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Significant impact on the oncologic outcomes with intensity modulated radiotherapy and conformational radiotherapy over conventional radiotherapy in cervix cancer patients treated with radiotherapy

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A B S T R A C T

Objective: We designed a retrospective cohort of women with cervix cancer treated by radiation therapy with an extended follow-up to evaluate if the incorporation of modern radiation techniques was a prognostic factor.
Material and methods: We studied a cohort of patients with cervix cancer FIGO stage I-IVa treated in the last fifteen years. Patients were treated with radiotherapy alone (RT) or chemoradiation alone (CRT) using conventional radiotherapy (2DRT), conformational radiotherapy (3DRT), or intensity-modulated radiotherapy (IMRT) followed by high dose rate brachytherapy. Univariate and multivariate analysis was conducted to identify significant prognostic factors ($p < 0.05$).
Results: 228 patients with cervix cancer were included. The treatment groups were CRT (64.8%), and RT (34.2%), with 31.6% submitted to 2DRT and 68.4% to IMRT/3DRT. The median follow-up was 6.3 years, the OS in 5 years according to the treatment groups was 48% for CRT, and 27.8% for RT ($p < 0.001$). The early-stage I-IIa ($p = 0.001$), CRT, and IMRT/3DRT were significant factors for better overall survival (OS) in the multivariate analysis. For the cancer-specific survival (CSS), chemoradiation, age <60 years, and IMRT/3DRT were significant. Treatment with IMRT/3DRT was the only prognostic factor associated with event-free survival (EFS).
Conclusion: In a long-term follow-up, chemoradiation, early-clinical stage, and age <60 years were significant factors associated with better OS and CSS at 5 and 8 years. The incorporation of new radiation techniques, such as IMRT/3DRT, over time has a significant impact on all endpoints (EFS, OS, and CSS) of this cohort. These outcomes are useful to decide about the radiation technique to achieve satisfactory oncological results outside a clinical trial.

1. Introduction

In the world, cervix cancer is third most common cancer and the fourth cancer-related cause of death in women.[1] In developing countries, it represents the third cause of cancer death, with the majority of cases diagnostic at locally advanced disease.[2]

The treatment of cervix cancer is guided by the clinical stage, age, the patient's clinical condition, and economic resources available.[3] In general, gynecology surgery is indicated as an upfront treatment for early staging disease (Ib1-IIa). After surgery, patients with adverse prognostic factors (positive margins, pelvic lymph node involvement, and compromised parametrial) need of adjuvant treatment.[4] Elderly patients or patients with a high surgical risk are better treated by radiation combined or not with chemotherapy. In the literature, the role of chemoradiation is well documented and established for patients with locally advanced disease.[5] Numerous randomized clinical trials and several meta-analyses have confirmed the significant benefit of the combined treatment for survival, disease-free survival, and cancer-specific survival.[5–8] Concerning the prognostic factors, staging, tumor volume, tumor regression after external beam radiation,

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overall treatment time, hemoglobin level, patients age, and other has been identified as significant factors related to overall survival, local control, and cancer-specific survival.[3,9–11]

Our institution is a tertiary hospital from a developing country with a high volume and a long history of treating cervix cancer. Over the years, we have followed the treatment guidelines indicating chemoradiation for locally advanced disease for patients with a good clinical condition to receive it, and according to the clinical judgment of the medical attendant, chemoradiation was delivered for the initial disease. After 2010, we have entirely abandoned the conventional radiotherapy (2DRT), and all patients have been treated by conformal radiotherapy (3DRT) or IMRT technique during the external beam treatment. There is compelling evidence showing that the four box field technique guided by bone landmarks provides suboptimal lymph node coverage and increases the risk of excessive normal tissue irradiation when compared with 3DRT.[12–16] Most recently, some studies have shown that IMRT is capable of significantly reducing the acute and late effects.[17] Although several studies are demonstrating that the incorporation of technology produces significant benefits for the reduction of collateral effects, better tumor coverage, better precision to deliver radiation treatment to the tumor target,[17–19] currently, scarce evidence shows an improvement of survival with technological incorporation to treat cervix cancer patients. Therefore, we designed a large cohort of cervix cancer patients treated by radiotherapy with a long term follow up to assess prognostic factors and to evaluate if 3DRT or IMRT results in better oncological outcomes than 2DRT.

