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ORIGINAL ARTICLE

Stage IB2 cervical cancer: brachytherapy followed by radical hysterectomy

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Summary

Purpose: *Stage IB2 squamous cell cervical cancer can be treated by radiation therapy alone or by radical hysterectomy and lymphadenectomy (pelvic±para-aortic). Preoperative radiation therapy followed by extrafascial hysterectomy has been recommended as an effective combined treatment method.*

Patients and methods: *During the period January 1994-January 2004, 114 patients with stage IB2 cervical cancer were treated with preoperative brachytherapy followed by radical hysterectomy (Piver class III) with pelvic lymphadenectomy.*

Results: *Histology showed that 56 (49%) patients were without cervical malignant disease. Positive lymph nodes were found in 5 (9%) of them and negative in 51 (91%). In 58 (51%) patients cervical cancer still existed after brachytherapy and among them 26 (45%) were with lymph node metastasis. Patients with residual cervical carcinoma and positive lymph nodes after brachytherapy were older than those with no residual carcinoma and negative lymph nodes.*

Conclusion: *Women with stage IB2 squamous cell cervical cancer primarily treated with brachytherapy must be assessed by appropriate diagnostic procedures to evaluate local effects of brachytherapy and the status outside the pelvis. Negative local findings with positive lymph nodes point to further treatment of patients, while positive local findings point to radical surgery which may increase recurrence-free interval.*

Key words: brachytherapy, cervical cancer, radical hysterectomy

Introduction

Invasive squamous cell cervical cancer still remains a most devastating disease affecting women's health worldwide, especially in developing countries, where it is still the most common cause of mortality in women [1]. There are 500,000 new cases diagnosed every year worldwide, with the vast majority of them in the developing world [1]. In developed countries, incidence and mortality rates of cervical cancer have declined dramatically, due to the effectiveness of screening programs with cervical cytology by Papanicolaou smear [2,3].

According to statistical data, in the Republic of Serbia for the period 1990-1994 approximately 1100 women died annually from malignancies of the genitals, and nearly half of them (45.3%) had cervical cancer. In the same period, approximately 5,000 new cases of malignant diseases of the genitals were detected annually, invasive cervical cancer accounting for 58.3% of all cases [4]. In the period 1985-1996 in Vojvodina, region of Serbia and Montenegro, 3,228 women were registered with cervical cancer. Cervical cancer ranks first with an incidence of about 41% among genital neoplasms, causing death in 51.15% of them. According to the Registry for malignant diseases of Vojvodina, Institute of Oncology Sremska Kamenica, cervical can-

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cer ranks third after breast and skin cancer among all tumor localizations in this region [5,6].

Both FIGO and TNM staging systems are used in the staging of cervical cancer [7,8].

In a large surgicopathological study of patients with clinical stage IB disease reported by the Gynecologic Oncology Group (GOG), factors that predicted most accurately lymph node metastases and decreased disease-free survival were capillary-lymphatic space invasion , tumor size and depth of stromal invasion, the latter being the most significant [9-11].

Treatment of patients with invasive cervical cancer depends on stage and can be radical surgery, radiotherapy or chemoirradiation. Stage IB2, or barrel-shaped cervical cancer, can be treated by radiation therapy alone or by radical hysterectomy and lymphadenectomy (pelvic ± para-aortic).

Preoperative radiation therapy followed by radical extrafascial hysterectomy has been recommended by several groups [12].

Patients and methods

During the period January 1994 - January 2004, patients with squamous cell cervical cancer, stage IB2, grade 2 and 3, were retrospectively analysed. Patients were treated with preoperative brachytherapy followed by radical hysterectomy (Piver class III) with pelvic lymphadenectomy. Preoperatively, patients were treated with Medium Dose Rate (MDR) brachytherapy administered by Selectron weekly in 3 applications. The dose administered was 1700 cGy per session. Intracavitary brachytherapy was carried out by using a caesium (Cs) 137 MDR remote-controlled afterloading system. Brachytherapy technique, including the use of intrauterine tubes, vaginal applicators and the remote-controlled afterloading system, was the same among all patients. During application patients were under general anesthesia.

Several gauze sponges were packed into the vagina to displace the rectum and bladder in all patients.

Four to 5 weeks after brachytherapy, radical hysterectomy (Piver class III) was performed. The mean duration of radical hysterectomy and pelvic lymphadenectomy was 150 min. When paraaortic lymphadenectomy was also done, the mean duration was 240 min. The average blood loss during radical hysterectomy and pelvic lymphadenectomy was 700 ml (range 400-2000).

