International Journal of Innovation and Scientific Research
ISSN 2351-8014 Vol. 27 No. 1 Oct. 2016, pp. 176-185

http://www.ijisr.issr-journals.org/

Epidemiology, Treatment and Outcome of Muscle invasive bladder cancer in north Tunisia

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ABSTRACT: *Introduction:* There have been only few data published reporting the clinical or pathological features of bladder cancer in Tunisia. Muscle invasive bladder is characterized by poor outcome despite systemic therapy. We aim to report the epidemiological, clinicopathological features and treatment of invasive bladder cancer in a Tunisian population. Materials and methods: A total of 141 patients diagnosed with invasive bladder cancer were included in the analysis. Data were collected and correlated with overall survival (OS). Kaplan Meier survival analysis was used to evaluate the median survival time and survivals were compared by the log-rank test. *Results:* Median age at diagnosis was 63 years old. Sex ratio was 14.6. Median follow-up duration was 22 months. Smoking was the most important risk factor in our series (81.6%) of cases followed by occupational exposure. Hematuria was the most common symptom reported in 93.6% of cases. Urothelial bladder carcinoma was the most common histologic subtype representing 93.5% of cases. Only 61 patients underwent curative surgery, followed by adjuvant gemcitabine-based chemotherapy in 32 cases. TNM staging was the most significant prognostic factor in our population ($p<0.001$). Median overall survival of the organ confined group was 60 months, in the locally advanced group was 36 months and in the metastatic group was 12 months ($p<0.001$). *Conclusions:* The increasing incidence of bladder cancer is due to ongoing high prevalence of smoking, which represents the main risk factor. Therefore primary prevention is crucial. Bladder cancer remains diagnosed in Tunisia at locally advanced and/or metastatic stages impairing the prognosis

KEYWORDS: bladder cancer; epidemiology; treatment; prognosis, outcome.

1 INTRODUCTION

Invasive bladder cancer is the most common urological cancer in Tunisia accounting for 347 new cases per year [1]. The incidence of bladder cancer is increasing; it varies by sex, about three times higher in men. Smoking, occupational exposure and certain genetic susceptibility are the main risk factors for this cancer. About 25% of newly diagnosed bladder cancers present with muscle invasion and need either radical surgery or radiotherapy but often still have poor outcome despite systemic therapy [2].

To our knowledge, there have been only few data published reporting the clinical or pathological features of bladder cancer in Tunisia. Therefore, we sought to study invasive bladder cancer cases seen over a five years period in order to help draw the epidemiological and clinicopathological features of this cancer in Tunisia along with its risk factors.

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2 MATERIAL AND METHODS

This is a retrospective study including all cases of invasive bladder cancer in north Tunisia. Patients were firstly diagnosed by urologists then only those who needed chemotherapy were transferred to Salah Azaiez Cancer Institute between the years 2009 and 2013. The medical records of these patients were reviewed and included in the present study. Clinicopathological data (size, site, morphology, multiplicity, stage, grade of tumor, etc.), epidemiological data (age, sex, occupation and smoking habit), investigations and treatment and follow-up data from the case notes were entered on a standard data collection sheet.

STATISTICAL ANALYSIS

Data were analyzed using SPSS software version 20 (IBM SPSS Statistics; IBM Corp, Armonk, NY, USA) and chi-square test was used to compare the variables. A p-value of 0.05 was taken as significant. Kaplan Meier survival analysis was used to determine the median overall survival (OS) and survivals were compared by the log-rank test.

3 RESULTS

3.1 PATIENT'S CHARACTERISTICS

A total of 141 patients were treated at the Salah Azaiez Cancer Institute in the period of the study. The distribution was quite homogeneous with an average of 28.2 cases per year (Range: 27 to 31) (figure1).

