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High-dose-rate interstitial brachytherapy for mucinous adenocarcinoma endocervical-type – a case study

Śródtkankowa brachyterapia HDR w leczeniu gruczolakoraka śluzowego typu szyjkowego – opis przypadku

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Abstract

Background: *Adenocarcinoma in cervical cancer has poorer response rate to treatment and requires longer time to achieve complete remission than squamous cell carcinoma [1]. Lower response to chemotherapy and radiotherapy is observed [2,3,4,5] and the optimal management remains undefined [1,4,6,7]. Case: We report a case of a 58-year-old woman with bulky mucinous adenocarcinoma endocervical-type G1, treated previously with radiochemotherapy with no visible response. After subsequent interstitial HDR brachytherapy (iHDR-BT) complete local remission was achieved.*

Conclusion: *Interstitial HDR brachytherapy in bulky mucinous adenocarcinoma endocervical-type may be the best treatment choice that allows to receive a complete local response.*

Key words: **interstitial HDR brachytherapy** / / **mucinous adenocarcinoma endocervical-type** /

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Streszczenie

Gruczolakoraki szyjki macicy charakteryzują się słabszą odpowiedzią na leczenie i w porównaniu do raków płaskonabłonkowych wymagają dłuższego czasu do uzyskania remisji [1]. Ten typ nowotworu gorzej odpowiada na chemioterapię oraz radioterapię [2, 3, 4, 5] a optymalny schemat postępowania terapeutycznego nadal jest pozostaje przedmiotem badań [1, 4, 6, 7].

Opis przypadku: *58-letnia chora na raka szyjki macicy IB2 (gruczolakorak śluzowy typu szyjkowego G1) leczona radykalnie radiochemioterapią (bez widocznego efektu klinicznego) została poddana uzupełniającej śródtkankowej brachyterapii HDR. Zastosowane leczenie pozwoliło uzyskać całkowitą remisję.*

Wnioski: *Śródtkankowa brachyterapia HDR w leczeniu gruczolakoraka śluzowego typu szyjkowego w stopniu IB2 pozwoliła uzyskać całkowitą, miejscową regresję zmian.*

Słowa kluczowe: **śródtkankowa brachyterapia HDR** / **gruczolakorak śluzowy** / **typ szyjkowy** /

Introduction

Adenocarcinoma of the cervix constitutes about 10-20% of all cervical carcinomas [6], and mucinous adenocarcinoma is the most common histological subtype [8, 9]. It has been known to show a poorer prognosis when compared with squamous cell carcinoma due to delayed tumor detection and poor response to radiotherapy [2, 3, 10].

A worse survival outcome was observed in early cervical adenocarcinoma than in squamous cell carcinoma [9, 11]. Also, in locally advanced disease, worse response rates to treatment and longer time to achieve complete remission were noted [1]. In patients with pelvic lymph node metastasis, adenocarcinoma was associated with less favorable outcomes than squamous cell carcinoma [4]. It is suggested that due to its low radiosensitivity, treatment of adenocarcinoma requires a new strategy [2]. So far, there has been no standard therapy procedure [7, 12]. In most trials, the number of patients with adenocarcinoma was insufficient to perform proper analysis and, as a consequence, the understanding of the natural history of adenocarcinoma of the cervix remains limited and optimal therapy unavailable. [6].

In Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology Gliwice Branch interstitial HDR brachytherapy (iHDR-BT) has been performed since early 90's. Usually after radiochemotherapy, interstitial HDR brachytherapy was performed for selected patients with bulky cervical cancer. IHDR-BT delivers a high dose of radiation strictly to the tumor, while sparing the adjacent healthy tissues, offering a good local control and individualized treatment over a short period of time [13, 14].

The aim of our study was to present the actual benefit of the interstitial HDR brachytherapy for a patient with bulky mucinous adenocarcinoma endocervical-type, previously treated with radiochemotherapy but with poor response.

Case report

Patient characteristic and preliminary proceedings

A 58-year-old woman with mucinous adenocarcinoma endocervical-type was treated at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology Gliwice Branch.

