

## The influence of adjuvant radiotherapy on ovarian function, menopausal symptoms and quality of sexual life in cervical cancer patients

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### Abstract

**Background:** Cervical cancer is the most common gynaecologic cancer in women worldwide. While majority of cervical cancer patients are premenopausal, preservation of ovarian function remains crucial to maintain overall quality of life without menopausal symptoms as well as their quality of sexual life. Ovarian function depletion following treatment of cancer due to pelvic irradiation is affecting the quality of survivals and is recognized issue and efforts should be made to help young women to retain also their fertility potential.

**Aim:** to analyse the influence of adjuvant radiotherapy in the treatment of cervical cancer on ovarian function, menopausal symptoms and quality of sexual life.

**Material and methods:** In a prospective case-control study 37 patients diagnosed with a cervical cancer were included - 29 patients receiving adjuvant radiotherapy in the study group and 8 patients without radiotherapy in the control group that were undergoing surgical treatment in Riga Eastern Clinical university hospital from year 2007 till 2011.

**Results:** Mean concentrations of folliculostimulating hormone were higher in patients who received adjuvant radiotherapy in comparison to patients who received only surgical treatment –  $94.12 \pm 44.16$  U/l (range 5.0 – 199.0) vs.  $6.08 \pm 2.90$  U/l (range 2.9 – 11.5) U ( $p < 0.001$ ). Higher concentrations of folliculostimulating hormone in serum correlated with adjuvant radiotherapy (0.683;  $p < 0.001$ ).

Patients who received adjuvant radiotherapy more often experienced symptoms related to the decreased oestrogen levels. Only for depressed mood, headaches and weight gain no differences between groups were observed.

Patients in the group with the adjuvant radiotherapy less frequently reported that their sexual life was fine; they were less frequently satisfied, more depressed, unconvinced and even felt anger concerning their sexual life.

37.5% patients in the surgery group and 20.7% patients in the combined treatment group had changed their sexual partners in the treatment period ( $p=0.36$ ).

**Conclusion:** Patients with more aggressive treatment have compromised quality of their sexual life and overall quality of life due to earlier onset of menopause. This can be explained by impaired ovarian function caused by external-beam radiotherapy. Combined surgical treatment following radiotherapy should be applied only in patients with high risk factors for cervical cancer recurrence; moreover, ovaries should be mapped with a metallic clipators for better visualization when planning adjuvant radiotherapy to preserve ovarian function in premenopausal women.

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**Key words:** cervical cancer, quality of sexual life, menopause

## **Introduction**

Cervical cancer is the most common gynaecologic cancer in women with 490,000 new cases and 270,000 deaths annually worldwide, despite a decreasing incidence in developed countries which is acquired due to vaccination and regular screening checkups.<sup>1-3</sup> Compared with other gynaecologic malignancies, cervical cancer develops in a younger population of women; more than 20% of these patients are below 40 of age.<sup>1,4</sup> There are two generally accepted cervical cancer treatment strategies with similar results in terms of survival - surgical approach and irradiation which nowadays very often is being combined with chemotherapy. Sometimes for high risk patients of cancer recurrence surgical and chemo-radiotherapy are being combined together. Despite that treatment results are similar for both treatment approaches; surgery is preferred in younger patients, because of lesser impact on quality of patient's sexual life. Microinvasive cervical cancer can be effectively treated surgically by either conisation or simple extrafascial hysterectomy. However, for those with advanced disease, chemoradiation may be applied as a neoadjuvant treatment.<sup>5-8</sup> Preservation of fertility potential is another important aspect for these patients. Infertility following treatment of cancer with radiotherapy is affecting the quality of survivals. For the first time ovarian transposition was proposed in 1958 by McCall *et al.* The results of this technique have been the subject of many studies in the context of ovarian function preservation.<sup>9-13</sup>

The goal of our study was to analyse ovarian function, menopausal symptoms and quality of sexual life after treatment of cervical cancer in patients with ovarian transposition who are receiving only surgical treatment and combined treatment with surgery and radiotherapy.

## Material and methods

In a prospective case-control study 37 patients diagnosed with a cervical cancer were included. All patients included in the study underwent surgical treatment in Riga Eastern Clinical university hospital from year 2007 till 2011.

