Three-Dimensional Conformal Radiotherapy for Stage IIB-IIIB Cervical Cancer: Experience of the Oncology Institute “Prof.Dr. Ion Chiricuta” Cluj-Napoca

Anamaria Sipos¹, Noemi Besenyodi¹, Claudia Ordeanu¹, Ovidiu Coza¹,², Victor Bogdan¹, Nicolae Todor¹, Viorica Nagy¹,²

¹) Oncology Institute “Prof.Dr.Ion Chiricuta” Cluj-Napoca; 2) University of Medicine and Pharmacy “Iuliu Hatieganu” Cluj-Napoca.

Introduction

Cervical carcinoma is still one of the most frequent and lethal malignancies in women worldwide, and it remains the second most common cause of cancer related death in women in Romania.

Pelvic external beam radiation therapy (EBRT) concurrent to chemotherapy (CT) and intracavitary brachytherapy (BT) continues to be the cornerstone in the primary treatment of locally advanced cervical cancer (1-3). Risk factors for morbidity include the volume of irradiated normal tissue, total tumor dose, EBRT dose, fraction size, and age (4-6).

In the late 1990s, the technique of three-dimensional conformal radiation therapy (3DCRT) emerged as a preferred technique of radiotherapy for cervical cancer, since it gave better and more precise target coverage (20% reduction in the risk of a geographical miss) and significantly reduced the volume of radiation-exposed normal tissues (bladder and bowel) (7,8). These results are consistent with the findings of reduced dose to normal structures such as the intestinal tract.

The objective of this study was to evaluate local tumor control, toxicity and overall survival in patients with stage IIB-IIIB cervical cancer.
IIB-IIIB cervical cancer, treated by 3D external beam radiotherapy (3DCRT).

Material and methods

In this retrospective study 209 patients were included, with histologically confirmed stage IIB-IIIB cervical cancer (FIGO staging modified by MD Anderson Cancer Center) (9), treated with 3DCRT, in the Oncology Institute “Prof. Dr. Ion Chiricuta” Cluj-Napoca (OICN), between 2011–2013.

Before treatment all patients had undergone thorough clinical examination, and several investigations as part of the initial workup: hematology and biochemistry profile, chest X-ray, abdominal and pelvic computed tomography (CT).

One hundred (48%) patients included in this study received neoadjuvant chemotherapy (NACT), two regimens: Paclitaxel 175mg/m² and Carboplatin AUC5(PC) or Topotecan 0.75mg/m² and Cisplatin 50mg/m² (TC) administered every three weeks. Three weeks after the completion of the last NACT cycle, all underwent concurrent radio-chemotherapy(RCT) with Cisplatin two regimens (20mg/m² x 5 days every three weeks or 40mg/m²/weekly) or Carboplatin AUC5/ weekly (Fig .1).

All patients underwent 3DCRT up to a total dose (TD) of 46Gy/23fr on the pelvis + 10Gy cervical boost (CB). All were evaluated and for those with favorable parametrial response, surgery (S) was performed comprising radical hysterectomy and pelvic lymph node dissection. Patients who did not undergo surgery continued with 3DCRT up to a TD of 60Gy/30fr/ the pelvis + 14-21Gy/ cervical boost.

For data acquisition all patients were positioned supine without thermoplastic mould, with knee rest for immobilization and underwent planning CT scan with i.v. and oral contrast, intravaginal marker, taking 5 mm thickness slices.

After imaging, contouring was done based on clinical findings for the primary and standard RTOG guidelines for the pelvic nodes (19). The gross tumor volume (GTV) included the cervical tumor and the local extension, determined clinical and imagistic according to TNM requirements. The clinical target volume (CTV) included the entire GTV (if not already included within GTV contour), the entire uterus, parametrium, ovaries, entire mesorectum if uterosacral ligament involved, and the vagina (if minimal or no vaginal extension: upper half of the vagina was included if upper vaginal involvement was present: upper two-thirds of the vagina was included; and in case of extensive vaginal involvement: entire vagina was included). The CTV also included the pelvic lymph nodes: common, internal and external iliac nodes, obturator, presacral and inguinal nodes.