2. Material and methods

This cohort study was designed to evaluate the overall survival of patients with cervical cancer treated in a single tertiary center from a developing country. To gather a large sample of cervix cancer patients with adequate follow-up time, we include patients treated in our institution over the last fifteen years. To guarantee an adequate follow-up time, we cross-check our database with the database from the regional cancer registry database. Our institution is linked to the State Department of Health, which receives cancer data from hospitals in our state through regional centers called Cancer Hospital Registries. It configures a cohort of secondary data, since the individuals diagnosed and treated at the hospital are followed up annually for the rest of their lives, after identifying and collecting information in the medical records.

The information was filtered, limiting the treatment period from 2000 to 2015, and cervix cancer cases that refer to ICDs c 53.0; according to the 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10). In the first step, we included all patients with histological diagnosis of cancer of the cervix with a clinical or pathological staging I-IVa treated with surgery followed by adjuvant treatment or treated with radiotherapy or chemoradiation alone. In the second step, we selected only patients who received radiotherapy alone or chemoradiation, excluding patients treated with adjuvant radiotherapy or chemoradiation. Between 2000–2015, 1998, and 2009 FIGO staging systems were used to stage patients into FIGO I-IVa. All patients were staged according to FIGO guidelines.

Regarding the radiotherapy schedule, only conventional fractionation was included. Only cases treated by radiotherapy alone or combined with chemotherapy in the intact cervix were included. During the long period, different radiation techniques were employed; therefore, conventional, conformational, and intensity-modulated radiotherapy (IMRT) techniques were included. We excluded patients with metastatic disease (FIGO stage IVb), or with positive paraaortic lymph node, patients treated with induction chemotherapy, or chemotherapy without cisplatin or patients treated with hypofractionation or palliative radiotherapy, or adjuvant radiotherapy.

The analyses performed were based on the information contained in the database, such as age, sex, morphology of the disease, topography, clinical-stage, treatments performed, follow-up time, and death.

The chemotherapy schedule consisted of weekly cisplatin with 40 mg/m^2 for six cycles beginning at day 1 of radiotherapy. In general, patients with staged as an initial disease (I-IIa) were treated by RT, and when the tumor was >4 cm, and the patient had a good clinical condition, the chemoradiation was indicated. Patients classified as an advanced disease (Ib-IVa) were treated by chemoradiation; however, elderly patients or patients in poor clinical condition were treated by RT exclusively.

The protocols for the radiotherapy treatment of uterine cervical cancer at our institution varied during the period of the study. In general, 2DRT was performed between 2000–2010, and 3DRT and IMRT from 2010 to 2015. 2DRT was planned by fluoroscopy; during the treatment simulation in all patients, the whole pelvis was included. The 3DRT and IMRT plan was designed using computerized tomography and delivered using a 6 or 10-MV X-ray beam linear accelerator (Primus or Oncor, Siemens, Germany). The 3DRT and IMRT followed the RTOG guidelines to draw the GTV and CTV. The PTV margins ranged 1–1.5 cm from the CTV. Patients with early-stage (I–IIa) tumors received 44–50 Gy in 22–25 fractions, and patients with advanced-stage (IIb-IVa) received 44–54 Gy in 22–27 fractions. Patients with parametrial involvement or pelvic lymphadenopathy were given external beam radiation boosts ranging from 9 to 14 Gy depending on the tumor size and location.