Eligible patients according to the study protocol were invited to participate in the study. Patient inclusion criteria were age from 18 till 45, histologically approved cervical cancer after radical hysterectomy type II with preserved ovaries. All patients were divided into two groups – patients with only surgical treatment (n=8) in the control group and patients with surgical treatment followed by adjuvant external-beam radiotherapy (n=29) in the study group.

During the case control appointment patients were visually examined, underwent abdominal and vaginal ultrasound examination to visualise their ovaries and they filled two forms one concerning their menopause symptoms and daily habits that can influence more rapid the ovarian function depletion and other concerning the quality of sexual life.

To assess ovarian function folliculostimulating hormone was analysed quantitatively in the patients serum using immunohaemofluorescence method. To analyse the differences in the concentrations of FSH *t-test* was applied. For the correlation analysis of folliculostimulating hormone concentration and radiotherapy *Pearson* test was used.

All patients were assessed for menopausal symptoms such as hot flushes, mood changes, sleeping disorders, vaginal dryness, decreased libido, urinary incontinence and weight gain. Answers to these symptoms were given matching „yes” or „no”, patient had to match the beginning of symptoms and severity. To compare differences in symptom appearance in study groups' values Mann-Whitney U test was applied.

Quality of sexual life was assessed using Sexual quality of life questionnaire developed by Pfizer Ltd in 1998 consisting of 18 questions.<sup>26</sup> Differences in answers to these questions included in the SQoL-F were analysed using Mann-Whitney U test. Answers to the questions included in the SQoL-F were given twice – for the period before the treatment and for the period after the treatment. Additionally patients were asked if their sexual partner has changed during the treatment.

## Results

All the patients included in the study were premenopausal and there were no differences in the mean age within the study groups –  $36.5 \pm 5.9$  (24 – 48) years of age in the surgery group vs.  $39.8 \pm 4.9$  (32 – 46) years of age in the combined treatment ( $p=0.148$ ).

Mean concentration of folliculostimulating hormone was higher in patients who received adjuvant radiotherapy in comparison to patients who received only surgical treatment –  $94.12 \pm 44.16$  U/l (range 5.0 – 199.0) vs.  $6.08 \pm 2.90$  U/l (range 2.9 – 11.5) U ( $p < 0.001$ ). Normal concentrations of folliculostimulating hormone according to the age had all patients in the surgery group, but only 10.3% patients in the group with adjuvant treatment. Higher

concentrations of folliculostimulating hormone in serum correlated with adjuvant radiotherapy (0.683;  $p < 0.001$ ).

Patients who have received adjuvant treatment with radiotherapy more often experienced symptoms related to the decreased estrogens levels. Only for depressed mood, headaches and weight gain there were no differences between the study groups observed (Table 1).

Patients in the group with the adjuvant treatment were even more sexually satisfied according to the frequency of sexual activities before the treatment ( $p = 0.04$ ), but situation completely changed after the treatment – these patients less frequently thought that their sexual life is enjoyable, they were less frequently satisfied, more depressed, unconvinced and even angry about their sexual life. These patients with the combined treatment more frequently had the feeling that they have lost something in their sexual life (Figure 1, Table 2).

Besides this, 37.5% patients in the patient group with only surgical treatment and 20.7% patients in the combined treatment group declared that they have changed their sexual partners in the treatment period ( $p = 0.36$ ).

## **Discussion**

Cervical cancer is the second most common cancer after breast cancer in female under the age of 40. In Latvia there are approximately 200 patients affected with this disease every year and a lot of them diagnosed in the early stages are suffering by complications caused of overtreatment. It has been already proven that cervical cancer in the early stages (IA2 – IIB) with no adverse risk factors for cancer recurrence can be treated either by surgery or radiotherapy with similar results, but combination of both treatments leads to doubling of complications related to the treatment.<sup>14-16</sup>

The diagnosis of menopause is confirmed by detection of elevated folliculostimulating and luteinizing hormone concentrations.<sup>17-18</sup> In our study only folliculostimulating hormone was measured to approve menopausal status, because the correlation between folliculostimulating hormone and menopausal symptoms have been proven earlier to be a reliable measurement to affirm menopause.<sup>19</sup>

