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Cervical Cancer: Prognostic and Evolution after Radiotherapy (Results from a Single Institution)

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Abstract

Introduction: In Morocco, cervical cancer is the second most common cancer,and the third cause of death. Our department recruits more than 500 patients each year and proximally half of the cases are diagnosed at an advanced stage.

Patients and methods: Between January 2011 and December 2011, all patients diagnosed with cervical cancer and treated with concurrent chemoradiotherapy were retrieved. We analyzed overall survival, local control, and defined prognostic factors influencing outcomes in this population.

Results: At 3 years the overall survival rate for the cohort was 89.8% and the overall LC rate was 80.8%. The most important prognostic factors for OS and LC were the pretreatment hemoglobin, total duration of treatment, and the use of brachyteherapy. Of the included patients, 20% experienced late Grade 3 or 4 toxicity.

Conclusion: The results of our study have shown that besides tumor stage, the use of brachytherapy, and lymphnode status, other factors such as pretreatment hemoglobin and treatment duration should be analyzed carefully and should be considered taking into consideration influence of all of the aforementioned factors.

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

Abbreviations: FIGO: Federation of Gynecology and Obstetrics; OS: Overall Survival; LC: Local Control; PFS: Progression Free Survival; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EORTC: European Oncology and Radiation Therapy Center; RTOG: Radiation Therapy Oncology Group; EBRT: External Beam Radiation; DF: Distant Failure; DSM: Disease-Specific Mortality; LACC: Locally Advanced Cervical Cancer

Introduction

Cervical cancer is not only one of the most widespread gynecological malignancies in women worldwide; but according to recent data it is the second most common cause of female cancer death [1].

While its incidence has widely decreased in developed countries, it is still rising in developing countries. In Morocco for example, cervical cancer is the second most common cancer and is the third most common cause of death [1].

Since the National Cancer Institute Alert in 1999 [2], chemotherapy concomitantly with radiation has become the standard of care for locally advanced cervical cancer.

Tumor size and stage, lymph nodes status and the pretreatment hemoglobin level are the most reported prognostic factors affecting cervical cancers' outcomes.

Our study is a population-based one aiming to evaluate the impact of different prognostic factors on overall survival and local control among patients receiving an optimal treatment for locally advanced cervical cancer.

Materials and Methods

Data collection

Our department recruits each year more than 600 women with cervical cancer. In our study, we analyzed the data of all the patients treated with for invasive cervical cancer between January 2011 and December 2011. We limited our selection to patients treated with primary chemo radiotherapy, and that were able to complete the total dose of radiotherapy (either by brachytherapy or external beam radiotherapy).

Patients

During the study period, 325 patients were identified. Patients were retrospectively identified using the available data on the national register of cancer and MOSAIQ data of our department. Of the 325 patients, we excluded 33 patients, because they did not complete the planned treatment. Of note, all the patients were previously informed of the necessity to continue their treatment. Eventually, 293 patients treated with concomitant chemoradiotherapy were included in our study. For each patient, the following data were collected for analysis of the prognostic factors: age, tumor stage, tumor size, histologic type, presence of lymphadenopathy evaluated either by pelvic CT or MRI, pretreatment hemoglobin level, mean hemoglobin during treatment, number of cycles of chemotherapy, external beam RT dose, brachytherapy when given, and overall treatment duration. The case notes were then evaluated for the main outcome measures: Overall survival (OS), local control (LC).

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Treatment modalities

In our department, the standard approach for locally advanced cervical cancer is concurrent chemo radiotherapy with weekly cisplatine in combination with brachytherapy. A total radiation dose of 70 Gy was delivered to all patients, either as a combination of external beam radiation therapy and brachytherapy or as EBRT alone when brachytherapy was not feasible. 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 5mm 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.

Chemotherapy

Concomitant chemotherapy was administered as a single agent. Cisplatin was most commonly used and was delivered once weekly throughout the course of RT at a dose of 40 mg/m^2 (maximum dose of 70 mg weekly) during radiotherapy as long as the treatment is tolerated. Carboplatine was prescribed only in the cases for whom renal failure (<40 ml/m^2) was diagnosed before starting the treatment.

Follow-up

The median follow up was 31months**.** After completion of treatment, oncologic surveillance was recommended every 3 months for 2 years, every 6 months for 3 years. Relapse was documented by positive biopsy, clinical examination, or radiographic findings.

