Original article

Tolerance and efficacy of preoperative intracavitary HDR brachytherapy in IB and IIA cervical cancer

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Abstract

Purpose: The aim of this work is to analyze the efficacy and tolerance of preoperative intracavitary HDR brachytherapy (HDR-BT) in patients with IB and IIA cervical cancer.

Material and methods: 139 patients with cervical cancer IB-IIA with preoperative HDR-BT, out of which 60 patients with cervical cancer IB (43.2%) and 79 with IIA (56.8%) were treated since 1996 to 2002. In preoperative BT total dose to point A ranged from 30-45 Gy in 6-9 fractions twice a week. The fraction dose was 4-5 Gy at point A. Six weeks after BT all patients underwent radical Wertheim-Meigs hysterectomy. Patients with disadvantageous risk factors or with positive specimen histology had a complementary therapy: external-beam radiotherapy (EBRT) given to the whole pelvic volume in daily fractions of 2 Gy up to total dose of 36-52 Gy (20 patients) or EBRT with cisplatin-based chemotherapy with the dose of 30-40 mg/m^2 in 5-7 fractions given weekly (7 patients) or chemotherapy (6 patients). Acute and late radiation toxicity was evaluated according to EORTC/RTOG.

Results: In postoperative specimen histopathology the number of 114 women (82%) had tumor-free specimen within brachytherapy target (in cervix and cavity), 96 women (60.1%) had tumor-free specimen both in and outside brachytherapy target (lymph nodes, parametra, adnexis). The 5-year and 10-year DFS were 93.8% and 88% for IB and 89.7% and 64.7% for IIA respectively. 7.9% of patients developed acute toxicity both in rectum and bladder (only in I and II grade of EORTC/RTOG). Late severe complication occurred in rectum in 2.2% of patients and in bladder 1.4%.

Conclusions: 1. Preoperative HDR-BT in patients with IB and IIA cervical cancer is an effective and well tolerated therapy with acceptable rate of side effects. 2. Preoperative HDR-BT followed by surgery in a group without risk factors is a sufficient treatment option with no additional adjuvant therapy requirement.

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Key words: cervical cancer, preoperative HDR brachytherapy.

Purpose

Cervical cancer is one of the most frequent cancer [1, 2]. It is estimated that about half a million women worldwide will be diagnosed with cervical cancer and more than half of them will die from the disease [3]. It is also very common problem in Poland and the leading cause of female cancer deaths [1]. According to the National Cancer Registration, cervical cancer constitutes about 7.6% of all gynecological carcinomas in Poland and comes third, after breast and pulmonary cancer as the most frequent cause of death [4]. In aspect of morbidity and mortality, Poland is on the intermediate position in the world, however the first in Europe [4].

For early stages of cervical cancer there are some potential treatment strategies available [1, 3, 5]. The basic way of treatment is radical Wertheim-Meigs hysterectomy after which – according to risk factors of recurrence – an adjuvant therapy such as EBRT and/or chemotherapy is applied. Another strategy is preoperative brachytherapy (BT) followed by radical Wertheim-Meigs hysterectomy and in case of the presence of risk factors, additional treatment with adjuvant therapy is applied. In similar clinical situations radiotherapy as a single way of treatment is performed [6]. Results of the therapy in early cervical cancer depend on prognostic factors. The most important are: tumor size, histopathology, clinical stage, lymph-vascular space invasion, lymph nodes involvement and the number of lymph nodes removed [6-8]. BT plays crucial role in the treatment of cervical cancer in all FIGO stages [9-12]. In our Center preoperative BT is one of the treatment strategies and it is very useful in sterilizing tumor cells in cervix and uterus (brachytherapy target) reducing the number of patients with an adjuvant therapy requirement [6, 10]. The aim of the study was to analyze the efficacy and tolerance of preoperative High-Dose-Rate brachytherapy (HDR-BT) in patients with IB and IIA cervical cancer. We analyzed the efficacy of this treatment strategy according to stages, risk factors and complementary therapy.