The CTV tumor site was expanded 3-dimensionally (3D) uniformly by 0.5mm and the nodal CTV was expanded by 0.7mm (3D) to define the planning target volume (PTV). Healthy organs at risk (OAR) contoured were: bladder, rectum, bowel and femoral heads.

Each patient was treated using 4 - field technique and high-energy, 16MV photon beams, with standard fractionation, 5 days a week.

Conformal plans were generated for optimal PTV coverage ensuring that 95% of the PTV received 95% of the prescribed dose and that no part of the PTV received more than 107% of the prescribed dose. The dose volume histograms (DVHs) were analyzed for PTV coverage and sparing of the organs at risk (bladder, rectum, bowel, femoral heads).

During the course of 3DCRT, patients were evaluated weekly with clinical examination, blood count and renal function.

Tumor response was evaluated according to the WHO criteria (10) defined as complete response – CR, partial response - PR, stable disease – SD and progressive disease – PD.

After the end of the treatment, the follow-up consisted of clinical examination every 3 months in the first 2 years, then every 6 months in the subsequent years. CT scan evaluation was performed yearly.

Fig. 1. Design of the study.
Treatment related toxicities were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Results

209 patients with locally advanced cervical cancer were included in this retrospective study: stage IIB 103 patients (49%), stage IIIA 62 patients (30%) and stage IIIB 45 patients (21%). Median age at diagnosis was 51 years (22-72 years old). The size of the tumor varied from 1 cm to 10 cm with a median of 4 cm; 87% of the tumors were squamous cell carcinomas, 10% adenocarcinomas and 3% were other histology. The baseline characteristics of the patients are presented in Table I.

Table I. Patients characteristics

<table>
<thead>
<tr>
<th>Period 2011 - 2013</th>
<th>209 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 51, Range 22-83</td>
</tr>
<tr>
<td>FIGO stage</td>
<td>IIB 102 (49%), IIIA 62 (30%), IIIB 45 (21%)</td>
</tr>
<tr>
<td>Tumor size(baseline) (cm)</td>
<td>min 1, max 10, median 4</td>
</tr>
<tr>
<td>Histology</td>
<td>squamos cell carcinoma 181 (87%), adenocarcinomas 21 (10%), other 7 (3%)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>min 9, max 47, median 26.7</td>
</tr>
</tbody>
</table>

One hundred (48%) from the 209 patients included in this study performed NACT, and the remaining 52% (109 patients) did not receive NACT. In terms of therapeutic sequences: 47 patients (23%) performed NACT + RCT, 53 patients (25%) NACT + RCT + S, 52 patients (24%) exclusive RCT and 57 patients (28%) RCT + S (Table II). More than half (55%) of the 110 operated patients presented pCR (pathological complete response).

Loco-regional failure at 2 years for stage IIB was 5%, for stage IIIA was 16%, and for stage IIIB was 24% (p=0.02). Comparing stage IIB with stage III (IIIA- IIIB), we found that the local failure rate was higher in stage III (20% vs 5%) (p<0.01), the difference is statistically significant (p<0.01), (Table III).

Table II. Therapeutic sequences of the patients included in the study

<table>
<thead>
<tr>
<th>NACT (48%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACT + RCT</td>
</tr>
<tr>
<td>NACT + RCT + S</td>
</tr>
<tr>
<td>No NACT (52%)</td>
</tr>
<tr>
<td>exclusive RCT</td>
</tr>
<tr>
<td>RCT + S</td>
</tr>
</tbody>
</table>