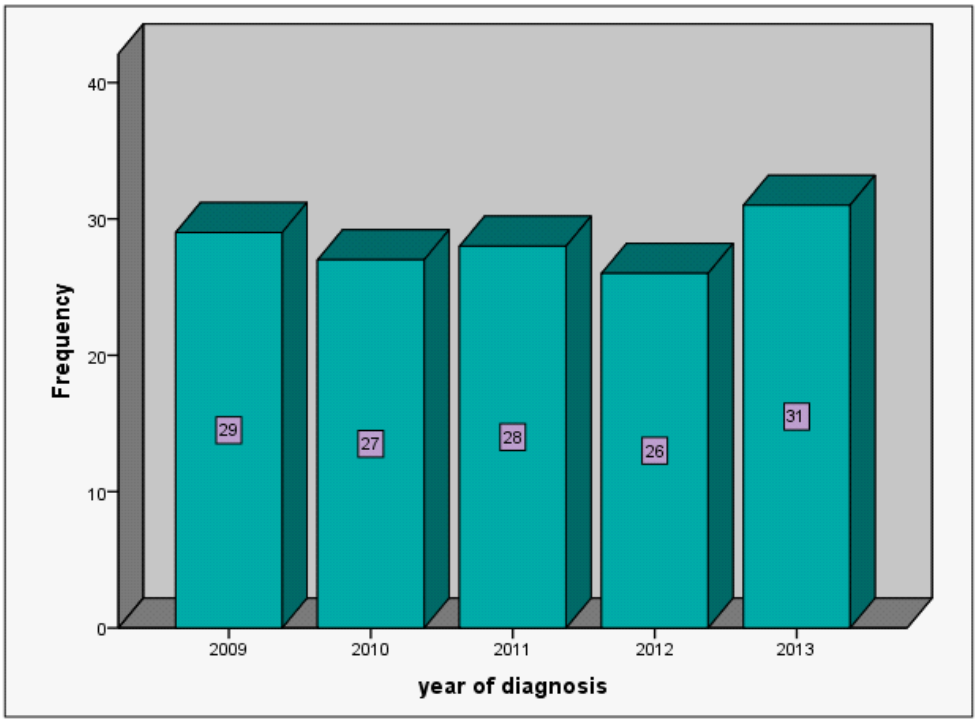

Fig. 1. Distribution of muscle invasive bladder cancer cases per year

Median age at diagnosis was 63 years old (Range: 38 to 85years). Sex ratio was 14.6. Risk factors in our population are shown in table I.

Table 1. Risk factors of invasive bladder cancer

	Male(132)	Female(9)	X2
Tobacco smoking	114(86.4%)	1(11.1%)	***P<0,001***
Familal History of bladder cancer	3(2.3%)	0(0%)	P=0.868
polycyclic aromatic hydrocarbons	22(16.6%)	1(11.1%)	P=0.55
Bilharzia	1(0.8%)	0(0%)	P=0.936

Smoking was the most important risk factor reported in 81.6% of cases. Hookah smoking was noticed in 20% of cases, snuff tobacco in only 3% of patients and the main form of smoking consisted of cigarettes (77%). Smoking was followed by the second most important reported risk factor for bladder cancer which is occupational exposure. In our series, 23 patients were exposed to polycyclic aromatic hydrocarbons and 7 were farmers. Our male patients were more exposed to this carcinogen compared to female patients (16.6% vs 11.1%). Only three male patients had a family history of bladder cancer and only one patient was subject to a parasitic infection and suffered from Bilharzia.

Mean time to diagnosis was 6.45 months (from 1 to 48 months). The most common symptom was hematuria in 132 patients (93.6%). Kidney failure was noticed in 9.9% of cases. All patients had a prior trans-urethral resection for diagnosis. Urothelial bladder carcinoma was the most common histologic subtype (93.5%) followed by non-urothelial carcinoma (adenocarcinoma in 5.1% and squamous cell carcinoma in 1.4%. Urothelial carcinoma was mostly found in a pure form (88.4%). Whereas divergent differentiation were found in the other cases (squamous differentiation 8.5%, glandular differentiation 1.6% and sarcomatoid differentiation 1.6%) (Figure 2).