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Material and methods

Patients characteristic

From January 1996 to December 2002 in Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, 139 women with operable, early stage of cervical cancer were treated with preoperative intracavitary HDR brachytherapy. Sixty women were in IB (43.2%) and 79 in IIA (56.8%) cervical cancer according to International Federation of Gynecology and Obstetrics (FIGO). The most frequent histopathological type of cancer was squamous cell carcinoma (128 women – 92.1%). The mean age in IB was 50 years (range 31-71 yrs) and 51.5 in IIA (range 35-74 yrs) (Table 1). All women underwent complete staging workups including physical examination, exo- and endocervical biopsies, cystoscopy, urography, chest X-ray as well as complete blood count and blood biochemistry. While establishing the FIGO stage, neither CT (computed tomography) nor MRI (magnetic resonance imaging) were routinely performed.

Methods of treatment selection

After clinical examination women were selected for preoperative BT. All patients had operable cervical carcinoma with clinically negative lymph nodes and the tumor size was between 2 and 5 cm. They were all qualified as IB1 with 50 of cases (36%), IB2 – 10 (7.2%) and IIA 79 of patients (56.8%). Women were treated according to two strategies: 121 of them (87.1%) in two steps – the first 3 fractions with intrauterine source, and next 6 fractions with vaginal source (according to the anatomical conditions of a patient, ring or plate applicator was selected) and 18 of cases (12.9%) in one step only with ring applicator (in order to shorter the time of treatment whenever possible). All women had the treatment planning based on X-ray simulation.

Methods of treatment

An uterovaginal brachytherapy was performed with afterloading 192 Ir source.

Treatment schedule contained: uterine cavity – intrauterine tube with 10 Gy/fr 1 cm from applicator surface (5 Gy in point A) in 3 fractions, twice a week (total dose of 30 Gy in reference points); vagina: ring or plate applicator with 7-8 Gy/fr 1 cm from applicator surface (4-5 Gy in point A), 6 factions twice a week (total dose 42-48 Gy in reference points). Total dose delivered to point A ranged from 30 to 39 Gy.

The average BT treatment time was 28 days (range 17-37 days). Six weeks after receiving BT treatment, all patients underwent laparotomy with radical Wertheim-Meigs hysterectomy (n = 136) or hysterectomy without lymphadenectomy (n = 3). Patients with risk factors of recurrence had an adjuvant therapy such as external-beam radiotherapy (EBRT), chemotherapy, or combination of both methods. There were 20 patients who received external-beam radiotherapy with either γCo 60 or 6-20 MV photons given to the whole pelvic volume in daily fractions of 2 Gy up to total dose of 36-52 Gy. 7 patients received EBRT with cisplatin-based chemotherapy with the dose of 30-40 mg/m^2 in 5-7 fractions given weekly, and 6 patients received chemotherapy. EBRT was administered through individually shaped portals using AP/PA technique. In ten patients with disadvantageous risk factors or with positive specimen histology no adjuvant therapy was applied, owning to the fact that the period between surgery and the first control visit in our department was too long – more than 3 months. In that group of patients no symptoms of recurrence at the time of control were observed.

Follow-up and statistical methods

Women were followed-up with 3-6 month intervals for the first 5 years, after that once a year. The median follow-up period from the beginning of treatment was 98 months (range: 56-144 months).

Pelvic recurrences were divided into local (vagina, vaginal cuff or central pelvis) and regional (sidewall, lymph nodes) failures. All non-pelvic recurrence were considered as distant failures.

Acute and late radiation toxicity on bowel and bladder was evaluated according to EORTC/RTOG scale [2].

Statistic analysis

A statistic analysis of results was carried out using Statistica 6.0 data analysis system. With reference to the most tested features, a major deviation from standard distribution was shown. Due to this fact, nonparametric tests were used to verify the assumptions: the U Mann-Whitney's test for two independent samples and the Wilcoxon's test for two linked samples. In order to characterize the tested features, while using nonparametric tests, the median was used as the middle value. The statistical verification was performed including the following thresholds of importance level: no statistical importance ($p > 0.05$), statistical importance ($p < 0.05$), high statistical importance ($p < 0.01$) and very high statistical importance ($p < 0.001$). The statistical analysis of dependence was conducted by measuring a correlation (Spearman's rank correlation coefficient) and regression (Pearson's linear model). The survival curves were determined with the Kaplan-Meyer method, and

