Journal of
Cancer Science & Therapy

Lmezguidi et al., J Cancer Sci Ther 2017, 9:6
DOI: 10.4172/1948-5956.1000463

Research Article OMICS International

Oncologic Outcomes after Radical Cystectomy: Comparison between Primary and Progressive Muscle Invasive Bladder Cancer

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Abstract

Background: Between primary and progressive muscle-invasive bladder cancer, in the current literature, data regarding the prognostic difference and survival between this two entities are controversial.

Objectives: To assess differences in survival between the primary and progressive MIBC and to determine main prognostic factors in muscle-invasive bladder tumors (MIBT).

Material and methods: All patients who were underwent radical cystectomy for MIBC in our institution between 1990 and 2014 were retrospectively evaluated using an institutional database. A total of 308 patients had met inclusion criteria, 218 (70,77%) (Group 1) with primary MIBC and 90 (29.22%) (Group 2) with progressive MIBC. The main variables studied were: age, sex, initial tumor stage of TURs in group 2, pathologic stage (T/N), type of urinary diversion and extent of LND. Survival rate was investigated with Kaplan-Meier method and a multivariate analysis using the Cox regression analysis was performed to evaluate potential prognostic factors.

Results: In Group 2, the median time of progression to invasive cancer was 32 months. 2, 3 and 5-year cancer specific survival rate after surgery was 77%, 63% and 51% in Group 1 and 59%, 49% and 32% in group 2, respectively ($p < 0.05$). Analyzing pN stage, overall 2,3 and 5-year survival rate were 75%, 62%, and 53% in group 1 and 61%, 49%, and 37% in group 2 respectively for pN0 ($P < 0.05$). On multivariate analysis, lympho-vascular invasion and pT stage of the primary tumor remained significant independent prognostic factors for cancer-specific survival.

Conclusions: Our study has shown that Progressive MIBC have a worse prognosis than Primary MIBC. Lympho-vascular invasion and Positive nodes in RC specimens seems to be an independent factor that decreases survival in patients with MIBC.

Keywords: Oncologic outcomes; Radical cystectomy; Primary; Progressive; Muscle invasive bladder cancer; Prognosis

Introduction

Bladder cancer is the second most common genitourinary malignancy, with transitional cell carcinoma (TCC) comprising nearly 90% of all primary bladder tumors [1]. Muscle-invasive bladder cancer (MIBC) can be classified into two categories: Primary, for those which are muscle-invasive at the time of the diagnosis, and Progressive, for those non-muscle invasive bladder cancers in their earlier stages that will become invasive during their follow-up stages. Approximately 30% of non-muscle invasive bladder (NMIBT) urothelial tumors progress to muscle-invasive tumors during their follow-up. Radical cystectomy (RC) with bilateral pelvic lymphadenectomy (LA) is the standard of care for muscle-invasive disease, various regimens of preoperative radiation were implemented but failed to demonstrate convincingly any additional benefit [2,3].

Different studies have evaluated the difference between these progressive and primary muscle-invasive tumors in terms of prognosis and survival and results remain controversial. While some studies have found differences in clinical outcomes, others did not.

In the pathologic stage, lymphovascular invasion and lymph node (LN) status have consistently been shown to be the most powerful independent predictors of long-term outcome following radical cystectomy (RC).

The aim of this study was to investigate if there was a difference in the clinical outcomes of patients with progressive and primary muscle-invasive bladder cancers. In addition, we analysed variables such as grade, age, sex, lymphovascular invasion (LVI), pathologic T stage, lymph node status (in the cystectomy specimen), and the detection of metastasis during follow-up (either local or distant) with the aim to bring out independent predictors of cancer-specific survival in muscle-invasive urothelial tumors.

Patients and Methods

Retrospective data was collected on all 308 patients who underwent RC for bladder urothelial carcinoma at our department from January 1990 to December 2014. Pathologic staging of bladder tumors and LNs was performed per the 2002 TNM classification. All cases treated before 2002 were reclassified. Reclassification per the 2010 TNM classification could not be performed because we had incomplete information on the precise localization of the positive LNs. To assess the maximum tumor stage, the tumor was classified after review of the TURBT and the RC specimens. Histologic grading was performed per the World Health Organization/International Society of Urologic Pathology Classification.

