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Surgical Resection after Concurrent Chemoradiotherapy for Locally Advanced Cervical Carcinoma

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Abstract

Background: Completion surgery after chemoradiotherapy (CRT) in management of locally advanced cervical cancers (LACC) still controversial. The aim of this study was to compare disease-free and overall survival rates in patients who had completion surgery and who were therefore treated conservatively by exclusive concomitant chemoradiotherapy (CCRT).

Materials and methods: This is a retrospective study from January 2005 to December 2014 included 130 patients with LACC, managed by standard CCRT followed by brachytherapy at the radiotherapy department of Military Hospital Mohamed V of Rabat in Morocco.

Inclusion criteria were the following: Biopsy-proven carcinoma of the cervix, FIGO stage IB2 to IVA and treatment with CCRT followed by brachytherapy. All patients had good response to standard CCRT, with a clinical decrease in tumor volume of more than 50%. Patients were divided into two groups depending on the authors practice: Group 1 consisted of patients without completion surgery who had theoretically a good response to standard treatment and Group 2 consisted of patients treated by completion surgery with pelvic control on final pathology.

One hundred and two patients are included in Group 1 and 28 in Group 2. The mean age of the patients was 50.9 years (range 29–82). Squamous cell carcinoma 115 (89.8%) was the leading histological type. Tumor size was 4.77 ± 1.44 cm clinically and 46.72 ± 15.42 mm in MRI. The parametrial was invaded in 113 (87.6%) of cases and the pelvic lymph nodes were suspected in 29 (23%) of cases.

Major of patients whom underwent a completion surgery showed a complete response on final pathology. Overall, 20.8% (27/130) of patients had a recurrence, with a median time to recurrence of 8 months [2-55]. With a mean follow-up of 44 months (2 to 118), the local control rate was 68.5% (n=89) and 20 (15.4%) patients were lost to follow-up.

The overall survival (OS) at 5 years in Group 1 and 2 was respectively 59.8% and 88.9% and the relapse-free survival (RFS) was respectively 73.3% and 88.9%. A significant benefit of completion surgery was seen only in OS (p=0.011).

Conclusion: completion surgery after CCRT has a place in the multimodality management of locally advanced cervical cancer with significant benefice in local control and OS.

Keywords: Cervical cancer; Completion surgery; Concomitant chemoradiotherapy

Abbreviations: CRT: Chemoradiotherapy; LACC: Locally Advanced Cervical Cancers; CCRT: Concomitant Chemoradiotherapy; RFS: Relapse-free Survival; OS: Overall Survival; DFS: Disease-Free Survival; MRI: Magnetic Resonance Imaging; SD: Standard Deviation; IQR: Interquartile Range

Introduction

Cervical cancer remains the second most common type of cancer and cause of cancer deaths among all types of cancer in women from developing countries [1]. Although the incidence of invasive cervical cancer has decreased thanks to screening and prevention programs, it is still not exceptional to find advanced cancers.

Prognosis for patients with cervical cancer depends on the stage of disease at diagnosis, based on the International Federation of Gynecology and Obstetrics staging system (FIGO), women with locally advanced cervical cancer (stage IB2 to IVA) have a higher rate of

recurrence and worse survival than those with early-stage disease (stage IA to IB1) [2,3].

Since the meta-analysis of Green et al. concomitant chemoradiotherapy (CCRT) has become the treatment standard for the management of locally advanced cervical cancers (LACC) [4]. In order to improve local control rate and to decrease the rate of distant failure, some authors have suggested the use of completion surgery after chemoradiotherapy (CRT), to remove potentially chemo and radio resistant foci. This approach, currently debated and not yet delineated in international guidelines, has shown encouraging results in terms of local control, with reported 78-90% of overall survival at 5th years [5-7].

The aim of this study was to compare disease-free and overall survival rates in patients who had completion surgery with less than 50% residual tumor and patients with a good response to CCRT who were therefore treated conservatively.

Materials and Methods

Population study

This is a retrospective study from January 2005 to December 2014 included 130 patients with LACC, managed by standard CCRT followed by brachytherapy at the radiotherapy department of Military Hospital Mohamed V of Rabat in Morocco. Inclusion criteria were the following: biopsy-proven carcinoma of the cervix, FIGO stage IB2 to IVA and treatment with concurrent chemoradiotherapy followed by brachytherapy.

Population management

The management protocol included external beam radiotherapy (EBRT) delivering 45 Gy in fractionated doses of 1.8 Gy, generally in four beams with 18 MeV photons using a linear accelerator after dosimeter under three-dimensional (3D) computed tomography (CT) scan.

Concurrent chemotherapy with cisplatin was associated with radiotherapy at a dose of 40 mg/m^2/week for five weeks. This standard treatment was followed by uterine and vaginal brachytherapy up to dose depending to completion surgery (14 Gy in preoperative) or not (24 Gy).

