

## **Evaluation of MDR brachytherapy and teletherapy results in patients with advanced cervical cancer**

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*Introduction.* Definitive radiation therapy has been established as an effective treatment in patients with advanced cervical cancer. The aim of the study is to evaluate the results of MDR brachytherapy and external beam radiation in patients with cervical cancer in stages II b and III.

*Material and methods.* Between 1981 and 1986 161 patients with advanced cervical cancer (34 – stage II b; 127 – stage III acc. to FIGO scale) were treated in the Institute of Oncology in Gliwice. The treatment was one of combined radiotherapy: external beam radiation (60Co photons) and original MDR brachytherapy 137Cs based on individually selected applicators and fractionation schedule.

*Results.* The 5-year disease-free survival rate for patients with stage II b tumours was 60%, with stage III – 41%. In 54 patients (33,5%) clinical examination after the completion of treatment revealed persistent disease, 26 patients (16%) developed local recurrences, 11 patients (7%) – distant metastases. Treatment tolerance in the analysed group was good. Severe postradiation complications were noted in 2 cases (1%).

*Conclusion.* The efficiency and tolerance of cervical cancer treatment combined with MDR brachytherapy was good and comparable with data reported in literature.

### **Ocena wyników brachyterapii MDR i teleradioterapii u chorych na zaawansowanego raka szyjki macicy**

*Wstęp.* Radioterapia jest podstawową metodą leczenia chorych na zaawansowanego raka szyjki macicy i polega na skojarzeniu napromieniania od zewnątrz i leczenia wewnątrzjamowego. Celem pracy jest ocena wyników brachyterapii średnimi mocami dawek (MDR BT) i teleterapii (TT) u chorych na zaawansowanego raka szyjki macicy.

*Materiał i metoda.* Materiał stanowiło 161 chorych leczonych radykalnie w Centrum Onkologii-Instytucie w Gliwicach w latach 1981-1986. U 34 chorych stwierdzono stopień zaawansowania II b, a u 127 – III według FIGO. Wszystkie chore poddano radykalnej TT (60Co) oraz MDR BT (137Cs), opartej o indywidualny dobór aplikatorów i oryginalny schemat frakcjonowania.

*Wyniki.* Prawdopodobieństwo pięcioletniego przeżycia bezobjawowego chorych na raka szyjki macicy w stopniu II b wynosiło 60%, w stopniu III – 41%. Niewyleczenie stwierdzono u 54 chorych (33,5%), wznówę w okresie obserwacji u 26 chorych (16%), a przerzuty odległe u 11 chorych (7%). Nie zanotowano ciężkich wczesnych odczynów popromiennych, a późne powikłania (III i IV stopnia według skali EORTC/RTOG) ze strony odbytnicy stwierdzono u 2 chorych (1%).

*Podsumowanie.* Skojarzona brachyterapia MDR i teleterapia w leczeniu chorych na zaawansowanego raka szyjki macicy charakteryzowała się dobrą skutecznością i tolerancją porównywalną z danymi literaturowymi.

**Key words:** uterine cervix carcinoma, MDR brachytherapy

**Słowa kluczowe:** rak szyjki macicy, brachyterapia MDR

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## Introduction

Carcinoma of the uterine cervix is still one of the most common malignant neoplasms in women. Definitive radiation therapy alone, combined with teletherapy (TT) and brachytherapy (BT) has been established as an effective form of treatment in patients with advanced cervical cancer (stage II b and III).

During the past 20 years, owing to the introduction of remote control afterloading into clinical practice, traditional brachytherapy based on Low Dose Rate technique (LDR  $0.4 \div 2$  Gy/h) has been gradually replaced with Medium Dose Rate (MDR  $2 \div 12$  Gy/h) and High Dose Rate technique (HDR  $>12$  Gy/h). Those modifications were caused mainly by such practical considerations as shortening application time and reducing the exposure of medical staff to ionizing radiation [1, 2]. Introduction of MDR and HDR into clinical practice influenced the necessity of the total dose fractionation [3, 4]. The Institute of Oncology was the first in Poland to introduce MDR brachytherapy with  $^{137}\text{Cs}$  source (Selectron MDR afterloader by Nucletron). There are only a few studies in literature concerning MDR brachytherapy in cervical cancer treatment.

