Adjuvant Therapy after Radical Surgery of Cervical Cancer: Zagreb Experience

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ABSTRACT

The results of the analysis of the treatment of 72 patients with carcinoma of the uterine cervix are presented. Seventy-two patients with Stage IB1 carcinoma of the cervix underwent a radical hysterectomy and pelvic lymphadenectomy. The low-risk group includes the patients without unfavourable prognostic factors that were treated by surgery alone. The high-risk group included women with pelvic node metastases, clinical tumour size greater than 3.0 cm, depth of stromal invasion greater than 1/3 of the cervical wall, Grade 3 tumours and the presence of lympho-vascular space involvement. High-risk patients received whole pelvic radiotherapy between two and four weeks following surgery. Thirty-four patients (47.2%) were in the low-risk group and thirty-eight patients (52.8%) were in the high-risk group. Locoregional recurrences were diagnosed in three cases (8.8%) in the surgery group and in four patients (10.5 %) assigned to postoperative radiotherapy. The incidence of distant metastases was 2.9% in the group treated by surgery alone and 5.3% in the group treated by surgery and radiotherapy. Overall survival at five years was 91.2% in the low-risk group and 89.5% in the high-risk group of patients. Five-year overall survival, locoregional and distant metastases were similar in the low-risk and high-risk groups of patients, which emphasizes the value of whole pelvic radiation in patients with one or more unfavourable prognostic factors after radical surgery in Stage IB1 cervical cancer.

Key words: *cervical cancer, risk factors, adjuvant therapy*

Introduction

Uterine cervical cancer is the most common gynecological cancer worldwide with a yearly incidence of 500, 000 cases[1]. It is an important women's health problem in developing countries. Risk factors for cervical cancer include early onset of sexual activity, multiple sexual partners, lower socio-economic group and history of sexually transmitted disease. Human papilloma virus has been implicated as the major causative agent in this disease. Squamous cell carcinomas account for 80–85% of cases with adenocarcinoma and adenosquamous carcinomas responsible for 15% and 3–5%, respectively[2]. At the FIGO Congress in Montreal 1994, the Gynecologic Oncology Committee made some changes in the staging for cervical cancer. Stage IB comprises patients with microscopic stromal invasion more than 5.0 mm or with horizontal spread more than 7.0 mm and clinically visible lesion confirmed to the cervix. Stage IB1 presents clinical lesions no greater than 4.0 cm in size and Stage IB2 clinical lesions greater than 4.0 cm in size[3]. Signs range from abnormal cervical smear only to a cervix with exophytic or crater-like type lesions. Symptoms include abnormal vaginal bleeding, postcoital spotting and vaginal discharge.

The algorithm for the management of Stage IB cervical cancer includes radical hysterectomy and pelvic lymphadenectomy. Patients with lymph node metastases are treated by postoperative adjuvant pelvic radiation[4]. Positive surgical margins, parametrial involvement, tumor diameter, depth of stromal invasion, tumor grade and lympho-vascular space involvement are also risk factors for recurrences. Gynecology Oncology Group (GOG) study in 1990, reported clinical tumor size, depth of invasion of the cervix and lympho-vascular space involvement as

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independent prognostic factors. Patients with negative lymph nodes in Stage IB cervical cancer have 25% high risk factors[5]. Another GOG study in 1999, suggested that postoperative pelvic radiation reduced the risk of recurrences in patients with at least two risk factors: large tumor diameter, more than 1/3 stromal invasion and lympho-vascular space involvement[6]. Women with Stage IB or II cervical carcinoma with lymph node metastases post Wertheim hysterectomy and pelvic lymphadenectomy who were given adjuvant radiotherapy treatment had better survival than those undergoing surgery only in a multivariate analysis. Patients without pelvic lymph node metastases but with parametrial extension, tumour size greater than 4 cm, full thickness cervical stromal invasion and DNA index more than 1. 3 had significantly better five-year recurrence free survival rate if receiving postoperative radiotherapy[7].