Patients were divided in two groups according to the pathological presence or not of residual tumor after brachytherapy. Group A consisted of patients without cervical neoplasia and group B included patients with residual cervical tumor. Age in relation to response to radiotherapy was examined. Fisher's exact test and t-test were used for statistical analysis.

Results

One hundred and fourteen patients were analysed. Their age ranged from 24 to 67 years (median 43.3). The median number of removed lymph nodes was 20 (range 12-40).

Postoperative biopsies showed that 56 (49.12%) patients had pathological complete response of cervical cancer and in 58 (50.87%) patients pathological residual disease was found (Figure 1).

Five (9%) of 56 patients with pathological complete response of the cervical tumor after brachytherapy had positive lymph nodes, while the remaining 51 (91%) patients had negative lymph nodes. Among 58 patients with residual cervical tumor 26 (45%) were with positive lymph nodes (Figure 2).

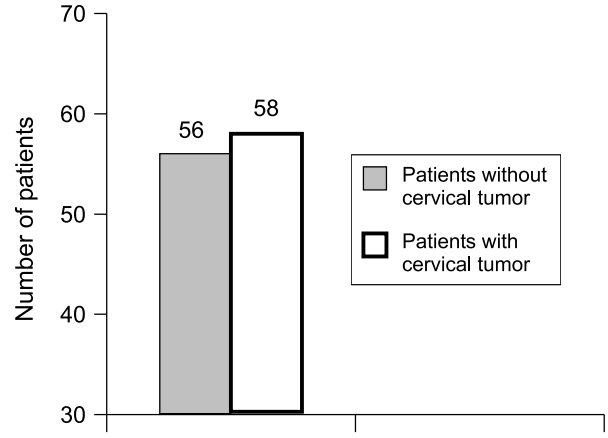

Figure 1. Histological findings of cervical disease after brachytherapy.

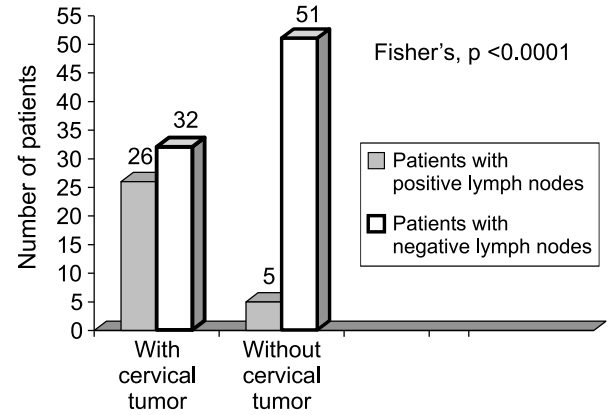

Figure 2. Lymph node status in relation to the response of the cervical tumor after brachytherapy.

Table 1. Results of brachytherapy in cervical carcinoma according to the age of the patients

Groups of patients	*Median*	*Age (years) Range*	*p-value*
Group A (n=56)	40.7	26-63	0.0318
Group B (n=58)	45.7	31-66	

The difference between the 2 groups was highly significant (Fisher's exact test, $p \leq 0.0001$; 95% C.I. 1.592-2.973).

Group A patients had significantly lower age compared with group B patients ($p < 0.0318$, Table 1).

Discussion

Stage IB cervical carcinoma is divided into IB1 (less than 4 cm in greatest dimension) and IB2 (greater than 4 cm). The treatment of these two substages is similar. Patients with stage IB can be treated effectively by either radical hysterectomy and lymphadenectomy (pelvic ± para-aortic) or by radiation therapy. Although surgery and radiation therapy produce similar survival rates, radical hysterectomy is considered by many to be the treatment of choice for young patients with IB1 lesions [13,14]. Landoni et al. concluded that overall survival (83%) and 5-year disease-free survival (74%) for the two groups were the same [15]. Currently, options for primary therapy of IB2-IIA include: a) primary chemoradiation; b) primary radical hysterectomy and bilateral pelvic lymphadenectomy, which usually is followed with adjuvant radiation; c) neoadjuvant chemotherapy (3 rapidly delivered courses of platinum-based chemotherapy) followed by radical hysterectomy and pelvic lymphadenectomy ± adjuvant postoperative radiation or chemoradiation [16-18].

