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ADJUVANT RADIOTHERAPY IN THE TREATMENT OF CERVICAL CANCERS STAGE IB1: A STANDARD FOR THE HIGH-RISK RECURRENCE GROUP WHAT ABOUT THE INTERMEDIATE RISK GROUP?

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INTRODUCTION

Radiation therapy occupies an important place in the treatment of gynecological cancers and especially the cervix. However, although it is associated with chemotherapy, the standard treatment of locally advanced forms surgery, remains paramount to the management of early forms. The therapeutic strategy adopted faced a problem concerning adjuvant treatment. The objective of this study is to evaluate the indications of post-operative radiotherapy for cervical cancer at an early stage.

MATERIALS AND METHODS

This is a retrospective bi-centric study in which the medical observations of patients that have been treated at the Radiation Therapy Department of Farhat Hached Sousse Hospital and the Ibn Khaldoun Private Medical Center were reviewed between 1995 and 2014. A total of 24 patients were included in the study. They had cervical carcinoma classified as stage IB1 according to the International Federation of Gynecologists and Obstetricians (FIGO 2009). And, all of them had the first surgery.

Epidemiological and clinical-radiological data were collected from the various observations. An analysis of histopronostic factors, including tumor size, degree of stromal invasion, presence of parametrial involvement, tumor surgical limit, vascular embols or lymphnodes involvement seperate the patients in 2 groups prognosis. Tumors are classified as high risk of loco regional recurrence in the presence of involved tumoral margins and / or microscopic parametrial involvement and / or histological lymph nodes involvement. Otherwise, they are considered as an intermediate risk of recurrence group. A GYNECOLOGIC ONCOLOGY GROUP STUDY score (GOG) of Delgado was carried out for this. It was obtained by multiplying the risks relatively to the different factors that are the tumor size, the degree of stromal invasion and the presence or not of vascular or lymphatic invasion. From this score, 3 prognostic sub groups were defined. (Table 1).

Table. 1: Score of prognosis sub groups.

Group 1	Group 2	Group 3
Score < 40	Score 40-120	Score > 120

Statistical analyses were carried out using the SPSS® software (Statistical Package for Social Sciences). The main objectives are to study the conformity of our therapeutic indications with the GOG score. Secondary goals are to calculate recurrence-free survival and overall survival. Overall survival is defined as the period from the pathologic diagnosis to the date of death and the recurrence-free survival to the onset of recurrence. Despite the small size of our population, the Kaplan-Meier method was used to estimate survival, and the Log Rank test to determine the correlation between risk factors and survival.

RESULTS

The average age of our 24 patients was 52 years [32-75years]. The mean size of the tumor at diagnosis was estimated at 2 cm [1-4cm]. After biopsy, the most frequent histological type was squamous cell carcinoma in 95.8% of cases.

All patients were operated, surgery was either a total colpohysterectomy with bilateral annexectomy and lymphadenectomy (83.3%), or an enlarged colpohysterectomy with bilateral annexectomy (4.2%) or an extra facial hysterectomy (4.2%) or interannexal hysterectomy (8, 3%).

Tumors were classified as having a high risk of recurrence, with a tumor surgical limit in 12.5% of cases, 4.2% of cases with parametrial involvement, and 25% of cases with lymph nodes involvement.

The mean histological size of the tumor was 2.07 cm [0.1-5 cm]. The upper third of the cervical stroma was invaded in 45.8% of the cases, the middle third in 29.2%

and the deep third in 12.5% of the cases. There were no cases of vascular emboli in our series.

The GOG score was calculated in 14 patients in the intermediate risk group. It was less than 40 in 30% of cases, between 40 and 120 in 70% of cases and no score was greater than 120.

Adjuvant treatment which is external radiation therapy was delivered to all our patients. It was a two-dimensional 2D type with cobalt 60, in 70.8% of cases, and three-dimensional 3D, with CLINAX iX, for 29.2% of the patients.

For the high-risk recurrence group, the target volume included the large pelvis alone in 70% of cases at doses ranging from 45 to 50.4 Gy, spraying with conventional fractionation (EFC: 1.8 Gy / fraction; days per week). In 30% of cases, it included the large pelvis followed by a complement, in external RT, on the vaginal vault (small pelvis) at doses ranging from 61.2 to 68.4 Gy in EFC. In 20.8% of cases, the vaginal complement was a low-dose brachy therapy. Concomitant chemo therapy was performed in 16.7% of cases and was of interest to high-risk patients.