In previously published studies patients with cervical cancer stage IB with unfavourable prognostic factors were classified in two groups, those who were and those who were not treated by radiotherapy after surgery. The five-year survival was significantly higher in those women who were treated compared to non-treated women by radiotherapy after surgery. Herein, we evaluate the whole pelvic radiation in women with vs. those without unfavourable prognostic factors after surgery of cervical cancer stage IB1. The recurrence of the disease was the endpoint of this evaluation.

Subjects, Material and Methods

Seventy-two patients were included into the study with a mean age 44.2±10.4 years. Initial evaluation included medical history, Pap smears and pelvic examination. When cytology has shown malignant cells in patients with no visible tumour we made diagnostic conization. In patients with clinically visible lesions confined to the cervix, diagnosis was confirmed by a directed punch biopsy. Preoperative evaluation included physical examination, complete blood count, blood chemistry tests, chest radiography, intravenous pyelogram, cystoscopy and sigmoidoscopy. All patients were treated by Wertheim hysterectomy and pelvic lymphadenectomy. When no residual tumour was found in the radical hysterectomy specimen, presurgical data from cone biopsies were used. The diagnoses of squamous cell carcinoma, adenocarcinoma or adenosquamous cervical cancer were made by a pathologist.

Low-risk group include the patients without unfavourable prognostic factors and they were treated only by surgery. High-risk group includes women with pelvic node metastases, clinical tumour size greater than 3.0 cm, depth of stromal invasion greater than 1/3 cervical wall, Grade 3 tumours and the presence of lympho-vascular space involvement. High-risk patients received radiotherapy between two and four weeks following surgery.

Postoperative radiotherapy was administered to the pelvic region according to a standardised protocol. The radiation was delivered by 4 fields' box technique or by *anteroposterior* and *posteroanterior* parallel-opposed pair of fields, using linear accelerator or cobalt-60 unit. The total tumour dose was 40–48 Gy in 20–24 fractions using 2 Gy daily fractions, five days a week.

Patients were evaluated by physical examination, ultrasound, Pap smear, blood counts, blood chemistries and chest radiography every three months for the first two years, every six months during the next three years and then annually. Computed tomography scan with contrast or magnetic resonance imaging of the abdomen and pelvis were done at six months and then yearly. Sites of recurrence were classified as local if detected in the pelvis or vagina, and distant if detected in extra-pelvic locations.

The differences were evaluated by Chi-square test with statistical significance set at $p<0.05$.

Results

From January 1995, to December 2001, seventy-two patients with FIGO Stage IB1 cervical cancer were primarily treated by radical surgery. The tumour cell type was squamous in sixty-one (84.7%) women, adenocarcinoma in nine (12.5%) and adenosquamous carcinoma in two (2.8%). Thirty-four patients out of 72 (47.2%) were low-risk and 38/72 (52.8%) were high-risk patients.

For the low-risk group of patients no further therapy was applied, while high-risk patients received postoperative whole pelvic radiation. The median interval between the operation and the first radiotherapy session was 24 days. During radiotherapy the patients were treated with medication or dietary measures, or both, for related symptoms.

Local recurrences in the pelvis or vagina were diagnosed in three patients (8.8%) in the group treated by surgery and in four patients (10.5%) treated by postoperative radiotherapy. Distant metastases involving the abdomen or lung, or both locations were analyzed. The incidence of distant metastases was 2.9% in the group treated by surgery alone and 5.3% in the group treated by surgery and radiotherapy (Table 1). No significant differences was observed (Chi-square=0,08, $p>0.05$).

In four patients there were grade 3 or 4 adverse effects, of which one out of 34 (2.9%) patient was treated by surgery alone and 3 out of 38 (7.9%) patients were treated by both surgery and radiotherapy.