Human oocyte is very sensitive to radiation and such doses as 6 Gy causes irreversible ovarian failure in almost all cases.<sup>20</sup> It was confirmed also by our study that the majority of patients who received pelvic irradiation had elevated concentrations of folliculostimulating hormone and symptoms characteristic for menopause despite ovarian transposition. It has been reported that permanent failure of ovarian function occurs approximately in half of patients undergoing adjuvant radiotherapy, but in our study almost all patients had lost function of their ovaries - only 11% of patients had normal concentrations of folliculostimulating hormone.<sup>21</sup> This can be explained by inappropriate ovarian transposition when they are stitched closer to the pelvic region. This problem also can be avoided if metallic clips are used to mark the translocated ovaries. Another option proposed by Farber et al. is to use smaller irradiation doses.<sup>22</sup>

In our study population majority of women received adjuvant radiotherapy, but there were no cases where concomitant chemotherapy was given, although it has been proven that simultaneous chemoradiation with cisplatin 40mg per square meter at weekly dosages is the standard of care in high risk population.<sup>23</sup>

Most of patients in the combined treatment group had worsened quality of their sexual life according to the survey results. Decreased quality of sexual life was connected with the onset of menopausal symptoms - lack of sexual desire or libido, lack of sexual arousal and vaginal dryness. Prolonged oestrogen deficiency, as occurs in menopause, results in atrophy, fibrosis and reduced blood flow to the urogenital tract, causing the symptoms of vaginal dryness, soreness and dyspareunia.<sup>24</sup>

In addition to decreased quality of patient's sexual life, 9 from 37 have changed their sexual partners during and after the treatment. There was no statistically significant difference between both study groups and therefore change of sexual partner cannot be attributed to the onset of menopause. Probably it is because of treatment itself is causing psychological trauma to patient, partner or both.

In the literature there are quite few data about the impact of surgical treatment on the sexual quality of life. Nappi has reported resembling findings that women with a surgically caused menopause feel more distressed about their sexual life.<sup>25</sup>

## **Conclusion**

Patients with more aggressive treatment have compromised quality of their sexual life and overall quality of life due to earlier onset of menopause. This can be explained by impaired ovarian function caused by external-beam radiotherapy. Combined surgical treatment following radiotherapy should be applied only in patients with high risk factors for cervical cancer recurrence; moreover, ovaries should be mapped with a metallic clipators for better visualization when planning adjuvant radiotherapy to preserve ovarian function in premenopausal women.

**Conflict of Interest:** All authors declare that they have no conflict of interest.

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**Table 1:** Frequency table showing menopausal symptoms in the surgical and combined therapy group

Symptoms	Surgery (n=8)	Surgery and radiotherapy (n=29)	P value *
Hot flushes	0	26	< 0.01
Increased sweating	2	25	< 0.01
Feeling concern, worried	1	18	0.01
Depressed mood	2	12	0.37
Concentration difficulties	0	16	< 0.01
Weakness	1	24	< 0.01
Skin dryness	0	12	0.03
Fragility of hair and nail	0	17	< 0.01
Increased heart rate	0	12	0.03
Headache	1	7	0.46
Frequent mood changes	1	16	0.03
Decreased libido	1	17	0.02
Sleep disorders	1	12	0.12
Urinary incontinence	1	12	0.12
Weight gain	2	10	0.57
Vaginal dryness	1	18	0.01

\*Mann-Whitney U test

**Table 2:** Comparison of Sexual quality of life in the surgical and combined treatment group before and after treatment