For the intermediate risk group, the target volume was the vaginal vault 40% of cases at doses between 50 and 61.2 Gy in EFC and pelvis in 60% of cases at doses ranging from 45 to 50,4 Gy in EFC. The mean time between surgery and radiotherapy was 2.67 months [1-5 months] with a median spread of 44 days [29-90days].

A cute toxicities were hematological in one patient, urinary in 33.3% of cases, rectal and / or intestinal in33.3% of cases. They were only seen in patients with large pelvic irradiation. No toxicity was detected in case of irradiation of the vaginal vault and no late toxicity was noted.

After a mean follow-up of 15.8 months [1-60 months], overall survival of 5 years was 65%, recurrence-free survival and 5-year survival without metastases were 82.5% for the entire population(Figure 1). They were 57.1%, 85.7% and 66.7% respectively for the high-risk group and 71.4%, 83.3% and 85.7% for the intermediate risk group(Figure 2). In the intermediate risk group, overall survival and metastasis-free survival were better with a score <40 compared to a score between 40 and 120 (SG 5 years: 100% VS 33.3%, p = 0, 07, SSM at 5 years: 100% VS 66.7%, p = 0.24) (figure 3).

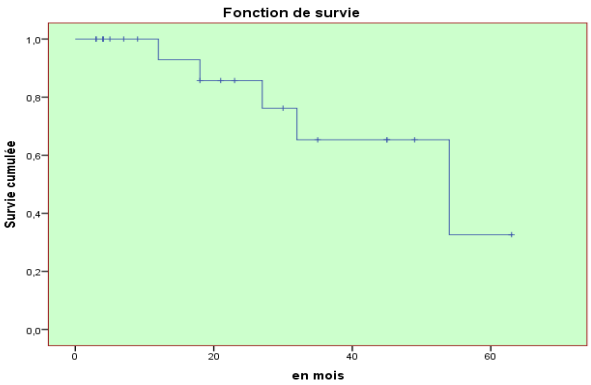

Figure. 1. A: Overallsurvival (OS).

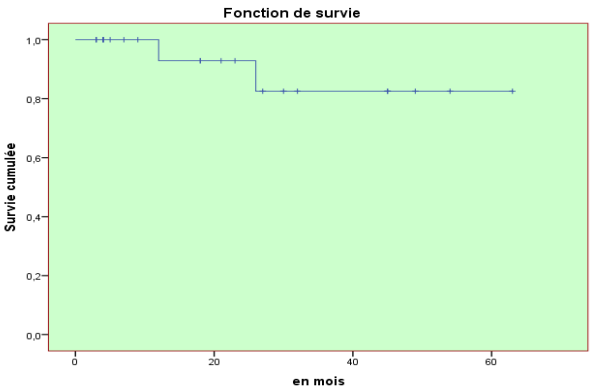

Figure. 1. B: Desease free Survival (DFS).

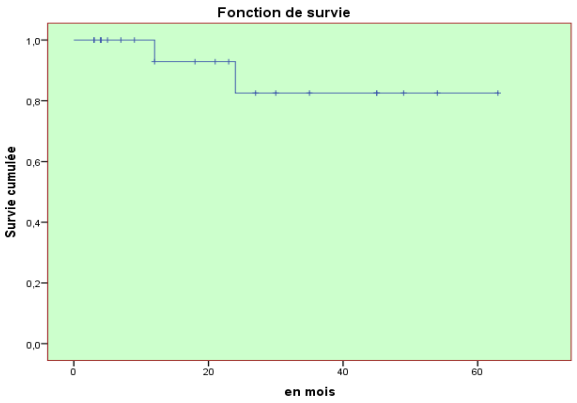

Figure. 1. C: Metastases free Survival (MFS).

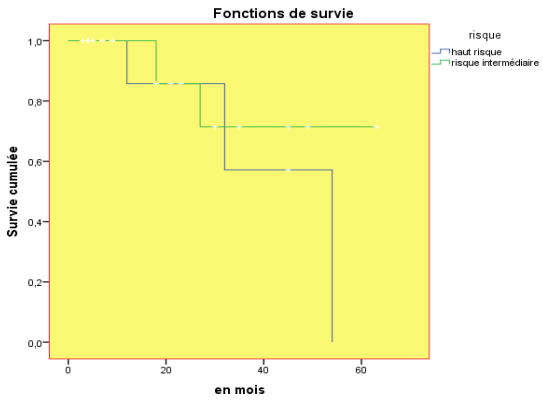

Figure. 2. A: Overall survival accordingrisk groups.