In January 2011 she was diagnosed with mucinous adenocarcinoma endocervical-type G1 (FIGO IB2). Gynecological examination revealed an exophytic, bleeding tumor with posterior vaginal gathering. Clinically, parametra were without infiltration. Inguinal lymph nodes were not palpable. No other pathological changes were found. Episodes of bleeding started a year before.

Urography and cystoscopy were normal except inflammatory changes in vesical urinary triangle.

The first Magnetic Resonance (MR) (02.03.2011) revealed a cervical tumor (7.3x6.3x4.8cm), infiltrating the posterior vaginal fornix and more than a half of the uterus. An unobtrusive infiltration to surrounding fat tissue of the cervix was found. One lymph node near the external iliac venous, 8x10mm in diameter, was observed (Figure 1).

The patient underwent radical radiochemotherapy. Radiotherapy: 20MV, total dose to the pelvis with tumor was 45Gy, boost up to 54Gy to tumor. Fraction dose was 1.8Gy. Chemotherapy: DDP 70mg weekly (six fractions). Overall treatment time was 44 days.

The second MR (06.05.2011), after 40Gy of EBRT, showed no remission, except for the fact that the previously enlarged lymphatic node was normal sized and no longer suspected of metastasis.

Due to no tumor response to radiochemotherapy, a radical hysterectomy was considered but the patient did not qualify for the procedure because of the size of the tumor and difficult anatomical conditions. Four weeks after radiochemotherapy, the patient was qualified to interstitial HDR brachytherapy.

Brachytherapy

Interstitial HDR afterloading brachytherapy with Ir^{192} source was delivered in local anesthesia. Implantation was performed at each brachytherapy fraction. Plastic needles were inserted into the cervical tumor. Total dose was 22.5Gy delivered in three fractions, one fraction per week, (implant of 5 needles was used for the first two fractions and for the last fraction 6 needles were implanted). Overall treatment time was 13 days.

The clinical target volume was determined either by clinical examination and CT imaging. Therapeutic dose was prescribed

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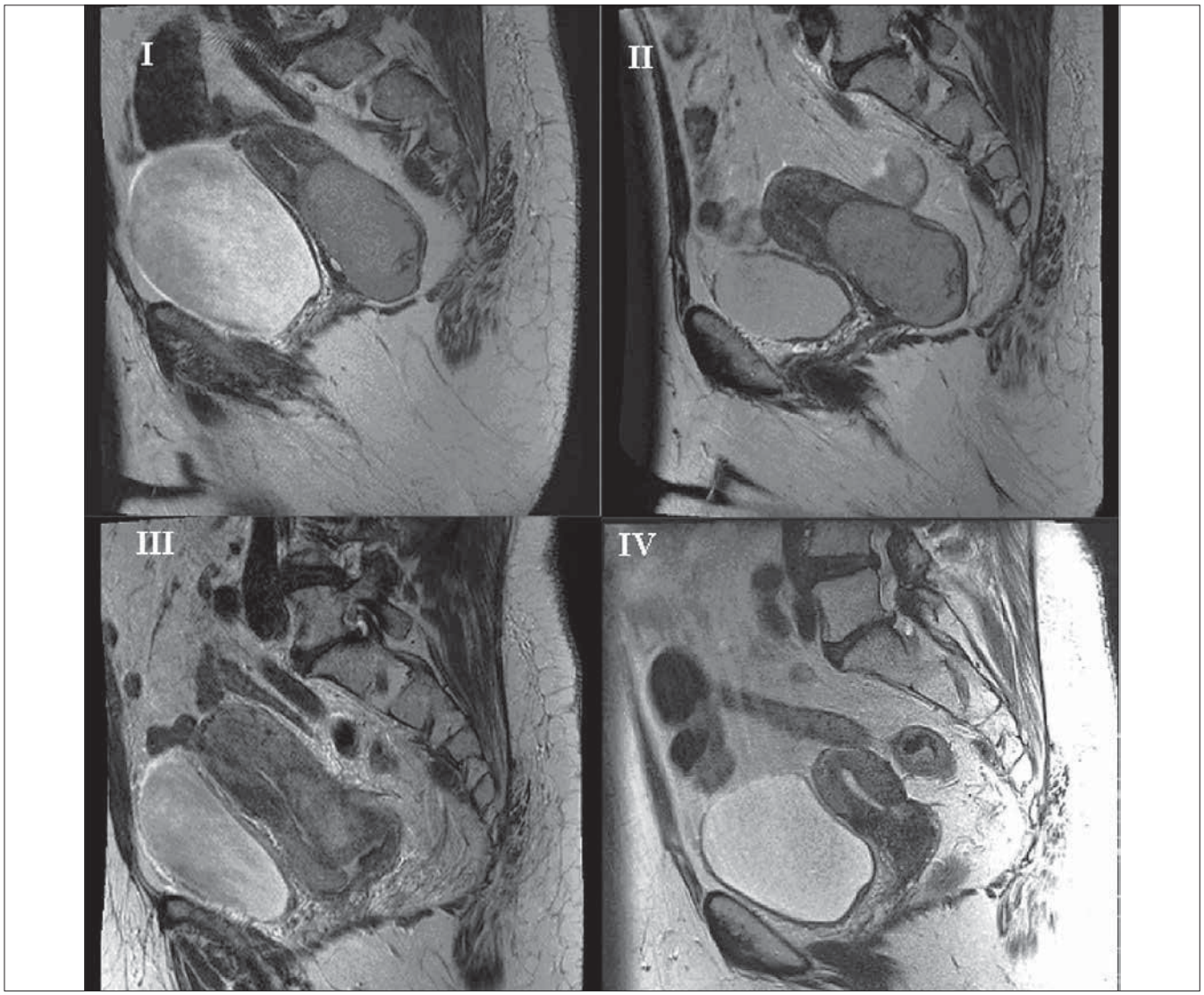

