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Original article

Quadrimodal Bladder-Preserving Treatment for Nonmetastatic pT2N0–1M0 Muscle-Invasive Urothelial Carcinoma: Experience of a Moroccan Oncology Center and Review of the Literature

Traitement quadri-modal conservateur du carcinome urothélial de vessie infiltrant le muscle pT2 localisé : expérience d'un centre d'oncologie marocain et revue de la littérature

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Résumé

Introduction : Le cancer de la vessie est le onzième cancer le plus fréquent dans le monde et représente un problème croissant de santé publique, notamment en Afrique du Nord. La cystectomie radicale est le traitement de référence des tumeurs infiltrant le muscle, mais les stratégies de préservation vésicale constituent une alternative chez des patients sélectionnés. Méthodes : Nous avons réalisé une étude rétrospective monocentrique au Centre Mohammed VI de Casablanca portant sur 109 patients atteints d'un carcinome urothélial pT2N0–1M0 traités entre janvier 2015 et décembre 2019. Le protocole associait une résection transurétrale maximale de la vessie, une chimiothérapie néoadjuvante par gemcitabine-cisplatine, puis une radiochimiothérapie concomitante. Résultats : L'âge moyen était de 63,15 ans et le suivi moyen de 30,94 mois. À la dernière évaluation, 88 patients (80,7 %) étaient vivants et 21 (19,3 %) étaient décédés. Quinze récidives ont été recensées, dont 13 avec un délai documenté. La présence d'une urétéro-hydronéphrose était associée à une survie globale plus courte (p = 0,006). Les toxicités sévères étaient peu fréquentes et tous les patients ont achevé la radiothérapie. Conclusion : Cette stratégie quadri-modale a donné des résultats encourageants et peut constituer une option de préservation vésicale chez des patients rigoureusement sélectionnés. Des études prospectives comparatives sont nécessaires.

Mots-clés : carcinome urothélial ; vessie ; traitement quadri-modal ; préservation vésicale.

Abstract

Introduction: Bladder cancer is the eleventh most common cancer worldwide and is an increasing public health concern, particularly in North Africa. Radical

cystectomy remains a standard treatment for muscle-invasive disease, but bladder-preserving strategies may be considered in selected patients. Methods: We conducted a retrospective single-center study at the Mohammed VI Center in Casablanca involving 109 patients with pT2N0–1M0 urothelial carcinoma treated between January 2015 and December 2019. Treatment combined maximal transurethral resection of the bladder tumor, neoadjuvant gemcitabine–cisplatin chemotherapy, and subsequent concurrent chemoradiotherapy. Results: Mean age was 63.15 years and mean follow-up was 30.94 months. At last follow-up, 88 patients (80.7%) were alive and 21 (19.3%) had died. Fifteen recurrences were recorded, including 13 with a documented time to recurrence. Ureterohydronephrosis was associated with shorter overall survival ($p = 0.006$). Severe toxicities were uncommon, and all patients completed radiotherapy. Conclusion: This quadrimodal strategy yielded encouraging outcomes and may provide a bladder-preserving option for carefully selected patients. Prospective comparative studies are required.

Keywords: urothelial carcinoma; bladder; quadrimodal treatment; bladder preservation.

Introduction

Bladder cancer is the eleventh most common cancer worldwide, with an increasing incidence in several regions, including North Africa [1,2]. In Morocco, it is the second most frequent urologic cancer and therefore represents an important public health problem [2]. The rising burden of urothelial carcinoma, particularly muscle-invasive bladder cancer (MIBC), highlights the need to optimize treatment strategies [3].

Risk factors include tobacco smoking, occupational exposure to harmful chemicals, and chronic infections such as schistosomiasis, all of which are particularly relevant in African settings [2,4]. A substantial proportion of bladder cancers in Morocco may be attributable to these exposures, supporting the need for targeted prevention [2].

