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Tumor Response after the First Serie of Treatment for Locally Advanced Cervical Cancer: A Retrospective Study (750 Cases)

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Abstract:

- ***Introduction:***

Tumor response after the first series of treatment is a predictive factor for outcomes in cervical cancer. There is a correlation between early tumor regression and the probability of loco-regional control.

This study aims to assess the tumor response following concurrent radio-chemotherapy in the treatment of locally advanced cervical cancer.

- ***Materials and Methods:***

This retrospective study includes 750 patients with locally advanced cervical cancer (started from IB) treated with concurrent radio-chemotherapy (46 Gy with weekly cisplatin) between January 1, 2018, and December 2022, at the National Oncology Institute in Rabat.

- ***Results:***

The patients' ages ranged from 22 to 85 years, with a median age of 50.67 years. The predominant histological type was squamous cell carcinoma (83%), followed by adenocarcinoma (16%). All patients received concurrent radio-chemotherapy with a dose of 46 Gy (2 Gy per fraction in 23 sessions), along with weekly cisplatin at 40 mg/m².

Tumor response after RCC was evaluated using clinical examination and\or pelvic MRI at the end of the treatment. In this study, 610 patients (81.33%) showed near-complete or complete tumor regression based and subsequently underwent intracavitary brachytherapy. Conversely, 140 patients (18.66%) presented significant residual tumors on pelvic MRI, rendering them ineligible for brachytherapy. These patients received additional irradiation using 3D conformal techniques, delivering a dose of 66–70 Gy in normo-fractionated sessions, combined with weekly cisplatin.

- ***Conclusion:***

Tumor response after the initial series of concurrent radio-chemotherapy serves as a key prognostic factor for locally advanced cervical cancer. Patients with significant tumor regression demonstrate favorable outcomes with brachytherapy, while alternative radiation techniques are required for those with residual tumors.

Keywords: *Brachytherapy, Cervical Cancer, Concurrent Radio-Chemotherapy.*

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I. INTRODUCTION

In Morocco, cervical cancer represents a major public health issue among women, ranking second after breast cancer. This type of cancer progresses slowly and is generally asymptomatic.

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Cervical cancer is typically an infectious disease with a progressive development. It has been established that Human Papillomavirus (HPV) plays a crucial role in its onset [1].

Squamous cell carcinomas present approximately 80% of cervical cancers, while adenocarcinomas account for 20% with less favorable prognosis [2]

The treatment of cervical cancer is multimodal and depends on the stage of the disease, including surgery, external radiotherapy, brachytherapy, and chemotherapy. Concomitant chemoradiotherapy, with or without brachytherapy, has become the standard treatment for locally advanced cervical cancer [3,4].

Tumor response after the first series of treatments (complete clinical response or CCR) is a predictive factor for outcomes in cervical cancer. There is a correlation between early tumor regression and the likelihood of locoregional control.

The objective of our study is to evaluate tumor response following the first series of concomitant chemoradiotherapy in the treatment of locally advanced cervical cancer at the Radiotherapy Department of the National Institute of Oncology in Rabat.

II. MATERIALS AND METHODS

This is a descriptive retrospective study including 750 patients with locally advanced cervical cancer (from stage IA) who received concomitant chemoradiotherapy from January 2018, to December 2022 at the National Institute of Oncology in Rabat.

All patients underwent a complete clinical examination at the initial consultation before treatment, including a gynecological examination (vaginal examination and speculum) with rectal examination, and palpation of the inguinal and supraclavicular lymph nodes.

- *Exclusion Criteria were:*

- Patients receiving primary surgery,
- Exclusive radiotherapy,
- Patients with metastases, and patients lost to follow-up during treatment.

- *The Parameters Studied were:*

Epidemiological, clinical, paraclinical characteristics, and therapeutic outcomes at the end of irradiation.

The evaluation was performed by gynecological examination and/or pelvic MRI at the end of the concomitant chemoradiotherapy.

- *External Radiotherapy:*

All patients were treated with three-dimensional conformal radiotherapy. During the dosimetric CT scan in the treatment position, they were lying on their backs with their hands placed on the chest, with foot and knee supports. The bladder was kept half full to protect the bladder and intestin, while the rectum was kept empty.

The gross tumor volume (GTV) is defined as the tumor of the cervix and its macroscopic and radiological extensions, including any pelvic lymph node with a diameter greater than 0.8 cm. The clinical target volume (CTV) includes the GTV, the entire cervix, the uterus, the adnexa, surrounding tissues, and the vagina, depending on the extent of the tumor.