Figure 1. Sagittal T-2 weighted MR (I - 02.03.2011; II - 06.05.2011; III - 22.07.2011 and IV - 30.01.2012) depicts the region of the cervical tumor.

5 mm from the surface of the applicator. Treatment plan was calculated with Oncentra MasterPlan v 3.xxx (Nucletron™) based on cone beam CT imaging (Simulix Evolution Nucletron™) (Figure 2).

Mean volume irradiated with the prescribed dose was 35.0 ± 10 ccm, while the volume of the hyperdose region (the volume surrounded by the 200% of the prescribed dose) was 7.5 ± 3.3 ccm.

Follow up and analysis

Two weeks after the interstitial HDR brachytherapy, the patient complained of polyuria, tenesmus and weakness. Tender necrotic tumor (4cm diameter), in the process of disintegration with stinking secretion and small bleeding was observed during a gynecological examination. Vagina toilet was performed with metronidazole and iodine rinse during each gynecological follow-up. Tumor bleeding, polyuria, tenesmus and weakness stopped.

The third MR (22.07.2011) showed partial remission, the largest dimension of cervical tumor was 5 cm. Advanced necrosis was observed in the tumor region and post-radiotherapy features in the surrounding tissues.

The next MR (30.01.2012) showed almost complete remission. A small suspected focus (high signal in T2), 11mm in diameter, was observed in the posterior wall between the cervix and the uterus (isthmus), without evident features of restriction of diffusion and without signal intensity after intravenous contrast.

The last MR (08.08.212) showed complete remission.

At present the patient is under periodical controls and remains in good overall condition. Other examinations showed no symptoms of an active disease.

Discussion

The ratio of adenocarcinoma to squamous cell carcinoma has increased from 5% to 25% in the last half of the century [11, 15]. The overall declining incidence of cervical cancer was observed. In contrast, an increasing number of adenocarcinomas and adenosquamous carcinomas, particularly in younger women, was noticed [6, 11, 16, 17].

