

The Outcomes of Extended Field Radiotherapy in Patients with Para-aortic Lymph Node Metastases of Cervical Cancer

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ABSTRACT

Purpose: Patients with advanced cervical cancer require interdisciplinary therapeutic treatment, after detailed diagnostics (CT, MR and also PET/CT), due to the high risk of metastases to the pelvic lymph nodes and/or para-aortic lymph nodes as well as supraclavicular region.

Aim: The aim of this retrospective study was to assess the response to treatment in women with cervical cancer with metastases to the para-aortic lymph nodes given radiotherapy or radiochemotherapy

Material and Methods: The study was conducted in 40 cervical cancer patients with para-aortic lymph node metastases undergoing radiation therapy with/without concomitantly a cisplatin-based chemotherapy. Subsequently, total doses were set for pelvic lymph nodes and para-aortic lymph nodes, and were between 45 Gy and 50.4 Gy with dose increase to the tumor and metastatic lymph nodes for a total dose of 48.6 Gy-60 Gy in 1.8 Gy-2.0 Gy fractionation.

Results: The analysis of overall survival demonstrates that OS was significantly longer in patients with local recurrence ($p=0.0165$) or distant metastases ($p=0.0266$) as compared to patients without recurrence or dissemination. An effect on overall survival (OS) was observed of emergency radiation therapy ($p=0.026$) but we did not observe anything particular for emergency chemotherapy. The analysis of disease-free survival time included the assessment of various parameters using the log-rank test to demonstrate that DFS was significantly longer in patients without local recurrence ($p=0.0452$) and distant metastases ($p<0.0001$) as compared to patients with dissemination. It was demonstrated that the presence of metastases caused a significantly higher risk of non-remission (OR=42.5; +/- 95% CI: 4.58-394.45; $p=0.001$), and the recurrence of the disease reduced the chance of remission (OR=0.35; +/- 95% CI: 0.15-0.83; $p=0.016$).

Conclusion: It is well-known that our study has several limitations which could have influenced the results we obtained, including the small number of patients and a non-homogeneous group: some patients were operated on prior to radiotherapy +/- chemotherapy; therefore it is advisable to continue testing on larger groups of patients.

Keywords: Cervical cancer; Radiotherapy; Para-aortic lymph node metastases

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INTRODUCTION

Patients with advanced cervical cancer require interdisciplinary therapeutic treatment, after detailed diagnostics (CT, MR and also PET/CT), due to the high risk of metastases to the pelvic lymph nodes and/or para-aortic lymph nodes as well as supraclavicular region [1]. Among patients with cervical cancer, every third relapse will occur within 2 years, and the percentage of 5-year survival is respectively for each degree according to FIGO IA 95%-100%, IB 75%-90%, falling to 50% in the case of metastasis to the pelvic lymph nodes [2]. Patients with metastatic lymph node metastases have a poor prognosis and it is considered an intermediate stage between locally advanced disease and its dissemination, according to the classification of the International Federation of Gynecology and Obstetrics (FIGO); metastasis in this location is noted in 5% of patients in grade IB, 16% in grade II and 25% in grade III [3,4].

An effective loco-regional treatment is sought that can effect better local control and longer survival. In order to obtain such an effect, larger areas of irradiation are used during radiotherapy [5], where the percentage of 5-year survival in these patients reaches 24%-57.1% and the percentage of distant metastases after radiotherapy with large volumes is 18.2%-54.9% [6].

The aim of this retrospective study was to assess the response to treatment in women with cervical cancer with metastases to the para-aortic lymph nodes given radiotherapy or radiochemotherapy.

MATERIAL AND METHODS

General information

The study was conducted in 40 cervical cancer patients with para-aortic lymph node metastases undergoing radiation therapy in the Department of Radiotherapy of the Oncology Center in Bydgoszcz between 2012 and 2017. The analysis covered patients with all T-stages of carcinoma, according to TNM classification. Patients with invasive squamous cell carcinoma or adenocarcinoma were included in the study, while other histopathological types were excluded, and women were not included in the study if they had distant metastases, synchronous malignancies or were treated with palliative intent. The patients' age ranged from 29 to 68 years.

