



The Influence of Adjuvant Radiotherapy on Physical Symptoms and Quality of Life In IB1 Stage Cervical Cancer Patients

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Abstract

Cervical cancer is the fourth most common cancer affecting women worldwide. Radical hysterectomy with pelvic lymphadenectomy with or without adjuvant radiation therapy is used as primary therapy for IB stage carcinoma of the cervix. The aim of this study was to compare the complications and quality of life of patients with stage IB1 cervical carcinoma treated by surgery or combined surgery and adjuvant radiotherapy. In a prospective case-control study 49 patients diagnosed with a cervical cancer were included - 37 patients receiving adjuvant radiotherapy in the study group and 12 patients without radiotherapy in the control group that were undergoing surgical treatment in Riga Eastern Clinical university hospital between January 2011 and December 2012.

Mean age was higher in patients who received adjuvant radiotherapy in comparison to patients who received only surgical treatment – 49,76±11,54 vs. 40,08±9,59 years (p=0,012).

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Higher stromal invasion was in adjuvant radiotherapy group comparing to surgical group- $12,44 \pm 5,05$ vs. $8,27 \pm 4,32$ mm ($p=0,02$). Patients who received adjuvant radiotherapy more often experienced symptoms related to the radiation influence on gastrointestinal tract and urinary system. Diarrhea during the treatment was statistically higher in adjuvant radiotherapy group ($p < 0,001$). In addition, dysuria after the therapy ($p=0,065$), dysuria at the time of interview ($p=0,078$) and legs edema at the time of interview ($p=0,080$) were more often observed in adjuvant radiotherapy group.

No differences between groups were observed for constipation ($p=0,123$), legs edema after the treatment ($p=0,305$) and diarrhea at the time of interview ($p=0,634$).

Keywords: cervical cancer, quality of life, radiation therapy, hysterectomy

1. Introduction

Cervical cancer with 528 000 new cases every year, is the fourth most common cancer after breast, colorectal, and lung cancers affecting women worldwide. It is also the fourth most common cause of cancer death (266 000 deaths in 2012) in women worldwide [1].

There is a lot of published research, which describes quality of life among women who received treatment for cervical cancer. In stage IB a similar therapeutic effect can be reached using either surgical or radio therapy: recurrence rate 15.5% (1-5 years interval) vs. 11% (5 years interval) [2; 3]. If a woman wants to preserve sexual function, the surgical therapy is recommended [4]. If it is unnecessary or cancer is widely spread (for example, there is metastasis in pelvic lymph nodes), radiotherapy should be done [5].

Our research did not include review of the quality of sexual life because it had been analyzed before. Sexual life quality and climacteric symptoms among women, who received surgical or combined surgical and radiotherapy treatment of cervical cancer, were studied in Riga Eastern Clinical university hospital in 2013. The research demonstrated that those women who had received dual therapy developed a premature menopause and an impairment of sexual life [6].

In our research we analyzed gastrointestinal and urinary system complications, as well as lymph drainage impairment after combination surgery and radiation therapy in IB1 stage cervical cancer patients.

2. Material and methods

Patients with primary diagnosed IB1 stage cervical cancer (tumor is visualized and is not larger than 4 cm in diameter) were included in the prospective study. All patients included in the study underwent treatment at Gynecological department Riga Eastern Clinical university hospital from January 2011 to December 2012. The stage of cervical cancer was determined according to International Gynecologists and Obstetricians FIGO staging system.

From the beginning, 62 patients with clinical stage IB1 were selected, of which 15 patients received surgical treatment and 42 patients received the combination treatment - surgery and adjuvant radiotherapy. Four patients received surgery, radiation and chemotherapy, and one patient refused any treatment. These 5 patients were excluded from the research. Only patients who could be reached by phone were included into the study. All patients were divided in two groups: patients who got only the surgical treatment (n=12) and patients who got the surgical treatment followed by the adjuvant radiotherapy (n=37). All patients have had radical hysterectomy type 2: total hysterectomy with or without adnexa uteri removal, excision of the parametrical tissues and lymphadenectomy of pelvic lymph nodes. In the study group with the adjuvant radiotherapy, all patients received the external-beam radiotherapy to small pelvis with the total dose of 45 – 50 Gy (dose was divided into 22 – 25 Gy fractions with 1,8 – 2,0 Gy amplitude) and the cavity radiotherapy with the total dose of 30 – 40 Gy.

