Radiation therapy complications in patients with primary invasive vaginal carcinoma

Powikłania radioterapii u chorych na pierwotnego inwazyjnego raka pochwy

Paweł Blecharz[1], Marian Reinfuss[2], Jerzy Jakubowicz[2], Piotr Skotnicki[3], Elżbieta Łuczyńska[4], Maciej Bodzek[5], Krzysztof Urbański [1]

[1] Department of Gynecologic Oncology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Krakow Branch, Poland
[2] Department of Radiation Oncology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Krakow Branch, Poland
[3] Department of Surgical Oncology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Krakow Branch, Poland
[4] Department of Diagnostic Imaging, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Krakow Branch, Poland
[5] Department of Obstetrisc and Gynecology, L.Rydygier Memorial Hospital, Krakow. Poland

Abstract

Objectives: *The aim of the study was to estimate acute and late complications of radiation therapy in primary invasive vaginal carcinoma (PIVC) patients.*

Material and methods: *The analysis was performed for the group of 152 PIVC patients given radical radiotherapy in the Krakow Branch of Centre of Oncology during the 1967–2005 period. Twenty five (16.5%) patients in I stage with primary tumour of the thickness not larger than 0.5 cm were treated with intracavitary brachytherapy alone; for 120 (78.9%) patients (stages I – IVA) intracavitary brachytherapy was combined with external radiation therapy; and 7 (4.6%) patients in stage IVA were given only external radiotherapy. In total, 145 (95.4%) patients were treated with intracavitary LDR brachyterapy by means of Ra-226 or afterloaded Cs-137 sources, and 127 (83.5%) received external radiation therapy using Co-60 and linac 10MV or 6MV photon beams.*

Results: *Early radiotherapy tolerance was good in the investigated group; 146 (96.1%) patients completed full planned radiation therapy treatment. Late complications of radiation therapy were observed in 21 (13.8%) patients: 3 (2%) patients reported mild complications, 12 (7.9%) moderate complications, and 6 (3.9%) severe complications. Severe complications of radiation therapy in the investigated group included: recto-vaginal fistula (5 patients) and vesico-vaginal fistula (1 patient). None of the patients in the group died of radiation therapy complications.*

Conclusions: *Early tolerance of radiotherapy in PIVC patients is generally good. Late radiation therapy complications, particularly the severe, are rare and can be efficiently managed with conservative therapy or surgical treatment.*

Key words: **radiotherapy** / **vaginal cancer** / **complications** /

Address for correspondence:
Paweł Blecharz
Department of Gynecologic Oncology, Centre of Oncology, Maria Sklodowska-Curie, Memorial Institute, Krakow Branch
Garncarska 11, 31-115 Kraków, Poland
phone: 501 223 772
e-mail: pawel.blecharz@interia.pl

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Streszczenie

Cel pracy: *Celem pracy była ocena wczesnych i późnych powikłań radioterapii chorych na pierwotnego inwazyjnego raka pochwy (PIVC).*

Materiał i metody: *Przedmiotem analizy była grupa 152 chorych na PIVC napromienianych radykalnie w krakowskim Oddziale Centrum Onkologii w latach 1967-2005. U 25 (16,5%) chorych na PIVC w I0 zaawansowania, ze zmianą pierwotną nieprzekraczającą 0,5cm grubości przeprowadzono wyłącznie brachyterapię dojamową, u 120 (78,9%) chorych (I0- IVA0) brachyterapię dojamową skojarzoną z teleradioterapią, a u 7 (4,6%) chorych w IVA0 zaawansowania wyłącznie teleradioterapię. W sumie, u 145 (95,4%) chorych zastosowano brachyterapię dojamową LDR radem-226 lub cezem-137, a u 127 (83,5%) teleradioterapię w warunkach telegammaterapii kobaltem-60 lub promieniowania X o energii 10MeV lub 6MeV z akceleratorów liniowych.*