The nodal CTV includes lymph nodes located in the internal iliac, external iliac, obturator, and presacral regions. The common iliac nodes are included in locally advanced stages or in case of positive adenopathy in the internal or external iliac regions. The paraaortic regions are targeted in the case of adenopathy in their level.

The planned target volume (PTV) is defined by adding a margin of 0.7 to 1 cm around the CTV. The organs at risk (OARs) include the intestine, rectum, bladder, and femoral heads.

Radiotherapy was delivered to a dose of 46 Gy at the ICRU 50 point on the pelvis, in 23 fractions of 2 Grays per day, five days a week, using photons from a high-energy linear accelerator (18 MV).

- *Chemotherapy:*

The chemotherapy protocol consists of the administration of cisplatin at a dose of 40 mg/m² per week (with a maximum of 70 mg per week) according to a weekly schedule throughout the course of external radiotherapy. Before each chemotherapy session, a complete blood count and renal function test were performed.

If the neutrophil count less than 1000/mm³, the platelet less than 100,000/mm³, the creatinine clearance was less than 60 ml/min, or in cases of anemia with Hb < 8 g/dl, chemotherapy was suspended until these abnormalities were corrected.

III. RESULTS

Our study included 750 patients, with an age range of 22 to 85 years and a median age of 50.67 years. The average consultation delay was 4 months (ranging from 1 to 18 months).

The clinical presentation consisted of metrorrhagia in 79.54% of cases, leukorrhea in 15.90%, and pelvic pain in 4.56% of cases. (Figure 1).

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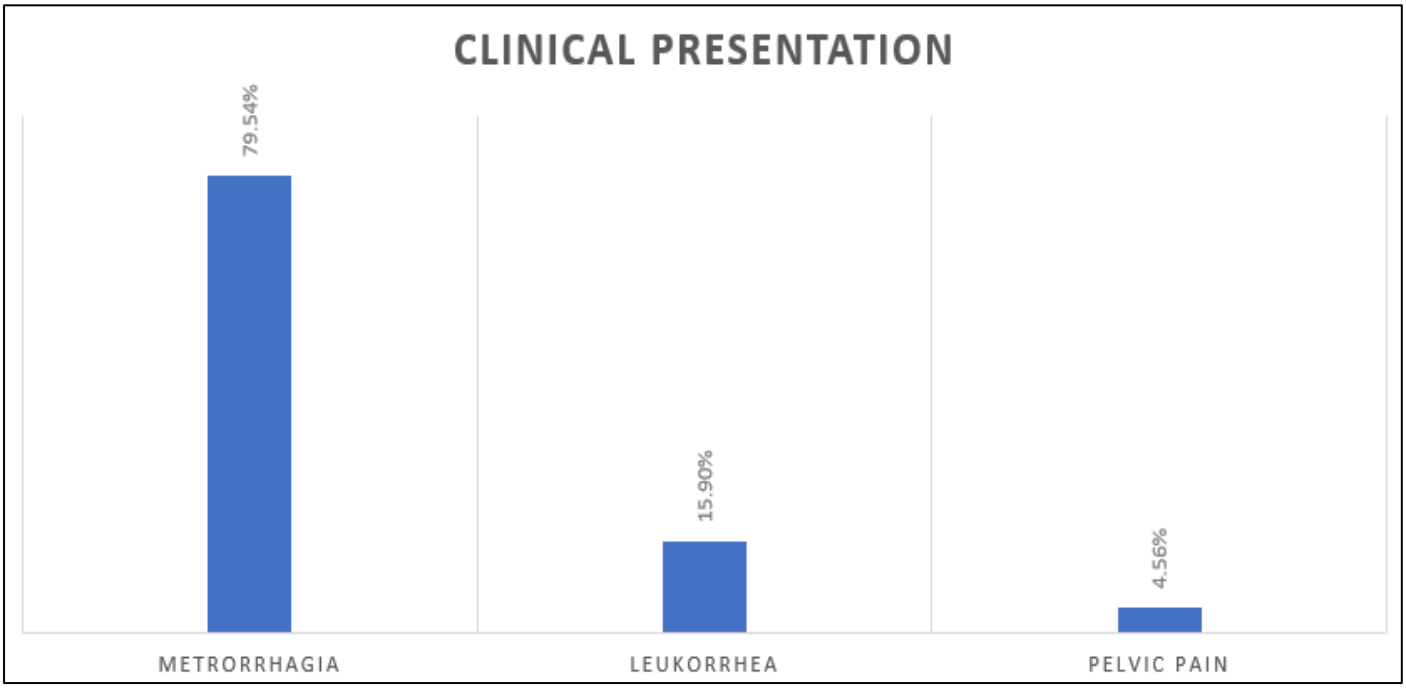

Fig 1 Clinical Presentation

The predominant histological type was squamous cell carcinoma, accounting for 83% of cases, followed by adenocarcinoma in 16%.