Treatment details

Before treatment all patients underwent pretreatment staging workup, including medical history, general physical and gynecological examination, tumor biopsy, comprehensive laboratory analysis. Tumor staging was defined according to the International Federation of Obstetrics and Gynecology (FIGO) and the TNM-UICC system. In addition, local tumor extension was assessed by MRI or 18FDG-PET/CT.

Patients were treated in line with the accepted management standard; in most cases, this included combination treatment. Surgical treatment was undertaken in patients (12 patients-30%) with adjuvant radiochemotherapy. The remaining patients received chemotherapy, most commonly platinum-based

regimens. Radiotherapy combined with systemic therapy as a basic treatment was administered to 28 patients (70%). Four patients had previous pelvic irradiation and then, in imaging and/or postoperative confirmation, metastatic lesions to para-aortic lymph node were confirmed; the interval between the first treatment using radiation and the second was from 3 months to 3 years.

Brachytherapy: Brachytherapy procedures were performed in all 40 patients with HDR (High-Dose Rate) brachytherapy with the after-loading method using the irradiation device with iridium radioisotope from microSelectron® HDRB; a 3D system (computed tomography) was used for treatment planning in accordance with the GEC-ESTRO guidelines.

In the case of supplemental brachytherapy with the use of cylindrical applicators, planning was enabled based on the radiation standards developed at the Brachytherapy Facility for individual applicator sizes. In these patients, vaginal brachytherapy was used at a dose of 15 Gy on a scar to a depth of 0.5 cm from the applicator surface in two fractions of 7.5 Gy. In the case of treatment with independent radiotherapy, probes with two ovoids or a ring applicator were used, together with needle guides.

Brachytherapy was used in all patients, of which: 16 (40%) had interstitial brachytherapy and 24 (60%) had intrathecal at a dose of 14 Gy-30 Gy in 2 to 4 fractions.

External beam irradiation: As standard in our clinic in the treatment of cervical cancer, 3D conformal radiotherapy is used IMRT (Intensity-Modulated Radiation Therapy)/SIB (Simultaneous Integrated Boost), IGRT (Image Guided Radiotherapy), which enables safe administration of a high and uniform dose in the irradiated volume with maximum protection of healthy tissues.

Before the start of radiotherapy each patient had a selected therapeutic position in which further stages of planning and treatment were carried out. In patients with pelvic neoplasms, a position on the back is usually used, because of the need to irradiate the para-aortic lymph nodes with the upper limbs raised above the chest, and then a computer tomography without contrast +/- PET/CT, +/- MR is performed. In the planning study the upper limit was above the twelfth thoracic vertebra and the lower covered the entire pelvis.

Radiotherapy planning was based on imaging studies with a full bladder, in a therapeutic volume of every 1 mm-3 mm (planning and implementation of the treatment was based on three-dimensional reconstruction of imaging tests), using the Eclipse Planning System, Varian Medical Systems, Palo Alto, CA, USA.

TARGET VOLUMES AND ORGANS AT RISK-PLANNING

Target volumes

In the obtained tomographic sections, the oncological radiotherapist outlined target volumes such as: a tumor or a box with a margin of healthy tissues and critical organs such as:

femoral head, bladder, rectum, intestines, core, kidneys, liver, pancreas and duodenum.

The first stage was defining GTV (Gross Tumor Volume), which is a macroscopically visible tumor based on clinical and pictorial data, CTV (Clinical Target Volume) including GTV and the whole uterus, parametrium and one third of the vaginal wall. In the case of neoplastic infiltration affecting the vaginal walls the area was widened by the entire length of the vagina, then the margin for organ mobility was added to 2 cm, thus defining PTV (Planning Target Volume).

The next stage was the contouring of regional lymph nodes: para-aortic (from the Th12/L1 vertebra), common hip, internal, external, frontal and curtilal. In patients where the vaginal wall infiltration was additionally covered by inguinal lymph nodes-CTV_n, a 7mm margin was added to define PTV_n. Metastatic para-aortic lymph nodes visible in imaging studies were contoured as GTV and then a margin of at least 0.5 cm was added to define CTV and PTV.

In 18 (45%) people, metastatic lesions to para-aortic nodes were located below the renal vessels, which affected the areas contoured by the leading physicians, where the target volumes along with the margin ended around the renal vessels.