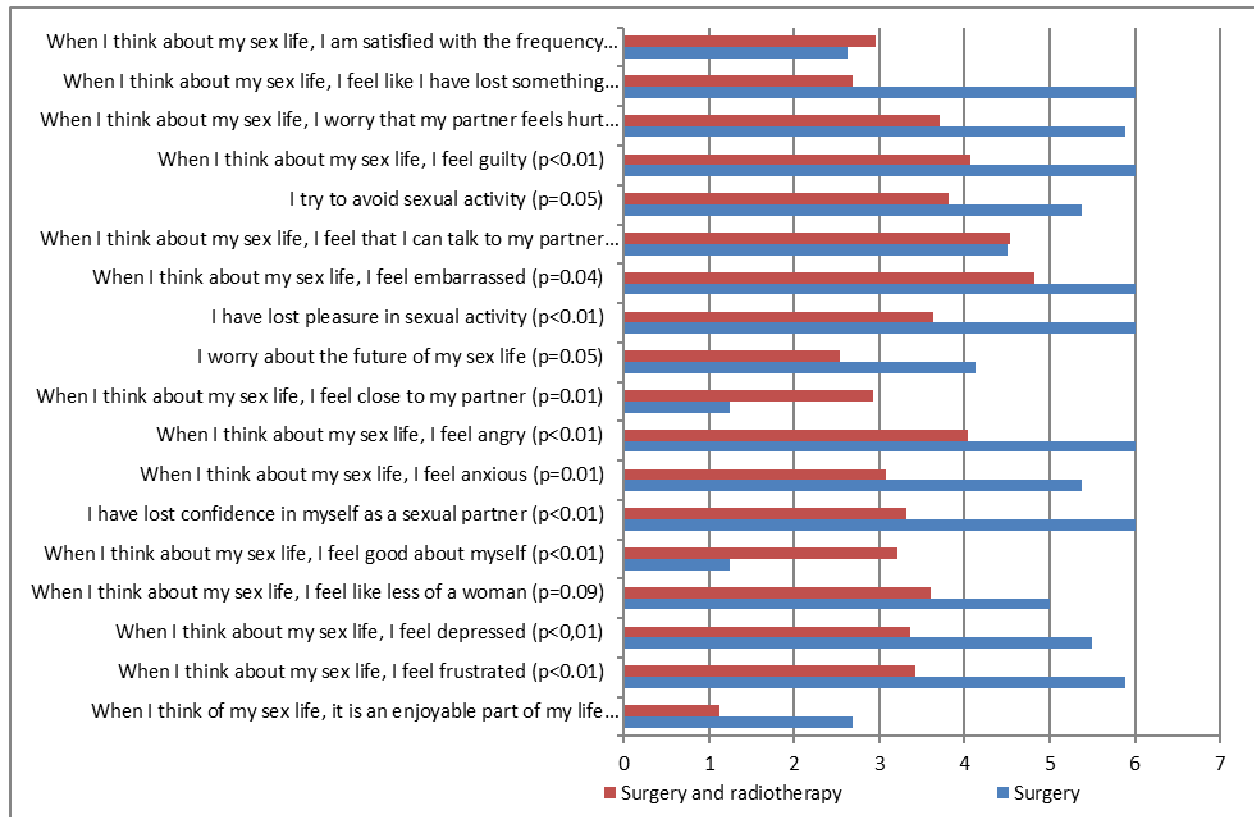
Questions	Surgery	Surgery and radiotherapy	p value**
When I think of my sex life, it is an enjoyable part of my life	2.68	1.13	0.03
When I think about my sex life, I feel frustrated	5.88	3.43	<0.01
When I think about my sex life, I feel depressed	5.50	3.36	<0.01
When I think about my sex life, I feel like less of a woman	5.00	3.61	0.09
When I think about my sex life, I feel good about myself	1.25	3.21	<0.01
I have lost confidence in myself as a sexual partner	6.00	3.32	<0.01
When I think about my sex life, I feel anxious	5.38	3.07	0.01
When I think about my sex life, I feel angry	6.00	4.04	<0.01
When I think about my sex life, I feel close to my partner	1.25	2.93	0.01
I worry about the future of my sex life	4.13	2.54	0.05
I have lost pleasure in sexual activity	6.00	3.64	<0.01



When I think about my sex life, I feel embarrassed	6.00	4.82	0.04
When I think about my sex life, I feel that I can talk to my partner about sexual matters	4.50	4.54	0.84
I try to avoid sexual activity	5.38	3.82	0.05
When I think about my sex life, I feel guilty	6.00	4.07	<0.01
When I think about my sex life, I worry that my partner feels hurt or rejected	5.88	3.71	0.01
When I think about my sex life, I feel like I have lost something	6.00	2.68	<0.01
When I think about my sex life, I am satisfied with the frequency of sexual activity	2.63	2.96	0.68

\*Mean score calculated using *t-test*

\*\**Mann-Whitney U test*



**Figure 1:** Comparison of Sexual quality of life in the surgical and combined treatment group after treatment

\*Lesser score indicates more agreement to each statement; to calculate mean score in the groups and compare them *t-test* and *Mann-Whitney U test* were applied