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Impact of Treatment Duration on Cervical Cancer Outcomes: Results from a Single Institution

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Abstract

Introduction: Treatment duration has always been related to treatment outcomes in cervical cancer. Our study is aiming to evaluate this parameter and its effect on treatments' results in patients with locally advanced cervical cancer treated with concurrent chemo radiation.

Patients and methods: Between January 2011 and December 2011, all patients diagnosed with cervical cancer and treated with concurrent chemo radiotherapy were retrieved. Treatment duration was calculated from the first day of EBRT to the last day of brachytherapy or EBRT, whichever was last to complete, Fifty-six days (8 weeks) was used as a limit, we analyzed the impact of treatment duration on the overall survival and local control.

Results: The median time to complete pelvis RT was 37 days (34-42 days). A median of 15 days (13-26 days) between the last day of Pelvic RT and the start of the first Brachytherapy fraction (Pelvis RT-BT interval) was noted. The median time to complete EBRT in association with BT was55 days (50-69 days) while the median total treatment duration was 61 days (53-71 days).

At 3 years the overall survival (OS) rate of the studied cohort was 89.8% and local control (LC) rate was 80.8%. In the univariate analysis, total treatment duration (>56 days) was found to be a significant factor impacting both OS (P=0.014)), and LC (P=0.014). Also in the multivariate analysis, total treatment duration was associated independently with prognosis, and affected both OS (hazard ratio [HR], 2.8; 95% CI, 1.07-7.54, P=0.035) and LC (hazard ratio [HR] 3.2; 95% CI, 1.57-6.64, P=0.001).

Conclusion: Extended treatment duration significantly affects treatment outcomes in cervical cancer, efforts should be made to shorten it in a way to improve cancer prognosis.

Keywords: Cervical cancer; Concurrent chemoradiotherapy; Treatment duration; Prognostic factors

Abbreviations: FIGO: Federation of Gynecology and Obstetrics; OS: Overall Survival; LC: Local Control; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; Gog: Gynecology Oncologic Group; Rtog: Radiation Therapy Oncology Group; Ebrt: External Beam Radiation; TD: Treatment Duration; Rt: Radiotherapy; Lacc: Locally Advanced Cervical Cancer

Introduction

Cervical cancer is not only one of the most widespread gynecological malignancies in women worldwide, but also one of the most common causes of cancer related death. In Morocco as an example, cervical cancer is the second most common cancer and is the second cause of cancer related death [1]. Its treatment is adapted to the clinical stage of the disease. Accordingly, concurrent chemoradiotherapy is the standard treatment in locally advanced cervical cancer. In fact, it has been established since the National Cancer Institute Alert in 1999 [2].

In a well conducted treatment, many factors affect treatment outcomes. In our study, we are going to focus on treatment duration. Based on a recent investigation, 19 days is sufficient to accelerate repopulation in cervical cancer [3], which underlines the important role of treatment duration in tumor control. Many studies have in fact investigated the "time effect" and demonstrated that extension of treatment duration of radiotherapy affects local control [4-7]. However, its relevance is not well established in the context of concurrent chemoradiation [8,9].

Our study is a retrospective analysis of patients with locally advanced cervical cancer treated with concurrent chemoradiation. Its main objective is to define the impact of treatment duration in this setting.

Materials and Methods

Patients

From the first of January 2011 till the 31th of December 2011, all patients diagnosed with locally advanced cervical cancer and receiving concurrent chemoradiation were identified. We then selected those who have completed the total dose of radiotherapy (either by brachytherapy or external beam radiotherapy).

Of the 325 patients selected, we excluded 32 patients, because they did not complete the planned treatment (Of note all the patients were informed of the necessity to continue their treatment).

At least, 293 patients were included in the study.

For each patient data were collected for analysis; it included: age, tumor stage, tumor size, histologic type, number of cycles of

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chemotherapy, external beam RT dose, time of both treatments' start and its ending to evaluate overall treatment duration and its impact on treatment outcomes.

Treatment modalities

The treatment adopted in our department is concurrent chemo radiotherapy with weekly Cisplatine.

Radiation therapy: A total dose of 70 Gy was delivered to all patients, using either a combination of external beam radiation therapy (EBRT) and brachytherapy or EBRT alone when brachytherapy was not feasible.

Both Low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy were performed. Four fractions of 7Gy were prescribed when HDR brachytherapy was performed or one fraction of 24Gy with LDR brachytherapy.