Subsequently, total doses were set for pelvic lymph nodes and para-aortic lymph nodes, and were between 45 Gy and 50.4 Gy with dose increase to the tumor and metastatic lymph nodes for a total dose of 48.6 Gy-60 Gy in 1.8 Gy to 2.0 Gy fractionation.

Organs at risk

Standard dose constraints were used to assess the administered dose for critical organs, including: V50<50% for the rectum traced to the sigmoid, for the bladder V65.92<50%, for femoral heads the maximum dose should not exceed 52.82 Gy, for intestines V 45.8 below 195 cm³. For the kidneys the mean dose <14.7 Gy, for the spinal cord the maximum dose <43.9 Gy, and for the healthy liver the average dose below 31.22 Gy.

Planning

The next stage was the preparation in the Department of Medical Physics of individual treatment plans for each patient and their acceptance by the leading physician based on the histogram of distribution of doses in individual target volumes and anatomical structures, the so-called critical organs.

In 4 patients previously irradiated in the pelvic area, additional attention was paid to whether therapeutic volumes overlap when planning radiotherapy for para-aortic nodes.

All patients were treated using multi-line linear accelerators with 6 MV and 15 MV photons. Patients on the therapy apparatus were positioned in relation to markers on the body. Before each administration of the therapeutic dose, photographs were made to check the patient's position using a portal cassette-an integral device on the therapeutic apparatus, or using the IGRT (Image Guided Radiotherapy) technique.

Chemotherapy

Patients with cervical cancer were given weekly cycles of cisplatin with a combination of minimum and maximum number of cycles of 3 and 5. Weekly cisplatin at a dose of 40 mg/m² was administered during radiotherapy; the first course of cisplatin was administered on day 1 of radiotherapy.

Follow up

Follow-up visits were held 4 weeks after completion of radiotherapy and then at 3-month intervals. Patient follow-up lasted at least 60 months. Two patients did not report for follow-up visits; further course of their disease remains unknown.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistica (TIBCO Software Inc. 2017, version 13). The association between overall survival rate, disease-free survival rate, progression-free survival rate and prognostic factors was estimated using the Kaplan-Mayer model. Differences between categorized groups were assessed using the log-rank and Cox-Mantel tests. Proportions of FIGO stage in 2010 and 2018 groups was assessed using the Chi-square test. Logistic regression model was used for remission chance assesment. Statistical significance was considered at p<0.05.

RESULTS

Patient clinico-pathologic features

The research was carried out on a group of 40 patients with cervical cancer. Patients were at the stage of FIGO III and IVa but the T-stage according to TNM was different and in T1 there were 2 (5%) women, in T2-19 (47.5%) patients, T3 was diagnosed in 8 (20%) people. In T4 stage, 10 (25%) patients were affected with local organs involvement, and one patient had unspecified T-trait (2.5%).

Among the 40 patients included in the study, the degree of G tumor differentiation was assessed in 27 women, in the remaining 13 (32.5%) patients the G trait was not determined. 5 (12.5%) people were diagnosed-G1, 16 (40%) patients-G2, 6 (15%) women had tumor malignancy grade-G3.

Pattern of failure

After completion of the therapeutic process, complete response (CR) was found in 16 (40%) patients, partial response (PR) for the therapy was found in 4 patients (10%). No response to treatment and further disease progression (PD) was noted in the remaining 20 women (50%).

In the group of 12 operated patients, complete response (CR) was confirmed in 6 (15%) patients and progression of the disease (PD) was diagnosed in 6 (15%) women. In 6 (15%) patients, radiotherapy for metastatic tumors was used and 7 patients (17.5%) received emergency chemotherapy.

Of the whole group of patients, 24 (60%) are still alive, the fate of one patient (2.5%) is unknown. Up to 20 (50%) women died

of primary disease, the most common relapse sites were: scalene nodes, lungs, bones, peritoneal, para-aortic nodes and skin.