Table 1. Patient and tumor characteristics

Characteristic	No of patients	IB	IIA	p
Number of patients:	139	60: IB 1-10 IB 2-50	79	$p > 0.05$
Age (years):				
mean	51	50	51.5	
median	49	49	50	$p > 0.05$
range	31-74	31-71	35-74	
Tumor size (cm):				
mean		3.01	3.31	
median		3	3.25	$p < 0.05$
range		2-4.5	2-5	
Histopathology:				
squamosus cell carcinoma	128	56	72	
adenocarcinoma	11	4	7	

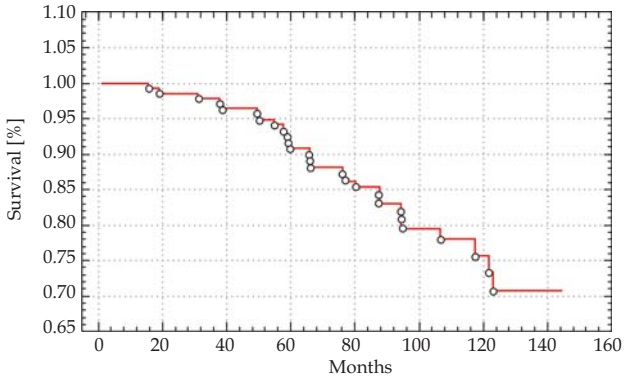

Fig. 1. DFS in whole group of patients with preoperative brachytherapy (n = 139)

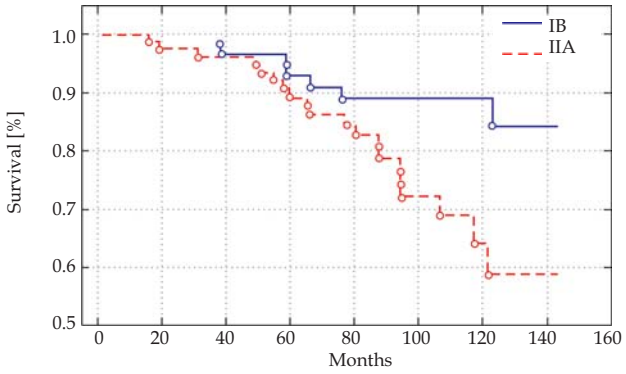

Fig. 2. DFS according to FIGO stage ($p < 0.03$)

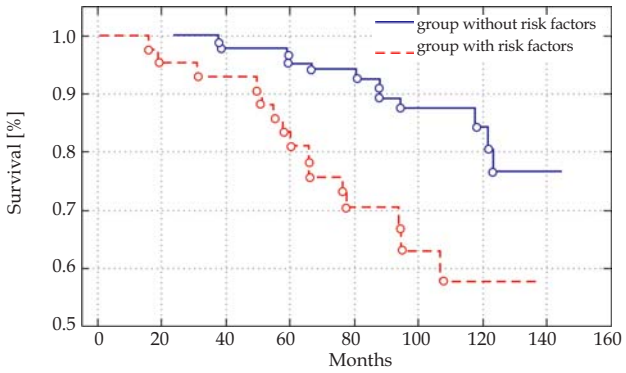

Fig. 3. DFS according to risk factors ($p < 0.003$)

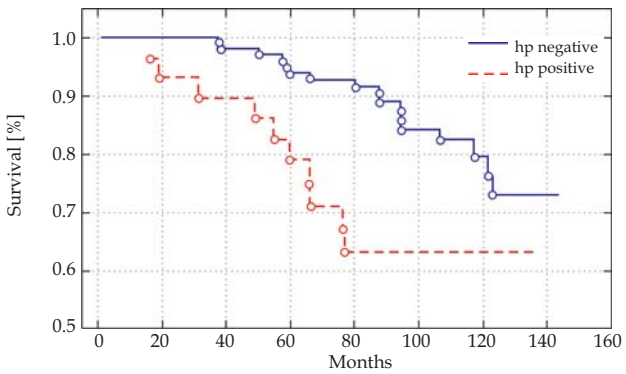

Fig. 4. DFS according to postoperative histopatology outside BT target ($p < 0.02$)

the survival rates were calculated from the beginning of the treatment.

