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Research Article

Management of Muscle-Invasive Bladder Cancer: Experience of Mohammed VI Cancer Treatment Center

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ABSTRACT

Background: Bladder cancer is the 10th most frequently diagnosed cancer in the world, with approximately 573,000 new diagnoses in 2020. The aim of our study is to detail the clinical-pathological characteristics, the treatments, in particular the benefits of CNA for muscle infiltrating bladder cancer and assess the efficacy and feasibility of concomitant radiochemotherapy as a good alternative to radical cystoprostatectomy in a large Moroccan cohort of 73 cases.

Results: Seventy-three patients were collected from 2015 to 2020 at the Mohammed VI oncology center at the Ibn Rochd University Hospital in Casablanca, Morocco. The median age was 62. The main clinical complaint was haematuria in 92% of cases. Most patients have a tumor classified as T2. Urothelial carcinoma was the exclusive histologic type. Management consisted in particular of radical cystoprostatectomy or concomitant radiochemotherapy preceded by neoadjuvant chemotherapy. The median follow-up was 20 months. The evolution was characterized by no local recurrence. Metastases occurred in 14% of patients treated with cystoprostatectomy and 17% with chemoradiation therapy.

Conclusions: The muscle infiltrating bladder tumor is a chemosensitive disease, the choice between CT and bladder preservation remains difficult to validate in RCP, future research for a better understanding of this disease as well as the selection of responders or not at scale. National or international are necessary to improve the therapeutic behavior and the prognosis of the patients, while waiting Let us continue to respect the standards of care.

Keywords: Bladder cancer; Neoadjuvant; Urothelial carcinoma; Chemoradiotherapy; Radical cystoprostatectomy

INTRODUCTION

Bladder cancer is a public health problem; it is the second urogenital cancer in men after prostate cancer. Urothelial carcinoma is the most predominant histologic type. Bladder tumors present in 30% of cases to the invasive stage of the muscle from the start. The standard treatment for muscle-infiltrating tumors (T_2-T_3-T_4) has been based on radical surgery for several years. However, over 50% of these patients will experience metastatic progression within 2 years of surgery [1]. This is the reason why several studies have evaluated the interest of Neoadjuvant Chemotherapy (NA) in locoregional treatment (cystectomy or radiotherapy), decided in principle for an extirpable tumor, it is considered as a standard since the publication of 4 randomized trials and two meta-analyzes, these studies compared cystectomy after cisplatin-based chemotherapy *versus* cystectomy alone, the results confirm the impact of NA chemotherapy with a gain in 5-year survival of 6.5% in the combined arm.

The objective of our work is to analyze the contribution of neoadjuvant chemotherapy in the treatment of urothelial cancer of the bladder localized and infiltrating the muscle treated by surgery or radiotherapy in the context of bladder preservation through a retrospective study conducted in within the Mohammed VI oncology center at the Ibn Rochd University Hospital.

MATERIALS AND METHODS

This is a retrospective, descriptive study of 73 cases, the main objective of which is to summarize the data on the benefits of neoadjuvant systemic chemotherapy for urothelial bladder cancer before cystectomy or radiochemotherapy. concomitant. This study was conducted within the Mohammed VI oncology center at the Ibn Rochd University Hospital, and included all patients with

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invasive bladder cancer, candidates for neoadjuvant chemotherapy for the period extending from January 2015 to December 2020. eligible patients with histologically confirmed muscle infiltrating bladder tumor on TURBT, with a general condition preserved: PS 0-2, including the following stages T_2-T_4, N_0-3, M_0, for which the decision to neoadjuvant chemotherapy was collegial after a multidisciplinary consultation meeting organized at the level of our structure.

The main exclusion criteria: were patients with an altered general condition due to a comorbidity that could not receive chemotherapy, the presence of distant metastases a histological type other than urothelial carcinoma, 7 patients were excluded and lost to follow-up during CNA. The data were collected from the computerized medical records of the patients allowed the evaluation of the epidemiological, clinical, pathological, and therapeutic characteristics of invasive bladder cancer. A descriptive analysis of the sample is made; the results are presented as a percentage. Data collection was carried out with respect for the anonymity of patients and the confidentiality of their information.