The Institute of Oncology in Gliwice has originally introduced the method, which is discussed here, i.e. in advanced cervical cancer treatment. It combines TT and MDR BT based on individually selected applicators. This method constituted an essential breakthrough in implementing of HDR BT in clinical practice in our Brachytherapy Department.

The aim of the study is to evaluate MDR brachytherapy combined with teletherapy in advanced cervical cancer patients treated in the Institute of Oncology in Gliwice.

## Material and methods

A retrospective analysis of 161 patients with histologically confirmed advanced cervical cancer treated with definitive radiation alone at the Institute of Oncology in Gliwice, Poland between the years 1981 and 1986 has been performed. The mean age of patients at the time of treatment was 56 years (range  $26 \div 81$  years). All patients were staged clinically according to the International Federation of Gynecology and Obstetrician (FIGO) system [5]. Distribution of the stages was as follows: 34 (21%) cases in II b and 127 (79%) in III (4 patients in IIIa and 123 in III b). Histological examination revealed squamous cell carcinoma in 149 (93%) patients, adenocarcinoma in 8 (5%) patients and solid tumor in 4 (2%).

All patients were treated with  $^{60}\text{Co}$  machine with anterior and posterior opposing fields to the whole pelvis. The total dose of 40-54 Gy was administered in 20-27 daily fractions, 2 Gy per fraction. Brachytherapy was introduced after completing 20Gy to the entire pelvis from TT and was performed twice a week with 3-day-intervals between insertions. The TT was continued on non-BT days with a 4-cm wide midline block to shield critical organs. The total TT time ranged from 4 to 6 weeks. One hundred and forty six patients completed this schedule. In 15 cases the total TT dose was below 40 Gy due to disease progression and/or poor performance status during the treatment.

MDR brachytherapy with  $^{137}\text{Cs}$  remote afterloader was performed according to the following rules:

- total dose divided into fractions,
- treatment twice a week,
- treatment separately in vagina (vaginal applicators) and in uterine cavity (intrauterine applicators).

Applied dose rate ranged from 8 to 10 Gy/h. The type of intrauterine tube depended on the uterine cavity length. Vaginal applicators were selected individually to match each patient's anatomical conditions and the extension of the tumor infiltration in vagina. Seventy one patients underwent intravaginal treatment with a 3-channel flat applicator, constructed in our Department (the tumour involved the vaginal walls), 45 with plate and 2 with multichannel cylinder. In case of changes in the anatomical conditions during treatment (vaginal stenosis, narrowing of the vaginal part of the cervix) the type of vaginal applicator was reselected (43 cases). The irradiation schedule (number of fractions, total dose from BT) depended on the stage of the disease and the degree of tumor regression during treatment. Dose per fraction was administered in reference points located 0.5 cm or 1 cm from the applicator surface. The prescription for total dose from BT in vagina varied from 26 Gy (reference points 1 cm from the applicator surface) to 98 Gy (reference points 0.5 cm from the applicator surface) applied in 3-15 fractions. The total dose from BT in the uterine cavity was escalated depending upon tumor extension in the cervical canal, metrorrhagia and early treatment complications. It ranged from 10 to 30 Gy applied in 1-3 fractions (reference points 1 cm from the applicator surface). In 1 patient the total dose from BT in uterine cavity was escalated to 45 Gy due to main tumor localization in the uterine cavity and bleeding from uterine canal. Four patients received 5 Gy in the uterine cavity and intrauterine BT was not continued due to early treatment complications. In 9 patients anatomical conditions rendered BT in the uterine cavity impossible.

The combined treatment effectiveness was analyzed basing on:

- 5 year disease free survival rate,
- number of persistent diseases (lack of total tumor regression in clinical examination within 6 months from the end of the treatment),
- number of local recurrences (recurrence of the disease after 6 months from the end of the treatment).