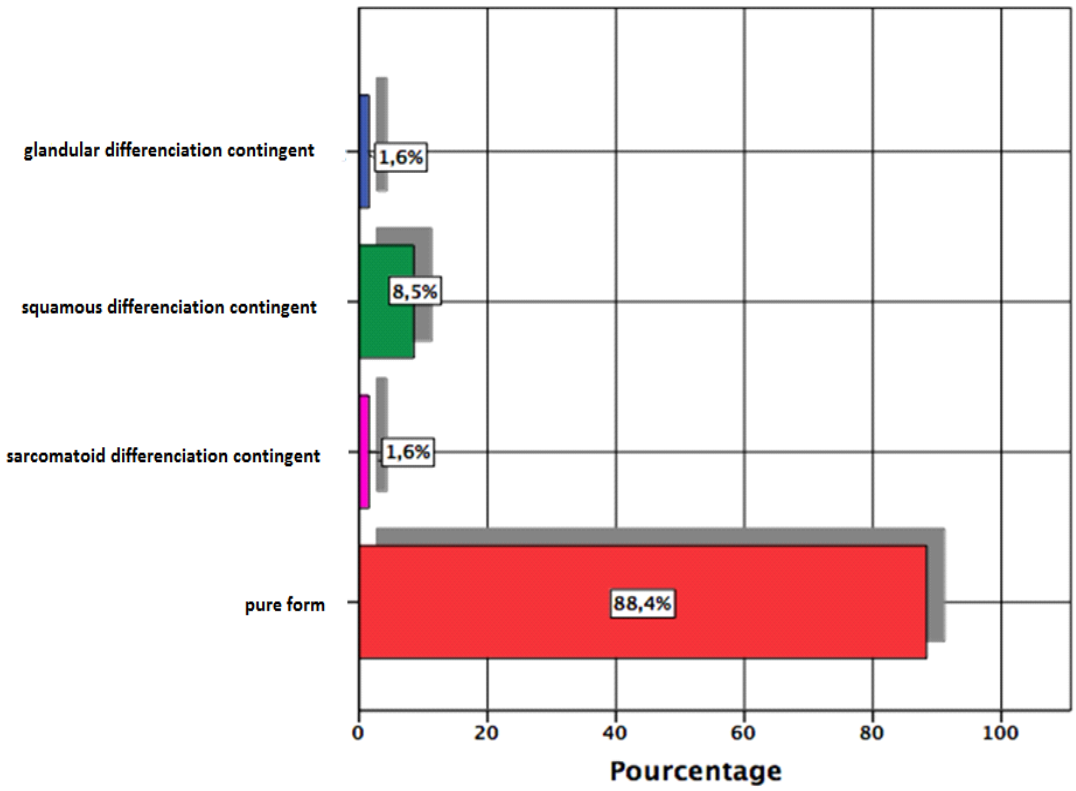

Fig. 2. Tumoral contingents

All patients had a body CT scan but only 42.6% had a bone scan. Organ-confined tumors (T2 N0) were present in 15 patients (11.1%). Non-organ-confined tumors (>T2 and/or N+) were found in 126 patients (88.9%), T3 in 65(48.1%) and T4 in 49 (36.3%) patients.

Fifty eight (41.1%) patients were metastatic at the time of diagnosis. The most frequent sites of metastasis at the diagnosis are lungs in 22 patients (40.7%) and bone in 14 patients (14.9%) (Figure 3).