RESULTS

Clinical characteristics

The use of the results of the 73 cases found that 90% of the patients were men, the median age was 62 years (range 42 years-78 years), The notion of smoking was found in 57 patients or 78% of cases, all of which were male. The presence of a risky profession was found in 12%, the main clinical complaint is macroscopic hematuria, found in 92% of cases, and this hematuria was only isolated in 26% present in 67% of cases, they were isolated and revealing in only 11% of cases. The physical examination noted on rectal examination a flexible bladder base in 71% of cases and an indurated bladder base in 29% of cases, paraclinical examination: biology: All our patients underwent a biological examination: It showed anemia in 39% of cases and kidney failure was identified in 23%. Urinary cytology has not been done in our patients.

The initial vesico-renal ultrasound and the uroscanner were done in all our patients (100%) had objectified a bladder thickening in all the patients, an impact on the upper apparatus in 48% of the cases, and an infiltration of the perivesical fatty tissue in 37% of cases and allowed to starify tumors of which: 56% patients had a cT_2 tumor stage, 37% of patients had a CT_3 tumor stage, and 7% patients had a cT_4 tumor stage. Endoscopic examination with early trans urethral resection is the key examination in the diagnosis of bladder tumor, it allowed us to appreciate the macroscopic characters: appearance, location and size. All of our patients underwent a cystoscopy with resection, in all of our patients, cystoscopy found a papillary and budding tumor with the most frequent location being at the lateral wall in 49% of cases. CT chest/abdominal/pelvis which was routinely requested in all patients. Lymph node involvement was found in 40%. No metastasis was objectified (Table 1).

Table 1: Clinico-pathological features.

	Years	Cases	Percentage
Age	40-50	5	7%
	51-60	18	24%
	61-70	37	51%
	71-80	13	18%
Sex	Men	66	90%
	Women	7	10%
Risk factors	Smoking	57	78%
	Professional Exposure	9	12%
	Other*	5	7%
Clinical Complaint	Hematuria	67	92%
	Signs of Bladder Irritation	55	76%
	Lower back pain	10	14%
	Renal colic	0	0%
	Acute urine retention	3	4%
Primary Tumor	CT_2	41	56%
	CT_3	27	37%
	CT_4	5	7%
Lymph node	N_0	44	60%
	N_1	7	10%
	N_2	20	27%
	N_3	2	3%
Histology	Urothelial carcinoma An associated lymph	73	100%
	Lymphovascular	7	10%
	Infiltration	24	33%

*Repeated Urinary tract infection family History of bladder tumor cis: Carcinoma *in situ*

Treatment

Chemotherapy (CMT) at conventional doses 43% of patients received CMT based on a combination of methotrexate, vinblastine, Doxorubicin (Adriamycin) and Cisplatin (H-MVAC) at High Dose (HD) associated with growth Factors, 19% patients benefited from the standard MVAC, 23% patients had received the Gemcitabine-Cisplatin protocol, these patients had a PS_2 that could not support the above protocols, 15% patients had received the Gemcitabine-Carboplatin protocol due to of an IR against indicating the use of cisplatin, The number of cures according to the type of neoadjuvant chemotherapy protocols varied between 2 and 5 cures, Concerning tolerance, hematological toxicity was the most frequent, in particular neutropenia which was observed in 36% of cases, 55% of patients presented a complete radiological response after neoadjuvant chemotherapy. 19% underwent total radical cystoprostatectomy after CNA with bilateral ilio-obturator, hypogastric and external iliac lymph node dissection. The average time between radical cystectomy and neoadjuvant chemotherapy in our patients was 2 months, obviously the procedure is completed by a urinary diversion; Transilean cutaneous ureterostomy (Bricker) was performed in 57%, a bilateral cutaneous ureterostomy

was performed in 43% and no patient had replacement enterocystoplasty, a complete histological response in 21% of cases, and 60% of patients received concomitant radiochemotherapy including; 73% patients who refused surgery and 11% patients were gg progression after CNA and 5% of patients had altered PS and considered inoperable, 11% had a still unresectable tumor, the combination used was Paclitaxel-CDDP in the majority of cases in 84% concerning the radiotherapy protocol,all our patients were treated by three-dimensional conformational radiotherapy at a dose of 46Gy on the bladder and lymph node areas followed by a complement of d up to 66Gy over the entire bladder, with classic 2 Gy/fraction.