All patients were contacted by phone. We used phone numbers mentioned on medical charts. A specially prepared questionnaire about patients' symptoms (urinary problems, diarrhea, constipation, legs edema), was filled during the phone interview.

During interview we collected information about beginning of symptoms and their level of severity. The severity of symptoms was classified as severe if repeated 7 and more times a day, moderate – 4 to 6 times a day, and mild - less than 4 times a day. Other clinical data were obtained from medical charts. The data were analyzed by SPSS 20.0 and Excel programs. Parametric and nonparametric statistics were analyzed by t-test and Chi-quadrat test. Statistically significant difference was assumed if $p < 0,005$.

3. Results

Patients in the combined therapy group were older than in the chirurgic therapy group: $49,76 \pm 11,54$ vs. $40,08 \pm 9,59$ ($p=0,012$). Mean invasion was higher in the combined therapy group ($12,44 \pm 5,05$) compared to the chirurgic group ($8,27 \pm 4,32$) with $p=0,02$. The histology and the number of removed lymph nodes were similar in both groups. One adenocarcinoma and 11 squamous cell carcinomas were in the surgery group, and 6 adenocarcinomas and 31 squamous cell carcinomas were in the combined therapy group ($p=0,445$). Tumor invasion $\leq 1/3$ were found in 8 patients in the chirurgic group and in 7 patients in the combined therapy group ($p=0,953$).

Metastatic lymph nodes were positive in one chirurgic patient and in 2 combined therapy patients (Table 1).

No significant difference in cancer morphology or metastatic lymph nodes number was observed between the two groups (Table 1). The loose stool after the treatment was more likely to occur in the combined therapy group ($p < 0,001$): 14% of patients noted severe, 37% - moderate and 49% - mild diarrhea. Symptoms associated with urination impairment and legs edema were observed more often in

patients in the combined therapy group but did not reach a statistically significant difference (Fig. 1).

Table 1. Patients' descriptive parameters in the surgical and the combined treatment groups

Analyzed parameters	Surgery group (n=12)	Combined therapy group (n=37)	p
Mean age, years	40,08±9,59	49,76±11,54	p=0,012
Cancer morphology			
- adenocarcinoma	1	6	p=0,445
- squamous cell carcinoma	11	31	
Cancer stromal invasion, mm	8,27±4,32	12,44±5,05	p=0,02
Cancer stromal invasion ≤1/3	8	7	p=0,953
Metastatic lymph nodes	1	2	p=0,946
Mean removed lymph nodes	16,10±5,78	11,13±11,19	p=0,189