Overall Survival (OS)

Parameters affecting the likelihood of survival were analyzed in the entire group, including: T-staging, tumor differentiation grade G, metastases status, treatment history including surgery, radiochemotherapy, chemotherapy, pelvic radiotherapy, local radiotherapy, para-aortic lymph node radiotherapy above vs. under kidney vessels, emergency radiotherapy, emergency chemotherapy, brachytherapy cavity, interstitial brachytherapy, numbers of courses of brachytherapy, nephrostomy, simultaneous radiotherapy of the pelvis and para-aortic lymph nodes, type of cancer, side-effects of radiotherapy.

The analysis of overall survival (OS) included the assessment of various parameters using the log-rank test to demonstrate that OS was not significantly longer in patients with operation as compared to patients without surgical treatment.

The analysis of overall survival demonstrates that OS was significantly longer in patients with local recurrence ($p=0.0165$) or distant metastases ($p=0.0266$) as compared to patients without recurrence or dissemination (Figures 1 and 2).

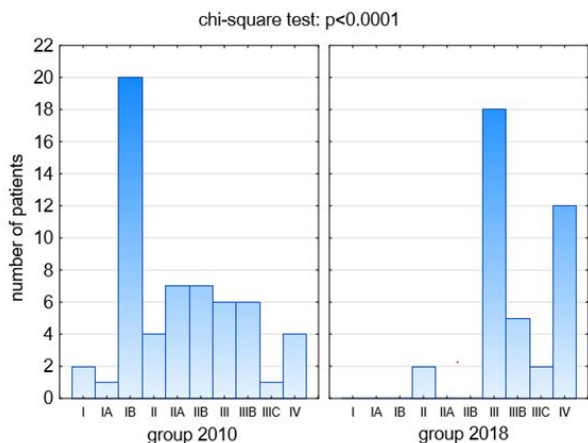


Figure 1: Comparison of results with patients from previous studies treated for cervical cancer but without metastases to the para-aortic lymph nodes. The patients were in all FIGO stages, although the lower stages were prevalent. The patients were treated according to accepted standards with both surgical treatment and radiotherapy and/or chemoradiation and brachytherapy.

The next step of statistical analysis included the assessment of the effect of emergency radiation therapy on patients. An effect on overall survival (OS) was observed in longer life ($p=0.026$) but we did not observe anything particular for emergency chemotherapy (Figures 3 and 4).

The study did not demonstrate any effect for pelvic radiation therapy, para-aortic node radiation therapy under or above kidney vessels, or local radiotherapy.

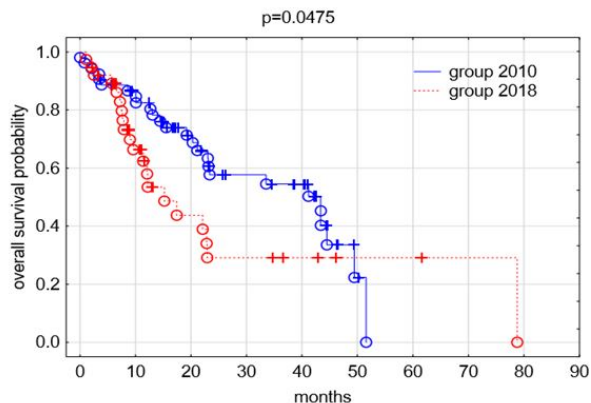


Figure 2: Comparison of results of overall survival of both groups 2010 vs. 2018.

Disease-Free Survival (DFS)

The analysis of disease-free survival time included the assessment of various parameters using the log-rank test to demonstrate that DFS was significantly longer in patients without local recurrence ($p=0.0452$) and distant metastases ($p<0.0001$) as compared to patients with dissemination.

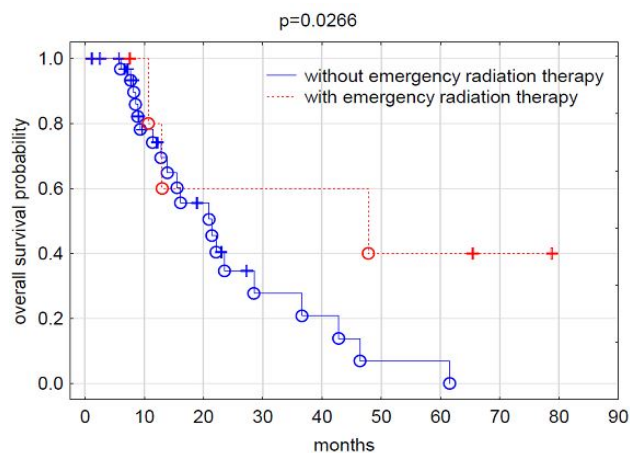


Figure 3: Effect of emergency radiation therapy on overall survival.