Treatment side effects were assessed basing upon revealed complications (type, grade, localization and time of occurrence) according to the EORTC/RTOG scale. Patients with treatment sequelae that occurred during treatment, or within 6 months from its termination were considered as early complication cases; those who revealed sequelae after 6 months from the termination of treatment – as late complication cases.

The probability of disease free survival was calculated by the Kaplan-Meier method.

## Results

The probability of 5-year disease free survival for cervical cancer was 0,6 for patients in stage II b and 0.41 in stage III, while the probability of 10-year disease free survival was 0.53 and 0.4 respectively (Fig. 1).

In the analysed group of 161 patients persistent disease was stated in 54 patients (33.5%), local recurrence in 26 patients (16%) and distant metastases in 11 patients (7%). The reasons of treatment failures are presented in table I.

Early irradiation sequelae grade I° and II° were observed in 22 patients (14 %) in the urinary bladder and in 22 (14 %) – in the rectum. No severe early side effects ra-

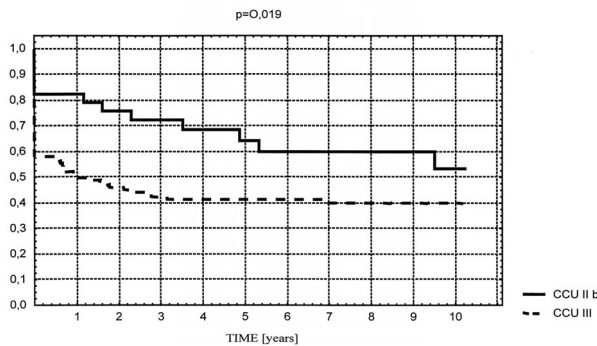


Fig. 1. Disease free survivals according to the FIGO staging system in advanced cervical cancer (CCU)

ted as grade III° and IV° were noted. Eight patients (5%) revealed grade I° and II° late bladder complications and 6 patients (4%) late rectal complications. No late complications rated as III° were recorded. Two patients (1%) revealed severe IV° late treatment complications – recto-vaginal fistula requiring surgical intervention and an artificial anus. In the first of these cases routine medical control examination held 10 months after treatment completion revealed anterior rectal wall ulceration with smooth margins. Once the fistula had been formed, surgical intervention was performed in the 15th month. In the second – 5 years after treatment completion the patient began to complain of strong pain in the lower abdomen and dyschezia. Microscopic examination of the excised rectal tissue confirmed chronic colitis. Despite intensive pharmacological treatment, a year later a recto-vaginal fistula developed and surgery (ending with an artificial anus) had to be performed. Both patients received equal total doses from TT (50 Gy) and from BT in vagina (30 Gy in reference point 0.5 cm from the applicator surface). The total dose from BT in uterine cavity differed: 30 Gy in the first case and 10 Gy in the second referred in points located 1 cm from the applicator surface.

## Discussion

Retrospective analysis of treatment results obtained for 161 patients with advanced cervical cancer treated at the Institute of Oncology in Gliwice between the years 1981 and 1986 constitutes a base for the evaluation of definitive irradiation combined with MDR BT and TT (60Co). Considering the fact that there are only a few literature reports describing the results of MDR brachytherapy in gynaecological malignancies, data related to HDR and LDR brachytherapy results was also taken into account [6, 7].

The probability of 5-year disease free survival in the analyzed group of patients was 0.6 in stage II b and 0.41 in stage III. The summarized data published in literature in relation to the results of definitive radiotherapy in advanced cervical cancer reported 5 year disease free survival probability in the range of 0.56-0.59 in patients with stage II b and 0.37-0.47 in patients with stage III [8-12]. A few randomized studies have been published comparing HDR and LDR brachytherapy for carcinoma of the cervix. No significant differences in local control and survival rates between HDR and LDR group were reported in these studies [13-15], however recently published studies indicated lower survival and pelvic control rates observed for stage III b patients treated with HDR brachytherapy [16].