Many IB2 tumors extend anatomically beyond the curative isodose curve of radiation, and contain central hypoxic areas that are resistant to ionizing radiation [19]. Decker et al. showed that for each 1 cm increase in cervical diameter (3-9 cm), there was a nearly 3-fold increase in the risk of recurrence. It was also confirmed that no residual carcinoma at the time of hysterectomy was associated with a significant decrease in the risk of recurrence [20].

Therefore, preoperative radiation therapy followed by extrafascial hysterectomy has been recommended by several groups [12,21]. Pelvic lymph node metastases are present in 20-25% of patients with stage IB2, which is more important for further therapy [22,23].

About 50% of the patients treated preoperatively with brachytherapy were without disease in the cervix and lymph nodes, showing considerable benefit from this treatment modality. This benefit poses, however, another question: can radiotherapy be considered adequate definite therapy? Many studies have shown that overall survival and 5-year disease-free survival for the two treatment modalities (surgery *versus* radiotherapy) were practically identical. Postirradiation adjuvant hysterectomy for patients without macroscopic disease outside the pelvis at the time of surgery is still a valuable treatment option and may improve survival in a select group of patients. Keys et al. noted a possible improvement in survival in patients with tumors <7 cm who underwent postirradiation hysterectomy in the only randomized prospective study done that compared radiation with radiation and completion hysterectomy as a combined modality [24]. It has not been proven to lengthen overall survival of patients with bulky cervical cancer, but there may be some benefit for patients with residual disease after chemotherapy and radiation. It is likely that patients with residual disease might have relatively worse survival without adjuvant hysterectomy [12,20,21,24].

These facts underline the importance of careful selection of patients where adjuvant hysterectomy will improve treatment results. These patients are with residual cervical disease without macroscopic disease outside the pelvis after preoperative treatment, since patients with disease outside the pelvis do not benefit from surgery. Inadequate choice of patients for surgery could increase morbidity uselessly [25,26].

It is widely accepted that intracavitary brachytherapy is an essential component of radical treatment of cervical cancer either alone or in combination with external beam radiation. Many authors have reported the optimal time-dose-fractionation relationship of high dose rate (HDR) brachytherapy, based on the cure rates and the incidence of late complications. External beam irradiation and HDR intracavitary brachytherapy constitute the integrated radiation therapy for cervical cancer [27-29]. HDR brachytherapy has been accepted as an alternative to low dose rate (LDR) brachytherapy and provides the advantage of shortened treatment periods [30].

The Decker's et al. study provided data on HDR *versus* LDR brachytherapy. Seventy-two percent of the patients who received HDR brachytherapy were alive with no evidence of disease, compared with 68% of patients who received LDR brachytherapy. The difference was not statistically significant because of the sample size, but the data in that study support the use of HDR with respect to survival and postradia-

tion morbidity plus the added advantage of shortened treatment periods [20]. However, the history of HDR brachytherapy is short and the treatment is still controversial.

What are the options if we prefer preoperative brachytherapy? Do we have to perform radical hysterectomy in all patients with preoperative brachytherapy?

Adjuvant hysterectomy is performed to decrease the risk of locoregional disease recurrence.

Evidence suggests improvement in pelvic control and progression-free survival in selected patients when combined therapy is used in bulky disease [12,21,24].

Women with stage IB2 cervical cancer treated primarily with radiotherapy have to be evaluated again. It is mandatory to distinguish patients with and without malignant disease outside the pelvis. Chemoirradiaton is a tailored treatment in these cases.

Many diagnostic modalities (cervical biopsy, nuclear magnetic resonance scan, PET scan, laparoscopy) can show the status of the cervix and pelvic lymph nodes [31,32]. Laparoscopy, as initial diagnostic procedure, could be useful in the differentiation between patients with pelvic and extrapelvic disease. Computerized tomography has not been helpful in the assessment of extrapelvic disease in bulky cervical cancer cases [33]. High percentages of false-positive or negative results decrease the sensitivity of the method just after radiotherapy.

Positive local findings point to radical surgery if there is no extrapelvic spread of the disease.

The patients' posttreatment morbidity, which is increased when preoperative and postoperative therapies are applied, has to be considered as an important factor in selecting patients for radical operations. Most complications are seen among patients who had preoperative brachytherapy followed by radical hysterectomy and postoperative radiotherapy [25,26].

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