TABLE 1
RECURRENCES OF IRRADIATED AND NONIRRADIATED GROUP OF PATIENTS

Site of recurrence	Surgery only (N=34)	Pelvic radiation (N=38)
Local	3 (8.8%)	4 (10.5%)
Distant	1 (2.9%)	2 (5.3%)
Total	4 (11.7%)	6 (15.8%)

TABLE 2
FIVE-YEAR SURVIVAL OF PATIENTS ACCORDING TO THE TREATMENT IN RELATION TO GOOD AND POOR PROGNOSTIC FACTORS

Prognostic factors	Number of cases	Pelvic radiation	5-year survival (%)
Low-risk group	34	No	91.2%
High-risk group	38	Yes	89.5%

Overall survival at five years was 91.2% in the low-risk group and 89.5% in the high-risk group of patients (Table 2); almost equal in both groups of patients.

Discussion

The role of postoperative irradiation was evaluated for patients with Stage IB cervical cancer with tumour-related risk factors. Three independent prognostic factors in the GOG study in 1990, clinical tumour size, depth of tumour invasion and lympho-vascular space involvement made GOG risk score. Score higher than 120 was correlated with 41% recurrence rate[5]. Sedlis et al. used a modification of the GOG scoring system and reported a 44% reduction of the risk of recurrences after adjuvant radiotherapy when a combination of three risk factors were present compared without postoperative irradiation[6]. Ayhan et al. reported that tumour size larger than 4 cm; lympho-vascular space involvement and vaginal involvement were independent prognostic factors in lymph node negative invasive cervical cancer. Depths of stromal invasion, parametrial, endometrial and myometrial involvement, however, were not independent prognostic factors. Women with one and two or more risk factors showed lower ratios of pelvic recurrences when receiving postoperative radiotherapy[8]. Pieterse et al. before 1996 received adjuvant radiotherapy for patients with pelvic node metastases, parametrial invasion or positive surgical margins. In 1997 they extended the indication for postoperative irradiation using a modification of the GOG scoring system. Patients with at least two of the three risk factors received total pelvic radiotherapy: pathologic tumour size greater than 40 mm, depth of invasion greater than 15 mm and presence of lympho-vascular space involvement. They found that a significantly larger percentage of the high-risk group of patients who did not receive radiotherapy had recurrence of disease (41% vs. 12%). Differences in five-year cancer specific survival and five-year disease free survival between the high-risk groups treated with radiotherapy and without radiotherapy after radical surgery were statistically significant[9]. In the recent study they found that adjuvant radiotherapy did not significantly increase the risk of bladder dysfunction, bowel symptoms, lymphedema and sexual function after 2-years follow-up[10]. Scharge et al. reported that lympho-vascular space involvement is an important prognostic variable and adjuvant pelvic radiation may decrease the risk of recurrence in this patients[11]. GOG study in 2005 suggests that pelvic radiotherapy after radical surgery significantly reduced the risk of recurrence and prolongs progression-free survival in women with Stage IB cervical cancer. Radiation appears to be particularly beneficial for patients with adenocarcinoma or adenosquamous carcinoma[12].

In another our study one hundred and forty eight patients with Stage IB squamous cell cervical cancer were primarily treated by radical surgery. Low-risk group included 70 patients without unfavourable prognostic factors that were treated by surgery alone. High-risk group included 78 women with one or more risk factors: pelvic node metastases, positive or close surgical margins, clinical tumour size greater than 4.0 cm, stromal invasion greater than 1/3 cervical wall, Grade 3 tumours and the presence of lympho-vascular space involvement. High-risk patients received postoperative whole pelvic radiation. Eleven (15.6%) women in the low-risk group developed cancer recurrences, nine (12.8%) local, and two (2.8%) distant. In high-risk patients there were sixteen (20.5%) cancer recurrences, eleven (14.1%) local and five (6.4%) distant. Overall survival at five years was 88.6% in the low-risk group and 84.7% in the high-risk group of patients[13]. More of recurrences in the high-risk group were seen in patients with IB bulky tumours and we reduced primarily radical surgery treatment for FIGO Stage IB1 cervical cancer.