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 intercurrent 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 0.05 as inclusion.

Results

Clinico-pathologic characteristics

The median age for the whole group of patients in this study was 51 (range 26–78years).

The most recorded predominant presenting symptom was vaginal bleeding (79%) either post coital (41%) or spontaneous bleeding (59%), vaginal discharge (70%) and pelvic pain (45%). A maximum duration of symptoms prior to presentation of 13 months, and a minimum of three weeks, with a mean duration of 4 ± 1.9 months was noted (Table 1).

On histologic evaluation, Squamous cell carcinoma was found in 94.9% of the cases (n=278), adenocarcinoma represented 5.1% of the cases (n=15).

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% .

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.

Radiological workup

74% of patients had an abdomino-pelvic CT to evaluate the loco regional extent and 26% of the cases had a pelvic MRI along with abdominal CT. All of the patients had an evaluation of thoracic metastases either by a chest x ray which was performed in 65% of the cases or a chest CT performed in 35% of the cases.

The presence of lymphadenopathy was noted in 22.5% (n=66) pelvien nodes found in 22.5% (n=66) and para aortic nodes in 3.8% (n=11).

Radiologic findings are summarized in (Table 2).

Biological workup

All of our patients had a blood cell account and a dosage of the urea and the creatinine levels, the hemoglobin level was below 12 g/dl in 44% of the cases and 31% of them had a renal failure with a creatinine clearance of less than 60 ml/m^2 biiologic findings are summarized in (Table 3).

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.

	N	%
Age (y)	50 [44–59]	
Histologic type		
Squamous cell carcinoma	278	94,9 %
Adenocarcinoma	15	5,1 %
Revealing symptom		
Metrorrhagia	231	79%
Leucorrhea	205	70%
Pelvic pain	131	45%
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%

Table 1: Clinicopathologic characteristics of the studied patients.

	N	%
Lymphadenopathy		
Pelvien	66	22.5%
Para aortic	11	3.8
Distance metastasis	0	0%
Pretreatment hemoglobin level		
<10 g/dL	60	20.3%
10-11.9 g/dL	103	34.9%
≥ 12	130	44.1%

Table 2: Radiological and biological characteristics of the studied patients.

		Univariate analysis	Multivariate analysis		
	%	p value	p value	HR	IC 95%
Age					
≤ 49 >49 55.6%	44.4 %	0.56	Not included		
Histolgic type					
Squamous cell carcinoma 94.9 % Adenocarcinome 5.1%		0.89	Not included		
Size					
≤ 4cm >4cm	45.4% 54.6%	0.003	0.75 **(NS)**	1.18	0.40-3.46
Lymphadenopathy					
No Yes	76.7% 23.1%	0.0001	0.08	1.9	0.91-4.14
Stage					
Local Locally advanced	58.3% 41.7%	0.0001	0.028	2.79	1.11- 6.97
Pretreatment hemoglobin level					
<10 g/Dl 10-11.9 g/dL ≥ 12 g/dL	20.3% 34.9% 44.1%	0.004	0.47**(NS)**	1.43	0.53-3.83
Number of cycle Of chemotherapy					
<4 ≥ 4	16.9% 82.4 %	0.028	0.059	2.15	0.97-4.76
Treatment duration					
≤ 56 days >56 days	38.3 % 61.7 %	0.014	0.035	2.84	1.07-7.54
Brachytherapy					
No Yes	29% 71%	0.0001	0.03 3.29 1.50-7.21		

Table 3: Uni and multivariate analysis for prognosis factors influencing OS.

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).

A total dose of 46 Gy 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).

Treatment results

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

Median total treatment duration was 61 days (53-71 hours) and was beyond 56 days in 61.7%. The median duration of the first phase of external radiotherapy (delivering a total dose of 46 Gy) was 37 days (34-42 days). The median duration between the end of radiotherapy (46 Gy) and the beginning of brachytherapy was 15 days (10-23 days).

46% of patients received additional on the parameters and / or the lymph nodes at the end of brachytherapy (after 7 days).

Brachytherapy was performed in 71% of the cases, Of the 208 patients who received brachytherapy, low-dose-rate (LDR) brachytherapy was used in 73.6% of the cases with a total dose of 24 Gy, and high-dose-rate (HDR) brachytherapy was used in the remaining 26.4% with four fractions of 7 Gy (two fractions per week for two weeks).