After completion of external beam irradiation, high dose rate intracavitary brachytherapy (HDR- ICBT) was delivered using an Ir-192 brachytherapy unit 1–2 times per week employing a Fletcher-Suit intracavitary applicator. The brachytherapy procedure and dose prescription followed the American Brachytherapy Society (ABS) recommendations. The brachytherapy dose was 30 Gy in 4 fractions for IIb-IIIb and IVa, 24−28 Gy in 4 fractions depending on the tumor size ($\geq$4 cm or <4 cm). The brachytherapy dose was prescribed in point A and point B, with rectal and bladder doses evaluated according to the ICRU 38 report.[20] During each session, meticulous gauze packing of the vagina was performed when necessary so that the bladder and rectal doses were less than 75% of the point-A dose.

2.1. Statistical analysis

The survival curves were created using the R Commander and Survival packages of the software R, which consists of a free programming environment for statistical and graphical computation. The survival analysis was counted from the end of radiotherapy treatment until death or the last information. The survival analysis was performed by the Kaplan–Meier estimator method. Event-free survival was considered as any event related to the disease, i.e., death from any cause and disease recurrence. The log-rank test was used to estimate the proportional survival rates between the treatment groups or variables. The recognized prognostic factors such as age (<60 or $\geq$60 years), histology type (CEC vs. adenocarcinoma vs. other), clinical-stage (stage I-IIa or stage IIb-IVa), upfront treatment (RT, CRT), the treatment technique (2DRT, 3DRT/IMRT) and year of treatment (2000–20004, 2005–2010, 2010–2015). Significant variables detected in the univariate analysis were selected to multivariate analysis with Cox regression. A p-value <0.05 and CI95% was considered statistically significant.

Table 1
Characteristics of women included in this cohort.

Variables	Mean/percentage (%)
Mean age (years)	58.3 ± 15.7
Follow-up (years)	6.3 ± 2.4
Histology	N (%)
Adenocarcinoma	18.9
SSC	75.0
Others	6.1
Stage	N (%)
IA1	0.4
IA2	0.5
IIA	11.8
IIB	27.2
IIIA	5.7
IIIB	44.3
IVA	10.1
Treatment	N (%)
RT	34.2
CTRT	65.8
Period	N (%)
2000–2004	13.2
2005–2009	18.4
>2010	68.4
Radiotherapy technique	N (%)
2DRT	31.6
3DRT/IMRT	68.4

3. Results

Between 2000–2015 a total of 426 patients were submitted to radiotherapy with a follow-up of more than 1 year due to cervix cancer. After applying the criterion of inclusion, 228 patients with intact cervix and diagnosed with uterine cervical cancer were selected to be included in the present cohort. In the entire period, the most common treatment employed was CRT (65.8%), followed by RT (34.2%). The mean age was 58.3 years, with the locally advanced stage being the most frequent (87.3%), and squamous cell carcinoma (SCC), the most common histology (75%), as described in Table 1. In the entire cohort, the median follow-up was of 6.3 years (1–18 years). In the RT group with 78 patients, the OS at 5 and 8 years was 27.8% and 18.5%, respectively, figure-1a. For the CRT group, the OS was 39 % at 5 - years and 27.9 % at 8-years. The CSS rate was 81.2% and 68.4% at 5 years, and 61.4% and 40.8% at 8 years, for the CRT and RT groups, respectively, figure-1b. In the univariate analysis for OS (Table 2), histological subtype and age did not present statistical significance, respectively. While early-stage ($p = 0.001$), age <60 years ($p = 0.001$), chemoradiation ($p = 0.001$) and IMRT/3DRT technique ($p < 0.001$) had better survival. For CSS, the univariate analysis showed that age <60 years, IMRT/3DRT, and CRT had a better outcome (Table 2). For EFS, IMRT/3DRT was the only factor associated with better EFS. In the multivariate analysis for OS, the clinical-stage, RT technique, and combined treatment were prognostic factors (Table 3). For CSS, the multivariate analysis showed that age, RT technique, and combined treatment had a better outcome (Table 4).