Table III. Local failure vs stage of disease.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Local failure</th>
<th>Local control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB</td>
<td>5 (5%)</td>
<td>97 (95%)</td>
<td>102 (100%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>10 (16%)</td>
<td>52 (84%)</td>
<td>62 (100%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>11 (24%)</td>
<td>34 (76%)</td>
<td>45 (100%)</td>
</tr>
</tbody>
</table>

p = 0.02

<table>
<thead>
<tr>
<th>Stage</th>
<th>Local failure</th>
<th>Local control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB</td>
<td>5 (5%)</td>
<td>97 (95%)</td>
<td>102 (100%)</td>
</tr>
<tr>
<td>IIIA-IIIB</td>
<td>21 (20%)</td>
<td>86 (80%)</td>
<td>107 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>26 (12%)</td>
<td>183 (88%)</td>
<td>209 (100%)</td>
</tr>
</tbody>
</table>

p < 0.01

Local control at 2 years was 88%. The 2 years disease free survival (DFS) was 90% and overall survival 86% (Fig. 2). Based on the stage the overall survival (OS) was 91% IIB, 84% IIIA and 76% for stage IIIB, at 2 years (p=0.02) (Fig. 3).

In terms of acute toxicity, the incidence of grade (G) 3-4 digestive and urinary toxicity was 0.48% and 0%, G3 radioepithelitis was 0.48%, and G3 radiodermatitis was 0.48% of the cases (Table IV). In terms of late toxicity, the incidence of G3-4 bladder and rectum morbidity was 0.96% and 0%, and G2 and G3 vaginal stenosis was 2.87% and 1.44%, and G3 fibrosis was 0.5% (Table V).

Fig. 2. Two years disease free survival and overall survival.
Discussion

Survival of patients with cervical cancer has been significantly improved in the last two decades as a consequence of early diagnosis, new therapeutic strategies and also with the development of the technology.

Results from 5 randomized trials published in 1999, including nearly 2000 patients, demonstrating that survival rate with concomitant RCT based on cisplatin was superior than that obtained with radiation alone (11-13). A meta-analysis published in 2005 based on 19 trials including 4580 patients, corroborated these findings confirming that RCT offers an absolute survival benefit of 12% at 5 years (14). An update of the aforementioned meta-analysis that includes 24 trials and 4921 patients strongly suggests that RCT improves overall survival and progression free survival (PFS), whether or not platinum was used, with absolute benefits of 10% and 13%, respectively (15). These trials demonstrated significant differences regarding eligibility criteria, treatment schedules, and overall design.

The OICN has established a remarkable tradition in the treatment of cervical cancer, with extensive experience, which is based on the large casework. A randomized phase III study, conducted in our institute and published in 2009, can be registered among the studies that confirmed the superiority of CDDP-based RCT compared to RT alone. In this study patients were randomly assigned to two treatment arms: RT (arm A) and RTCT with cisplatin 20mg/m2 x 5days, every 21 days (arm B). The treatment schedule consisted of external-beam RT to the pelvic region delivered with 15MV X-rays, using linear accelerator. Pelvic radiation was given using four-field technique (anterior and posterior portals: 0.6 Gy, lateral portals: 0.4Gy). A less known CT schedule was used: CDDP, 20 mg/m2 x 5 days every 21 days.

This study proved the obvious superiority of concurrent RCT with 5-day cisplatin over RT alone in patients with locally advanced cervical carcinoma regarding local control (78% for RTCT vs 67% for RT) and 5-year survival rates (74% for RTCT vs 64% for RT), (P<0.05). The rate of acute G 3 or 4 toxicity was higher for the concurrent RTCT group as compared to the RT group (35% vs. 16%). Gastrointestinal toxicity was more frequent in the RTCT group (G3 in 37 patients and G4 in six patients) than grade 4 at one patient). Grade 3 and 4 genitourinary toxicity was observed in 12 patients with RT alone versus 6 patients with RTCT (16).

Although cisplatin-based RCT was largely accepted, as the standard of care for patients with locally advanced cervical cancer whose treatment required radiation, an optimal chemotherapy regimen has not been established yet.