The basic cause of treatment failure in advanced cervical cancer is either persistent disease or local recurrence. According to data from literature no regression is observed in some 15÷30% patients with stage II b and 36÷43% in stage III treated with HDR BT [17]. The incidence of no response in the analyzed group was 23% in II b and 44% in III. Pelvic recurrences are reported within the range of 23% in IIb and 42% in III [18, 19], however in our material local recurrence was recognized in 21% in II b and 17% in III. The incidence of pelvic failure is

Tab. I. Treatment failures in advanced cervical cancer (CCU) patients treated with definitive radiotherapy

DISEASE STAGE	TREATMENT FAILURES	persistent disease number of patients (%)	local recurrence number of patients (%)	distant metastases number of patients (%)
CCU II b	18 / 34 (52.9%)	8 / 34 (23.5%) *	7 / 34 (20.6%) *	3 / 34 (8.8%) *
	⇒ vagina 1 (3%) ⇒ parametrium 3 (8.5%) ⇒ parametrium and vagina 3 (8.5%)  ⇒ parametrium, vagina and cervix 1 (3%)		⇒ vagina 3 (9%) ⇒ parametrium 2 (6%) ⇒ parametrium and vagina 1 (3%)  ⇒ parametrium and cervix 1 (3%)	⇒ bones 1 (3%) ⇒ distant lymph nodes 1 (3%) ⇒ skin in pubic symphysis region 1 (3%)
CCU III	73 / 127 (57.5%)	46 / 127 (36.2%) *	19 / 127 (15%) *	8 / 127 (6.3%) *
	⇒ vagina 14 (11%) ⇒ parametrium 18 (14%) ⇒ parametrium and vagina 2 (1.5%) ⇒ parametrium and cervix 3 (2.5%) ⇒ parametrium, vagina and cervix 9 (7%)		⇒ vagina 3 (2%) ⇒ parametrium 10 (8%) ⇒ vagina and parametrium 6 (5%)	⇒ lungs 4 (2.5%) ⇒ disseminated 2 (1.5%) ⇒ distant lymph nodes 1 (1%) ⇒ bones 1 (1%)
TOTAL	91 / 161 (56.5%)	54 / 161 (33.5%)	26 / 161 (16.2%)	11 / 161 (6.8%)

\* Note: percentage values in brackets are given approximately

comparable in groups treated with HDR and LDR BT [13, 14]. A relatively low percentage of local recurrences together with a high percentage of treatment failures in patients with stage III of the disease may be connected with the period of 6 months, during which no regression is classified as persistent disease. Distant metastases are a rather uncommon reason of treatment failures in cervical cancer patients. The incidence of distant metastases in literature is between 8 and 34%, while in the analysed group – only 7% [10, 20].

The analysis of treatment toxicity, as reported in literature, is difficult due to lack of a single commonly used radiation morbidity scoring system [21]. Early complications grade I and II were observed in 14% of the cases both in the bladder and in the rectum. No severe early complication was noted. Literature reports present complication rates to be between 10 and 25% for stage II b and III [10, 22, 23]. In the analysed material the incidence of late complication rate was 9% including 1% of IV grade side effects.

## Conclusion

Our results suggest, that Medium Dose Rate brachytherapy has good efficacy and tolerance in definitive radiotherapy of advanced cervical cancer.