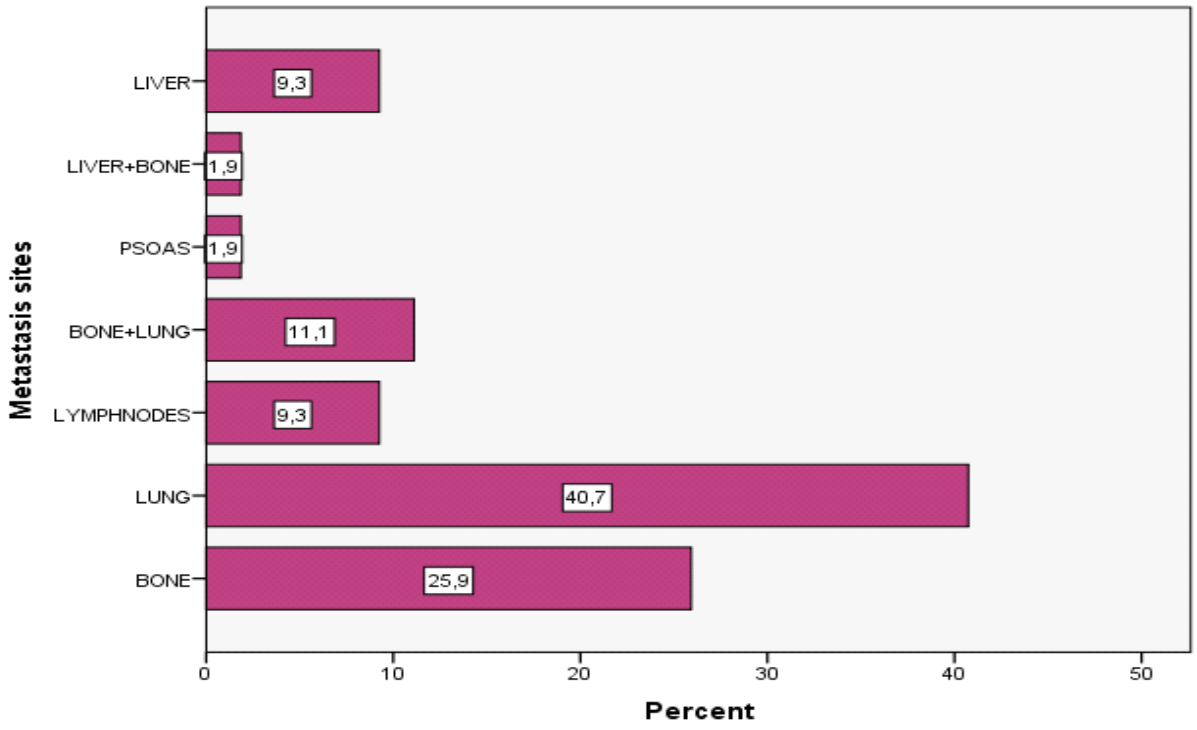

Fig. 3. Metastasis sites

3.2 TREATMENT

Among the eighty-three non metastatic patients only seventeen (20.48%) received gemcitabine-based neoadjuvant chemotherapy. Sixty-one patients had surgery consisted of a radical cystectomy with lymph-node dissection. Operated patients characteristics are show in Table II.

Table 2. Clinicopathological Characteristics of operated Patients

	AC After RC	RC Alone
No. of Patients	32	29
Male/Female	29/3	27/2
Age, Median	59	61
Acute Renal Failure	0	1
Performance Status		
<1	31	28
2	1	1
pT Stage		
<pT2	1	4
pT2	2	5
pT3	17	10
pT4	12	10
pN		
pN0	17	20
pN1	6	4
pN2	9	5
pN3	0	0
Nuclear Grade		
High	27	1
Low	5	28
Cisplatin-Based AC		
MVAC	0	
GC	32	
Median AC cycles	4(1-7)	
Form of Urinary Diversion		
Ileal conduit	30	28
Ileal neobladder	2	1
Open surgery	32	29

Abbreviations: AC=adjuvant chemotherapy; GC=gemcitabine and cisplatin; MVAC=methotrexate, vinblastine, doxorubicin, and cisplatin; RC = radical cystectomy

Three patients had a neobladder reconstruction and fifty eight had Briker urinary derivation. Thirty two patients had gemcitabine based adjuvant chemotherapy.

Forty four metastatic patients received palliative chemotherapy consisted of gemcitabine-based regimen (gemcitabine and cisplatin or carboplatin) in 43 cases, MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) in 1 case. Fourteen patients didn't receive chemotherapy due to a poor PS (3/4).

3.3 SURVIVAL

Statistical analysis showed that patients younger than 65 years had a better outcome than those aged more than 65 years but this difference wasn't statistically significant (P=0.094). Distant metastasis (p=0.02) and T3/T4 stage (p=0.02) were associated with reduced OS. However lymph node involvement didn't impair the OS. TNM staging was the most significant prognostic factor in our population (p<0.001). Median overall survival of the organ confined group was 60 months, in the locally advanced group 36 months and in the metastatic group was 12 months (p<0.001) (figure4).