The next step of statistical analysis included the assessment of the effect of emergency radiation therapy or systemic therapy on patients: no better effect on DFS was observed ($p=0.0575$).

Odds ratio

The study analyzed the odds of non-response considering such variables as: stage of TNM, degree according to FIGO, length of irradiated areas, trait G, trait M, surgery, chemotherapy, combination chemotherapy, number of brachytherapy fractions, type of brachytherapy applicators, emergency radiotherapy, emergency chemotherapy, radiation reactions.

It was demonstrated that the presence of metastases caused a significantly higher risk of non-remission (OR=42.5; +/- 95% CI: 4.58-394.45; $p=0.001$), and the recurrence of the disease reduced the chance of remission (OR=0.35; +/- 95% CI: 0.15-0.83; $p=0.016$).

The influence of brachytherapy on the results of treatment was analyzed: the odds of cure were the same regardless of the number of brachytherapy fractions used, although the results were not statistically significant.

In the next stage, the odds ratio was compared depending on the stage of advancement. In the study the same chances for remission were obtained for patients in Grade III as well as for patients in Stage IV according to FIGO, although the result was not statistically significant.

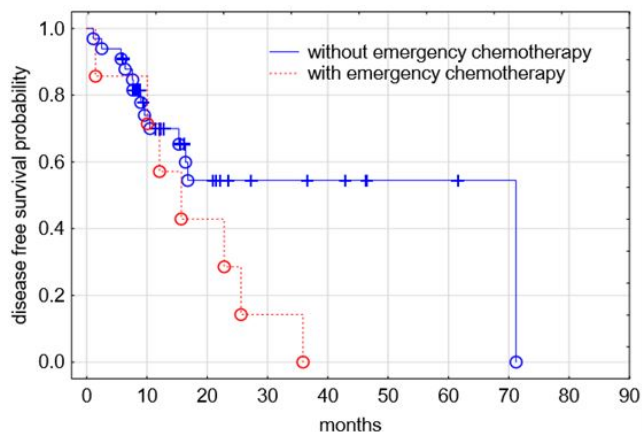


Figure 4: Effect of emergency chemotherapy on disease-free survival time.

Comparison with patients with cervical cancer without metastases to para-aortic lymph nodes

In the next stage, the obtained results were compared with patients from previous studies treated for cervical cancer but without metastases to the para-aortic lymph nodes. The patients were in all stages according to FIGO, although the lower stages were prevalent. The patients were treated according to accepted standards with surgical treatment and radiotherapy and/or chemoradiation and brachytherapy.

In the statistical analysis Gehan-Wilcoxon's test showed that in the overall survival, the curves of both groups "parted" in the period between eight and forty months ($p=0.04750$) so that the overall survival would be at a similar level. It may be the result of the fact that in 2010 patients were treated with a clearly lower degree of progression according to FIGO.

In contrast to the overall survival, the groups of patients treated in 2010 and 2018 did not differ with the time of disease-free survival $p=0.7423$.

Adverse events

Treatment was well tolerated; side effects were observed in patients undergoing radiotherapy as well as in patients with combination therapy. Regarding skin, the EORTC reaction was 0-1, including 18 in the first degree. In the lower gastrointestinal tract 0-3, in 2 patients it was degree 3, in 4 it was degree 2, and in 26 patients degree 1 was observed. Regarding the urinary tract 0-2, in one patient there was degree 2 and in 20 degree 1. In the upper gastrointestinal tract the tolerance was good and amounted to 0-1 according to the EORTC scale; one person had the first degree. Regarding hematology, there were no significant

side effects in the platelet count and hemoglobin concentration; side effects were 0-3 in the white blood cells, degree 2 in 2 patients and in one patient degree 3. There was no treatment-related death (TRD) observed. In 4 patients, fistula was observed as a late effect after chemoradiation.