4. Discussion

Radiotherapy has advanced greatly over the last decades, leaving behind the conventional radiotherapy (2DRT) passing through conformational radiotherapy (3DRT) until the development of the IMRT.[21] The 2DRT is a traditional technique of radiation to treat cervix cancer, which involves a four-field plan with customized blocks to shield the organs at risk, and with the bone, landmarks to guide the boundaries of the treatment fields.[13] The 3DRT is an advancement of 2DRT, using the computerized tomography images to plan instead of bone marks from x-ray, giving more accuracy to deliver the radiation to the tumor and lymphatic drainages.[22] IMRT is an evolution from 3DRT, which allows a more conformal shaping of radiotherapy dose to a specified target, intending to reduce high-dose exposure to surrounding organs at risk, including the small bowel, sigmoid bowel, bladder, rectum, femoral heads, and pelvic bone marrow.[18] Recently, retrospective and prospective studies have suggested that IMRT in the postoperative setting for gynecologic malignancies produces excellent rates of local control with reduced rates of toxicity.[17,18] Thus, IMRT is now considered standard in postoperative settings where removal of the uterus results in the displacement of small bowel into the pelvis. However, for definitive cervix cancer treatment, the survival benefit using 3DRT and IMRT over 2DRT is scarce and controversial.[18]

In our institution, we have testified the radiotherapy evolution in our clinical practice treating women with cervix cancer over the years. Therefore, we designed the present study with three objectives: 1- to evaluate prognostic factors associated with survival. 2- to assess whether the incorporation of the modern radiation techniques would be related to survival, and 3- to correctly evaluate the relation of these factors in the univariate and multivariate analysis. Our data confirm that the advanced stage, age, chemoradiation, and radiation technique were significant factors for OS and CSS in the multivariate analysis for women treated by radiation. All these factors have been constantly described as a significant factor for survival in patients receiving radiation alone or chemoradiation.[3,5,9–11] However, the radiation technique was the only significant factor in achieving significant statistical differences for EFS.

An optimal lymph node coverage is crucial for the success of the radiation treatment of cervical cancer.[23] The adequate radiation dose delivered to the lymphatic drainages has the capability of sterilizing microscopic disease in the nodes.[23] Moreover, pelvic failure is associated with decreased survival. The inadequacy of the 2DRT fields for target volume coverage with underdosing in lymph node regions is about 30–40%.[23] Kim et al. noted that margins were inadequate in up to 50% of patients.[15] Russell et al. also reported that the rate of missed therapeutic margins and the rate of incomplete coverage of the uterine fundus was as high as 24% and 62.5%, respectively.[24] Even using generous margins with 4-field radiation to the pelvis, the risk of inadequate inclusion of anatomic drainage without a CT scan continues elevated. The incidence of inadequate margin ranged from 39% to 50% and was independent of the stage of the disease, with the rectum as the most common site of inadequate margin.[22]

Curiously, in our data, chemoradiation and the advanced clinical stage had no significance in the EFS rate at 5 years. How to explain this finding? The interpretation is linked to the influence of 2DRT on the treatment group (radiotherapy alone and chemoradiation) and clinical stage (early and advanced). New radiation techniques as 3DRT/IMRT are more precise, reducing the volume of tumors receiving underdose of treatment when compared to 2DRT.[25] As a proportion of patients with an early clinical stage and chemoradiation in our cohort received 2DRT, these subgroups with theoretically better EFS than advanced stage and radiotherapy alone suffered the influence of 2DRT reducing the impact of these variables on the EFS to show a significant difference between them. Table 5 summarizes the proportion of patients receiving chemotherapy and the clinical stage in both groups 2DRT and 3DRT/IMRT. In our study, 78% of 2DRT vs. 61% of 3DRT/IMRT underwent chemoradiation. The disproportion between the groups is the possible explanation for the non-significant effect of the combined treatment in the univariate analysis for the EFS mainly due to local failure (Fig. 1c).