In the recent study the low-risk group includes 34 patients without unfavourable prognostic factors who were treated by surgery alone. The high-risk group includes 38 women with one or more risk factors: pelvic node metastases, tumour size greater than 3.0 cm, stromal invasion greater than 1/3 cervical wall, Grade 3 tumours and presence of lympho-vascular space involvement. The high-risk patients received postoperative radiotherapy. Four (11.7%) women in the low-risk group developed cancer recurrences, three (8.8%) local, and one (2.9%) distant. In the high-risk group of patients there were six (15.8%) cancer recurrences, four (10.5%) local and two (5.3%) distant. Local relapses were treated by surgery and patients with distant metastases received chemotherapy. Women with squamous cell carcinomas received cisplatin-based regiments and patients with adenocarcinoma or adenosquamous type tumours received paclitaxel-based chemotherapy[14]. Five-year overall survival rate in the low-risk group treated by surgery and high-risk, surgery and radiotherapy treated group was similar, 91.2 and 89.5%, respectively. The adverse effects were not more expressed in the group of patients treated by adjuvant total pelvic irradiation after radical surgery. This emphasizes the value of whole pelvic radiation in patients with unfavourable prognostic factors in Stage IB1 cervical cancer.

Conclusion

In this study on a relatively small number of patients with cervical cancer stage IB1 with one or more unfavourable prognostic factors we intended to show the

value of postoperative adjuvant radiation. Our findings indicate that the number of local and distal metastasis were similar to those patients without unfavourable prognostic factors. The five year survival is also similar in both groups of patients. The adjuvant total pelvic irradiation after radical surgery might represent over treatment in some women but did not generate any side effects. From all these observations we consider that it is prove enough to practice whole pelvic radiation in patients with one or more unfavourable prognostic factors after radical surgery in Stage IB1 cervical cancer.

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ADJUVANTNA TERAPIJA NAKON RADIKALNE OPERACIJE RAKA VRATA MATERNICE

SAŽETAK

Prikazani su rezultati analize naše studije liječenja 72 bolesnice s rakom vrata maternice. Sedamdeset i dvije pacijentice s IB1 stadijem raka vrata maternice podvrgnute su radikalnoj histerektomiji i zdjeličnoj limfadenektomiji. Skupinu niskog rizika čine bolesnice bez nepovoljnih prognostičkih čimbenika i liječene su samo operacijom. Skupinu visokog rizika tvore žene s presadnicama u zdjeličnim limfnim čvorovima, veličinom tumora preko 3,0 cm, dubinom invazije strome većom od 1/3, nezrelim tumor ima i nazočnošću tumora u limfo-vaskularnim prostorima. Visoko rizične bolesnice primile su zračenje izvana na zdjelicu između dva i četiri tjedna nakon operacije. Trideset četiri bolesnice (47,2%) bile su niskog rizika, a trideset i osam (52,8%) ih je bilo visokog rizika. Lokalni recidiv bolesti je dijagnosticiran u tri slučaja (8,8%) u operiranoj skupini i u četiri bolesnice (10,5%) koje su određene za radioterapiju. Incidencija udaljenih metastaza bila je 2,9% u operiranoj skupini i 5,3% u operiranoj i zračenoj skupini. Peto-godišnje preživljenje je bilo 91,2% u skupini bolesnica s niskim rizikom, dok je u skupini bolesnica s visokim rizikom bilo 89,5%. Petogodišnje preživljenje, lokalne i udaljene metastaze bile su slične u bolesnica s niskim i visokim rizikom. Ovo ističe vrijednost zračenja zdjelice u bolesnica s jednim ili više nepovoljnih prognostičkih čimbenika nakon radikalne operacije IB1 stadija raka vrata maternice.