Radical cystectomy remains a standard treatment for localized MIBC [3,5], but it is an invasive procedure that may have major functional and psychological consequences [6–8]. The desire to preserve quality of life has prompted the development of less invasive approaches [8]. Standard trimodality therapy combines maximal transurethral resection of the bladder tumor (TURBT) with concurrent chemoradiotherapy and can provide effective bladder preservation in appropriately selected patients [9,10].

More recently, quadrimodal treatment has attracted interest. In addition to maximal TURBT and concurrent chemoradiotherapy, it incorporates neoadjuvant chemotherapy as a fourth component [3,5]. The objective is to achieve early systemic control, reduce the risk of distant relapse, and improve locoregional response before chemoradiotherapy [11–16].

This study evaluated the effectiveness and tolerability of a quadrimodal strategy in 109 patients with nonmetastatic pT2N0–1M0 MIBC treated at the Mohammed VI Center for Cancer Treatment in Casablanca.

Methodology

Study design

This retrospective, single-center study was conducted at the Mohammed VI Center for Cancer Treatment in Casablanca. It included patients managed between January 2015 and December 2019 for muscle-invasive urothelial carcinoma of the bladder treated with bladder-preserving intent using a quadrimodal strategy.

Study population

Inclusion criteria were age ≥18 years; histologically confirmed urothelial carcinoma invading the detrusor muscle; nonmetastatic pT2N0–1M0 disease according to the 2018 TNM classification; initial TURBT followed by neoadjuvant chemotherapy and concurrent chemoradiotherapy; available pretreatment clinical, laboratory, and imaging assessment; and usable post-treatment follow-up data.

Patients were excluded for any of the following

reasons:

- Metastatic disease at diagnosis (M1);
- Pure or predominant non-urothelial histology, including pure squamous cell carcinoma, adenocarcinoma, or small-cell carcinoma;
- Medical contraindication to cisplatin-based chemotherapy, pelvic radiotherapy, or both;
- Severely impaired performance status or uncontrolled comorbidity precluding the planned protocol;
- Incomplete medical records or insufficient follow-up data for outcome assessment.

A total of 109 patients met these criteria and were included in the analysis.

Definition of quadrimodal treatment

Quadrimodal treatment consisted of four sequential components:

- Maximal TURBT, with removal of all macroscopically visible tumor whenever technically feasible;
- Neoadjuvant cisplatin–gemcitabine chemotherapy;
- External-beam pelvic and bladder radiotherapy;
- Concurrent radiosensitizing chemotherapy during irradiation.

This strategy differs from classic trimodality bladder preservation, which combines maximal TURBT with concurrent chemoradiotherapy without routine neoadjuvant chemotherapy. The neoadjuvant sequence was intended to improve early systemic control and locoregional response.

Transurethral resection of the bladder tumor

All patients underwent initial TURBT for diagnostic and therapeutic purposes. Maximal resection of visible tumor was attempted, and detrusor muscle was included in the specimen to confirm muscle invasion. Pathologic review documented histologic type, tumor grade, carcinoma in situ when available, and muscular invasion. Staging included thoracoabdominopelvic computed tomography and/or pelvic magnetic resonance imaging to exclude metastatic disease.

Neoadjuvant chemotherapy

After TURBT, eligible patients received neoadjuvant gemcitabine and cisplatin. Gemcitabine 1,000 mg/m² was administered intravenously on days 1 and 8. Cisplatin 70 mg/m² was administered intravenously on day 1, or 35 mg/m² on days 1 and 8 when fractionation was required because of renal function or clinical status. Cycles were repeated every 21 days, for a planned total of three cycles. Dose modification, delay, or early discontinuation was determined by the medical oncologist according to clinical tolerance, hematologic and nonhematologic toxicities, renal function, and performance status.