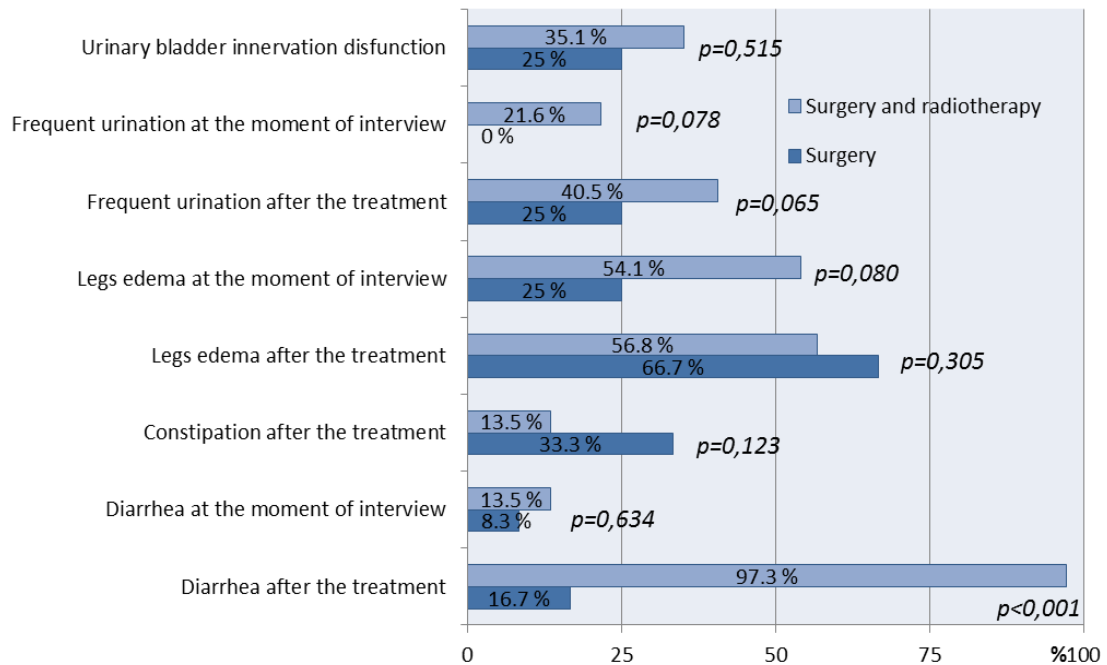


Figure 1: Comparison of complications in the surgical and the combined treatment groups after treatment

In the combined therapy group, diarrhea and frequent urination was longer while the legs edema in both study groups remained equally long (Fig. 2).

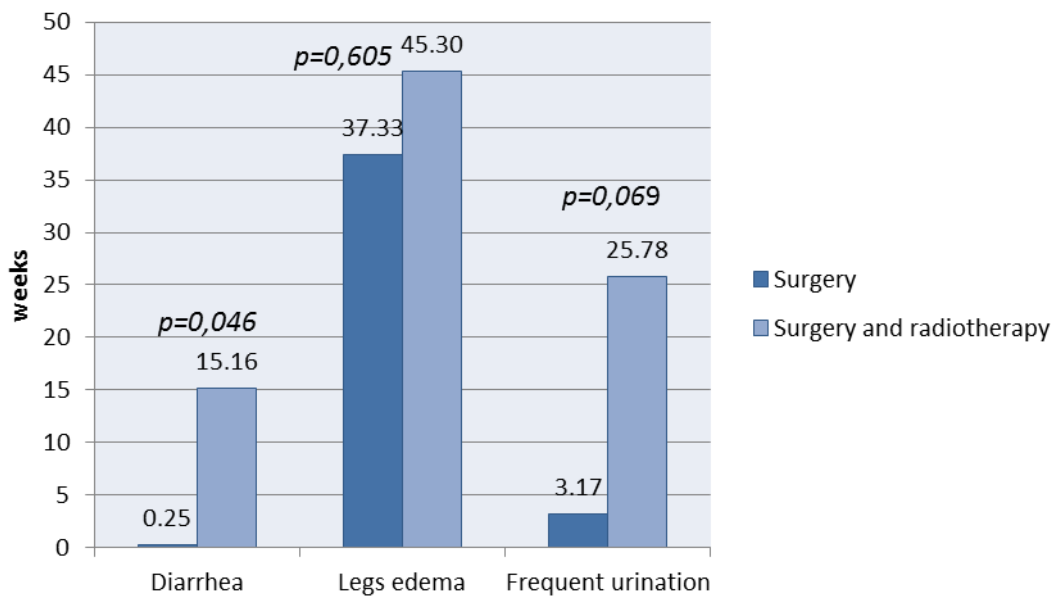


Figure 2: Comparison of symptoms duration in the surgical and the combined treatment groups after treatment

4. Discussion

Our research examines the most common complaints associated with cervical cancer treatment. We observed an increased incidence of diarrhea in patients who underwent a combined treatment of surgery and radiotherapy as compared to the group of patients who was treated only by the surgery. In addition, diarrhea in the combined therapy group of patients was more prolonged as compared to the other group.

According to Maduroa et al., diarrhea after radiotherapy was observed in 61 % of patients, while Bergmark et al. observed it in 46 % of the patients [7; 8]. In our study, the more frequently observed diarrhea was due to the fact that we also documented mild diarrhea cases, which occurred in nearly all patients during the second or third week after the start of radiotherapy and lasted for at least 3 weeks after completion of the radiation therapy. Diarrhea after radiotherapy can be explained by several pathophysiological mechanisms: bile and lactose malabsorption, intestinal motility changes and disbacteriosis [9]. Such kind of diarrhea can be treated with opioid derivate loperamide and bile absorbent smecta [9].

Severe diarrhea was observed in 14 % of patients. That coincided with the data published by other authors e.g. in the Bergmark et al. study analyzing 78 patients, severe diarrhea was observed in 22% of cases [8]. Severe diarrhea is often seen in patients who receive aggressive radiation therapy. Zelefsky et

al. found that diarrhea occurs more frequently in patients receiving > 70 Gy total dose of radiation and in patients with diabetes [10].