Wyniki: *Bezpośrednia tolerancja radioterapii w badanej grupie chorych była dobra; pełną zaplanowaną radioterapię przeprowadzono u 146 (96,1%) chorych. Późne powikłania napromieniania stwierdzono u 21 (13,8%) chorych: u 3 (2%) były to powikłania o średnim nasileniu, u 12 (7,9%) znacznym nasileniu i u 6 (3,9%) – o bardzo ciężkim nasileniu. Ciężkie powikłania radioterapii w badanej grupie chorych to: przetoka pochwowo-odbytnicza (5 chorych) i przetoka pochwowo-pęcherzowa (1 chora). Żadna chora z badanej grupy nie zmarła z powodu powikłań radioterapii.*

Wnioski: *Bezpośrednia tolerancja radioterapii chorych na PIVC jest zasadniczo dobra. Późne powikłania radioterapii, szczególnie ciężkie są rzadkie i mogą być skutecznie leczone zachowawczo lub operacyjnie.*

Słowa kluczowe: **radioterapia** / **rak pochwy** / **powikłania** /

Introduction

Radiation therapy is the treatment of choice for most of the primary invasive vaginal carcinoma (PIVC) patients [1-10]. Of the essential importance is intravaginal treatment. The source of ionizing radiation in intracavitary brachytherapy is radium (Ra-226) (rarely used nowadays) and afterloaded caesium (Cs-137) or iridium (Ir-192); interstitial brachytherapy is performed by means of permanent implants of radioactive gold (Au-198) or iodine (I-125), and temporary implants containing radioactive iridium (Ir-192). Both brachytherapy modalities are combined for part of the patients. In cases of vaginal vault involvement additional intrauterine applicator is used [6, 8-16]. Generally, PIVC patients are advised low-dose rate (LDR, 0,4-2Gy/h) treatment and rarely medium-dose rate treatment (MDR, 2Gy – 12Gy/h). In recent years, a growing number of institutions uses iridium sources of a high-dose rate (HDR, over 12Gy/h). For most of the patients intravaginal brachytherapy is supplemented with external radiation therapy [6, 16-19]. Selected non-advanced PIVC patients with small (up to 0.5 cm) superficial neoplastic lesions may be treated with brachytherapy alone [6, 10, 11, 16, 18, 19].

Objectives

The aim of the study was the analysis of acute and late complications of radiation therapy in PIVC patients. There are many controversies on the subject in the literature and their main reasons include rare occurrence of PIVC, differences in clinical profile and radiotherapy techniques advised in analyzed groups of patients, diverse type and severity assessment scales of the complications [6, 15, 17, 19-25].

Material and methods

The detailed analysis was performed for the group of 152 PIVC patients given radical radiotherapy in the Krakow Branch of Centre of Oncology (COOK) during the 1967–2005 period. Demographic, clinical and histopathological characteristics of the investigated group have been presented in detail in earlier work, "Prognostic factors for vaginal carcinoma patients".

Radiotherapy modalities

Table I presents radiotherapy modalities applied in the investigated group of patients in relation to FIGO stage of neoplastic disease.

Table I. Radiotherapy modalities applied in the group of 152 PIVC patients.

FIGO stage of PIVC	Radiotherapy modality	Numer of patients	
		No.	%
I^0	intracavitary brachytherapy	25	16.5
	intracavitary brachytherapy + external radiotherapy	14	9.2
II^0 and III^0	intracavitary brachytherapy + external radiotherapy	91	59.8
IVA^0	intracavitary brachytherapy + external radiotherapy	15	9.9
	external radiotherapy alone	7	4.6
Total		**152**	**100.0**

Hundred and forty five (95.4%) patients were treated with intracavitary LDR brachytherapy using radium-226 (manual loading) or cesium-137 (Selectron LDR/MDR afterloader) sources, among which 131 (90.3%) patients were given a single-fraction treatment and 14 (9.7%) a 2-fraction course with a 3-week-interval. For 25 (16.5%) patients of 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 2 cm in its largest dimension. The treatment was performed using vaginal colpostat (2 applicators along vagina axis with 2 additional dome applicators in cases of upper vagina involvement). Total radiation dose to primary tumor calculated at 0.5cm distance from vaginal mucosa was 65-70 Gy; vaginal mucosa received dose of 95-100 Gy. Remaining 14 (9.2%) patients in stage I^0 PIVC with primary tumour exceeding 0.5 cm thickness were additionally given external radiation therapy involving whole pelvis minor irradiation to 50 Gy in 25 fractions within 5-week-period.