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## References

- Rattka P. Die Therapie des Kollumkarzinoms mit High-Dose-Rate Seletron. In: Hammer J et al., *Fortschritte in der interstitiellen und intracavitären Strahlentherapie*. München – Bern – Wien – San Francisco: Verlag; 1988, s. 203–207.
- Rattka P. Experience in treatment of cancer of cervix using HDR brachytherapy in Gliwice. In: Mould RF, *Brachytherapy 2*. Nucletron 1988; 296–300.
- Rattka P. Brachytherapy in the Centre of Oncology in Gliwice, Poland. *Activity* 1990; 4: 26–29.
- Rattka P. Clinical investigation and fractionation schemes in the treatment of cervix carcinoma with HDR afterloading at the Centre of Oncology in Gliwice. In: Vahrson H, *High Dose Rate Afterloading in the Treatment of Cancer of the Uterus, Breast and Rectum*. München – Wien – Baltimore: Urban and Schwarzenberg; 1988, s. 173–176.
- International Federation of Gynecologists and Obstetrician (FIGO). Changes in the definitions of clinical staging for the cervix and ovary. *Am J Obstet Gynecol* 1987; 56: 263–264.
- Bates TC, Beery RJ. High dose rate afterloading in treatment of cancer of the uterus. *Brit J Radiol (Special Report)* 1980; 17: 1–89.
- Taina E. High versus low dose rate intracavitary radiotherapy in the treatment of carcinoma of the uterus. *Acta Obstet Gynecol (Suppl)* 1981; 113, 12–13.
- Arthur D, Kaufman N, Schmidt-Ullrich R, et al. Heuristically derived tumor burden score as a prognostic factor for stage III B carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 1995; 31: 743–751.
- Delaloye JF, Coucke PA, Pampallona S, et al. Effect of total treatment time on event-free survival in carcinoma of the cervix. *Gynecol Oncol* 1996; 60: 42–48.
- Kapp KS, Stueckelschweiger GF, Kapp DS, et al. Carcinoma of the cervix: analysis of complications after primary external beam radiation and Ir-192 brachytherapy. *Radiother Oncol* 1997; 42: 143–153.
- Lorvidhaya V, Tonusin A, Changwiwit W, et al. High-dose-rate afterloading brachytherapy in carcinoma of the cervix: an experience of 1992 patients. *Int J Radiat Oncol Biol Phys* 2000; 46: 1185–1191.
- Yoonessi M. Treatment of advanced invasive cervical cancer. Changing times and trends. *J Surg Oncol* 1984; 26: 161–167.
- Patel PD, Sharma S.C., Negi PS, et al. Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: A clinical trial. *Int J Radiat Oncol Biol Phys* 1994; 28: 335–341.
- Teshima T, Inoue T, Ikeda H, et al. High-dose-rate and low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: Final results of Osaka University Hospital. *Cancer* 1993; 72: 2409–2414.
- Wen-Lin H, Ching-Jung W, Yee-Min J, et al. Twice-per-day fractionated high versus continuous low dose rate intracavitary therapy in the radical treatment of the cervical cancer: A nonrandomized comparison of treatment results. *Int J Radiat Oncol Biol Phys* 1995; 32: 1425–1431.
- Petereit DG, Sarkaria JN, Potter DM, et al. High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer: analysis of tumor recurrence. *Int J Radiat Oncol Biol Phys* 1999; 45: 1267–1274.
- Arai A, Nakano T, Morita S, et al. High dose rate remote afterloading intracavitary radiation therapy in the treatment of carcinoma of the cervix: A 20-year experience. *Cancer* 1992; 69: 175–180.
- Perez CA, Breaux S., Madoc-Jones H, et al. Radiation therapy alone in the treatment of carcinoma of uterine cervix. Analysis of tumor recurrence. *Cancer* 1983; 51: 1393–1402.
- Perez CA, Grigsby PW, Camel HM et al. Irradiation alone or combined with surgery in stage IB, IIA, and IIIB carcinoma of the uterine cervix: Update of nonrandomized comparison. *Int J Radiat Oncol Biol Phys* 1995; 31: 703–716.
- Fagundes H, Perez CA, Grisby PW, et al. Distant metastases after irradiation alone in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1992; 24: 197–204.
- Sismondì P, Sinistrero G, Zola P, et al. Complications of uterine cervix carcinoma treatments: The problem of uniform classification. In: Mould RF, *Brachytherapy 2*. Nucletron; 1988; 349–356.
- Pedersen D, Bentzen SM, Overgaard J. Early and late radiotherapeutic morbidity in 442 consecutive patients with locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1994; 29: 941–952.
- Rodrigus P, De Winter K, Venselaar JL, et al. Evaluation of late morbidity in patients with carcinoma of the uterine cervix following a dose rate change. *Radiother Oncol* 1997; 42: 137–141.

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