Results

Postoperative specimen histopathology

In 96 of women (69.1%) no tumor cells in postoperative specimen histopathology was detected and this group was classified as a group without risk factors of recurrence.

In 114 women (82%) tumor-free specimen in brachytherapy target were observed (in cervix and cavity), however 18 of them (12.9%) had tumor cells outside the BT target such as lymph nodes, parametrium or adnexis. Other women had tumor cells both inside and outside BT target (11 women – 7.9%) or only inside BT target (11 women – 7.9%). Three women underwent hysterectomy without lymphadenectomy (2.2%). 43 women (39.9%) with tumor cells inside BT target, outside BT target or both and women without lymphadenectomy, with positive margins, lymphovascular space invasion and deep stromal invasion of tumor were classified as a group with risk factors for recurrence. In IB group 9 women (15%) and in IIA 17 women (21.5%) had positive lymph node ($p > 0.05$). In our group parametrium involvement was observed in 3 cases (2.2%) classified as IIA before hysterectomy. According to postoperative histopathology 43 of women (30.2%) were classified as a group of high risk factors of recurrence or dissemination. 33 women with risk factors (76.7%) had an adjuvant therapy, out of which 20 patients were treated with EBRT, 7 patients with EBRT with cisplatin-based chemotherapy and 6 patients with chemotherapy as a single way of treatment.

Overall survival

Among 139 patients the amount of 25 women died (17.9%) out of which 13 of them (52%) as a result of cervical cancer. The 5- and 10-year rates for overall survival according to FIGO staging system were 92.8% and 86.8% for stage IB and 89.4% and 71.2% for stage IIA, respectively.

Disease-free survival

The 5-year and 10-year disease-free survival (DFS) for all patients was 90.7% and 75.6%, respectively (Fig. 1). The 5- and 10-year rates for DFS according to FIGO staging system were 92.8% and 88.8% for stage IB and 89.2% and 64% for stage IIA, respectively. Statistically significant difference was observed in DFS groups that were divided according to FIGO stage ($p < 0.03$) (Fig. 2). The 5- and 10-year rates for DFS according to risk factors were 95.4% and 84.2% for group without risk factors and 80.8% and 55.7% for group with risk factors, respectively. Statistically significant difference in DFS among these two groups ($p < 0.003$) was observed (Fig. 3). The 5- and 10-year rates for DFS according to postoperative histopathology outside BT target were 94.0% and 79.4% for group without tumor cells outside BT target and 79% and 63.2% for group with tumor cells outside BT target, respectively. There was a statistically significant difference between those groups ($p < 0.02$) (Fig. 4).

There were no statistical differences in DFS according to tumor size, women age and postoperative specimen histopathology inside BT target ($p > 0.05$). The 5- and 10-year rates for DFS in relation to postoperative histopathology inside BT target were 90.9% and 78.6% for group without tumor cells inside BT target and 86.9% and 55.7% for group with tumor cells inside BT target, respectively (Fig. 5).

Patterns of failures

In the group without risk factors (n = 96) the number of six cases with local recurrence (6.25%) and 2 with distant metastases were observed (2.1%). They appeared within 10 months (range: 8-17 months) and 12 months after the treatment (range: 9-20 months) on average, respectively. In group with risk factors (n = 43) there were seven women with local recurrence (16.3%) and 5 with distant metastases (11.6%). They appeared within 8 months (range: 7-19) and 12 months after the treatment (range: 7-18 months) on average, respectively (Fig. 6).

Acute and late toxicity

Acute toxicity was observed in 7.9% of cases in both rectum and bladder (only in grade I or II according to EORTC/RTOG scale). Late toxicity in bladder was observed in 7.1% of cases, although late severe toxicity only in third grade (1.4%). One case of bladder tear and one case of urethral stricture were recorded (Fig. 7). Late toxicity in rectum occurred in 10.7% of all cases, and late severe complications in 2.8%. In two cases recto-vaginal fistula and proctitis were observed (Fig. 8). The total number of late toxicity of both bladder and rectum was 17.8% of patients and severe late toxicity was 4.2% of cases.