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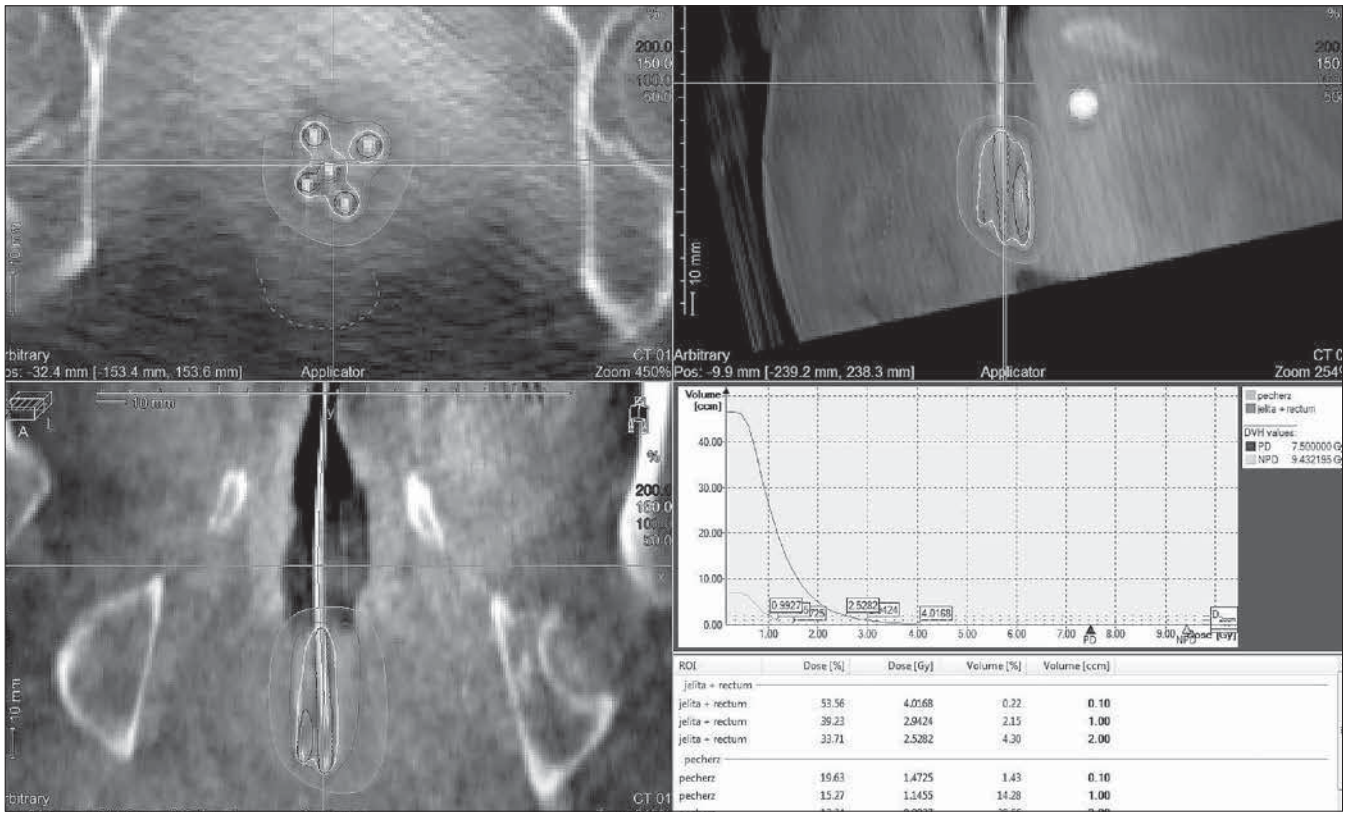

Figure 2. Dose distribution (top), dose volume histogram (lower left) and 3D dose (lower right) calculated for the interstitial implant for brachytherapy of the cervical cancer. Red line represents the reference isodose of 22.5 Gy. 3D-view green tubes represent implanted needles reconstructed in the treatment planning system.

The number of cases of mucinous adenocarcinoma increased from 1–3 cases per year between 1973–1975 to 11-17 per year between 2000–2002 [16].

Screening for early glandular lesions is suggested to have a low sensitivity, and adenocarcinomas might be easily missed by conventional screening methods, possibly due to their location higher in the cervical canal [16].

Five types of mucinous adenocarcinomas may occur in the cervix: endocervical, intestinal, signet ring cell, minimal deviation adenocarcinoma and villoglandular. The endocervical type accounts for 70% of cervical adenocarcinomas [18] and is characterized by cells with pale granular cytoplasm and basal nuclei resembling the cells of the endocervix [8].