Of the five planned cycles of concurrent cisplatin chemotherapy, 243 patients (82.4%) received four or more cycles. The main reason for patients having reduced number of cycles was acute hematologic toxicity.

OS and LC

The overall 3-year survival rate was 89.8%, and the overall LC rate was 80.8% at 3 years (Figures 1 and 2).

Univariate analysis

The univariate analysis examined prognosis factors affecting the aforementioned variables.

OS was significantly affected by tumor size (p=0.003), the presence of positive lymph nodes (P=0.001), pretreatment hemoglobin (p=0.004), total treatment duration (>55 days (P=0.014)), number of cycles of chemotherapy completed (less than four) (p=0.028), and the use of brachytherapy (p=0.0001).

Also LC was significantly affected by tumor size (p=0.005), the presence of positive lymph nodes (P=0.017), pretreatment hemoglobin (p=0.033), the total treatment duration (>56 days (P=0.014), and the number of cycles of chemotherapy completed (less than four) (p=0.025) (Table 4).

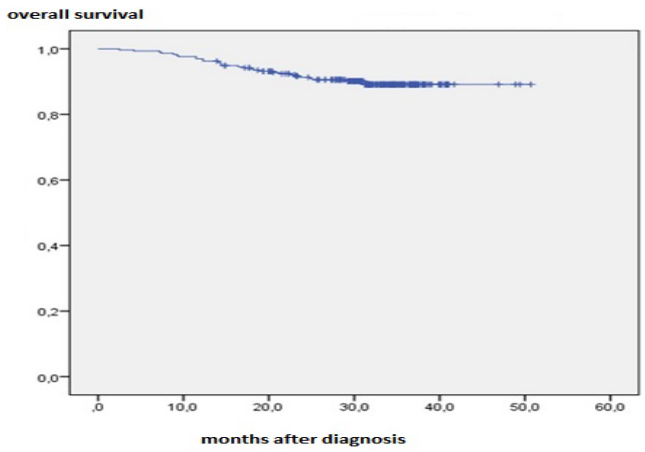

Figure 1: Three year overall survival for the studied cohort.

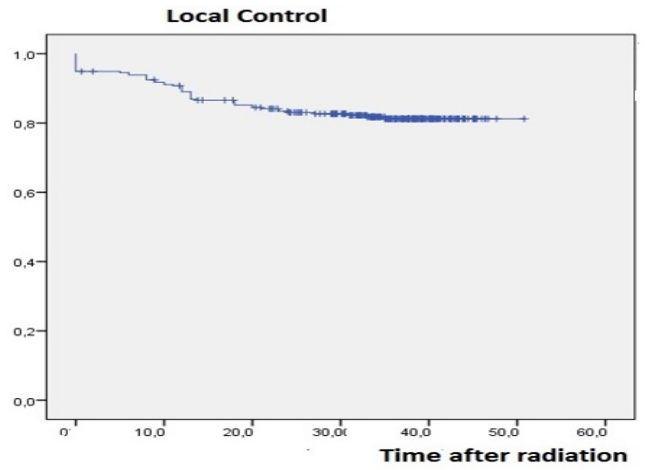

Figure 2: Local control for the studied cohort.

The use of brachytherapy as a component in the treatment was also found to be a significant factor influencing LC (p=0.001) (Figures 3 and 4).

Young age and histological type were identified with non significant p either for OS and LC.

Multivariate analysis

With the use of the Cox regression model, The only independently significant variables identified for OS were the number of cycles of chemotherapy completed (less than four) (p=0.05), the total treatment duration (>56 days) (P=0.035), and the use of brachytherapy (P=0.03) (Table 4).

Also for LC the only independently significant variables identified were the number of cycles of chemotherapy completed (less than four) (p=0.05), the total treatment duration (>55 days) (P=0.001), and the use of brachytherapy (P=0.005).

Discussion

Concurrent chemoradiation is the standard treatment of locally advanced cervical cancers [3-6].

Despite the satisfactory rate of local control after treatment carcinomas of the cervix, locoregional and distant relapse are not uncommon and are the major cause of failure. The occurrence of tumor progression and relapses depends on several prognostic factors, the most reported are: tumor size, lymphnode status, and hemoglobin levels [7].

Locoregional recurrences occur in two thirds of cases within 2 years after initial treatment and in 90% of cases within 3 years [8-10].

Through this chapter, we will analyze each prognostic factor that we found reported in the literature.

		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					
≤ 4 cm >4 cm	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 LC.