Concurrent chemoradiotherapy

After neoadjuvant chemotherapy and clinical and radiologic reassessment, patients received curative-intent external-beam radiotherapy with concurrent radiosensitizing chemotherapy. Radiotherapy was delivered using intensity-modulated radiotherapy or volumetric-modulated arc therapy with 6–18 MV photons. The initial target volume included the bladder and pelvic nodal regions at risk, with a subsequent boost to the whole bladder or tumor bed according to tumor location and response.

The fractionation schedule was:

- Pelvic irradiation: 45 Gy in 25 fractions of 1.8 Gy, five fractions per week;
- Boost to the bladder or initial tumor volume: 10–20 Gy in 5–10 fractions;
- Total bladder dose: 55–64 Gy in 30–35 fractions.

Dose constraints were applied to the rectum, small bowel, femoral heads, and pelvic bone marrow. Concurrent radiosensitization consisted of weekly cisplatin 40 mg/m², with administrations adapted to hematologic, renal, and clinical tolerance.

Follow-up and outcome measures

After treatment, patients were followed every three months for the first two years and every six months thereafter. Follow-up included clinical examination, assessment of urinary function, cystoscopy with urinary cytology according to local practice, and thoracoabdominopelvic imaging when recurrence was suspected.

The main outcomes were overall survival and recurrence-free survival. Recurrence was defined as

local intravesical, locoregional nodal, or metastatic relapse after treatment completion. Acute and late toxicities were extracted from medical records, chemotherapy reports, and radiotherapy files and graded according to the Common Terminology Criteria for Adverse Events, version 5.0, when sufficient detail was available. Acute toxicity occurred during treatment or within 90 days after radiotherapy; later events were classified as late toxicity.

Data collection and statistical analysis

Data were retrospectively extracted from clinical records, pathology reports, radiotherapy files, and follow-up registers. Collected variables included demographic characteristics, comorbidities, WHO performance status, tumor characteristics, TNM stage, TURBT details, chemotherapy and radiotherapy parameters, treatment response, recurrence, toxicity, and vital status at last follow-up.

Quantitative variables were summarized as mean ± standard deviation or median and range, according to distribution. Qualitative variables were reported as counts and percentages. Categorical associations were examined using the chi-square or Fisher exact test, as appropriate. Overall and recurrence-free survival were estimated by the Kaplan–Meier method and compared using the log-rank test. Statistical significance was set at $p < 0.05$.

Ethical considerations

The study was approved by the ethics committee of the Mohammed VI Center for Cancer Treatment in Casablanca. Because of the retrospective design, the requirement for individual informed consent was waived in accordance with the procedure applied by the committee. Data were anonymized before analysis.

Results

A total of 109 patients were included. Descriptive characteristics are presented in Table I.

Table I. Descriptive patient and clinical characteristics

Variable	N	Minimum	Maximum	Mean	SD
Age (years)	109	40	92	63.15	9.617
Smoking exposure (pack-years)	77	7	120	32.95	15.552
Time from treatment completion to cystoscopy (months)	109	2	6	4.27	0.929
Time to recurrence (months)	13	4	12	7.00	2.944
Follow-up (months)	109	4	60	30.94	13.747

Table II. Distribution of patients by occupation

Occupation	Frequency	Percentage
Farmer	20	18.3%
Manual worker	14	12.8%
Merchant	10	9.2%
Homemaker	8	7.3%
Other occupations	13	11.9%
Not specified	44	40.4%
Total	109	100%