The most frequent reason for being unable to perform intracavitary treatment was inability to cannulate the cervical os. The os was either obstructed by residual tumor or had disintegrated, leaving a large hole. This was the reason noted in 44 patients (21.1%).

Other reported technical limitation was the absence of interstitial catheters in our department, enabling us to perform brachytherapy when an involvement of the lower vagina with a thickness of more than 5 mm was reported (18% of the cases) and also in the cases where the uterus was involved (8% of the cases), because of the difficulty to ensure a full coverage of the tumor without interstitial catheters.

When parametrial involvement was documented, an additional dose of 10 Gy in five fractions was delivered. Also, an additional dose of 14 to 20 Gy was systematically delivered to any proven positive lymph nodes. Otherwise, positive lymph nodes were included in the target volume of the second phase of the EBRT treatment.

Chemotherapy: As to concomitant chemotherapy, Cisplatin was the most commonly used drug and was delivered weekly throughout the course of RT at a dose of 40 mg/m^2 (maximum dose of 70 mg weekly) as long as the treatment was well tolerated.

Carboplatine was prescribed only in the case of renal failure or an Eastern Cooperative Oncology Group performans status score ≥ 2 (13% of the cases).

Follow-up: After completion of treatment, oncologic follow up was recommended every 3 months for 2 years, every 6 months for 3 years.

Median follow up was 31 months.

Relapse was documented by positive biopsy, clinical examination, or radiographic findings.

Treatment duration: Treatment duration was calculated from the first day of EBRT to the last day of brachytherapy or EBRT, whichever was last to complete.

Fifty-six days (8 weeks) was used as a limit, as it was the recommended time to complete RT in contemporary Radiation therapy oncology group (RTOG) and Gynecology oncologic group (GOG) [10,11].

We divided patients into two groups: one with a TD≤56 days and another with TD > 56 days.

Statistical analysis

Statistical analysis was performed with SPSS software. Patient disease-specific survival distribution was calculated using the Kaplan–Meier method. Patients who died of general disease or who were lost to follow-up were censored at the time of last known follow-up. The significance of the survival was tested by log-rank test. A value of $P < 0.05$ was considered statistically significant. Multivariate analysis was performed using the Cox proportional hazard regression analysis in a forward stepwise manner with a P value of 0.2 as inclusion.

Results

Tumor and patient characteristics are summarized in Table 1. Median age at diagnosis was 49 years. Squamous cell carcinoma was the most common histological type; it was identified in 93% of the cases. All the patients were staged according to the FIGO staging system of 2009, stages IB, IIA, IIB, IIIA, IIIB et IVA were found in 9.5%, 4.4%, 44.4%, 0.7%, 38.6% and 1.7% of the cases.

To evaluate the tumor size, both of physical exam and radiologic findings were used, tumor size was superior to 4 cm in 54,6%. Parametrial involvement was recorded in 78.9%.

Seventeen percent of the studied cohort had positive pelvic lymphnodes (LN) based on pelvic computed tomography scan or pelvic Magnetic resonance imaging findings.

Radiation technique

External beam radiotherapy (EBRT): EBRT was delivered using linear accelerators. High-energy photon beams (10 MV or higher) were used in this setting.

When given alone radiation therapy was delivered in two phases of treatment to a total dose of 70Gy. CT-based treatment planning and conformal blocking were both used in this setting. A fusion with MRI images was realized whenever MRI was available.

In the first phase, target volume included the gross disease, parametria, uterosacral ligaments, and a vaginal margin of 3 cm from the gross disease. Concerning the nodal target volume, for patients with negative nodes on radiologic imaging, the radiation volume included the entirety of the external iliac, internal iliac, and obturator nodal basins. For those deemed at higher risk of lymph node involvement (bulky tumors; suspected or confirmed nodes confined to the low true pelvis), the radiation volume was increased to cover the common iliacs as well. In patients with documented common iliac and/or para-aortic nodal involvement, extended-field pelvic and para-aortic radiotherapy was used, up to the level of the renal vessels (or more cephalad as directed by involved nodal distribution).

	N	%
Age (y)	50 [44–59]	
Histologic type		
Squamous cell carcinoma	278	94,9%
Adenocarcinoma	15	5,1%
Tumor size		
<4 cm	133	45.4%
>4 cm	160	54.6%
Stages		
IB	28	9.5%
IIA	13	4.4%
IIB	131	44.4%
IIIA	2	0.7%
IIIB	114	38.6%
IVA	5	1.7%
Lymphadenopathy		
Pelvien	66	22.5%
Para aortic	11	3.8

Table 1: Patient and Disease Characteristics.

