12)	1991	116	–	82.0	53.0	50.0	22.0
Eddy *et al*. (14)	1991	91	46.2	73.0	IIA^0 – 47.0 IIB^0 – 35.0 39.0	38.0	25.0
Vavra *et al*. (53)	1991	434	–	76.7	44.5	31.0	18.2
Stock *et al*. (45)	1992	49	38.0	44.0	48.0	40.0	0
Leung and Sexton (29)	1993	84	39.0	68.0	68.0	35.0	–
Stock *et al*. (46)	1995	102	46.1	67.0	53.0	0	15
Leminen *et al*. (28)	1995	46	38.0	55.0	22.0	9.0	17.0
Ali *et al*. (1)	1996	40	40.0	100.0	53.0	25.0	0
Fine *et al*. (16)	1996	55	–	42.0	68.0	58.0	0
Chyle *et al*. (7)	1996	301	60.0	70.0	60.0	42.0	34.0 - IVA0
Kirkbride *et al*. (23)	1996	153	66.0	78.0	77.0	58.0	41.0 - IVA0
Urbański *et al*. (52)	1996	125	42.4	72.7	54.1	22.5	0
Schäfer *et al*. (42)	1997	39	41.0	62.0	44.0	25.0	0
Perez *et al*. (36)	1999	212	54.0	80.0	55.0 – IIA^0 35 – IIB^0 48.0	38.0	0
Pingley *et al*. (38)	2000	75	50.0	40.0	IIA^0 – 55.0 IIB^0 – 60.8	50.0	25.0
Stryker (47)	2000	34	58.8	78.0	63.0	$III^0 + IV^0$ – 33.0	
Kucera *et al*. (26)	2001	110	39.1	81.0	44.0	35.0	15.0
Beller *et al*. (3)	2001	192	42.2	67.0	39.0	33.0	19.0 - IVA^0 0 - IVB^0
Tawari *et al*. (49)	2001	71	58.0	100.0	IIA^0 – 60.0 IIB^0 – 61.0	30.0	0
Tabata *et al*. (48)	2002	39	54.3	82.0	70.0	0	14.0
Mock *et al*. (32)	2003	86	41.0	41.0	43.0	37.0	0
Otton *et al*. (34)	2004	70	-	71.0	48.0	–	–
Hellman *et al*. (21)	2006	314	45.0	75.0	36.0	36.0	IVA^0 – 19.0 IVB^0 – 0
Tran *et al*. (51)	2007	78	64.1	71.0	74.0	46.0	14.0
De Crevoisier *et al*. (10)	2007	91	63.7	75.0	75.0	48.0	0
Lian *et al*. (30)	2008	55	55.6	83.3	79.2	22.2	0
Sinha *et al*. (43)	2009	44	68.2	92.3	80.0	20.0	0
Blecharz *et al*. presented paper	2012	162	46.3	76.2	52.5	27.0	8.3-IVA^0

carcinoma were of independent and statistically unfavourable impact on treatment results.

In the investigated group, five-year disease-free survival was observed in 64.9% of patients younger than 60 years, and 30.7% of patients aged 60 years 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 the age, the better the prognosis [6, 13, 18-20, 33-39]. Vavry *et al.* reported five-year survival for 50% and 34% of patients younger and older than 60 years, respectively; whereas Frank *et al.*, 50% and 34.3% [19, 39]. In Hellman *et al.* research, multifactoral analysis showed that – apart from carcinoma stage and primary tumour size – age was the third independent prognostic factor [37]. Worse survival of patients > 65 years was also observed by Wu *et al.* during research in American population [6]. Malmstrőma *et al.* recorded five-year survival amounting to 43% in the group of patients younger than 70 years, and 21% for patients older than 70 years [38]. Some of the authors question independent prognostic significance of age and emphasize that its impact on treatment results is often shown in single factor analyses [2, 4, 10, 25, 40].

FIGO Stage of carcinoma is primary prognostic factor, never raising doubts in the literature [2-4, 8, 10-13, 15-17, 19, 20, 24-26, 35-39, 41-47].