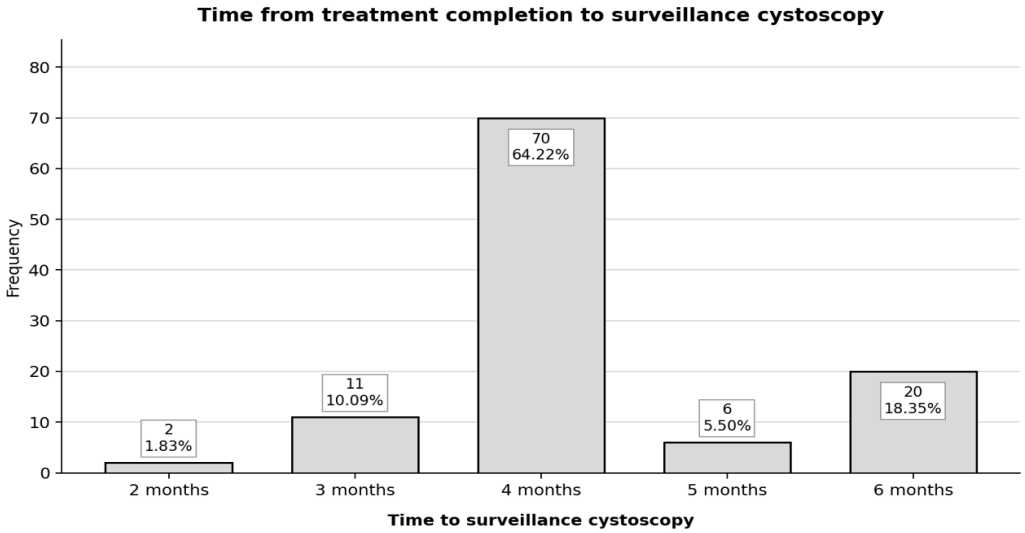

Figure 1. Distribution of patients according to the interval between treatment completion and surveillance cystoscopy.

Table III. Summary of demographic and clinical characteristics

Category	Variable	Frequency	Percentage
Age group	≤55 years	26	23.9%
	>55 years	83	76.1%
Sex	Male	100	91.7%
	Female	9	8.3%
Smoking status	Yes	75	68.8%
	No	34	31.2%
Smoking exposure	<40 pack-years	50	45.9%
	≥40 pack-years	27	24.8%
	Nonsmokers	32	29.4%
WHO performance status	0	66	60.6%
	1	43	39.4%
Ureterohydronephrosis	Present	37	33.9%
	Absent	72	66.1%
Type of ureterohydronephrosis	Unilateral	30	27.5%
	Bilateral	7	6.4%
	Absent	72	66.1%
Severity	Severe	24	22.0%
	Moderate	13	11.9%
Urinary diversion	Nephrostomy	25	22.9%
	Double-J stent	12	11.0%
	No ureterohydronephrosis	72	66.1%
Histologic grade	Grade 2	14	12.8%
	Grade 3	95	87.2%
Recurrence	Local	3	2.8%
	Metastatic	12	11.0%
	No recurrence	94	86.2%

The source dataset reports 75 current/former smokers by smoking status but 77 patients with a recorded pack-year exposure; this discrepancy could not be resolved without the individual-level database.

At last follow-up, 21 patients (19.3%) had died and 88 (80.7%) were alive.