On the other hand, 2DRT was a significant factor for a worst EFS rate, i.e., patients treated by 2DRT developed more local or regional failure, a clinical situation that the salvage treatment is limited, resulting in a reduced survival which explains the bet-

Table 2
Univariate analysis of factors related to overall survival, cancer specific survival and event free survival.

Variable	Ntotal	OS 5 years	OS 8 years	P value	EFS 5 years	EVS 8 years	P value	CSS 5 years	CSS 8 years	p Value
Age										
<60	118	37.2%	20.9%	p = 0.18	35.8%	33.8%	p = 0.60	83.2%	46.8%	p = 0.03
≥60	110	31.6%	13.9%		48.7%	44.6%		64.0%	28.1%	
Stage										
Early	29	51.0%	25.5%	p = 0.03	53.8%	47.8%	p = 0.26	85.2%	42.6%	p = 0.53
Advanced	199	30.9%	12.9%		37.4%	35.6%		71.2%	33.7%	
Histology										
SSC	171	34.7%	18.5%	p = 0.51	40.4%	38.3%	p = 0.34	72.5%	38.7%	p = 0.52
Adenocarcinoma	43	45.3%	26.8%		38.7%	34.8%		78.6%	29.5%	
Period										
2000–2004	30	19.7%	14.8%	p < 0.01	34.2%	28.5%	p < 0.01	54.3%	40.8%	p = 0.05
2005–2009	42	25.4%	22.1%		37.4%	33.2%		67.5%	37.5%	
>2010	156	44.6%	39.3%		42.6%	39.4%		83.5%	53%	
Treatment										
RT	78	27.8%	18.5%	p < 0.01	41.5%	37.4%	p < 0.38	61.4%	40.9%	p < 0.01
CRT	150	38.0%	28.3%		40.4%	38.4%		81.2%	64.8%	
RT Technique										
2D RT	72	22.9%	11.0%	p < 0.01	33.9%	31.5%	p = 0.03	62.5%	30.0%	p = 0.02
3D RT / IMRT	156	44.6%	33%		43.6%	41%		83.5%	52%	

Table 3
Cox multivariate analysis of significant factors for overall survival.

Variables	N	%	HR	95% CI	p-Value
Age [R. <60]			lower- upper		
<60	118	51.8	0.358	0.104–1.059	p = 0.15
≥60	110	48.2			
Stage [R. Early]					
Early	29	12.7	0.570	0.312–1.042	p < 0.05
Advanced	199	87.3			
Treat. [R. RT]					
RT	78	34.2	0.706	0.472–1.056	p < 0.05
CRT	150	65.8			
RT Tec. [R. 3D – IMRT]					
2D	72	31.5	0.546	0.341–0.875	p < 0.05
3D – IMRT	156	68.5			
Histology [R. SSC]					
Adenocarcinoma	43	18.9	0.800	0.519–1.235	p = 0.314
SSC	171	75.0			

R. = reference.

Table 4
Cox regression multivariate analysis of significant factors for cancer-specific survival.

Variables	N	%	HR	95% CI	p-Value
Age [R. < 60]			lower- upper		
<60	118	51.8	1.661	0.098–5.672	p < 0.05
≥60	110	48.2			
Stage [R. Early]					
Early	29	12.7	0.692	0.247–1.935	p = 0.48
Advanced	199	87.3			
Treat. [R. CRT]					
RT	78	34.2	0.402	0.186–0.868	p < 0.05
CRT	150	65.8			
RT Tec. [R. 3D – IMRT]					
2D	72	31.5	0.388	0.160–0.940	p < 0.05
3D – IMRT	156	68.5			
Histology [R. SSC]					
Adenocarcinoma	43	18.9	0.965	0.412–2.260	p = 0.93
SSC	171	75.0			
R. = Reference					