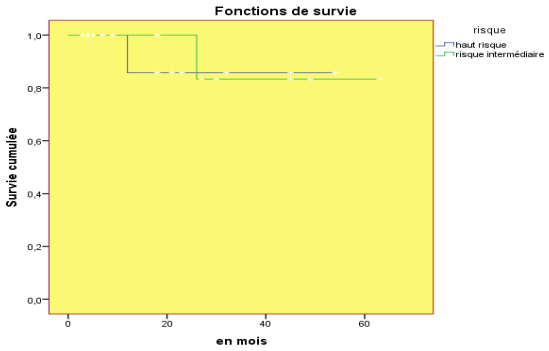

Figure. 2. B: Desease free survival according risk. Groups.

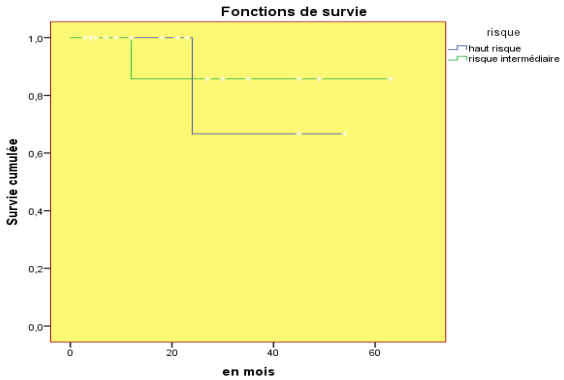

Figure. 2. C: Metastases free Survival accoring risk groups.

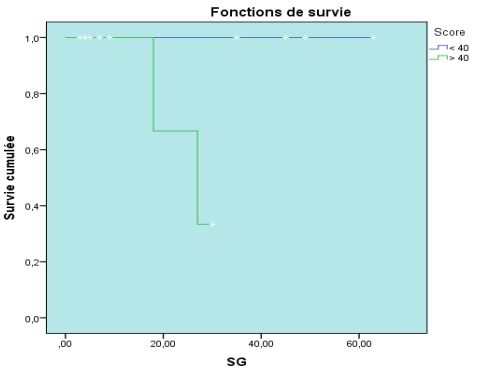

Figure. 3A: Overall survival according GOG score.

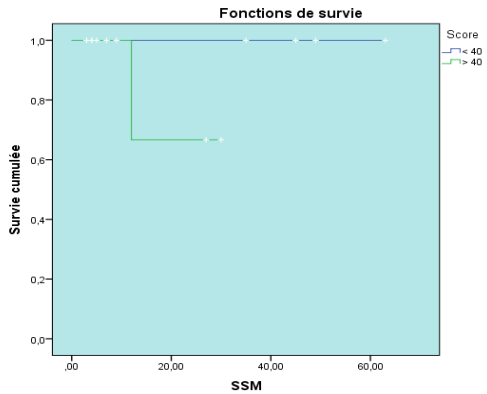

Figure. 3B: metastases free Survival according GOG score.

A tumor size less than 2 cm was not correlated with better overall survival, recurrence or metastasis. The study of the degree of stromal invasion showed that overall survival, recurrence free survival and metasases free survival were better if this latter did not exceed upper third (SG 5 years: 100% VS 33 , 3% p = 0.07, 5% SSR: 100% VS 75% p = 0.48, SSM at 5 years: 100% VS 66.7% p = 0.248).

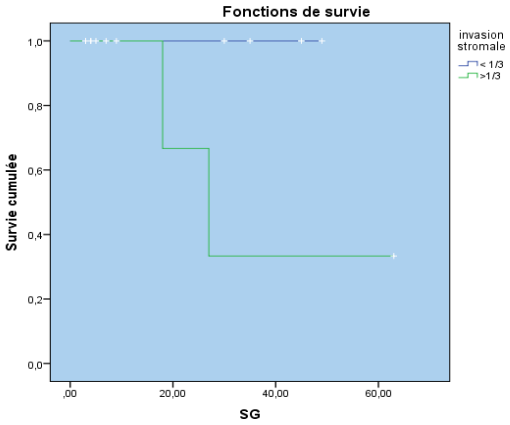

Figure. 4A: Overall surrvival according stromal invasion.

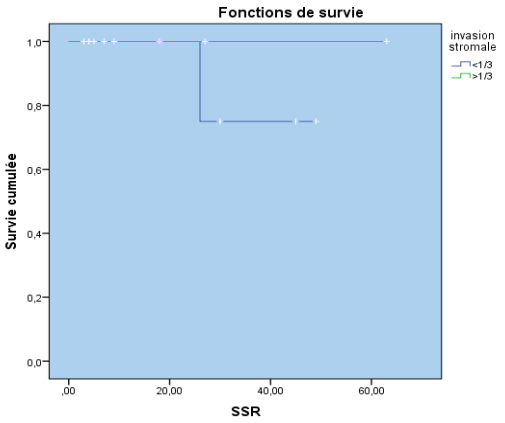

Figure. 4B: Desease free survival according stromal invasion.