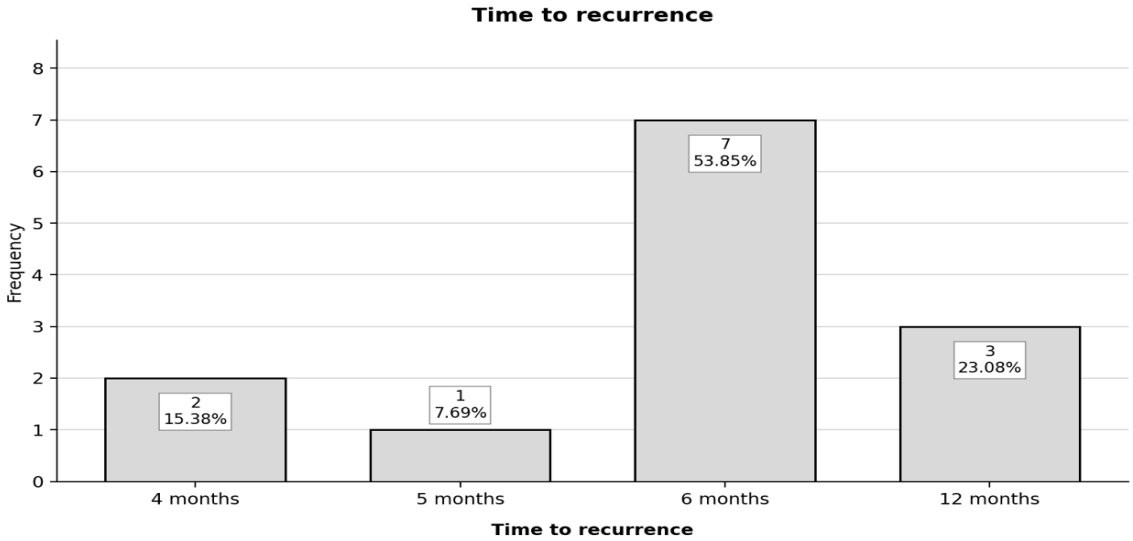

Figure 2. Distribution of the 13 patients with a documented time to recurrence.

Table IV. Univariate analysis of prognostic factors for overall survival

Factor	Category	Total N	Deaths	Censored (%)	Mean survival (months)	p value
Age	≤55 years	26	7	73.1	51.945	0.985
	>55 years	83	14	83.1	51.792	
Sex	Male	100	20	80.0	51.113	0.533
	Female	9	1	88.9	54.000	
Smoking	Yes	75	16	78.7	50.940	0.595
	No	34	5	85.3	51.917	
Pack-years	<40	50	11	78.0	50.118	0.930
	≥40	27	6	77.8	51.440	
WHO PS	0	66	14	78.8	50.585	0.459
	1	43	7	83.7	53.012	
Ureterohydronephrosis	Present	37	12	67.6	43.838	0.006
	Absent	72	9	87.5	54.715	
Severity	Severe	24	9	62.5	40.794	0.214
	Moderate	13	3	76.9	44.308	
Recurrence type	Local	3	1	66.7	48.000	0.212
	Metastatic	12	5	58.3	38.400	

PS = performance status.

Smoking-status counts in this survival table are reproduced from the source analysis; the descriptive smoking-exposure counts are shown in Tables I and III.

Treatment tolerance and toxicity

During neoadjuvant chemotherapy, the main hematologic toxicities were anemia in 11/109 patients (10.1%), neutropenia in 19/109 (17.4%), and thrombocytopenia in 10/109 (9.2%). Grade ≥3 hematologic toxicity occurred in 9/109 patients (8.2%): neutropenia in five, thrombocytopenia in two, and anemia in two. No dose

reduction or permanent chemotherapy discontinuation was required, but all patients with grade 3 toxicity had a one-week cycle delay.

During concurrent chemoradiotherapy, acute grade 1–2 gastrointestinal toxicity occurred in 3/109 patients (2.7%) and grade ≥3 toxicity in 1/109 (0.9%). Acute genitourinary toxicity occurred at grade 1–2 in 5/109 patients (4.6%) and at grade ≥3 in 1/109 (0.9%). Temporary interruption of radiotherapy or concurrent chemotherapy was required in one patient (0.9%). All patients completed the prescribed radiotherapy course.

Late genitourinary toxicity was documented in 5/109 patients (4.6%), and late gastrointestinal toxicity in 1/109 (0.9%). Detailed manifestations were not consistently recorded in the source files. No treatment-related death (grade 5 toxicity) occurred.

Discussion

Epidemiologic profile

MIBC is an aggressive disease with substantial risks of progression and recurrence. Management must balance oncologic control with preservation of urinary function. Radical cystectomy remains a reference option, but its morbidity and functional impact support the evaluation of bladder-preserving strategies in selected patients [17].