At the initial clinical examination, the mean tumor size was 4 cm (ranging from 1 to 8 cm). Vaginal involvement was limited to the upper third in 209 patients (27.86%), extended to the middle third in 430 patients (57.33%), and reached the lower third in 56 patients (7.46%). No vaginal involvement was observed in 80 patients (10.66%). Parametrial involvement was bilateral in 46.81% of patients, unilateral in 38.40%, and absent in 14.77%.

The staging assessment evaluated both locoregional and distant tumor spread, primarily based on pelvic MRI and thoracoabdominal CT. In our study, pelvic MRI was performed in 96% of patients, with tumor staging classified according to the 2018 FIGO system (Figure 2).

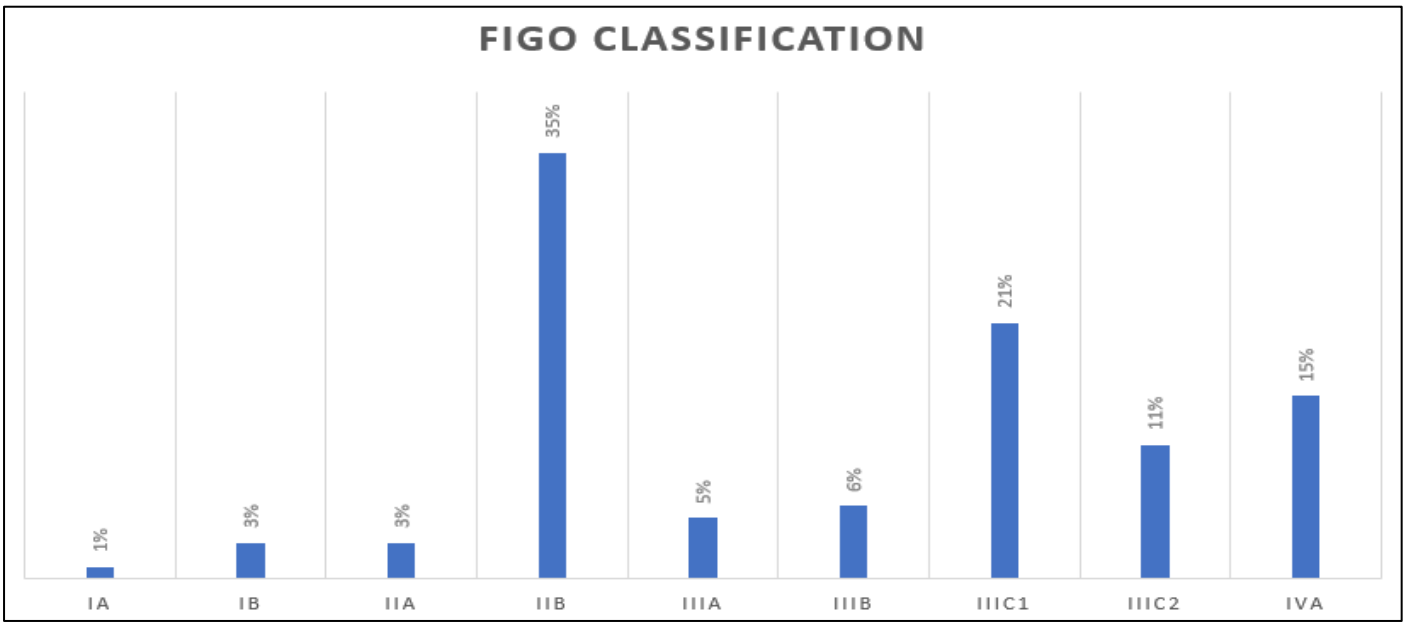

Fig 2 FIGO Classification

All patients received 3D conformal radiotherapy at a total dose of 46 Gy, delivered in 2 Gy fractions, 5 days per week over 5 weeks. This was combined with concomitant chemotherapy based on cisplatin at a weekly dose of 40 mg/m², not exceeding a cumulative dose of 70 mg/m².