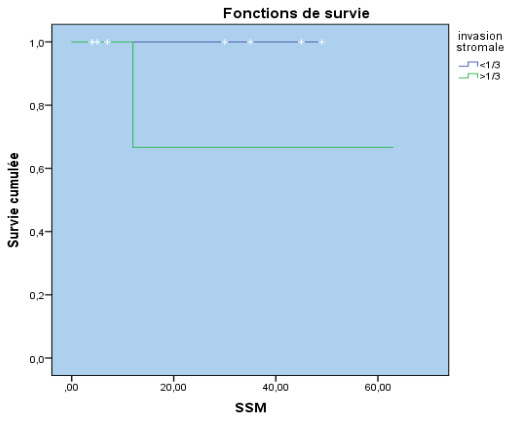

Figure. 4C: Metastases free survival according stromal invasion.

DISCUSSION

The histopronostic factors of loco regional recurrence of cervical cancer stage IB1 (FIGO 2009) are determined from the data of the anatomopathology. They represent the criteria for the indication of an adjuvant treatment. In our series, the tumor size of more than 2 cm did not stand out as a factor of recurrence where as there was a non significant influence of the degree of stromal invasion. This can be explained by the small number of our serie.

In the prospective study of Delgado, which included 732 patients with stage I cervical cancer, the factors that affected disease free survival (SSM) were parametral involvement, positive surgical margins, lymph node involvement, high histological grade, vascular or lymphatic invasion, tumor size greater than 3 cm and degree of stromal invasion.

Several studies have investigated the prognosis value of stromal invasion. Delgado showed that SSM was correlated to the degree of invasion in millimeters and that from a superficial third to a deep third, there was a loss of 11.5% of SSM at 3 years. Shimada study of nearly one hundred early-stage cervical cancer patients excluded this factor from the indication of adjuvant radiotherapy. It was demonstrated, only in univariate analysis, that patients with deep stromal invasion had a worse prognosis than those without deep invasion of the stroma (survival rate at 5 years, 69.8% VS 98.0%). Stromal invasion is more likely to be a predictor of lymph nodes involvement and parametrial extension.

In the US retrospective study of Ruldge, a comparison between stages IB1 and IB2 showed that parametrial involvement and stromal invasion> 2/3 were significantly more frequent in tumor sIB2 which would indicate more frequently, adjuvant radiotherapy.

While neither tumor size nor lymph nodes involvement were independent factors of progression free survival.

Factors classifying the tumor at high risk of recurrence, which are the presence of a parametrical extension, a tumor surgical margin or a nodal involvement, indicate an adjuvant treatment based on radiotherapy (Marrow 1980, Kinney 1989). The addition of concomitant chemotherapy provides better overall survival and better disease free survival, according to the Peters trial in 2000 and the Rosa meta-analysis in 2009.

The other histo pronostic factors, especially the degree of stromal invasion, vascular invasion and tumor size are not independent factors of recurrence. The interpretation should be awerned with a cumulative risk estimation by associating them.

A score was established in this direction, it is the GOG score elaborated from the Delgado study (Figure 5). This score is obtained by multiplying the relative risks of recurrence of each factor.

Table 1
Delgado's prognostic risk scoring system.

Relative risk of recurrence after radical hysterectomy for cervical cancer	
Variable	Relative risk
Depth of tumor penetration (mm)	
Superficial	
3	1.0
4	3.0
5	7.2
6	14
7	21
8	26
10	21
Middle	
5	20
6	22
7	23
8	25
10	28
12	32
14	36
Deep	
7	28
8	30
10	34
12	37
14	41
16	45
18	49
19	54
Clinical tumor size (cm)	
Occult tumor	1.0
1	1.6
2	1.9
3	2.4
4	2.9
6	4.4
8	6.6
Capillary/lymphatic space involvement	
No	1.0
Yes	1.7

"GOG score" is calculated by multiplying the relative risk for the depth × tumor size × capillary space involvement e.g. 8 mm superficial tumor, measuring 2 cm with LVSI would be 26 × 1.9 × 1.7 = 84.

Figure. 5: GOG Score Parameters.