All patients had a good response to standard CCRT, with a clinical decrease in tumor volume of more than 50%. Patients were divided into two groups depending on the authors practice:

- Group 1 consisted of patients without completion surgery who had theoretically a good response to standard treatment. The disease response is determined by clinic and MRI when possible, just before brachytherapy.
- Group 2 consisted of patients treated by completion surgery with pelvic control on final pathology. Pelvic control was defined as absence of residual tumor or microscopic residual tumor<1 cm or macroscopic residual tumor ≥ 1 cm. In this group, the disease response is assessed by pathology.

Statistical analysis

Statistical analysis of the data was carried out by the SPSS for Windows (SPSS, Inc., Chicago, IL, USA). Qualitative variables were presented as number and percentages. Quantitative variables were presented as mean ± standard deviation (SD) for variables with normal distribution, and as median and interquartile range (IQR) for variables with skewed distributions. The survival rate was analyzed with the Kaplan-Meier method.

Results

Patient's characteristics

Patient characteristics for each group are given in (Table 1). One hundred and two patients are included in Group 1 and 28 in Group 2. The mean age of the patients was 50.9 years (range 29–82).

Squamous cell carcinoma 115 (89.8%) was the leading histological type, whereas adenocarcinoma contributed 11 (8.6%) and 2 (1.6%) were adenosquamous carcinoma. Based on International Federation of Gynecology and Obstetrics classification for staging cervical cancer (ACS, 2008), 13 (10%), 3 (2.3%), 80 (61.5%), 4 (3.1%), 29 (22.3%) and 1 (0.8%) of cases, cancer stages were respectively IB2, IIA, IIB, IIIA, IIIB and VIA. Tumor size was 4.77 ± 1.44 cm clinically and 46.72 ± 15.42 mm in MRI.

The parametrial was invaded in 113 (87.6%) of cases and the pelvic lymph nodes were suspected in 29 (23%) of cases. We don't found any statistically significant difference between the two groups, for these characteristics.

	Group 1	Group 2	Total
Completion surgery	No	Yes	
Number of patients	102	28	130
Mean of age°	51.62 ± 10.01	48.29 ± 7.61	50.90 ± 9.62
Histologic type (%)*			
Squamous cell carcinoma	93 (92.1)	22 (81.5)	115 (89.8)
Adenocarcinoma	7 (6.9)	4 (14.8)	11 (8.6)
Adenosquamous carcinoma	1 (1)	1 (3.7)	2 (1.6)
Stage*			
IB2	11 (10.3)	2 (7.1)	13 (10)
IIA	1 (1)	2 (7.1)	3 (2.3)
IIB	61 (59.8)	19 (67.9)	80 (61.5)
IIIA	3 (2.9)	1 (3.6)	4 (3.1)
IIIB	25 (24.5)	4 (14.3)	29 (22.3)
IVA	1 (1)	0	1 (0.8)
Initial tumor size (cm) °	4.77 ± 1.45	4.79 ± 1.44	4.77 ± 1.44
MRI tumor size (mm) °	48.33 ± 15.76	41.33 ±13.25	46.72 ± 15.42
Parametrial invasion*	89 (88.1)	24 (85.7)	113 (87.6)
Pelvic lymph node Invasion*	24 (24.2)	5 (18.5)	29 (23)

*Qualitative variables presented as number and percentages n (%), °Quantitative variables presented as mean ± standard deviation (SD).

Table 1: Patients characteristic.

Major of patients whom underwent a completion surgery showed a complete response on final pathology. Results are shown in (Figure 1).

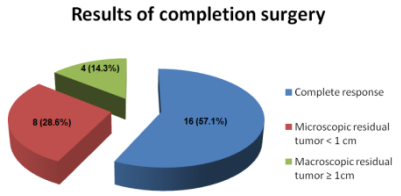

Figure 1: Results of completion surgery

Patients follow-up

Overall, 20.8% (27/130) of patients had a recurrence, with a median time to recurrence of 8 months [2-5]. Of the patients who had completion surgery (Group 2), 10.7% (3/28) had recurrence compared with 23.5% (24/102) of those who did not have surgery (Group 1).

Results according to location of recurrence are shown in (Table 2). With a mean follow-up of 44 months (2 to 118), the local control rate was 68.5% (n=89) and 20 (15.4%) patients were lost to follow-up. Khi-2 test shows statistically significant difference between the 2 groups only in local control in favor to Group 2 (p=0.033).

DFS and OS were analyzed to evaluate the impact of completion surgery and are shown in (Figure 2 and 3). The overall survival (OS) at 5 years in Group 1 and 2 was respectively 59.8% and 88.9% and the relapse-free survival (RFS) was respectively 73.3% and 88.9%. A significant benefit of completion surgery was seen only in OS (p = 0.011).

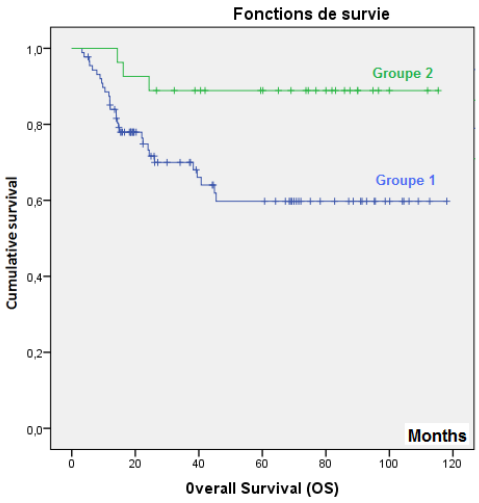

Figure 2: Overall survival according to the presence of surgery or not.