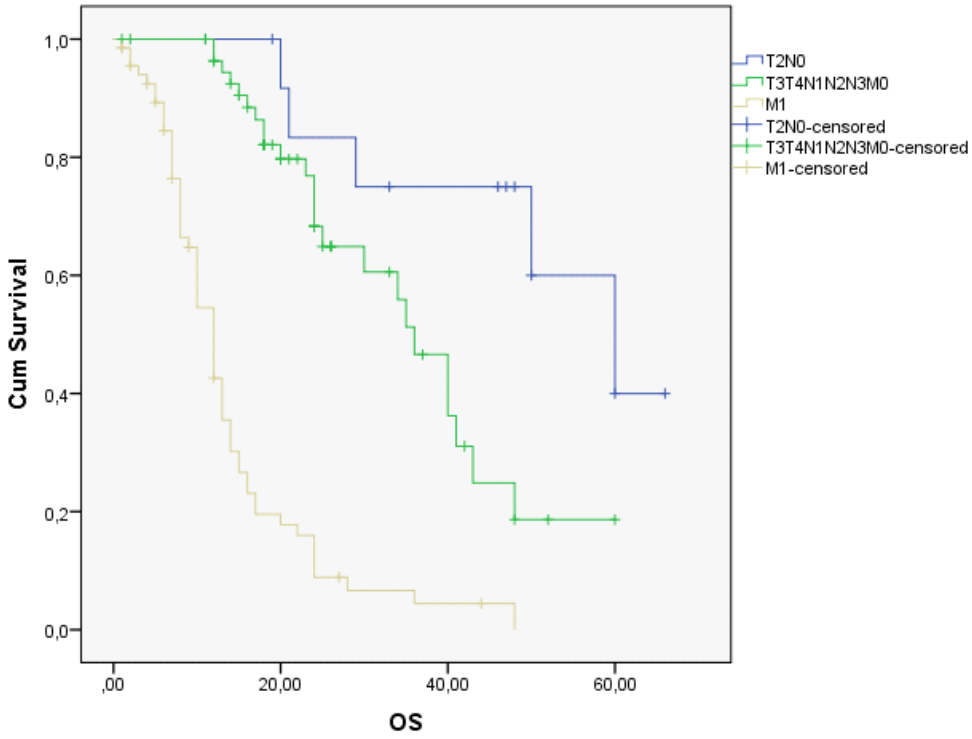

Fig. 4. Kaplan-Meier survival curves in muscle invasive bladder cancer according to TNM stage

Whereas for Disease free survival (DFS), the organ confined group presented better DFS (18 months) than the locally advanced patients (11 months) but this difference wasn't statistically significant p=0.355.

In the operated group, patients who had adjuvant chemotherapy seemed to have better overall survival (60 months) than patients who did not received chemotherapy (40 months) p=0.406 (figure 5).