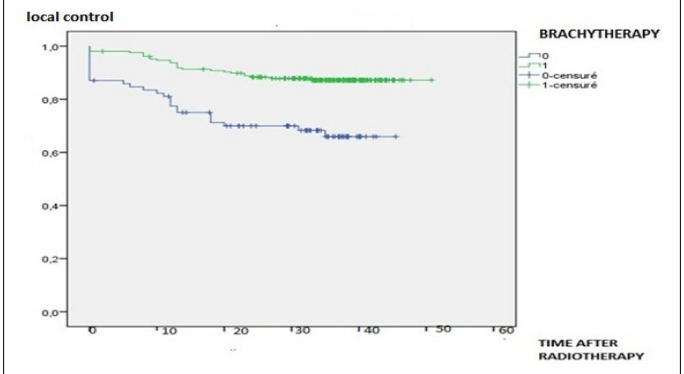

Figure 3: Graph shows effect of brachytherapy on local control.

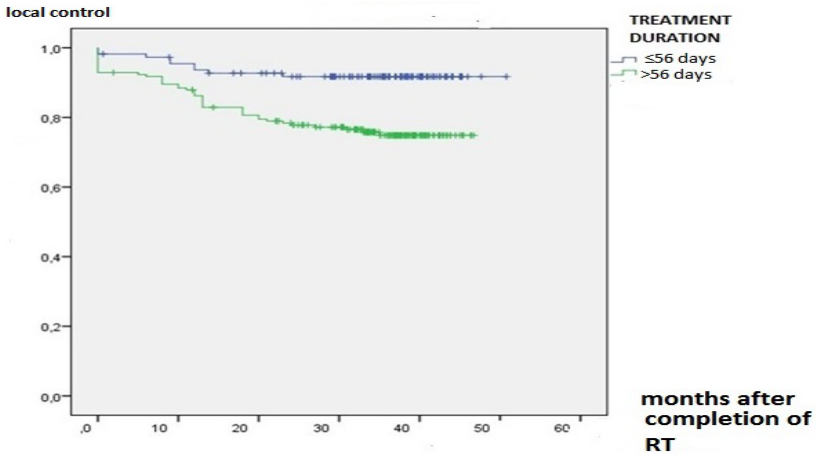

Figure 4: Graph shows effect of time to completion of radiotherapy (RT) on local control: ≤ 56 days versus >56 days.

Age

The median age of our patients was 50 years. In our study, age did not have any impact either on OS or LC. Our results are different from those reported in the literature where worse outcomes were seen in young patients [11,12], and patients aged 50 years or above respond better to radiotherapy [13-15].

Histological type

Squamous cell carcinomas is the most common histological type of cervical cancer accounting for approximately 80% of all cervical cancers. As to adenocarcinoma, its incidence has increased over the past 3 decades, and is considered as the second most common histological type accounting for approximately 20% of the cases [16,17]. Many published reports [18,19] suggested assuming that adenocarcinoma was associated to a worse prognosis, in the contrary other reports do not support this hypothesis. Therefore, the impact of the histological type on outcomes is still controversial. In our study, neither OS nor LC was affected by the histological type.

Tumor size

Tumor volume is an important predictor of progression free survival [20]. Also, local control has been reported to be inversely proportional to tumor volume [21]. The definition of tumor volume "Bulky" has varied in the literature; it is in some situations defined as 4 cm or 5 cm and very often as 6 cm.

At an equal stage, tumor size greater than 4 cm is associated with worse survival rates and local control rates when compared to smaller lesions [22].

Nodes involvements

In numerous series, the presence of pelvic lymphadenopathy impacts local control rates [20]. In this setting, many factors have been identified to significantly affect survival rates .It includes number of involved lymph nodes, bilaterality, the size of the lymph node metastasis, and the invasion or not of para-aortic lymph nodes.

In our series, OS and LC were affected by the presence of lymphadenopathy only in the univariate analysis. In the multivariate one, the influence of the lymphnode status was not significant. The main criticism of our results is the modality that we used to identify the lymphnode status. In fact, we used only conventional imaging (pelvic CT or MRI), which is currently considered to be insufficient. In fact, surgical staging and PET-CT have proven superiority in nodal assessment, and are currently adopted by international guidelines [23,24].

Pretreatment hemoglobine level

Anemia is frequent in the cervix cancer; its cause is often multifactorial: bleeding, iron deficiency, inflammation and infection. Its frequency is correlated with tumor stage [25].