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Received October 18, 2017; **Accepted** June 20, 2017; **Published** June 23, 2017

Citation: Lmezguidi K, Hajji F, Janane A, Alami M, Ameur A, et al. (2017) Oncologic Outcomes after Radical Cystectomy: Comparison between Primary and Progressive Muscle Invasive Bladder Cancer. J Cancer Sci Ther 9: 485-489. doi: 10.4172/1948-5956.1000463

LVI was defined as the presence of tumour cells within an unequivocal endothelium-lined space with no underlying walls of smooth muscle cells, in standard haematoxylin and eosin (H&E)- stained sections. In selected cases, immunohistochemistry for endothelial cells was done.

To analyze a homogeneous population, all our patients met the following inclusion criteria:

- Primary malignant tumor of the bladder.
- Urothelial carcinoma (UCa).
- No neoadjuvant radiotherapy and/or chemotherapy.
- No adjuvant radiotherapy and/or chemotherapy.
- RC with bilateral PLND.
- No positive surgical margins (R1/R2).

Patients undergoing palliative cystectomy and those with upper urinary tract tumors or non-transitional cell carcinoma were excluded.

None of the enrolled patients had LN metastases outside the true pelvis or distant organ metastases in the preoperative assessment or intraoperatively. Our standard preoperative assessment protocol included physical examination, chest x-ray, computed tomography of the pelvis, ultrasonography of the abdomen, bone scan, and excretory urography.

The first group (group 1) included 218 patients with primary muscle-invasive bladder tumors. This group contained patients in whom invasion into the muscular layer was detected at the primary transurethral resection (TUR).

The second group (group 2) was comprised of 90 patients who had intially had a non-muscle-invasive bladder tumor that progressed to muscle-invasive carcinoma during follow-up. The diagnosis of superficial tumor was done by evaluation of the specimen collected after TUR. These patients received additional adjuvant therapy consisting of intravesical instillation with bacille Calmette-Guérin and maintenance therapy or intravesical chemotherapy per their risk stratification. All patients in group 2 underwent cystectomy after Stage T2 disease had been documented pathologically from the specimen collected at the last TUR. Patients with carcinoma in situ or those who had undergone RC for refractory NMIBC were excluded from the study.

All operations, including control cystoscopy, initial transurethral resection, and final radical surgery, were performed at our institution.

Patients with local or distant metastasis detected during follow-up were given chemotherapy. The vinblastine, doxorubicin or epirubicin, and cisplatin regimen were used. After 2002, the gemcitabine and cisplatin regimen were used.

The follow-up strategy after radical surgery consisted of: office visits, serum chemistries, abdominal imaging, and chest radiography every 3-6 months for the first 3 years, with increasing intervals thereafter. Bone scans were ordered when clinically indicated.

Continuous normally distributed variables are presented as the mean (SD), and those not normally distributed as the median (interquartile range). The correlation of the clinical and pathologic variables with survival was investigated by the Cox proportional hazards test. The Kaplan-Meier method was used to derive the cumulative cancer-specific survival (CSS) with the log-rank test used to compare curves of two or more groups. Univariable Cox regression analyses were used to identify differences within pathological variables, and a multivariable Cox regression analysis to identify prognostic factors. All *P* values were two-sided and a value of <0.05 was considered to indicate significant differences between groups.

Results

The present study cohort consisted of 308 patients (Table 1); 13 females (4.22%) and 295 males (95,77%). Of the 218 patients in group 1 and the 90 in group 2, 10 (3.67) and 5 (5.55) were women, respectively. The mean patient age at surgery was 61.5 years and the mean follow-up time was 72.6 months for group 1. The mean age at surgery was 60.3 years and the mean follow-up time was 85.4 months for group 2 ($P>0.05$). During follow-up, 88 patients died of tumor progression.

The initial tumor stage in the progressive group was pTaG1 in 4 (4.44%), pTaG2 in 20 (22.22%), pT1G1 in 4 (4.44%), pT1G2 in 34 (37.77%), and pT1G3 in 28 (31.11%) patients. The median duration between the resection of the first noninvasive tumor and the diagnosis of Stage T2 disease (last TUR before cystectomy) was 32.3 months, ranging from 6 to 178. For pTa tumors, the median duration was 85.6 (ranging from 43 to 190), although it was 27.5 (ranging from to 76) months for pT1 tumors ($P<0.05$).

In group 1, the distribution of cases per the pathologic stage was as follows: 122 (55.96%) had pT2, 58 (26.60%) had pT3 and 38 (17.43%) had pT4. In group 2, 50 (55.55%) had pT2, 24 (26.66%) had pT3, and 16 (17.77) had pT4.