There is no standard treatment for cervical adenocarcinoma. A relatively low number of trials does not allow to document the most appropriate therapeutic modalities [6].

Adenocarcinoma histology negatively impacts survival for both early and advanced-stage carcinomas [17].

Many authors showed that cervical adenocarcinoma is resistant to radiation therapy [4, 19]. Also, among patients receiving post-operative radiotherapy, the survival rate for adenocarcinoma was significantly poorer than for patients with squamous cell carcinoma [4, 9]. Poujade et al., indicated factors associated with a significantly decreased sensitivity to neoadjuvant chemoradiotherapy i.e. menopause, parametrial invasion, lymphovascular space invasion and mucinous subtype [5].

In our case, there was also no visible response to chemoradiotherapy.

Some authors suggest that primary radical surgery followed by adjuvant therapy, which is the same treatment strategy as for squamous cell carcinoma, may be acceptable for adenocarcinomas with tumor size 2–4 cm in diameter as well [20]. A surgery for early stage adenocarcinoma of the uterine cervix in carefully staged patients is recommended [19]. Primary chemoradiotherapy remains the second best alternative for patients unfit for surgery; chemoradiation is probably the first choice in patients with (MR or PET-CT-suspected) positive lymph nodes [12]. The optimal treatment of women with advanced adenocarcinoma of uterine cervix remains undefined [1, 2, 5].

Our patient with bulky cervical tumor was disqualified from surgery due to difficult anatomical conditions. Tumor volumes of cervical adenocarcinomas are usually large, but in about 15% of patients there are no visible lesions [10]. In our cases the tumor was 7.3x6.3x4.8cm (in first MR). Tsubamoto et al., suggest that neoadjuvant chemotherapy (NAC) followed by radical hysterectomy (RH) for bulky cervical adenocarcinoma could be an alternative therapy to primary radiation [3].

Data on high-dose-rate interstitial brachytherapy (iHDR-BT) for mucinous adenocarcinoma endocervical-type are scarce [13]. A high rate of pelvic control and overall survival, with acceptable level of late toxicities, were obtained for patients with advanced cervical carcinoma treated with iHDR-BT [13, 14].

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Brachytherapy delivers a high dose of radiation strictly to the tumor while sparing the adjacent healthy tissues, because of rapid fall in dose outside the target. It offers good local control with functional and anatomical organ preservation.

In our study iHDR-BT was generally well tolerated by the patient although local acute toxicity was observed (I° EORTC – bladder – polyuria).

We used magnetic resonance to evaluate tumor regression. MR is believed to be the best method of assessing the stage of cervical cancer. T2-weighted images are used for assessment of the organ morphology, particularly the three primary layers of the uterus [21]. Adenocarcinoma appears on T2-weighted images as an area of high intensity, solid or cystic, mixed solid, or cystic cervical mass located in the endocervical canal. Typically, the mass is barrel-shaped, with preservation of the endocervical epithelium [22]. The cervical adenocarcinoma in MR shows higher SI than squamous cell carcinoma on FSE T2WI. Chung JJ et al., observed that if the SI ratio of the tumor was more than 3.0, adenocarcinoma could be diagnosed with a sensitivity of 68.8% and a specificity of 100% [10].

Adenocarcinoma of the uterine cervix has a tendency to early lymph node metastasis [3] and the incidence of lymph node involvement is significantly higher in patients with adenocarcinoma than in those with squamous cell carcinoma (31.6%vs 14.8%) [4]. Adenocarcinomas have also higher risk of recurrence [9].

In case of our patient, the PET-CT performed at the beginning of radiochemotherapy revealed no symptoms of lymph node involvement or distant metastasis. The follow up is 6 months and there are no symptoms of an active disease.

Oświadczenie autorów:

1. Sylwia Kellas-Ślęczka – współautor koncepcji i założeń pracy, opracowanie danych, przygotowanie manuskryptu i piśmiennictwa – autor zgłaszający i odpowiedzialny za manuskrypt.
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