A study published in 2007 which compared two concomitant RTCT in locally advanced cervical cancer (5-day vs. weekly cisplatin), demonstrated that patients

<table>
<thead>
<tr>
<th>Acute toxicity</th>
<th>Digestive n</th>
<th>%</th>
<th>Radioepithelitis N</th>
<th>%</th>
<th>Radiodermatitis n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>51</td>
<td>24%</td>
<td>144</td>
<td>69%</td>
<td>154</td>
<td>74%</td>
<td>200</td>
<td>96%</td>
</tr>
<tr>
<td>1</td>
<td>82</td>
<td>39%</td>
<td>60</td>
<td>29%</td>
<td>35</td>
<td>17%</td>
<td>5</td>
<td>2%</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>36%</td>
<td>5</td>
<td>2%</td>
<td>19</td>
<td>9%</td>
<td>3</td>
<td>1.5%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.5%</td>
<td>1</td>
<td>0.5%</td>
<td>1</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late toxicity</th>
<th>Rectal n</th>
<th>%</th>
<th>Bladder N</th>
<th>%</th>
<th>Fibrosis n</th>
<th>%</th>
<th>Vaginal stenosis n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>185</td>
<td>89%</td>
<td>203</td>
<td>97%</td>
<td>189</td>
<td>90%</td>
<td>179</td>
<td>86%</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>6%</td>
<td>5</td>
<td>2%</td>
<td>15</td>
<td>7%</td>
<td>21</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>5%</td>
<td>1</td>
<td>0.5%</td>
<td>4</td>
<td>2%</td>
<td>6</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1%</td>
<td>1</td>
<td>0.5%</td>
<td>3</td>
<td>1.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Two years overall survival vs stage of disease.
who received weekly cisplatin had a shorter 3-year progression-free survival (90% vs. 76%) and significantly more acute toxicities (17).

In 2012 was published a phase III randomized study, performed in our institution, including 326 patients. Patients were randomly assigned to 2 therapeutic arms: arm A (5 days) concurrent RT with cisplatin, 20 mg/m²/day, days 1 to 5 every 21 days; or arm B (weekly), concurrent RT with cisplatin, 40 mg/m²/day weekly during radiotherapy. EBRT to the pelvic region was delivered using 15-MV X-rays, given using four-field technique (anterior and posterior portals: 0.6 Gy, lateral portals: 0.4 Gy). The main objective of the study was the analysis of the treatment toxicity and the patients’ quality of life treated through the 2 RCT regimens (CDDP, 20 mg/m² x 5 days every 21 days, and the other with CDDP, 40 mg/m² per week), the results were published in 2007 (18), and the secondary objective was the comparison of the 2 RCT regimens by evaluating the local and distant failure as well as the overall and disease-free survival (DFS). The results obtained for the entire group of patients were very good: OS was 75% , DFS at 5 years 71%, and 19% of the patients presented locoregional recurrences.

The results of this study demonstrate that RCT with cisplatin, 20 mg/m² x 5 days every 21 days, is superior regarding local efficacy and is less toxic compared with the weekly chemotherapy regimen (19).

Also the results of the study published in 2012 (the patients performed 2DRT), the 2 years DFS was superior in the 5-day CDDP arm (82%) vs weekly CDDP arm (78%); p<0.01 and OS was superior in every stage for arm A (5 days), in this study (in which patients performed 3DCRT) the 2 years DFS was 90% and OS 86%, based on the stage the OS was 91% for stage IIIB, 84% in stage IIIA and 76% for stage IIIB, at 2 years (19).

In this study, the local control was 88%, DFS 90% and OS 86% but these are results at 2 years, and we used 3DCRT.

In recent years NACT before RT was important topic as it may facilitate local therapy by tumor size reduction, increase radiosensitivity and reduce the risk of relapse by the eradication of micrometastases. Even though there are many published trials with NACT before surgery, and recently data from several trials of NACT before RT became available, no NACT regimen has emerged, and no consensus has been established. All NACT regimens are platinum based and administered before RT leads to a high response rate with manageable toxicity, but randomized, larger trials and long term evaluation trials are necessary in order to confirm these data (20).

The technical and radiobiological improvements in the science of radiotherapy, coupled with the use of cisplatin-containing regimens concurrent with radiation therapy, have improved dramatically the cure rate and quality of life for cervical cancer survivors.