ter OS and CSS for IMRT/3DRT, chemoradiation, and early stage. Therefore, the correct definition of the lymph node structures to be included in the radiation treatment plan is vital for cervical cancer patients. Recently, a systematic review with meta-analysis, including six studies (retrospective and prospective studies) with a total of 1008 patients, showed no significant difference comparing IMRT vs. 3DRT or 2DRT in terms of survival and disease-free survival.[18] The data reported by Lin Y et al. in this meta-analysis was one of the main reasons for us to analyze 3DRT and IMRT in the same group. First, because the coverage with 3DRT and IMRT looking at 95% of the isodose curve in the PTV is very close to the vast majority of the cases.[12] Second, the basic principle to point out some difference between 2DRT and 3DRT or IMRT is the same, i.e., 2DRT has a great inadequacy to deliver dose to lymphatic drainage and tumor, while IMRT/3DRT treat the target more adequately. Furthermore, the studies included in the meta-analysis had a small sample, short follow-up (median three years), different design (retrospective and prospective), and heterogeneity sample in the comparison

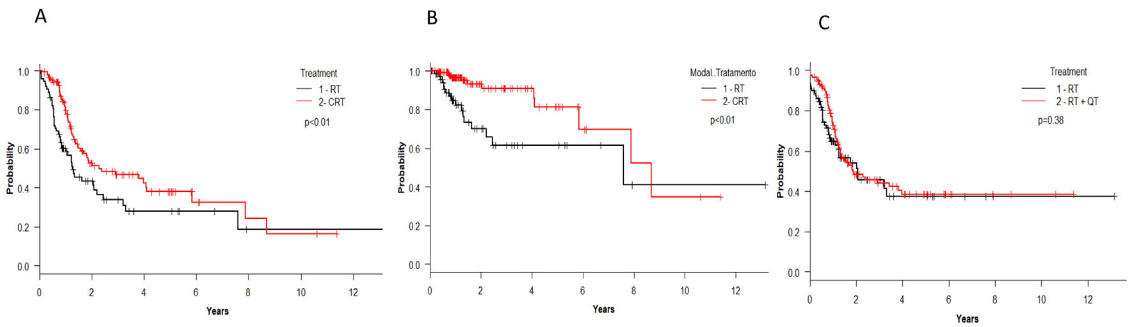

Fig. 1. (a, b, c) Kaplan–Meier estimation of overall survival, cancer specific-survival and event-free-survival comparing RT group with CRT using long-rank method.

Table 5
Characteristics of the 2DRT and 3DRT/IMRT groups.

Variables	2DRT (78)	3DRT/IMRT (150)	P Value
Age (mean)	58 ± 14	59 ± 15	NS
RT alone	17 (22%)	58 (39%)	0.012
CTRT	61 (78%)	92 (61%)	
Stage			0.004
Ia-IIa	17 (22%)	13 (9%)	
IIb-IIIb	59 (64%)	124 (82%)	
IVa	11 (14%)	13 (9%)	
Follow up months	59 ± 16	60 ± 14	NS

arms. Consequently, we choose to design a cohort study to consider the incorporation of technology over time as a prognostic factor with its weight estimated by the multivariate analysis for different endpoints.

The present cohort has limitations inherent to the study design. First, the acute and late toxicities were not collected and not considered in our analysis. Second, the presence of comorbidities, such as hypertension or diabetes mellitus, could be a factor influencing survival. However, it is unlikely that these limitations change the interpretation of the findings of our study.

5. Conclusion

The present cohort confirms the influence of significant prognostic factors such as chemoradiation, advanced stage, and advanced age for survival, and cancer-specific survival in women with cervix cancer treated by radiation with a long follow-up. The incorporation of new radiation technique over time (3DRT/IMRT) had a strong influence over all the endpoints evaluated in our study resulting in improvement of event-free survival, overall survival, and cancer-specific survival when compared to the conventional technique (2DRT). These outcomes can be useful and valuable for radiation oncologists, and patients from developing countries to choose adequate radiation techniques to produce satisfactory oncological results, as technological resources and radiotherapy facilities are many a time scarce in these countries.

Authors' contributions

All authors participated the study design, data extraction and analysis.

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None declared.

Conflict of interest

None declared.

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