DISCUSSION

In cervical cancer metastasis to the para-aortic lymph nodes is associated with worse prognosis and their detection requires extended field radiation therapy [5]. In order to obtain better effects of radiotherapy in the treatment of advanced cervical cancer, several groups in cooperation, including the Gynecologic Oncology Group (GOG), the National Cancer Institute of Canada (NCIC), Southwest Oncology Group (SWOG) and Radiation Therapy Oncology Group (RTOG), recommend using radiation with simultaneous chemotherapy [7].

There are also works in which prophylactic radiotherapy of the area of para-aortic lymph nodes is recommended, which is explained by the fact that for confirmed pelvic lymph node metastases, even 50% of cases can be metastatic, even if there is no lymphadenopathy in the para-aortal region [2].

On the other hand, there are, among others, Park et al., where no gain in total survival times or time free from disease in a group with prophylactic irradiation of the para-aortal lymph nodes were confirmed, and a multivariate analysis showed that a significant effect on the overall survival time was: low degree of advancement, good general condition of the patient and simultaneous chemotherapy. Two factors influenced the time free from the disease: histopathological type-squamous cell carcinoma and simultaneous chemotherapy [8].

The Sapienza study [9] is the first systematic review and meta-analysis that relates to the benefits of using broad fields in radiotherapy-EF-RT (extended field radiotherapy) in the treatment of advanced (stage \geq IB2) cervical cancer. The current significant benefit for distant metastases confirms the hypothesis that the para-aortic region is a mainstay of microscopic disease that further increases the incidence of distant metastases. Although the involvement of lymph nodes in the aorta is considered to be a metastatic disease, this area is usually the first station of the systemic disease and allows the inclusion of localized treatment, which may involve the reduction of distant metastases, as noted in the Sapienza analysis [9].

In two multicenter studies, there was a tendency for EF-RT to have a positive effect on the control of para-aortic nodes and distant metastases. However, a gain of 11% in 10-year survival in RTOG7920 has not been demonstrated in the EORTC study. Since the RTOG study did not include Grade III patients, and further demonstrated survival benefit, it was hypothesized that sterilization of microscopic para-aortic disease is more effective in a patient with a higher probability of local pelvis control [10-12].

In the GOG study presented results for patients with FIGO stage IIIB cervical cancer and biopsy of para-aortal nodes, prognosis in these patients was poor and the average survival was 15.2 months with a presumed 25% 3-year survival [Berman]. And in an earlier GOG study in 86 patients with lymph node

metastases, 39% of the total reached 3-year survival, and those having 3-year progression-free was 34% [7].

Interesting results were published in the RTOG 9001 study, which showed an advantage in patients with pelvic radiotherapy in combination with chemotherapy over radiotherapy alone for extended areas (areas of the pelvis and para-aortic lymph nodes). The reduction in distant metastases was associated with a reduction in the number of distant metastases and local recurrences. Research suggests that better pelvis coverage with the use of chemo-radiotherapy reduces the uncontrolled spread of pelvic disease and distant metastases at diagnosis [13,14].

In the meta-analysis by Sapienza [9] et al., there was a significant reduction in the failure of the para-aortic nodes (OR 0.35 [0.19-0.64], $p=0.0006$) and the incidence of distant metastases in favor of the group with EF-RT (extended field radiotherapy) (OR 0.69 [0.50-0.96], $p=0.03$). Because the control and experimental groups (EF-RT) received the same pelvic treatment, there was no difference in local pelvic recurrences (OR 1.06 [0.80-1.42], $p=0.67$) [9].

Furthermore, there was a tendency to reduce mortality due to cancer in the case of EF-RT (OR 0.68 [0.45-1.01], $p=0.06$), but only two studies (RTOG 7920 and Chang Gung University) provided data on the percentage of deaths due to neoplastic disease [9].

In addition to the size of the volumes, an important factor is the total dose administered during treatment, along with the development of planning techniques, it is recommended in the cases of bulky tumors and/or lymph nodes to administer above the total dose from 54 Gy to even 60 Gy. Ariga analyzed the total dose administered to lymph nodes of 56 Gy vs. 60 Gy and did not show statistically significant differences in the OS or DFS [15].