A total dose of 46Gy was delivered with a box technique using four fields (Anterior-posterior and two laterals), conformal blocking was used in all the cases to maximally spare the bowel and bladder and normal bone structures.

The second phase consisted on a boost of 24 Gy delivered to the gross tumor volume defined by MRI when available, otherwise the volume include the whole cervix. A margin of 2 cm is then added. Treatment was delivered using a four field technique (Anterior-posterior and two laterals).

Nodal and parametrial irradiation: When the combination of EBRT and brachytherapy was used, an additional dose of 14 to 20 Gy was systematically delivered to any proven positive lymph nodes. Otherwise, positive lymph nodes were included in the target volume of the second phase of the EBRT treatment.

Also, when parametral involvement was documented, an additional dose of 10 Gy in five fractions -delivered with reduced anteroposterior portals (8 by 12 cm for unilateral and 12 by 12 cm portals for bilateral parametrial coverage)- A central midline block was placed to protect the bladder and rectum.

Brachytherapy: HDR or LDR brachytherapy were used .Intracavitary approach was used in all the cases. Applicator was chosen depending on the patient and tumor anatomy. Tandem and ovoids were used in 38% of the cases, each time the largest ovoid diameter that can be accommodated in the fornices without displacement was used. The ring applicator was useful when the vaginal fornices were asymmetric or absent, it was used in 19% of the cases. Applicators placement was performed in a dedicated operative room and an Epidural anesthesia was applied in all the cases. The rectum was displaced away from the applicator by using an in-built rectal retractor, the bladder was displaced using an anterior vaginal packing (32% of the cases where the anterior wall was not involved) (Table 1).

Treatment results

29% of patients were treated by EBRT alone (70Gy).

The median time to complete pelvis RT was 37 days (34-42 days). A median of 15 days (13-26 days) between the last day of Pelvic RT and the start of the first BT fraction (Pelvis RT-BT interval) was noted. The median time to complete EBRT in association with BT was 55 days (50-69 days) while the median total treatment duration was 61 days (53-71 days) (Table 2).

Treatment toxicities

Toxicities were graded using the EORTC radiation toxicity scale. Acute toxicities (Table 3). 74% of the admitted patients were closely monitored; they had a weekly evaluation along with a blood cell account and a dosage of urea and creatinine levels. We could not find any data concerning the remaining patients.

The most common acute adverse effects were gastrointestinal (n=185; 63.1%) (diarrhea in 52 women, and nausea and vomiting in 133 women), hematological (n=139; 46%), infections (n=81; 27.5%), and skin reactions (n=101; 34.4%). The most common hematological toxicity was anemia (n=126; 43%); 117 women developed grade 1 or 2 toxicity, and 8 women developed grade 1 or 2 neutropenia.

The most common acute grade 3 or 4 toxicity was hematological (n=35; 11.9%), with 20 (6.8%) women experiencing grade 3 or 4 neutropenia, 9 women experiencing grade 3 or 4 anemia, and 6 women experiencing grade 3 or 4 thrombocytopenia. No women died from hematological toxicity, and it was reversible in all the cases. Twelve women (4%) had acute grade 3 or gastrointestinal toxicity, and four (2%) women developed thromboembolic complications.

We report no died during treatment in our series.

OS and LC

The median follow up was 31 months.

The overall 3-year survival rate was 89.8%, and the overall local control (LC) rate was 80.8% at 3 years.

Univariate analysis

The univariate analysis examined prognosis factors affecting the aforementioned variables.

OS was significantly affected by tumor size (≤ 4 cm or >4 cm) (p=0.003), the presence of positive lymph nodes (P=0.001), the stage (p=0.0001), pretreatment hemoglobin (p=0.004), number of cycles of chemotherapy completed (less than four) (p=0.028), and the use of brachytherapy (p=0.0001) (Table 4).

Also LC was significantly affected by tumor size (p = 0.005), the presence of positive lymph nodes (P=0.017), the stage (p=0.0001), pretreatment hemoglobin (p = 0.033), the use of brachytherapy (p=0.001), and the number of cycles of chemotherapy completed (less than four) (p = 0.025) (Table 5).

Total treatment duration (>56 days) was found to be a significant factor impacting both OS (P=0.014)), and LC (P=0.014) (Figure 1).