Prolonged diarrhea in our study was observed in 13.5 % of patients. The long-term diarrhea is a diarrhea that lasts at least 120 days [11]. In the study by Andreyev et al., 57-67 % of the women pointed out that the long-term diarrhea had significantly impaired their quality of life [12]. In 23-26 % of cases, prolonged diarrhea was complicated by hemorrhagic colitis, and in 1-5 % of cases hemotransfusion was required [12].

In our study, the diarrhea was seen in 16.7 % (2 /12) of patients after surgical therapy that is in agreement with the survey by Bergmark et al. where diarrhea after surgical treatment was observed in 18% of patients [8]. Only one patient treated exclusively by the surgery, had a prolonged diarrhea. Diarrhea after the surgical treatment can be due to a diet change, medication (mainly antibacterial therapy) as well as thyroid dysfunction, and celiac and other intestinal diseases, which are manifested after operative intervention [12].

The second most common combination therapy complication was an increase in the urination frequency. It was observed in 25 % and 40.5 % of women who underwent the surgical and the combination therapies respectively, This coincides with the Bergmark et al. study: 27% and 44 % respectively [8]. Frequent urination after surgical treatment is due to the small bladder nerve damage during the surgery [13]. In patients from the combination therapy group, urinary problems occurred on average 15 % more frequently that could be explained by the effects of radiation on the bladder wall e.g. aseptic inflammation, tissue fibrosis and bladder volume decrease [14].

Legs edema at the time of the interview was noted in 66.7 % of women after surgery and in 56.8 % of women after combined therapy that is more often than reported in the literature: 37.6 % and 40 % [20; 8]. Legs edema incidence is increased by the lymph nodes removal and is related to the number of lymph nodes removed [20; 15]. Edema treatment is a long and complicated process that involves lymph drainage, compression socks, skin care and special exercises [15].

In Riga Eastern Clinical university hospital, patients with cervical cancer stage IB1 are offered a radical hysterectomy as the primary treatment. When postoperative histology is received, the use of radiation therapy is approved by the council. In this study, 7 patients whose tumor invasion was $\leq 1/3$ of the cervical stroma and 7 patients with the tumor invasion $\leq 1/2$ received the adjuvant radiotherapy. Of these 14 patients, none had iliac metastasis and the tumor resection line was clean from cancer cells. Unfortunately, pathological reports were not available for lymphovascular space involvement.

European Association of chemotherapists (ESMO) guidelines [16] in considering the use of adjuvant radiation therapy refer to the Rotman et al. study criteria, a combination of two or more risk factors of recurrence: tumor cervical invasion more than $1/3$ of the cervical stroma, lymphovascular space involvement and tumor size greater > 4 cm [17].

International Gynecologists and Obstetricians (FIGO) published guidelines recommend adjuvant radiotherapy for patients with large primary tumors (> 4cm), lymphovascular space involvement and tumor invasion to the outer third of the cervix.

NCCN guidelines stress that patients with a tumor size less than 4 cm in diameter should be observed after surgery without radiotherapy. Radiation therapy can be used only for patients with high recurrence risk factors such as large primary tumor, deep tumor stromal invasion and / or lymphovascular space involvement [18].

All these guidelines mention large primary tumors, which were not observed in this study. Deep stromal tumor invasion to the cervix was observed in only 23 of 37 patients in the combined therapy group, where it exceeded 10 mm. In our study, lymphovascular space involvement was not investigated. One may think that the radiation treatment to the 14 patients was given because of the lymphovascular space involvement. However, Okazawa et al. showed that in the medium risk group of patients with only one risk factor, lymphovascular space involvement, there was no difference in survival rate between patients who received and who did not receive the adjuvant radiotherapy [19].

Three patients had a histologically verified tumor metastasis in lymph nodes. According to ESMO, FIGO and NCCN, and NCI guidelines, these patients should receive not only radiotherapy, but also chemotherapy in the postoperative period.

5. Conclusions

Women who had received a combination of surgical treatment and radiotherapy had side effects more frequently. Diarrhea and urinary system disorders were the most frequent side effects of the combined therapy. Often radiotherapy is used when patients have low risks of recurrence. However, patients, who have a high recurrence risk after surgery, get inadequate treatment i.e. radiotherapy without chemotherapy.

Acknowledgments

The authors sincerely thank the gynecology team at Gynecological department Riga Eastern Clinical University hospital.

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