Discussion

HDR-BT has been used for more than 30 years. Intracavitary techniques are based on afterloading sources, with different type of applicators. Brachytherapy plays an important role in treatment of patients with cervical cancer [6, 9, 12]. In IB-IIA cervical cancer BT can be used prior or after hysterectomy as well as combine treatment with radiotherapy and/or chemotherapy. In early cervical cancer there is no standard therapy protocol [10]. In case of high risk factors of recurrence BT can be combined with EBRT and/or chemotherapy. Preoperative BT is applied to decrease the number of patients who require an adjuvant therapy after surgical procedures. Furthermore, it reduces the number of patients with radiotherapy indication. BT sterilizes the tumor cells in BT target such as upper vagina, cervix and uterus [6].

The results of postoperative histopathology revealed that in 82% of patients no tumor cells in BT target were detected. For 60.1% of women no additional adjuvant therapy was required and they remained under regular medical control. In postoperative specimen no tumor cells were found (negative histopathology results inside and outside BT target). In other publications the findings were usually inadequate [12], however they might be related to a group of patients selected to this kind of treatment.

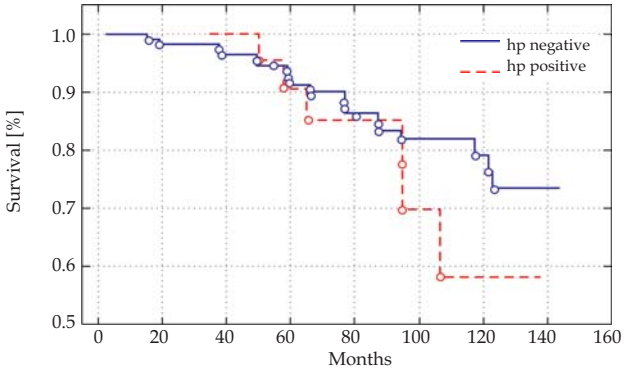

Fig. 5. DFS according to postoperative histopatology in BT target ($p > 0.05$)

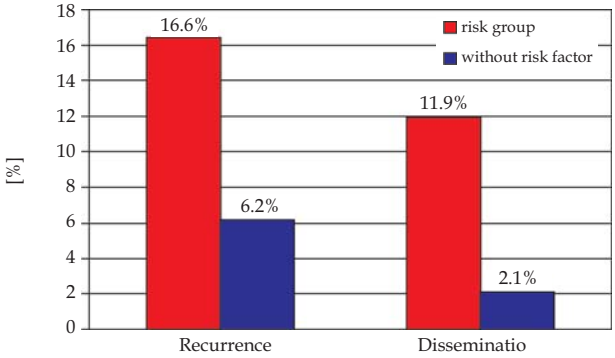

Fig. 6. Failures in whole group of patients group with preoperative brachytherapy (n = 139)

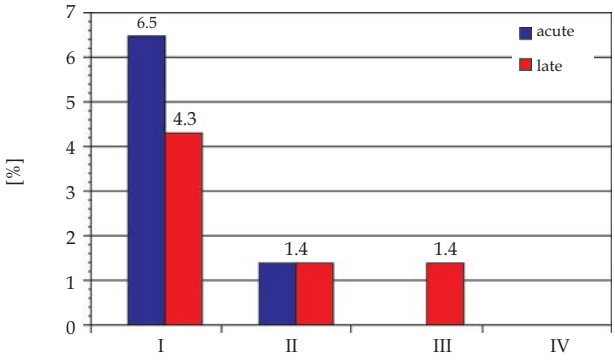

Fig. 7. Acute and late toxicity in bladder in percents according to EORTC/RTOG scale (n = 139)

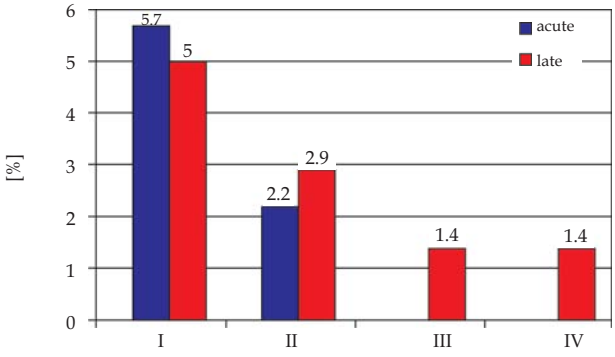

Fig. 8. Acute and late toxicity in recturn in percents according to EORTC/RTOG scale (n = 139)