The 2, 3, and 5-year cancer-specific survival rate was 59%, 49%, and 32% for the patients with progressive tumors and 77%, 63%, and 51% for patients with primary tumors, respectively. All differences in the cancer-specific survival rates were statistically significant between groups 1 and 2, ($P<0.05$). The mean survival time was 61.3 ± 7.34 months for group 1 and 89.1 ± 15.44 months for group 2. Using the log-rank test, the difference observed in terms of the mean survival time was statistically significant ($P=0.01$; Figure 1).

Of the 90 patients in the progressive group (group 2) and the 218 patients in the primary group (group 1), 73 (81.8%) and 156 (71.55%) had no positive pelvic lymph nodes after pathologic evaluation (pN0), respectively. For lymph node-negative tumors (pN0), the 2, 3, and 5-year cancer-specific survival rate was 79%, 67%, and 57% in group 1 and 61%, 49%, and 37% in group 2, respectively. The difference was statistically significant between two groups with the mean survival time (68.2 ± 6.44 months for group 1 and 87 ± 14.34 months for group 2; $P=0.034$, log-rank test) (Figure 2).

On multivariate analysis, none of the variables, including sex, age, or tumor grade identified from the cystectomy specimen were significantly associated with patient outcome. Thus, none were believed to be predictive of patient survival. However, lymph node tumor involvement, LVI and the pT stage of the primary tumor remained significant independent prognostic factors for cancer-specific survival. In addition, the detection of local and/or distant metastasis during follow-up significantly shortened the cancer-specific survival of patients with muscle-invasive bladder cancer (Table 2).

Discussion

The current study shows a large and clinically significant difference in disease-specific survival between primary and progressive muscle-invasive bladder cancer patients, favouring the primary group. The disease- specific survival is significantly high in the primary group always during follow-up. The 2, 3, and 5-year survival rates are 77%, 63% and 51% respectively for patients with a primary invasive tumour

Groups of BCa	Groupe 1 (n=218)	Groupe 2 (n=90)	p-value
Age (yr) Mean ± SD	61.5 ± 5.2	69.5 ± 6.7	0.09
Gender n (%)			
Male	210 (96.33)	85 (94.44)	0.43
Female	10 (3.67)	5 (5.55)	
Smoking history n (%)	156 (71.55)	60 (66.66)	0.15
History of pelvis irradiation n (%)	12 (5.5)	2 (2.22)	0 .06
Follow-up duration (months) mean ± SD	72.6 ± 5.3	85.4 ± 6.2	0.08
Initial tumor stage n (%)			
pTaG1		4 (4.44)	--
pTaG2		20 (22.22)	
pT1G1		4 (4.44)	
pT1G2		34 (37.77)	
pT1G3		28 (31.11)	
Duration between 1st TURBT and stage 2: Median (IQR)			
pTa	--	85.6 (43-190)	--
pT1	--	27.5 (7-76)	
Total	--	32.3 (6-179)	
Pathologic stage			
pT2	122 (55.96)	50 (55.55)	0.57
pT3	58 (26.60)	24 (26.66)	
pT4	38 (17.43)	16 (17.77)	
Type of urinary divesion n (%)			
Ileal conduit	86 (39.44)	35 (38.88)	0.46
Orthotopic neobladder	4 (1.83)	2 (2.22)	
Continent cutaneous reservoir	87 (39.90)	20 (24.44)	
Data unavailable	41 (18.80)	33 (36.66)	
Extent of LND n (%)			
Standard	111 (50.91)	45 (50.00)	0.77
Extended	65 (29 .81)	30 (33.33)	
None	25 (11.46)	11 (11.00)	
Data unavailable	17 (7.79)	4 (4.44)	

Abbreviations: SD=Standard Déviation; IQR=Interquartel Range; TURBT=Transurethral Resection of Bladder Tumor; LND=Lymph-Node Dissection; Bca: Bladder Cancer

Table 1: Patient characteristics.