Several studies have been interested in testing the application of the GOG score, such as the Richard study conducted in 2011 which included 126 patients with IB-IIA FIGO, treated with CHL without lymph nodes involvement.

A score of less than 40 did not indicate adjuvant radiotherapy, between 40 and 120 small pelvic radiotherapy (FIGURE 6A) and a score greater than 120 indicated a large pelvic type radiotherapy (FIGURE 6B). The doses used are 45 to 50.4 Gy in external radiotherapy followed by brachy therapy HDD 10 Gy in 2 fractions.

In our series, all the patients with intermediate group were irradiated, although the score was only 40 in 70% of the cases; no patient had a score greater than 120. Large pelvic irradiation were delivered for 60% of the patients.

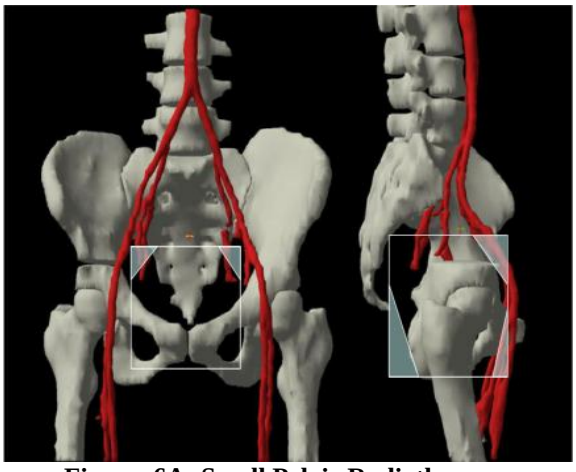

Figure. 6A: Small Pelvic Radiotherapy.

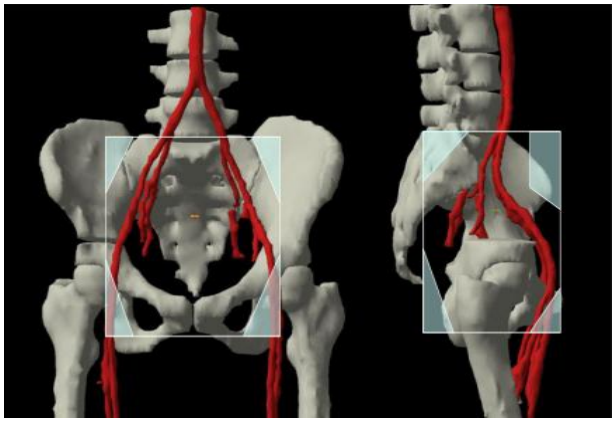

Figure. 6B: large pelvic radiotherapy.

The GOG92 study, updated in 2006, included patients with stage IB FIGO with negative lymph node dissection and at least 2 risk factors among vascular or lymphatic invasion, deep stromal invasion and tumor size greater than 4 cm. Then, they were randomized in 2 arms, radiotherapy or surveillance. The radiotherapy arm provides a statistically significant reduction in the risk of recurrence ([RR] 0.54, 90% confidence interval [CI] 0.35 to 0.81, p = 0.007) and progression-free survival (HR 0.58, 90% IC 0.40 to 0.85, p 0.009).

On the other hand, in 1982, Bilelek was unable to demonstrate a benefic effect of post operative radio therapy after radical hysterectomy and pelvic lymphadenectomy for tumors classified as pT1bNoMo (TNM).

The combination of the results of these two trials, in a meta-analysis of the Cochrane group, found a non-significant difference in the risk of death at 5 years between arms radiotherapy versus monitoring (RR 0.8, 95% CI of 0, 3 to 2.4). Contrasting with, irradiated patients had a significantly lower risk of disease progression (HR 0.6, 95% CI 0.4 to 0.9) without any increase in toxicity. The combination of chemotherapy for this group of patients is currently being tested in GOG 263. It is phase III trial with inclusion criteria that associates stages I-IIA with at least 2 factors of the three. Patients are randomized to 2 arms: the control arm for radiotherapy alone and the test arm represented the concomitant radio chemotherapy type cisplatin weekly.

CONCLUSION

These studies have been carried out with a view to reduce the indications for post-operative radiotherapy. The rigorous application of the GOG score may also limit the use of adjuvant therapy, as well as the optimization of target volume of radiotherapy. This reduction was imposed by concern for toxicity. However, current advances in radiotherapy, and mostly the use of conformational radiotherapy with modulation of intensity, could be an alternative allowing us to keep our indications and to deliver 54 Gy in post-operative position at the level of the pelvis while keeping an acceptable level of toxicity (Barillot 2009).