All of the 91 patients with stage II^0 and III^0 PIVC were treated with the combination of intracavitary brachytherapy and external radiotherapy. Intracavitary brachytherapy dose to infiltration base was 65-70Gy. Dose to Manchester A points varied from 44 to 62Gy (mean value of 52Gy) with the overall irradiation time of 72 up to 132 hours, most commonly within 96-120 hours range. Rectal mucosa dose received due to intracavitary brachytherapy was 31 to 56Gy; for most of the patients it stayed within 35-40Gy range. If the primary tumour was located in the upper third of vagina, vaginal colpostat was used together with intrauterine applicator.

Fifteen (9.9%) of 22 IVA^0 stage PIVC patients were advised intracavitary brachytherapy (as in case of I^0 and III^0 stage) in combination with external radiotherapy; 7 (4.6%) 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.

In total, 127 (83.5%) patients received external radiotherapy treatment: 58 (45.7%) were irradiated with Co-60 beams and the remaining 69 (54.3%) with 10MV or 6MV linac photon beams.

Patients were treated with four external beams: anterior field, posterior field and two opposite lateral fields (so called box technique).

AP-PA fields covered the area from the lower edge of obturator foramens up to L4-L5 junction level with lateral boundaries extending 1-1.5cm sideways outside the pelvic brim. Lateral fields were limited in the anterior direction by the pubic symphysis.

Entry field size was 15x15cm to 15x18cm for AP-PA fields, and 15x8cm to 15x10cm for lateral fields. Pelvis minor area determined this way was irradiated with daily dose of 2Gy to total dose of 50Gy in 25 fractions within 5-week-period.

Tumour dose was calculated at the intersection of AP-PA and lateral fields axes. It was assumed that all the beams had equal dose contribution of 12.5Gy. All the fields were irradiated during one session a day. Patients with primary tumour in the lower third of vagina were advised elective inguinal irradiation.

Four patients with histopathology confirmed PIVC metastasis in inguinal lymph nodes were given additional 15-20Gy dose ("boost") to that area using smaller fields of 15MeV electron beams. Seven IVA^0 stage PIVC patients treated with external radiotherapy alone were given 15-20Gy boost using "shrinking-field technique" up to total dose of 65-70Gy.

Of the 152 patients in the investigated group, 70 (46.1%) had 5-year disease-free survival (DFS), 74 (48.7%) died of PIVC during the 5-year follow-up period, and 8 (5.2%) died of other cause. Detailed analysis of treatment results has been presented in earlier work, "Prognostic factors for vaginal carcinoma patients".

Treatment course and complications

All the patients of the investigated group developed symptoms of postradiation reaction with 69 (45.4%) cases of considerable severity, mainly including loose stool, diarrhoea, abdominal pain, pollakiuria, difficulty and pain during micturition, purulent or bloody-and-mucoid vaginal discharge. Advised treatment involved diet control, administration of antidiarrhoeic drugs, analgesics and antibacterial drugs, vagina irrigation, etc. In definite majority of the patients (94.7%) the symptoms subsided within 2-3 months from the completion of radiotherapy; in several cases it lasted a little longer.

Table II presents the course of radiotherapy treatment in the investigated group of patients.

Table II. Course of radiotherapy treatment of 152 PIVC patients.

Radiotherapy treatment course	Numer of patients	%
Full planned radiotherapy treatment completed without interruptions	142	93.5
Full planned radiotherapy completed with an interruption during the treatment	4	2.6
Planned brachytherapy completed without completing external radiotherapy	6	3.9
Total	**152**	**100.0**

Data presented in Table II suggest that the radiotherapy tolerance in the investigated group of patients was good. Hundred forty six (96.1%) patients completed full planned radiotherapy. Six (3.9%) patients completed planned brachytherapy, but were not given full planned external radiotherapy dose due to condition deterioration (2 patients), exacerbation of accompanying disease symptoms (3 patients) and further radiotherapy refusal (1 patient). In all these cases patients received at least 2/3 of the planned external radiotherapy dose.