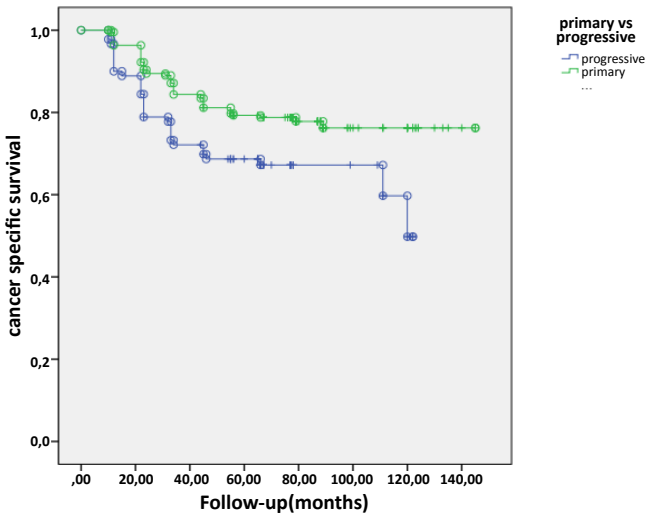

Figure 1 : Kaplan-Meier curve comparing primary and progressive tumors.

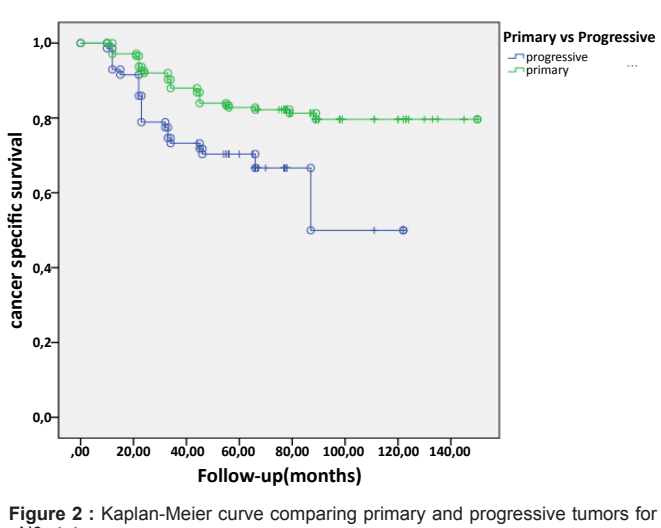

Figure 2 : Kaplan-Meier curve comparing primary and progressive tumors for pN0 status.

and 59%, 49%, and 32% respectively for patients with a progressive invasive tumour. This trend in survival difference between the two study groups was observed by Schrier, et al. [4] who examinated Nijimen and Rotterdam population showing that the disease- specific survival

Variables	Hazard ratio	P-value	95% Confidence Interval
Age	1.09	0.13	0.88-1.2
Sex	0.85	0.65	0.6-1.8
Tumor grade	1.01	0.78	0.7-1.6
pT stage	1.43	0.034°	1.1-1.5
LN status (pN+)	1.56	0.04°	1.2-2.5
Metastasis during follow-up	8.45	0.001°	5.4-16.2
LVI	2.8	0.003°	1.2-5.1

LN=Lymph Node; LVI=Lymphovascular Invasion
°P<0.05

Table 2: Multivariable analysis results.

appears to be approximately twice as high in the primary group. The 3 and 5-year survival rates are 67% and 55% respectively for patients with a primary invasive tumour and 37% and 28% respectively for patients with a progressive invasive tumour. Vaidya et al. [5] found a 2-year survival rate of 49% for those with primary (de novo) invasive tumors and 79% for those with progression from less than T2 at presentation concluding that progressive tumors had a worse prognosis than initially muscle-invasive tumors. Like this finding, Parra-Lopez, et al. [6] retrospectively reviewed the records of patients undergoing radical cystectomy. Their overall survival rate after 1 and 3 years of surgery was 86.9% and 70.2% for primary muscle-invasive tumors and 75.7% and 32.4% for progressive tumors. While these studies show significant differences between two study groups, Soloway [7] argued regarding the presence of difference. Türkölmez [7] examinating oncological outcomes after surgery between two groups, they found the 2, 3, and 5-year cancer-specific survival rate was 72%, 61%, and 43% for patients with progressive tumors and 75%, 62%, and 54% for patients with primary tumors, respectively and no statistically significance exists between these results. They conclude that patients with progressive muscle-invasive urothelial tumors do not have a worse prognosis than do those with primary tumors.