The mean age in our cohort was 63 years, and most patients were older than 55 years, consistent with the usual epidemiology of MIBC. Smoking exposure was frequent, confirming its major role in urothelial carcinogenesis [18]. The large proportion of patients with WHO performance status 0 reflects selection of patients with nonmetastatic disease who were considered fit for cisplatin-based chemotherapy and chemoradiotherapy. Ureterohydronephrosis was present in approximately one-third of patients and is clinically relevant because it may reflect more extensive local disease, impair renal function, and limit treatment options [19–21].

Oncologic outcomes

At last follow-up, 80.7% of patients were alive. This favorable crude vital-status proportion suggests that the quadrimodal strategy was feasible in a carefully selected population and allowed preservation of the native bladder in patients with local control. It should not be interpreted as a 60-month survival estimate, and the absence of a radical-cystectomy comparator precludes any conclusion of equivalence.

The strategy combined initial TURBT, neoadjuvant gemcitabine–cisplatin, and concurrent chemoradiotherapy. Compared with classic trimodality therapy, neoadjuvant chemotherapy constituted the fourth modality and was intended to treat occult micrometastatic disease before locoregional chemoradiotherapy [22].

The first surveillance cystoscopy was performed a mean of four months after treatment. Among the 13 patients with a documented interval, mean time to recurrence was seven months, emphasizing the need for close surveillance. Cystoscopy, ideally combined with urinary cytology and clinically indicated imaging, remains essential for early detection of intravesical, locoregional, or metastatic recurrence [23,24].

Factors associated with survival

Smoking status and pack-year exposure were not significantly associated with overall survival in the univariate analysis. This finding must be interpreted cautiously because of the limited sample size, patient selection, retrospective exposure assessment, and inconsistent smoking counts across source tables. It does not demonstrate an absence of prognostic effect [25].

Ureterohydronephrosis was associated with shorter overall survival ($p = 0.006$), with a mean survival of 43.8 months among affected patients. This association is clinically plausible because ureterohydronephrosis may indicate greater local extension or ureteric obstruction and may impair renal function, thereby limiting optimal cisplatin delivery [26]. Severity showed a nonsignificant trend toward shorter survival ($p = 0.214$). Recurrence type was also not significantly associated with overall survival ($p = 0.212$). These exploratory results derive from univariate analyses.

Tolerance and comparison with the literature

Retrospectively collected tolerance data support the overall feasibility of the quadrimodal strategy. Toxicities were mainly hematologic during neoadjuvant chemotherapy and gastrointestinal or genitourinary during chemoradiotherapy. Severe events were uncommon, and all patients completed radiotherapy. Comparisons with published series require caution because of differences in patient selection, systemic regimens, radiation doses and techniques, and toxicity ascertainment. In one retrospective bladder-preservation cohort, acute grade ≥2 genitourinary or gastrointestinal toxicity occurred in approximately 45.2% (38/84) of patients receiving chemoradiotherapy [27]. Published data underscore the need for systematic assessment of gastrointestinal, genitourinary, and hematologic toxicity [25,28].

Limitations

The retrospective single-center design entails selection bias and heterogeneity in the completeness and quality of clinical, treatment, and follow-up data. Low-grade and late toxicities may have been underestimated because they were not consistently recorded. The cohort size and limited number of events precluded a robust multivariable Cox analysis; adding several covariates would have risked overfitting and unstable estimates. The observed univariate associations, particularly for ureterohydronephrosis, should therefore be considered exploratory. Finally, the absence of a comparator group treated with radical cystectomy or classic trimodality therapy limits comparative interpretation. Prospective multicenter studies with standardized toxicity and quality-of-life assessment are needed.

Conclusion

Quadrimodal bladder-preserving treatment combining maximal TURBT, neoadjuvant chemotherapy, and concurrent chemoradiotherapy yielded encouraging institutional outcomes in selected patients with nonmetastatic MIBC. It may offer effective tumor control while preserving bladder function, but further prospective comparative research is required to confirm benefit, define optimal selection criteria, and standardize treatment protocols.

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Conflict of interest : None

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