Table 6 presents causes of radiotherapy failure in PIVC patients as reported by the literature. According to data in Table 6 as well as other literature data, the primary cause of treatment failure in PIVC patients is failure to achieve lo-

Table 6. — *Causes of radiotherapy treatment failures in PIVC patients.*

Authors and reference entry n.	Publication date	N. of patients	% of treatment failure	Loco-regional failures	Distant metastasis	Loco-regional failures + distant metastasis
Kirkbride *et al*. (23)	1995	153	42.0%	32.0%	7.0%	3.0%
Chyle *et al*. (7)	1996	301	35.0%	21.0%	11.0%	3.0%
Urbański *et al*. (52)	1996	125	53.0%	41.0%	8.0%	4.0%
Perez *et al*. (36)	1999	212	42.0%	13.0%	12.0%	17.0%
Pingley *et al*. (38)	2000	75	32.0%	17.3%	12.0%	2.7%
Tabata *et al*. (48)	2002	51	53.0%	41.0%	8.0%	4.0%
Frank *et al*. (17)	2005	193	25.3%	12.4%	6.7%	13.0%
de Crevoisier *et al*. (10)	2007	91	34.1%	26.6%	4.4%	3.1%
Tran *et al*. (51)	2007	78	33.3%	20.5%	6.4%	6.4%
Lian *et al*. (30)	2008	55	27.3%	12.8%	10.9%	3.6%
Sinha *et al*. (43)	2009	45	25.0%	12.0%	8%	5.0%
Blecharz *et al*. Present paper	2012	162	48.1%	37.0%	7.4%	3.7%

coregional disease control; its risk increases in advanced stages of neoplastic disease [1, 8, 9, 12, 13, 18-20, 40, 43]. Chyle *et al.* observed failure in locoregional control in 15%, 18%, 35%, and 60% of PIVC patients in Stages I^0, II^0, III^0, and IV^0, respectively [8]; Tabata *et al.* recorded 36% of the failures in Stages 0-II^0; and 50%, in Stages III^0 and IV^0 [27]. Frank *et al.* found nine percent of locoregional failures in the group of 147 PIVC patients in Stages I^0 and II^0; and 24%, in the group of 46 patients in Stages III^0 and IV^0 [19]. It should be emphasized that 66% of locoregional failures are vaginal [12, 43-45, 48, 49]. Data presented by Dixit *et al.* show that 68% of locoregional failures in PIVC patients in Stage III^0 are cases of incomplete local regression of disease, despite radical radiation treatment given [44]. Research by Yeh *et al.* proved that 85% of locoregional failures occur within irradiated area [50].

Distant metastases in PIVC patients are observed in 8%-30% of the cases [11, 24, 26, 43-45]. Most of them develop in patients with PIVC in Stages III^0 and IV^0 [8, 11, 19, 20, 25, 27, 40, 43]. In material presented by Perez *et al*. in 1999, distant metastases were observed in 8%, 13%, 27%, and 20% of PIVC patients in Stages I^0, IIA^0, IIB^0, and III^0, respectively [40]. Tabata *et al.* recorded distant metastases in 42% of patients in Stages III^0 and IV^0; in the group of patients in early Stages (0^0 - II^0), distant metastases were not observed [27]. In the group of patients presented by Davis *et al.*, distant metastases developed in five percent of Stage I^0 PIVC cases, and in 20% of Stage II^0 [43]. In the material analyzed by Chyle *et al.*, distant metastases were found in 7% of patients in Stage I^0; 18% in Stage II^0; 38% in Stage III^0; and also 38% in Stage IV^0 [8]; whereas in the group presented by Mock *et al.* the numbers were as follows: 0% for Stage I^0, 10% for Stage II^0, and 20% for Stage III^0 [19] The most frequent location of distant metastasis include bones, lungs, liver, large intestine, brain, and mediastinal lymph nodes [17, 43-45, 49, 51].

In the investigated group of 162 PIVC patients, the primary cause of treatment failure was failure to achieve locoregional disease control, which was observed in 66 (40.7%) patients. Distant metastases developed in 18 (11.1%) patients and in 12 (7.4%) cases it was the only cause of treatment failure. Hence, causes of failure in the investigated group are similar to that reported in the literature.

Perez *et al.* analyzed a group of 100 PIVC patients with primary tumour site in upper or middle third of vagina. Despite the fact that inguinal and femoral lymph nodes were not irradiated, none of the patients developed metastasis in the lymph nodes during many years of follow-up. However, metastases in inguinal and femoral lymph nodes were observed in 10% (three of 29) of patients with primary tumour located in lower third of vagina. Of seven patients with confirmed metastasis in lymph nodes at the time of presentation and given radiation doses of around 60 Gy, the nodal failure was recorded in just one case [25, 40]. Similar observations were made by Stock *et al*. as well as Stryker *et al.* [12, 24]. In the investigated group, patients with primary tumour located in lower third of vagina were given elective irradiation of inguinal lymph nodes, and four patients with PIVC metastasis in these lymph nodes were given boost up to 60 Gy dose using electron fields covering the lymph node region. No failures in disease control in inguinal and femoral lymph nodes were observed.

Conclusion

Radiotherapy is effective management of PIVC patients providing the chance for five-year disease-free survival for around half of them. In early Stage (I^0, II^0) patients below 60 years of age, it is possible to achieve 70% of disease control. The primary cause of radiotherapy treatment failure in PIVC patients is failure to achieve locoregional disease control.

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