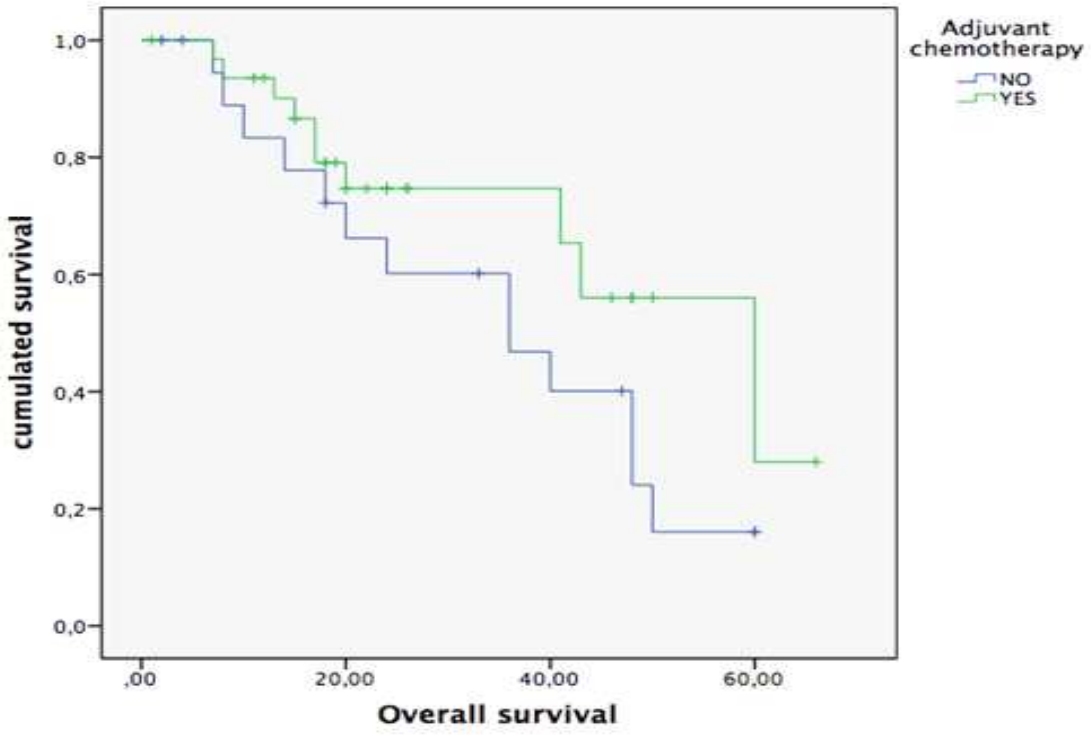

Fig. 5. Kaplan-Meier survival curves in muscle invasive bladder cancer according to adjuvant chemotherapy.

On the other hand, metastatic patients who received chemotherapy seemed to have a better overall survival (12 months) than patients who did not receive chemotherapy (8 months) p=0.318.

4 DISCUSSION

Bladder cancer is the 9th cancer worldwide [3], it is more common in men than females, ranked 7th when compared to all male cancers while its ranked 17th in women cancers [4, 5]. About 25% of newly diagnosed bladder cancer present with muscle invasion.2 Median age at diagnosis worldwide is 67 years.6 Unlike, in our population median age was 63 years. The incidence and prevalence of bladder cancer are seen in the sixth decade of life, with a peak in the seventh and eighth decade. Thus, is it mainly an elderly disease [6].

In Tunisia, the incidence of bladder cancer in men is among the highest incidences in the world; 15.6 / 100 000. According to the north Tunisia cancer register (RCNT 1999-2003 within 10 Governorates) published in 2007, the sex ratio of this pathology remains very high (close to 10) [1].

There are multiple possible reasons for the observed preponderance of bladder cancer in males. In fact, men are more exposed to industrial carcinogens and to exogenous estrogen than females which explains the low incidence of bladder cancer in females [7]. Additionally, smoking is more common in males compared to females, which is a well-established and important risk factor for bladder cancer [8].

Bladder cancer is a multifactorial disease. Nowadays, several risk factors are known and well established namely, Cigarette smoking and occupational exposure to aromatic amines which represents the most important ones [9].

Smoking is the main risk factor for bladder cancer; it is present in 50% of male cases, 35% of female cases and 65% of invasive bladder cancer [10]. Moreover, the risk of developing bladder cancer is 2-4 times higher in smokers compared to nonsmokers and this risk is directly proportional to the intensity and/or duration of smoking [11]. At the cessation of exposure, the risk decreases by more than 30% after 1 to 4 years and more than 60% after 25 years but it doesn't reach that of nonsmokers [12]. In our series, 81.6% of patients were exposed to tobacco. Following smoking and as seen in our study, occupational exposure to carcinogens is viewed as the second most important risk factor for bladder cancer. Roughly 20% of all bladder cancers have been suggested to be related to such exposure, mainly in industrial areas processing paint, dye,

metal, and petroleum products [13]. Moreover association between specific pesticides exposures and bladder cancer risk has been observed among agricultural populations [14]. Two studies have shown a link between farming and bladder cancer among non-smokers, which highlights the difficulty of trying to study the effect of other exposures on smoking-related cancers [15], [16] .The risk of death from bladder cancer appears to be elevated for more than 30 years after cessation of exposure to occupational carcinogens [17].