Late complications of radiation therapy were observed in 21 (13.8%) patients of the investigated group. Table III presents reported complications as defined by the glossary by Chassagne *et al.* published in 1993 [20].

Late radiotherapy complications in the investigated group included G1 complications observed in 3 (2%) patients, G2 in 12 (7.9%) patients, and G3 in 6 (3.9%) patients. There were no G4 complications in the group so that none of the patients died directly of radiotherapy complications.

Eleven patients had rectal complications in the form of recto-vaginal fistula (G3a) – 5 patients, chronic rectal bleeding periodically requiring hospitalization and blood transfusion (G2a) – 3 patients, and pain and tenesmus associated with necrotic rectal ulceration (G2b) – 3 patients.

Bladder complications were observed in 5 patients: vesico-vaginal fistula (G3d) in 1 patient, hematuria periodically requiring

Table III. Late radiotherapy complications in the group of 152 PIVC patients.

Organ	Severity (number of patients)		
	G1	G2	G3
Rectum	-	6	5
Bladder	1	3	1
Vagina	2	3	-
Total	**3**	**12**	**6**

hospitalization and blood transfusion as well as intensive antibacterial treatment (G3a) in 3 patients, and occasional incontinence (G1c) in 1 patient.

Vagina complications observed in 5 patients included vaginal narrowing and shortening to more than half the original dimensions (G2a) – 2 cases, symptomatic vulval fibrosis (G2c) – 1 case, and vaginal narrowing and shortening to less than half the original dimensions (G1b) – 2 cases.

Late radiotherapy complications occurred in the investigated group of patients 7 to 34 months after the treatment completion with 2/3 of the cases manifesting after 10 to 13 months.

All the G1 and G2 complications were managed with conservative therapy. Chronic rectal bleeding and hematuria were treated with blood transfusion, bladder infusions and enemas of agents controlling bleeding and accelerating ulceration healing, antibiotic treatment, analgesic and anti-inflammatory drugs; tenesmus patients were advised dietetic and antidiarrhoeic treatment. Inflammatory condition in vagina was reduced by general anti-inflammatory treatment and regular vagina irrigation. Attempts were made to prevent vaginal narrowing by regular vagina dilatation as well as local application of oestrogen creams or pentoxifylline with vitamin E. In most of the cases the conservative treatment proved to be effective and the symptoms subsided within few months or were considerably reduced (e.g. vagina narrowing).

Six patients in the group developed fistulas (5 cases of 3a grade recto-vaginal fistula and 1 case of 3d grade vesico-vaginal fistula). Three of these patients (III^0 and IVA^0 stage PIVC) died of locoregional failure (2 patients) and simultaneous distant metastasis (1 patient). Remaining 2 patients with recto-vaginal fistula underwent surgical treatment; one of them was disease-free for 5 years, the other died 4 years after the radiotherapy was started and 18 months after the surgery due to locoregional recurrence.

Cox multifactoral regression analysis did not result in any statistically significant, independent prognostic factors either for acute postradiation reaction or late radiotherapy complications.

Discussion

All 152 patients of the investigated group developed symptoms of postradiation reaction with 69 (45.4%) cases of considerable intensity, which is consistent with other reports [2, 4, 22, 26-29].

In some patients ineffective repair process is responsible for late radiotherapy complications. In vagina, fibrosis, vaginal narrowing and/or shortening, vaginal dryness, elasticity loss, ulceration and even necrosis are observed. Postradiation recto-intestinal complications include persistent and bothersome diarrhoea, relapsing inflammations, chronic bleeding, and intestinal and rectal stenosis; complications in bladder and ureter include relapsing bladder mucosistis, chronic dysuria, hematuria and ureteral stenosis with progressive hydronephrosis.