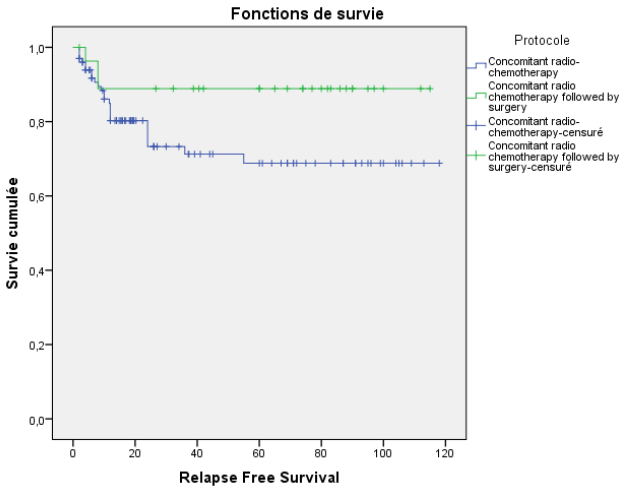

Figure 3: Relapse free survival according to the presence of surgery or not.

	Group 1	Group 2	Total
Recurrence*	24 (23.5)	3 (10.7)	27 (20.8)
Pelvic recurrence	15 (15.6)	3 (11.5)	18 (14.8)
Metastasis	11 (11.6)	1 (4)	12 (10)
Local control*	65 (63.7)	24 (85.7)	89 (68.5)
Lost to follow-up*	18 (17.6)	2 (7.1)	20 (15.4)
*Qualitative variables presented as number and percentages n (%).			

Table 2: Patients follow-up.

Discussion

CCRT represents the treatment of choice for the management of LACC [4]. To date, very few papers were published about the results of completion surgery after CCRT. However, data confirm that this approach can achieve OS and RFS rates at least comparable to exclusive CCRT [7-9]. Our study, confirm this benefice in local control, with reported 88.9% of overall survival at 5 years.

In the literature, major causes of treatment failure in advanced cervical cancer are pelvic failure, which according to: age, cancer stage, initial tumor size, lymph node invasion and residual tumor volume after CRT [10-12]. In our study, we don't found any significant predictors factors of recurrence. Tumor size after standard CCRT was not evaluated. However, all patients had a good response to standard CCRT, with a clinical decrease in tumor volume of more than 50%.

Furthermore, residual tumor on surgical specimen ranges in literature from 32% and 60% depending on the radiation dose and FIGO stage [12-15]. In our study, we demonstrated an 85.7% of pathological complete response or persistence of only microscopic disease, suggesting that the local control achieved with this schema is very high and at least comparable to that obtained by other groups using preoperative CRT. The fact that a residual tumor is often present

after CRT advocates for the hypothesis that an adjuvant surgical resection could improve local control, the DFS and the OS. Keys et al [13]. Reported an advantage in terms of local recurrence rate and 5-year DFS in patients treated with completion surgery versus those treated with exclusive CCRT. In other study, this approach has shown encouraging results in terms of local control, with reported 78–90% of overall survival at 5 years [6]. In current multicenter retrospective study, including 111 patients with LACC, treated by standard CCRT followed by brachytherapy, found that completion surgery does not improve OS but may improve DFS [16]. However, our study showed a significant benefit of completion surgery only in OS (p=0.011).

The evaluation of tumor response is crucial for subsequent treatment planning after initial CCRT because of the difficulty of correctly differentiating between residual tumor and post radiation changes. Magnetic resonance imaging (MRI) has been shown to be an excellent imaging technique in evaluating tumor response to CCRT in cervical cancer [17]. A recent retrospective analysis of prospectively data from 41 patients with cervical cancer who underwent MRI after CCRT showed a high negative predictive value and low risk of false negative results [18]. Unfortunately, in our study no patient underwent a MRI after CCRT and only 78 (60%) patients underwent MRI initially to treatment. Therefore, the role of conventional MRI combined with functional techniques should be more evaluated in patients with LACC treated with CCRT and completion surgery.

The major concern about this treatment could be the morbidity related to surgery after chemoradiation. In our series we have not evaluated acute and long-term morbidity. However, some authors confirm that surgery is feasible after CCRT and brachytherapy without undue increase in morbidity [13].

Conclusion

Completion surgery after chemoradiation therapy has a place in the multimodality management of locally advanced cervical cancer with significant benefice in local control and OS. Nevertheless further investigations are needed, particularly with collaborative studies, to analyze the real impact of such surgery on morbidity.

Competing Interests

We (authors) declare that we have no conflict of interest.

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Authors Contribution

A.M. and M.E, performed research and share the first position on article; M.E., A.M. and E.M., collected and analyzed clinical data statistically; K.A, A.B., I.L., K.H, H.S, N.Z and H.M, designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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