Multivariate analysis

Multivariate analysis of those prognostic factors that were identified in the univariate analysis showed that total treatment duration was associated independently with prognosis, and affected both overall survival (hazard ratio [HR], 2.8; 95% CI, 1.07-7.54, P=0.035) and local control (hazard ratio [HR], 3.2; 95% CI, 1.57-6.64, P=0.001), also, were identified the number of cycles of chemotherapy completed (less than four) and the use of brachytherapy (Tables 4 and 5).

	Median	IQR
Whole pelvis RT time	37 days	34-42
Time between RT and Brachytherapy	15 days	13-26
Brachytherapy time	55 days	50-69
Total RT time	61 days	53-71

Tables 2: Treatment duration in days.

	N	%
Gastrointestinal	**185**	**63.10%**
Diarrhea	52	28.10%
Nausea–vomiting	133	45.40%
Hematologic toxicities	**159**	**54.20%**
Neutropenia	**28**	**9.50%**
Grade 1 or 2	8	2.70%
Grade 3 or 4	20	6.80%
Anemia	**126**	**43%**
Grade 1 or 2	117	40%
Grade 3 or 4	9	3%
Thrombopenia	**5**	**1.70%**
Grade 1 or 2	2	0.60%
Grade 3 or 4	3	0.90%
Renal insufficiency	**62**	**21.10%**

Table 3: Treatment-related acute toxicities.

		Univariate analysis	Multivariate analysis		
	%	P Value	P Value	HR	IC 95%
Age					
≤49 >49	44.4% 55.6%	0.20	Not included		
Histolgic type					
Squamous cell carcinoma Adenocarcinome	94.9% 5.1%	0.886	Not included		
Size					
≤ 4cm > 4cm	45.4% 54.6%	0.005	0.63 (NS)	1.18	0.59-2.36
Lymphadenopathy					
No Yes	76.7% 23.1%	0.017	0.98	0.99	0.52-1.87
Stage					
Local Locally advanced	58.3% 41.7%	0.002	0.008	2.3	1.24-4.28
Pretreatment hemoglobin level					
< 10 g/Dl 10-11.9 g/dL ≥12 g/dL	20.3% 34.9% 44.1%	0.033	0.99(NS)	0.99	0.51-1.94
Number of cycle of chemotherapy					
< 4 ≥ 4	16.9% 82.4%	0.025	0.056	1.82	0.98-3.37
Treatment duration					
≤56 days >56 days	38.3% 61.7%	0.0001	0.001	3.23	1.57-6.64
Brachytherapy					
No Yes	29% 71%	0.001	0.005	2.33	1.30- 7.21

Table 4: Uni and multivariate analysis for prognosis factors influencing OS.

Discussion

The role of TD in patients with cervical cancer has been extensively studied in the context of radiotherapy alone. These studies have demonstrated that prolonged treatment duration significantly increased local relapse rate and decreased survival rate. It was mainly explained by cellular proliferation that is accelerated after radiation; in fact in the investigation of Huang et al. [3] the onset time of accelerated repopulation was directly derived from the clinical data by using the Linear Quadratic model. They showed that 19 days is sufficient to accelerate repopulation in cervical cancer, which is relatively short when compared to other cancer types.

Fyles et al. were the first to report loss of local control with prolonged time duration; it was estimated of 1% per day for a prolongation beyond 30 days [4].Those results were later on confirmed by Girinsky et al., with a threshold of 52 days [5]. Also, Petereit et al. [6], in their series of 209 patients treated with RT suggested a strong correlation between treatment duration and relapse, and by the same way survival rates. As results, extended time duration (TD ≥ 55 days was adversely associated with survival and pelvic relapse. Similarly, Chen et al. [7] observed that a TD ≥63 days was associated with increased pelvic relapse rates and low 5-year cause-specific survival rates. The main particularity of Chen's study is that adverse effects of extended TD were observed later in the treatment course than previous studies. They attributed this discrepant finding to their use of HDR brachytherapy and the potential greater efficacy of HDR, compared with LDR brachytherapy, in counteracting tumor repopulation.