The most severe radiotherapy complications observed in PIVC patients include complete vaginal stenosis, vaginal necrosis, small bowel obstruction, intestinal perforation, and recto-vaginal, vesico-vaginal or uretero-vaginal fistula [1, 2, 4-6, 8, 9, 11, 16, 17, 19, 21, 22, 24, 25, 27, 28, 30, 31].

As reported in the literature, severe radiotherapy complications develop in 5-19% of PIVC patients [2-5, 8-11, 15-17, 19, 21, 24, 25, 27, 28, 30, 32]. In the investigated group, severe complications occurred in 11.8% of patients.

One of the most frequent late radiotherapy complications in PIVC patients is various grade vaginal stenosis reported in the literature in 10-50% of the patients [2, 22, 33-37]. Obviously, much increased (G3) vagina narrowing is significantly rarer in larger groups, e.g. in 55-patient group analyzed by Lian *et al.* it was observed in 3 cases i.e. in 5.5% of the patients [5]. In the group analyzed in this work vagina narrowing and shortening of a higher grade (G2a) had 2 (1.3%) patients and of a lower grade (G1b) additional 2 patients. Vagina necrosis occurs rarely; Hegemann *et al*. reported 1 case in a 41-patient group, and Chyle *et al.* recorded 8 cases in presented group of 301 patients [4, 11]. Single necrotic loci in vaginal mucosa are more frequent and reported in the literature in 4-15% of PIVC patients treated with brachytherapy combined with external radiation therapy [2, 34, 38]. In the investigated group, there were no cases of postradiation necrosis in vagina.

Developing a fistula or fistulas (recto-vaginal, vesico-vaginal, uretero-vaginal or cutaneous-vaginal) is a severe radiotherapy complication and its frequency is reported in the literature as 1-8% [5, 26, 34, 36, 39]. In the investigated group there were 6 cases of postradiation fistula: 5 recto-vaginal and 1 vesico-vaginal, which constituted 3.9% of the patients.

In the investigated group there were 3 cases of a severe chronic rectal bleeding and 3 cases of pain and tenesmus associated with necrotic rectal ulceration, which constituted 3.9% of patients. Though, there were no cases of severe intestinal complications requiring surgical treatment, i.e. extensive ulceration, perforation or high grade stenosis, reported by other researchers [11, 26, 30].

Some authors emphasize the relation between severe postradiation complications occurrence and initial stage of neoplastic disease; there is no doubt that for III^0 and IV^0 stage PIVC patients who were given radical radiotherapy the risk of these complications is much higher [11, 21, 26, 30, 33].

The literature reports much more factors potentially increasing late postradiation complication risk in PIVC patients such as smoking, earlier surgical treatment, inflammations in pelvic area, immunosuppression conditions, low body weight, advanced age, accompanying diseases (diabetes, hypertension) etc. Their impact has not been commonly proved, though it has been observed by some researchers [17, 21, 26, 30].

Mock *et al.* have analyzed HDR brachytherapy treatment administered alone or in combination with external radiation therapy and found no pre-therapeutic factors affecting the frequency of late severe postradiation complication occurrence, as also did de Crevoisier *et al.* and authors of this work [2, 6].

Late radiotherapy complications generally develop 6 months to 2 years after the radiation treatment with the average of 1 year; more than 95% of the complications occur within the first 5 years, however, the complications may occur even 16 years after the treatment [29, 39]. Late radiotherapy complications occurred in the investigated group of patients 7 to 34 months after the treatment completion with 2/3 of the cases manifesting after 10 to 13 months.

Decrease in the frequency of late postradiation complications occurrence in PIVC patients might probably be achieved by the introduction of modern radiotherapy techniques, particularly IMRT [17, 40, 41].

Conclusions

Radiation therapy is effective and well-tolerated therapeutic management for PIVC patients. Late radiotherapy complications occur in several per cent of the cases, and severe complications, mainly of grade 3, only in few per cent of the patients. Providing appropriate conservative or surgical treatment (fistulas), the complications are not life-threatening for the patients.

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