Niibe et al. [16] showed that dosing to 60 Gy did not increase the percentage of severe late complications; furthermore, the analysis showed that a dose above 51 Gy on the metastatic lymph nodes improved survival rates compared to women receiving less than 50 Gy. In the Grigsby et al. [17] study there were attempts to escalate the dose up to 74.1 Gy on metastatic lymph nodes, but the analysis did not show an improvement in local control, and also increased the toxicity of treatment [17].

Shimada et al. [18] presented an interesting analysis of patients with squamous cell carcinoma (SCC) vs. cervical gland (AC) cancer. The histological type did not affect the outcome of treatment of patients with FIGO stage I disease; however, patients with stage II cervical gland cancer showed significantly worse 5-year survival rate (OS) compared to patients with squamous cell carcinoma. Among patients with lymph node involvement, patients with AC showed a significantly worse 5-year survival rate in comparison with persons with SCC (46.4% vs. 72.3% respectively, $p=0.0005$). Among patients receiving adjuvant radiotherapy, people with glandular cancer were more likely to have relapses than people with SCC, especially in the pelvic cavity, including vaginal and/or pelvic stump (24.6% vs. 10.5% respectively, $p=0.0022$). In contrast, the histological type did not affect the incidence of recurrences in para-aortic lymph nodes and/or distant metastases [18].

The authors emphasize that after radiotherapy of large volumes, patients have problems due to side effects of radiotherapy, including gastrointestinal complications and/or duodenal damage. This is why Choi et al. used in their work the so-called semi-extended field radiotherapy (SEFRT) where the upper limit was set to the level of the second lumbar vertebra [2]. What could be an interesting alternative: in our work some patients had radiotherapy to the level of kidney vessels and the results in both groups did not differ significantly in terms of statistics and there was good tolerance on the part of the upper gastrointestinal tract [2].

It should be emphasized that some of the available studies present the results still using old radiotherapy techniques like 2D with the use of shields. In this form of therapy, it was not possible to estimate the doses deposited in healthy tissues, in addition, the lack of protection of healthy tissues prevented administration of higher doses than 45.0 Gy-50.4 Gy to the therapeutic volume. Technological progress, including the era of new therapeutic devices and the development of techniques for planning and implementing radiotherapy, allowed the use of 3D planning, but most importantly, the administration of much higher doses with good tolerance from organs and healthy tissues. As in the case of our study, where in addition to administering 45 Gy-50.4 Gy dose to the pelvic area and para-aortic lymph nodes, the total dose was increased to the tumor area and/or metastatic lymph nodes to a total dose of 48.6 Gy-60 Gy in fractions of 1.8 Gy-2.0 Gy.

In the EORTC and RTOG studies, there was an increase in the number of cases of Grade 5 toxicity (death related to treatment) due to EF-RT, but these were not statistically significant results (OR 2.12 [0.71-6.27], $p=0.18$). In the Osaka study, more bone fractures were found in the EF-RT group (4 in the control group and 0 in the experimental group), but not in the EORTC study (2 in the control group and 3 in the experimental group). Other types of toxicity were primarily of gastro-intestinal origin. However, the heterogeneity of the scales limited the compilation of data on side effects as a result of radiotherapy [9].

Recent studies suggest tolerable EF-RT toxicity using the IMRT technique, with 3.9% at Grade 3 gastrointestinal toxicity, and no Grade 4 or 5 events in the Pittsburgh study, and 6.5% late gastrointestinal toxicity in the groups from Boston [19,20].

CONCLUSION AND LIMITATIONS

It should be emphasized that our study has several limitations that could have influenced the results we obtained, including the small number of patients and a non-homogeneous group: some patients were operated on prior to radiotherapy +/- chemotherapy; therefore it is advisable to continue testing on larger groups of patients.

In half of the patients the disease progressed, the potential factors responsible for failure include: tumor resistance to radiotherapy and/or chemotherapy, inaccurate estimation of disease severity both local and in lymph nodes, geographic error during radiotherapy planning or insufficient total dose especially in large bulky tumors where often critical organs limit the possibility of depositing a suitably high dose, which is why it

is so important to precisely determine the severity of the disease and select the appropriate comprehensive treatment for its extent.

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