Recent data published by Moschini et al. [8] with a large sample of 768 consecutive patients treated with radical cystectomy following primary or progressive MIBC, they found That The 10-year RFS, CSM and OM rates for primary vs. progressive status were 43 vs. 36% (P=0.01), 43 vs. 37% (P=0.01), and 35 vs. 28% (P=0.03), respectively. They suggested that progressive status was associated with a higher CSM, OM and recurrence rate after RC

When we excluded the patients with positive lymph nodes in the cystectomy specimen and re-evaluated the outcomes statistically, similar Kaplan-Meier curves were reached with the 2, 3, and 5-year cancer-specific survival rate being 79%, 67%, and 57% in group 1 and 61%, 49%, and 37% in group 2, respectively. The same results are shown in the study of Lopez, et al. [6] after analyzing pN stage, the overall 1-year and 3-year survival rate were 90.7% and 64.3% for pN (+) tumors and 77.7% and 48.2% respectively for pN (-).

The mechanism behind this observed difference is not so easily understood. Since survival figures of the primary invasive patients is comparable with the literature, the explanation for the significant differences between the two groups must be found in the worse survival of patients with progressive muscle-invasive bladder cancer. One possible explanation could be that in high risk superficial bladder tumours both therapy-sensitive and -insensitive cells coexist. Intravesical therapy given to patients with high-risk superficial bladder cancer might select for resistant clones, and the more aggressive tumor cells might continue to grow and lead to the development of a progressive tumor.

Another possible explanation could be a finding published by El-Abbady, et al. [9]. They compared 16 patients with progressive invasive tumours with 20 patients who were diagnosed with primary invasive tumours, all undergoing cystectomy. On meticulous histopathological examination, they found that patients who underwent previous transurethral resections had significantly more local spread of malignant cells into the bladder muscle as compared to patients with primary invasive tumours. Since they could demonstrate that intravesical pressure reaches as high as 80 cm water, they suggested some malignant cells penetrated through the denuded urothelium during resection because of high intravesical pressures. Similarly, random biopsies during resection of superficial tumours might cause tumour cell implantation at the site of the damaged mucosa, and influence the prognosis. However, two large series clearly demonstrated that the risk of recurrence and the risk of progression is almost the same comparing a “biopsy policy” with a “no biopsy policy” [10,11].

It has been previously reported that the pathological stage and the nodal status are the most important prognostic factors for patients undergoing RC for bladder cancer [12-14]. In the present study, as would be expected, pT stage was an idependant prognostic factor of survival after RC as well as lymph node status. The appearance of local and/or distant metastasis during follow-up dramatically shortened the life of patients with cystectomized bladder cancer in our study population (hazards ratio 8.45).

On multivariable analysis, our study shows an idependent prognostic value of lymphovascular invasion. In a multicentre study Bolenz, et al. [15] identified the presence of LVI in the surgical specimen as an independent predictor of survival in patients with node-negative UBC treated with RC and pelvic LA. They identified LVI in 26.8% of patients with node-negative disease, which is in line with the proportion reported in other studies, specifically the studies of Lotan et al & Harrada, et al. [16,17]. LVI occurred more frequently in tumours with higher stage and grade, but also β≈30% of pT1 tumours showed LVI, indicating metastatic potential despite a low stage. The same results are shown in other large previous studies [17-20]. Controversially, Bassi, et al. [21] and Hara, et al. [22] established that LVI was not a predictor of survival.

The process of LVI remains poorly understood but there is a consensus that it represents an early step in the systemic spread of malignant cells [22,23]. LVI can be regarded as a surrogate marker for the presence of lymphatic micrometastases at the time of RC. In a large multicentre study, Lotan, et al. [16] previously evaluated 151 LVI-positive patients with node-negative UBC after RC and showed that LVI is a predictor of recurrence, CSS, and OS. In their study, the prevalence of LVI increased with higher pathological stage and grade. The presence of LVI retained independent prognostic value in

competing- risks regression models in which other-because mortality was considered as a competing risk. Given these findings and some confirmatory retrospective studies [16,20,23], LVI has been suggested to be included in clinical staging models of UBC.

Conclusion

Our study has shown that patients with progressive muscle-invasive urothelial tumors have a worse prognosis than those with primary tumors. Therefore, in high risk patients with recurrent or persisting tumours at initial evaluation, radical surgery should be seriously considered. For both groups, pT stage, LN status and LVI seem to be independent predictors of decreased cancer-specific survival.

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Citation: Lmezguidi K, Hajji F, Janane A, Alami M, Ameur A, et al. (2017) Oncologic Outcomes after Radical Cystectomy: Comparison between Primary and Progressive Muscle Invasive Bladder Cancer. J Cancer Sci Ther 9: 485-489. doi: 10.4172/1948-5956.1000463