Tumor response was assessed at the end of the first treatment cycle, either through clinical examination in 481 patients (64.13%) and/or pelvic MRI in 269 patients (35.86%). (Table 1)

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Table 1 Tumor Response after First Treatment

Tumor Response	Number (n)	Percentage (%)
Complete response (100%)	150	20.00
Partial response (70–90%)	420	56.00
Partial response (50–65%)	40	5.33
Response < 50%	97	12.93
No response	43	5.73

During concomitant chemoradiotherapy, acute toxicity was observed in 20.27% of cases, primarily gastrointestinal and hematologic toxicities. (Figure 3).

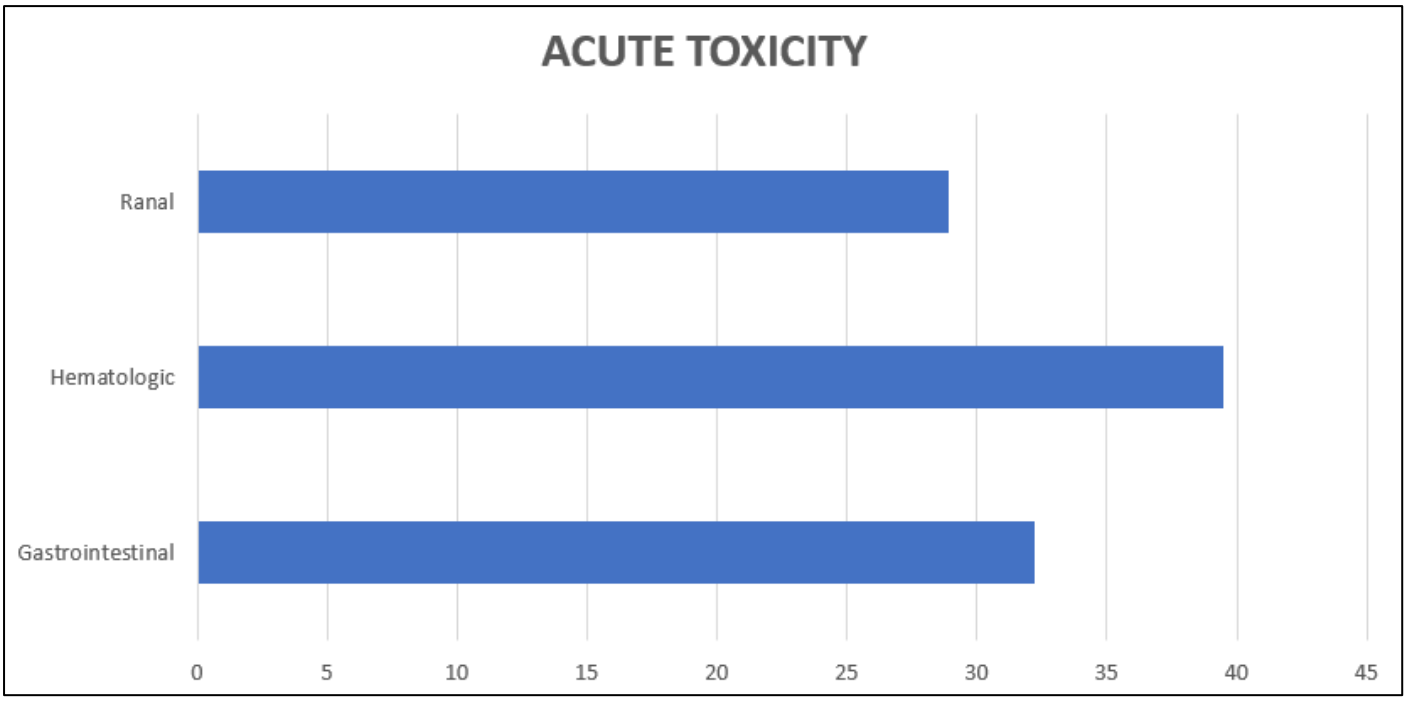

Fig 3 Acute Toxicity

IV. DISCUSSION

In Morocco, cervical cancer is the second most common cancer among women. The average age of onset is 55 years [5], whereas in our study, the mean age was 50.67 years.

The typical clinical presentation includes spontaneous metrorrhagia, along with other symptoms such as abdominopelvic pain, leukorrhea, cystitis, hematuria, pollakiuria, and pyelocaliceal dilatation, which may indicate an advanced pelvic disease [6]. In our study, 79.54% of patients presented with metrorrhagia, 15.90% with leukorrhea, and 4.56% with pelvic pain.