The primary surgery gives more accurate estimation of disease extension and the risk of failure. This kind of treatment is recommended for young women in order to preserve the ovarian function [6]. In our group the average age was 51 and included mostly women in menopause. The role of preoperative BT is to deliver high dose of radiation directly to the tumor while sparing the adjacent healthy tissues. The ideal placement of uterine applicator produces a pear-shaped isodose distribution, delivering high-dose radiation to BT target. Since there is no standard scheme, different fractionation schedules are available [13-15]. However, in our department we have our own treatment schedule. In preoperative HDR-BT the total dose to point A range from 30-45 Gy in 6-9 fractions delivered twice a week. The fraction dose was 4-5y at point A. In radiotherapy the treatment time is always crucial and the potential risk of its prolongation in cervical cancer has been reported in many studies. Such bad prognostic factor is effecting the treatment results [16, 17], with estimated loss of local control ranging from 0.3 to 1.6% per day of treatment prolongation [18]. In our studies the average HDR-BT treatment time was 28 days (range 17-37 days). The most common histopathological cancer type was squamous cell carcinoma (92.1%), and it was similar to other publications [3, 14, 19]. Only 7.9% of patients had the adenocarcinoma histopathology. It was shown by some investigators that the biology and prognosis of adenocarcinoma of the uterine cervix is different from the squamous cell carcinoma [14]. Nonetheless, such prognostic factor was unlikely to be evaluated, since the number of patients was not sufficient enough.

Certain risk factors concerning higher risk of recurrence within the group of patients with cervical cancer are most likely to be define. Among well known are the tumor size, histopathology, clinical stage, lymph node involvement, total number of metastatic lymph nodes and lymph-vascular space invasion [14, 19, 20]. Clinical stage is one of the most important factor in survival rate in patients with cervical carcinoma [19]. The results from different oncologic centers vary, nevertheless they are connected to many factors such as method of treatment, combination and sequences of different types of therapy as well as fractionation and total doses. In our study we observed a statistically significant difference in DFS among groups that were divided according to FIGO stage ($p < 0.03$). 5 and 10-year DFS were 93.8% and 88% for IB and 89.7% and 64.7% for IIA stage, respectively. Other authors also observed statistically significant differences between FIGO stage groups [19] with several of lower percentage [21].