Radiotherapy 4-field box arrangement using conventional portals based on bony anatomy as seen on X-ray simulation, used for pelvic irradiation in carcinoma cervix, have been demonstrated to be inadequate in comprehensive nodal coverage. Optimal nodal coverage is critical in the treatment of cervical cancer and RT has been shown to decreases recurrences on regional lymph nodes. Moreover, pelvic failure is associated with decreased survival.

With the use of CT simulation, it is possible to identify and delineate the pelvic blood vessels, and these can be used as surrogates for localizing the adjacent lymphatics and lymph nodes. The inadequacy of the standard fields for target volume coverage and underdosing in lymph node regions in around 30–40% of patients has been reported and Kim noted that margins are inadequate in 39–50% of cases (21).

Since computed tomography (CT) scans have become available in many radiotherapy departments, several attempts to improve treatment planning have been made by taking into account the anatomy of individual patients. Because sectional CT enables the visualization and delineation of the cervix, uterus, vagina, iliac vessels, and organs at risk such as bladder, rectum, and bowel, 3D CRT has become a preferred treatment for gynecologic malignancies. It gives better, more precise target coverage while reducing the risk of a geographical miss by 20% (22). Although 4-field radiation technique spares the small bowel anteriorly and a portion of the rectum posteriorly, it is potentially uncertain to use the 4-field pelvic technique without knowledge of the precise tumor volume. Therefore, Kim (23) strongly recommended CT treatment planning. With more targeted treatment, better results can be predicted.

Studies have shown that 3DCRT improves dose reduction to healthy organs for curative treatment in cervical cancer (24). Also Gerstner and colleagues reported that 3DCRT (compared with 2DRT) significantly reduces the volume of radiation exposure in the bladder (up to 34%) and bowel (up to 254 cm²) of cervical cancer patients (7, 8).

Toxicity is an important criteria in treatment evaluation. Besides therapeutic efficacy, toxicity quantification is crucial in estimating new therapeutic modalities and treatment individualization.

There are two GOG randomized trials that have used concomitant 2DRT and weekly cisplatin 40mg/m² in cervical cancer. The GOG 120 study included stages IIB, III and IV A cervical cancer, and had 3 randomized arms, one of which used weekly cisplatin. In this arm G2 gastrointestinal toxicity was 16%, G3 5%, and G4 2% (25). In the 2- arm GOG 123 trial RT with weekly cisplatin followed by surgery was used in one arm, G2 gastrointestinal toxicity was seen in 27% of the patients, G3 in 9% and G4 in 5% (26).

Gonzalez et al in their randomized study which used in one arm 40mg/m² cisplatin weekly, reported 5% G3 gastrointestinal toxicity (27). Green at all metaanaylsed 17 trials with concomitant cisplatin-based CT/RT in cervical carcinoma and noted acute G3-4 gastrointestinal toxicity 9% (28).
In our current study, side effects of 3DCRT were significantly lower: the incidence of acute toxicity of grade (G) 3-4 digestive and urinary toxicity was 0.48% and 0%, G3 radioepithelitis was 0.48%, and radiodermatitis G3 was 0.48% of the cases and the incidence of late toxicity G3-4 bladder and rectum morbidity was 0.96% and 0%, and vaginal stenosis G2 and G3 was 2.87% and 1.44% at 2 years. In our study, the use of CT simulation for a treatment plan allowed superior visualization of the pelvic lymph nodes and improved the PTV coverage, mainly by reducing the chances of geographical miss to a minimum compared with 2D plans based on bony anatomy as seen on X-ray simulation which does not allow an accurate view on the pelvic lymph nodes. This may translate into superior loco-regional control and even superior survival.

**Conclusion**

3DCRT gives a good target coverage and leads to a good local control and survival for cervical cancer patients. It also has caused a low incidence of grade 3-4 toxicity in the bladder and rectum, demonstrating the main objective indication of 3DCRT, in terms of minimizing the complications in healthy tissues.

**References**

3. Davidson MTM, Yuen J, Souza DPD, Batchelor DL. Image-guided cervix high-dose-rate brachytherapy treatment planning: does custom computed tomography planning for each insertion provide better conformal avoidance of organs at risk? Brachytherapy 2008; 7:37–42.