For Toxicity related to radiotherapy: the most frequent toxicity was radiodermatitis which was observed in 18% of patients followed by cystitis found in 11% of cases adjuvant RTH was performed in 5 patients.

A complete radiological response in 68% of cases. The evolution was favourable in the majority of cases. For the rest of the patients 3% are declared HDR after the CNA, 7% received palliative care (palliative CHT or palliative RTH), 7% refused any treatment after the CNA. 4% are lost to follow-up after being referred for surgery (Table 2).

Table 2: Most common adverse events during the overall treatment period (neoadjuvant chemotherapy and chemoradiotherapy).

Any adverse event	Neoadjuvant chemotherapy: MVASdd (n: 31), MVAC (n:14), Gemcitabin Cisplastin (n:17), Gemcitabin Carboplastin (n:11)	Chemoradio-therapy: paclitaxel-Cisplastin (n:38) paclitaxel-Carboplastin (n:8)
Neutropenia	27 (36%)	6 (11%)
Anemie	23 (30%)	11 (23%)
Thrombopenia	13 (18%)	1 (2%)
Asthenia and fatigue	14 (19%)	6 (14%)
Nausea, Vomiting	13 (18%)	5 (11%)
cystitis	12 (15%)	5 (11%)
Acute renal insufficiency	5 (6%)	-
Stonatitis	3 (4%)	-
Diarrhoea	-	4 (9%)
Radiodermatitis	-	8 (18%)
Death	0	0

Post-treatment follow up has been characterized by: distant metastasis was observed in 18% No local recurrence was observed in the patients. The follow-up was 9 months to 72 months with an average of 20 months for the patients in our series and the evolution was marked by 73% of the patients are still alive including 64% in maintained complete remission and 9% lived with a metastasis remotely 18% were lost to follow-up. The death of 4 patients or 9% of cases (cause of death linked to their disease) (Table 3).

Table 3: Evolution of patients according to the treatment received.

	-	Radial Crytoprostatectomy	Chemoradiotherapy
Living	Completed remission	71%	64%
	With metastatis	7%	9%
Death	-	7%	9%
Distant metastatis	-	14%	18%
Lost to follow-up	-	14%	18%

DISCUSSION

The Muscle-infiltrating bladder cancer is relatively common, including a rate of 30% to 35% of bladder cancer patients, first appearing with already T_2 cancer. It is an aggressive malignant disease with a high rate of early spread and the prognosis of these patients is highly dependent on possible lymph node metastases and the local pathological stage of the disease. This justifies the use of complementary treatments, in this case neoadjuvant selection, in order to eliminate the micrometastatic disease.

Before the 1980s, a percentage of 50%-57% is the overall 5-year survival rate obtained with radical cystectomy [2], considered at the time to be the only chance of a cure in order to improve the results of this survival of pioneering work. Data from prospective randomized trials and meta-analyzes have shown that administration of neoadjuvant chemotherapy leads to a significant improvement in Overall Survival (OS) at 5 years, and they support the preoperative application of platinum-based chemotherapy in all patients. We will follow the chronological order of the studies and metanalyses: the first 1999 EORTC/MRC study a study conducted with 976 patients in 106 institutes in 20 countries with T_2 T_3 T_4a No, Mo stages, who received either Cisplatin, Methotrexate and Vinblastine (CMV), i.e. no chemotherapy before radical cystectomy or radiotherapy, shows an improvement in 5-year survival of 6% in favor of CNA, a subsequent update of the data confirmed the benefit of CNA with a 10-year survival improvement of 30% to 36% [3,4]. The second SWOG 8710 phase 3 study, the inclusion of 126 centers was slow and carried out over 11 years, using the MVAC protocol then cystectomy versus cystectomy alone, already at five years, 57% of patients in the CNA group were alive, against 43% of those in the cystectomy group, the risk of death was reduced by 33%, in the M-VAC group who underwent cystectomy, 38% of the surgical samples were pathologically cancer-free (pT_0) at the time of surgery [5]. It is true that we always find this MA the ABC (Advanced Bladder Cancer) which was published now several years ago but nevertheless it is the reference with a great potential of 3005 patients having benefited from the CNA plus a local treatment versus the same local treatment alone in invasive bladder cancer, They noted an absolute overall survival benefit of 5% and a 14% reduction in the risk of death in patients who received combination chemotherapy based on platinum [6]. Preservation of the bladder is a reasonable alternative to cystectomy for well-selected patients: unifocal tumor, maximum T_2 stage, absence of CIS, absence of hydronephrosis, complete resection possible, in