Haematuria is the most common symptom of bladder cancer [18], representing 93.6% in our series. The most frequent pathologic subtype in our series was urothelial carcinoma (93,5%) like most north African countries and worldwide except for Egypt where the endemic infestation of shistosomiasis explain why squamous cell carcinoma is the most frequent histological subtype[19, 20, 21]. Other types of bladder cancer, i.e. squamous cell carcinoma and adenocarcinoma have much lower relative frequency. These findings are in line with our study results. In all "Cancer Incidence in Five Continents" (2016) registries, squamous cell carcinoma accounts for 1.1% and 2.8% of all bladder cancers in men and women respectively. Adenocarcinoma of the bladder constitutes respectively 1.5% and 1.9% of all bladder tumors worldwide (2016) [20].

Controversy regarding surgery has emerged concerning the best surgical approach (open versus robotic), and the optimal extent of lymph-node dissection. Robotic surgery is the new tendency in radical cystectomy even if there is no evidence in better outcome or complication rate in the robotic radical cystectomy group [22]. There are many options of adjuvant treatment for bladder cancer. Adjuvant chemotherapy (AC) after radical cystectomy in the treatment of muscle-invasive bladder cancer is controversial. There are ten main randomized trials that evaluated the role of AC. The most recent trial is the EORTC30994, who recruited only 284 of the planned 660 patients in locally advanced muscle invasive bladder cancer. Immediate AC was compared to deferred therapy upon relapse. Median overall survival was prolonged with AC (6.75 vs 4.6 years). However, results did not reach statistical significance for OS (HR 0.78, 95% CI 0.56e1.08, p = 0.13) [23] .

Furthermore, Kanatani et al suggested that postoperative cisplatin-based AC gives patients a survival advantage in locally advanced or node positive bladder cancer, especially in node-positive cases as reported in our study [24]. The most recent meta-analysis of nine trials showed overall survival benefit of adjuvant chemotherapy (pooled HR 0.77, 95% CI 0.59e0.99, p = 0.049). This meta-analysis did not include the last EORTC trial. Moreover, this meta-analysis is not reliable because it included unpowered trials with insufficient cohorts and heterogeneous populations [25]. In our series, AC seems to improve overall survival, although the non-receiving chemotherapy group had more organ-confined tumors, less metastatic nodes and a lower histological grade. Whereas, other options than chemotherapy are being discussed in adjuvant setting such as radiotherapy or chemoradiation. Recently, Zaghloul M published an abstract in ASCO GU 2016 comparing these three options. The trial demonstrated no difference in outcome but a better local control with protocols using radiotherapy. Furthermore, this trial had a larger proportion of squamous cell histotype explaining why the radiotherapy is so efficient [26]. All patients with locally advanced or metastatic disease received gemcitabine-cisplatin (GC) regimen. GC was compared with MVAC in two major randomized trials comparing locally advanced and metastatic patients, shown no outcome difference with a better risk/benefice ratio with GC , additionally, this regimen was better tolerated [27], [28]. These findings support our use to the GC regimen in the palliative settings.

5 CONCLUSIONS

To our knowledge, our study is the largest series published in Tunisia. Most available data are based on retrospective analysis. Bladder cancer remains diagnosed in Tunisia at locally advanced and/or metastatic stages impairing the prognosis. Moreover, the increasing incidence of bladder cancer is due to ongoing high prevalence of smoking, which represents the main risk factor. Therefore primary prevention is crucial, and smoking cessation programs should be encouraged and supported.

Besides Quitting tobacco smoking, avoiding occupational exposure to aromatic amines and other related chemicals are some of the ways to avoid increasing the risk of developing bladder cancer. On the other hand, pesticide exposure may be an overlooked risk factor in bladder cancer. More efforts must be done by public authorities regarding prevention and particularly reducing tobacco consumption. Despite the results of randomized trials and expert recommendations regarding neoadjuvant chemotherapy almost all patients in Tunisia receive only adjuvant chemotherapy. Further clinical trials exploring new treatment modalities such as robotic radical cystectomy and adjuvant radiotherapy are warranted.

CONFLICTS OF INTEREST

None

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