Endometrial extension of carcinoma of the uterine cervix is associated with decrease in overall survival in women treated in the same FIGO stage [22] and is associated with the risk of detected lymph node metastases and poor prognosis [23]. In our group uterine cavity was involved in 1.4% of the cases with additional lymph node connection. Lymph node status is the major prognostic factor and an important factor in selection of appropriate therapy and treatment planning [19, 24-26]. In IB pelvic lymph node metastases are detected in 0-17% and in IIA in 12-27% of cases [19, 24]. In our group lymph node involvement in IB was observed in 15% of patients and in IIA – 21.5%. High percentage might be associated to the fact that in the past not all women went through MRI or CT examination before the treatment. One of the most important aspect in cervical cancer patients is the evaluation of parametrial and pelvic sidewall invasion and the status of lymph nodes. In defining tumor extension and volume as well as depth of stromal invasion and parametrial invasion, MRI is more valuable than CT procedure [25]. On the other hand, the usefulness of MRI in preoperative diagnosis in pelvic and para-aortal lymph node assessment is still controversial [25]. CT and MRI imaging, based on measurements of node size and the diameter greater than 1 cm short-axis, are the most accepted criterions for nodal involvement. Even though there are some limitations of this kind of methods, since metastases in normal size nodes could be missed and reactive lymph node enlargement can be defined as a metastatic tumor [27]. The most valuable way of detecting staging of lymph node in patients with early-stage cervical cancer is PET/CT [25, 27]. Other diagnostic strategy is the laparoscopic sentinel node biopsy. This method can reliably determine lymph node status in early-stage cervical cancer [24]. In our group statistically significant difference were observed in DFS among women with and without high risk factors of failure, where lymph node involvement was the most common risk factor ($p < 0.003$). Another very important factor of recurrence and decreased survival is parametrial spread. Parametrial involvement is correlated with other high-risk factors of recurrence, and such patients are more likely to have pelvic and paraaortic nodal connection [3]. In our group we observed parametrial tumor spread in 2.2% of cases. Some other authors observed parametrial involvement in 4-39% of patients with early stage of cervical cancer [3]. Patients with cervical carcinoma may develop pelvic recurrence, distant metastasis or either. The majority of failures appear within the first two years from diagnosis [23], similarly in our observations. The incidence of failures after radical hysterectomy with lymphadenectomy depends on patient specific risk factors. In our study within the group without risk factors, such failures were associated with approximately 8% of patients. Furthermore, even in the absence of risk factors such as large tumor size, deep stromal invasion, lymphovascular involvement, positive margins, parametrial and lymph node invasion, a small percentage of patients will develop a failure [20]. In women with IB and IIA with no evidence of lymph node involvement, 10-20% recurrence has been reported after primary surgery or radiotherapy [23]. In the group with risk factors, failures occurred in about 28% of cases. Pelvic recurrences according to FIGO stage was detected in IB – 10% and in IIA – 17% of patients [8]. Toboul *et al*. observed that there was no difference in terms of either locoregional or distant metastatic recurrence free survival between patients treated with peroperative BT or primary surgery [6].

In our group the 5- and 10-year rates for overall survival according to FIGO staging system were 92.8% and 86.8% for stage IB and 89.4% and 71.2% for stage IIA, respectively. The 5- and 10-year rates for DFS according to FIGO

were 92.8% and 88.8% for stage IB and 89.2% and 64% for stage IIA, respectively. Our results are comparable to results from other publications with some are even more accurate [6]. Our group of patients contained 10 women with IB2 cervical cancer, although no statistical differences were observed in DFS according to tumor size. That could be related to a small group of patients with large tumor. Another author observed differences in OS and DFS in women in IB2 cervical cancer according to FIGO stage [6]. Pelvic lymph node metastases are present in 20-25% of women with IB2 cervical cancer and they are a very important factor for follow-up therapy [12]. Nowadays, a number of special procedures are offered to a patient with large tumor including preoperative radiochemotherapy [12, 28]. Since the nature of our study is retrospective, no preoperative (EBRT) or radiochemotherapy were applied within the study group.

The rapid dose fall-off allows the delivery of very high dose to the tumor and- to a certain extend-sparing organs at risk such as: bladder, rectum, sigmoid and small bowel [9]. We observed acute toxicities both in bladder and in rectum, but only in grade I and II according to EORTC/RTOG scale in similar percentage. All acute toxicities were relieved spontaneously or with the help of medications. No women showed grade III or IV acute toxicity in bladder and rectum. Total late toxicity both in bladder and rectum was 17.8% and severe in 4.2% of patients. Late serve complications in bladder was bladder tear and urethral stricture, and in rectum in two cases recto-vaginal fistula and proctitis. Various authors have reported similar incidence of severe late complications and it was 3-11% of all cases [14, 29]. Some authors observe higher number of severe late complications [12, 19]. The rates of side effects are influenced by single and total doses for organ at risk, depending on the treated volume, type of fractionation [15] method and sequence of treatment. In our study we used reference point according to ICRU 38 recommendations [30]. At the present time many oncological centers are using 3D image which is based on 3D treatment planning [9].

We are constantly working on discovering the best predictor factors for recurrence [7] as well as improving the treatment strategies [5, 11]. However now, the results of treatment of locally advanced cervical cancer are still suboptimal due to high rate of failures.

Conclusions

1. Preoperative HDR-BT in patients with IB and IIA cervical cancer is an effective and well tolerated therapy with acceptable rate of side effects.
2. Preoperative HDR-BT followed by surgery in group without risk factors is a sufficient treatment option and no adjuvant therapy required.

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