the absence of major functional impairment of the bladder , in a well-informed and compliant patient (rigorous follow-up) [7,8]

In another MA Fahmy, et al. involving 30,293 patients and comparing Trimodal Treatment (TMT) and Radical Cystectomy (CR) with or without neoadjuvant chemotherapy alone, concluded that La at OS at 5 years was significantly higher in patients treated with ANC and OS and Disease Free Survival (DFS) were comparable between TMT and CR [9].

Neoadjuvant chemotherapy is not recommended routinely in well-selected patients, but can be offered on a case-by-case basis and under the same modalities as before local treatment by surgery [10].

As well as ANC followed by concomitant radiochemotherapy is an option to surgery offering the possibility of organ conservation while maintaining the same survival rates Appropriate use of this treatment regimen in carefully selected patients may omit the need for morbid surgery, in our study 68% of patients were in complete remission after concomitant radiochemotherapy, this result is consistent with the literature where the CR rate after end of treatment evaluation ranges from 62% to 80% [11,12].

Ding, et al's meta-analysis showed that TMT was associated with better sexual function and better body image perception compared to CR, TMT had better overall quality of life compared to CR and higher physical, social, emotional and cognitive functioning TMT was associated with better bowel function and fewer bowel symptoms [13].

On the other hand a lot of questions which have been asked as being CNA disadvantages: chemotherapy delays surgery? it increases perioperative morbidities? The answer to the first question Bruins et al demonstrated in their article that non-responders were the same poor responders to surgery [13], for the 2nd question Johnson et al found that exposure to Neoadjuvant chemotherapy is not associated with an increased risk of postoperative morbidity and mortality [14].

Regarding the timing of the surgery dice the anathamopathologic results are in favor of a muscle invasive bladder cancer and if a CTN is to decide must be instituted quickly as soon as possible and not more than 8 weeks to avoid the upstaging which is to be respected in our series [15].

Therefore, neoadjuvant chemotherapy should be considered a safe approach in patients with muscle-infiltrating bladder cancer. Thus, because of their apparent efficacy in some patients and their relatively well tolerated toxicity profile, international guidelines recommend the use of neoadjuvant cisplatin-based chemotherapy in T2a-T4a bladder cancer if the patient is in good general condition and no impairment of renal function is detected. Regarding the protocols of neoadjuvant chemotherapy, M-VAC and GC are the two most commonly used regimens for bladder cancer in modern oncology are the same protocols used frequently in our series.

Despite the evidence suggesting that genetic and molecular characteristics may help identify patients who may benefit from neoadjuvant chemotherapy, these data have not yet translated into clinically useful tools. Many efforts have been and continue to be made to identify and validate the biomarkers predictive of the response to neoadjuvant chemotherapy. However, until today, the optimal timing of neoadjuvant therapy and the drugs used in the regimen, as well as their dosage and timing, are still under debate.

CONCLUSION

At the end of this study and on the basis of these studies, it is evident that ANC combined with local treatment is the current standard treatment for muscle-infiltrating urothelial cancers Although CR remains the usual treatment for IMTD, concomitant radiochemotherapy is an option to surgery offering the possibility of organ conservation while maintaining the same survival rates. However, it should be noted, we should adopt multidisciplinary consultation with experts, and also take into account the patient's expectations of treatment and financial situation, which can allow bladder cancer patients to access optimal treatment.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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