More recently, many interesting publication revising the role treatment duration in the setting of concurrent chemotherapy were published. Shaverdian et al. [8] recently stated that time duration had no significant impact on neither OS nor local relapse when concomitant chemotherapy was delivered with radiation. Adversely, Song et al. [9] -in their series of 103 patients treated with concurrent chemoradiation- found that treatment time >56 days is detrimental to pelvic control but is not associated with an increase in distant failure (DF) or disease-specific mortality (DFM). According to Shaverdian [8], the difference between the two series was related to a number of methodologic

		Univariate analysis	Multivariate analysis		
	%	P Value	P Value	HR	IC 95%
Age ≤ 49 % >49	44.4 55.6%	0.20	Not included		
Histolgic type Squamous cell carcinoma Adenocarcinome	94.9% 5.1%	0.886	Not included		
Size ≤ 4cm > 4cm	45.4% 54.6%	0.005	0.63 (NS)	1.18	0.59-2.36
Lymphadenopathy No Yes	76.7% 23.1%	0.017	0.98	0.99	0.52-1.87
Stage IB IIA IIB IIIA IIIB IVA	9.5% 4.4% 44.4% 0.7% 38.6% 1.7%	0.001	0.28	0.30	0.03-2.67
Pretreatment hemoglobin level < 10 g/Dl 10-11.9 g/dL ≥12 g/dL	20.3% 34.9% 44.1%	0.033	0.99(NS)	0.99	0.51-1.94
Number of cycle Of chemotherapy < 4 ≥ 4	16.9% 82.4%	0.025	0.056	1.82	0.98-3.37
Treatment duration ≤56 days >56 days	38.3% 61.7%	0.0001	0.001	3.23	1.57-6.64
Brachytherapy No Yes	29% 71%	0.001	0.005	2.33	1.30-7.21

Table 5: Uni and multivariate analysis for prognosis factors influencing LC.

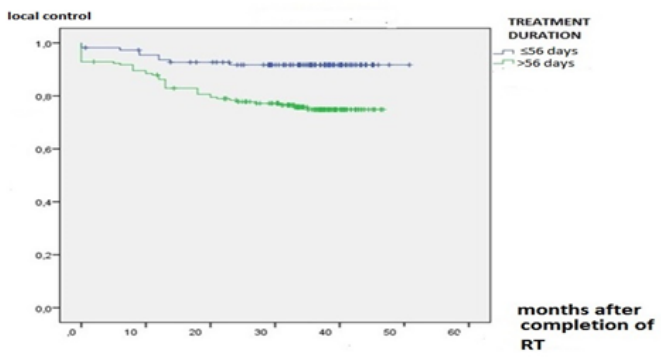

Figure 1: Graph showing the impact of time (≤ 56 days versus >56 days)to completion of radiotherapy (RT) on local control.

differences in Song et al. study. On one hand, the parametrial EBRT boost was administered after completion of cervical brachytherapy, and on the other hand TD from the beginning of pelvic EBRT to brachytherapy completion was significantly longer when compared with Shaverdian series (median TD 60 days vs median TD 51 days). Finally, 95% of patients in the Song et al study were treated with LDR brachytherapy while 85% of the CRT patients in the Shaverdian study were treated with HDR brachytherapy. Although interesting, these findings warrant further investigation and more studies.

In our series, both OS and LC were significantly negatively affected by treatment duration (> 56 days) in the univariate and the multivariate analysis that was similar to the finding of song et al and different from Shaverdian. This finding can be explained partially by the use of the parameter boost after brachytherapy.

The reasons explaining treatment prolongation were multifactorial, absence of patient was reported in 15% of the cases and it was mainly due to familial issues, manipulators' strike was also noted during the period of the study. Also for the 71% of the cases who received brachytherapy, the TD for patients HDR brachytherapy were higher than the others with LDR brachytherapy.

We acknowledge the limitations of this study, including the retrospective nature of the review, and relatively short follow-up period that was 3 years, longer follow up is necessary to draw conclusions.

Actually many studies with more sensitive approaches, including serial MRI throughout treatment to evaluate the role of TD on tumor response [3].

Conclusion

In our country cervical cancer is still diagnosed at an advanced stage, and outcomes are still poor. To improve its prognosis, treatment duration should be shorten by the sensibilisation of patients of the necessity to don 't stop their treatment and also reduce the time between the different treatment phases and to administrate the parametrial EBRT boost before brachytherapy.

Informed Consent

Written informed consent was obtained from the patients for publication of this case report and accompanying images.

A copy of the written consent is available for review by the Editor-in-Chief of this journal

Authors' Contributions

NS and JK contributed in the analysis of patients charts, in the literature review and in writing the manuscript.AM and KY participated to the data collection, HE and SE corrected the manuscript before submission. TK and NB participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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