According to the literature, squamous cell carcinoma is the most common histological type, accounting for approximately 80% of cases, while adenocarcinomas represent about 15% [7]. In our cohort, squamous cell carcinoma was found in 83% of cases, whereas adenocarcinoma accounted for 16%.

Locoregional staging primarily relies on pelvic magnetic resonance imaging (MRI) [8,9], which is used to assess tumor volume and its extent (including parametrial, isthmic, uterine, pelvic wall, bladder, and rectal involvement). However, MRI does not replace gynecological examination in this assessment. In our study, pelvic MRI was performed in 96% of cases.

Concomitant chemoradiotherapy (CCRT) is the standard treatment for locally advanced cervical cancer. The addition of chemotherapy to radiotherapy has been shown to significantly improve overall survival and progression-free survival compared to radiotherapy alone [10,11,12]. The first review of clinical trials, published by Green et al. in 2001 [13], analyzed 19 trials including 4,580 patients and was updated in 2005 [14,15] to include five additional studies, totaling 4,921 patients. It demonstrated that concurrent chemotherapy increased the likelihood of overall survival by 12% and progression-free survival by 16%, while significantly reducing the risk of distant metastases.

Cisplatin is the most effective cytotoxic agent in this setting. When administered concurrently with radiotherapy, it enhances tumor radiosensitivity by inhibiting DNA synthesis, preventing DNA damage repair caused by radiation, and increasing the sensitivity of hypoxic cells, thereby promoting cell death [16].

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In our study, all patients received 3D conformal radiotherapy at a total dose of 46 Gy, delivered in 2 Gy fractions, five days per week over five weeks. The entire pelvic region was treated using a four-field technique (anteroposterior and opposed lateral fields), which offers the advantage of sparing portions of the small intestine and bladder anteriorly, as well as the rectum posteriorly, while ensuring optimal tumor coverage. Dosimetric CT-based planning further optimized this technique by precisely localizing the tumor and its relationships with surrounding normal structures [17,18].

Radiotherapy was combined with concurrent cisplatin-based chemotherapy at a dose of 40 mg/m² per week, not exceeding a cumulative dose of 70 mg/m², starting from the first day of radiotherapy. Chemotherapy was well tolerated in 79.73% of patients. However, 20.27% experienced acute gastrointestinal and hematologic toxicities, necessitating hospitalization and treatment discontinuation in 13.06% of cases.

Early tumor response after the first cycle of treatment has been identified as an important prognostic factor [19]. Patients achieving a complete response at the end of the first treatment cycle had a 3-year overall survival rate of 95%, compared to 65% for those who achieved complete response only three months after treatment completion [20].

Similarly, Grossman et al. [21] confirmed the findings of Marcial et al., reporting poorer outcomes in patients with inadequate tumor response within the first 4 to 8 weeks of radiotherapy. Several studies [22,23] have shown that tumor regression at the end of CCRT is a strong predictor of disease progression, compared to tumor regression assessed after brachytherapy [24].

In our study, tumor response was evaluated after the first treatment cycle through clinical examination in 481 patients (64.13%) and/or pelvic MRI in 269 patients (35.86%). Among them, 150 patients (20%) achieved a complete response, while 420 patients (56%) showed a tumor reduction between 70% and 90%. Additionally, 40 patients (5.33%) had a response between 50% and 65%, whereas 97 patients (12.97%) had a response below 50%. In contrast, 43 patients (5.73%) exhibited stable disease.

Among the 18.66% of patients with a response below 50% or stable disease, 95 patients were at stage IVa, with bladder and/or rectal involvement. Furthermore, 45 patients received only one cycle of chemotherapy due to hematologic complications, including anemia in 26.66% of cases and febrile neutropenia in 44.44%. Gastrointestinal toxicity, including vomiting and diarrhea leading to electrolyte imbalances, was observed in 8.88% of cases, while renal toxicity occurred in 26.66% of cases during cisplatin administration.

Our study demonstrated the effectiveness of concurrent chemoradiotherapy, with a favorable tumor response rate of 81.33% after the first treatment cycle.

V. CONCLUSION

Our retrospective study demonstrated the significant effectiveness of concurrent chemoradiotherapy, with a notable tumor response after the first cycle of treatment.

The protocol, combining 3D conformal radiotherapy and cisplatin-based chemotherapy, showed encouraging results, although acute toxicity was observed in 20.27% of patients. These findings highlight the importance of a multidisciplinary and personalized approach to optimize therapeutic outcomes and minimize side effects.

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