Oxygen effect in radiation therapy is an important factor and the hemoglobin may compromise the effectiveness of the radiotherapy.

In a retrospective study by Mark et al. [26] showed that a hemoglobin level of less than 10 g/dl is associated to a low survival rate.

Girinski et al. [27] showed in their retrospective study of 386 patients treated at the Institut Gustave-Roussy between 1973 and 1983 that anemia during radiation therapy led to a relative risk of local relapse of 1.6 and metastatic relapse of 1.8 [28].

In a more recent and interesting study by Bishop et al., hemoglobin level (<10 g/dl) was not found to be an independent prognostic factor. Authors concluded that the effect of the level of Hg itself is probably overstated and that other factors such as the tumor size should be taken into consideration when assessing the role of the hemoglobin level [29]. In our series, hemoglobin level independently affected both of local control and overall survival in the univariate analysis but it was not significant in the multivariate analysis. It would be interesting to analyze the role of the hemoglobin level by subgroup according to tumor stage; the influence of tumor stage would be certainly more relevant.

Treatment duration

Treatment duration is an important prognostic factor found in several clinical studies. In fact, recent data suggests a period of 19 days required for accelerating the repopulation in cervical cancer which reflects the necessity in shortening treatment duration [30].

Petereit et al. [31], in their series of 209 patients treated with RT illustrated this correlation; between treatment duration and relapse and by the same way survival rates. As results to their study, extended time duration (TD) ≥ 55 days was adversely associated with survival and pelvic relapse. Similarly, Chen et al. [32] observed that a TD ≥ 63

days was associated with increased pelvic relapse rates and low 5-year cause-specific survival rates.

Shaverdian et al. [33] recently stated that time duration had no significant impact on both OS and local relapse when concomitant chemotherapy was delivered with radiation. Adversely, Song et al. [34] in a series of 103 patients treated by chemoradiation found that treatment time >56 days is detrimental to pelvic control but is not associated with an increase in DF (distant failure) or DSM (disease-specific mortality). Although interesting, these findings warrant further investigation.

In our series, the OS and LC were significantly negatively affected by treatment duration (>56 days) in the univariate and the multivariate analysis [35].

Brachytherapy

Brachytherapy is considered as an important component of treatment mainly because of its dosimetric benefits allowing the possibility to deliver a locally high dose to the site of disease with a surrounding rapid dose fall-off; sparing adjacent critical structure (small bowel, rectum, sigmoid, and bladder).Many studies have associated the use of brachytherapy with improved patient outcomes [36-41].

In a recent report by Han et al. [45] brachytherapy treatment was associated with higher 4-year cause-specific survival (CSS; 64.3% vs 51.5%, P<.001) and overall survival (OS; 58.2% vs 46.2%, P<.001). Brachytherapy treatment was independently associated with better CSS (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.57-0.71), and OS (HR 0.66; 95% CI, 0.60 to 0.74).

In a report by Gill et al. [42], omission of brachytherapy was associated with a survival detriment stronger than that associated with excluding chemotherapy (hazard ratio 0.65, 95% confidence interval, P<.01).

In our series, brachytherapy was found as an independent factor for Overall survival and Local control (P<0.02), in fact local control was reduced by a factor of 2.33 when brachytherapy was omitted.

Chemotherapy

Concurrent chemoradiation is the standard of care for locally advanced cancer [23,24]. Cispaltine or the combination of 5FU-Cisplatine is the most recommended.

In a randomized phase III trial conducted at the MD Anderson cancer center, Morris et al., compared radiotherapy alone with the combination of chemotherapy (Platine and 5FU based regimen) and radiation. At 5 years, PFS was 67% with the association of chemotherapy and radiation while it reached only 40% with radiotherapy alone (P<0,001). Overall survival rates were respectively 73 and 58% (P=0,004)[36]. Other randomized trials have confirmed these results [35].

Conclusion

Cervical cancer is mostly diagnosed at an advanced stage, and outcomes are still poor. The use of brachytherapy in combination with EBRT and the treatment duration were the most important prognostic factors identified in our series. Our results reflect the importance of brachytherapy as a component of the treatment, and also the need to shorten the treatment duration.

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 patient's charts, in the literature review and in writing the manuscript. HE and SE corrected the manuscript before submission.AL and RR participated in the statistics analysis of this series. 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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