Original Study

Impact of Age on Outcomes of Patients With Pure Carcinoma In Situ of the Bladder: Multi-Institutional Cohort Analysis

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Abstract

The aim of our multicenter study is to investigate the role of age in the oncologic outcomes of carcinoma in situ (CIS) of the bladder. One hundred and seventy-two patients with CIS from 8 centers were analyzed. Patients > 70 years reported a lower recurrence free survival and progression free survival compared to younger patients, respectively 41.7% versus 60%, and 68.3% versus 86.04%.

Introduction: The aim of this multicenter study was to investigate the role of age (cut-off 70 years) at diagnosis in predicting oncologic behavior of pure carcinoma in situ of the bladder. **Material and Methods:** Inclusion criteria were: patients with pure CIS confirmed and that followed intravesical BCG treatment. Pure CIS was defined at any CIS not associated with another urothelial cancer. Exclusion criteria were: any CIS associated with invasive urothelial carcinoma. A total of 172 with pure CIS treated between January 1, 2002 and December 31, 2012 at 8 academic institutions met the inclusion criteria. The maintenance schedule was generally according to the EAU guidelines at the time **Results:** A total of 99 (57.6%) patients had an age >70 years prior to TURBT. There was no difference between clinico-pathologic features among groups (group 1, age $\leq$ 70 years and group 2, age > 70 years), except that patients aged $\leq$ 70 years presented a larger size of CIS (35.6% vs. 21.2%), $P = .02$. In multivariable Cox regression analyses, the same clinico-pathologic factors (age, multifocality, and recurrent tumor state) were independently associated with worse RFS. Harrell's C-index was 65.75.In multivariable Cox regression analyses in addition to age ($P = .006$) and multifocality ($P < .001$)

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also BMI ($P = .04$) was independently associated with worse PFS. Harrell's C-index was 74.71 **Conclusion:** Advanced age at diagnosis appears to be associated with an increased risk of recurrence and progression of pure carcinoma in situ of the bladder. Elderly patients might fail to respond to BCG therapy.

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Introduction

Bladder Cancer (BC) represents a serious disease, which has an estimation of 83,730 newly diagnosed cases in 2021, accounting, with more than 62,000 new cases, as the 4thmost common cancer among males in the United States (US).[1] Furthermore, according to GLOBOCAN,BC represents, with an estimated incidence of 573,278 new cases, the 12th most common cancer.[2]

Approximately 3/4 of patients with BC have a disease confined to the mucosa (stage Ta, CIS [carcinoma in situ]) or submucosa (stage T1) at diagnosis[3]; in younger patients (< 40) this percentage is even higher.[4] CIS is a flat, high-grade tumor, confined to the mucosa classified as primary: isolated CIS with no previous or concurrent papillary tumors and no previous CIS; secondary: CIS detected during follow-up of patients with a previous tumor that was not CIS; or concurrent: CIS in the presence of any other urothelial tumor in the bladder.[5]

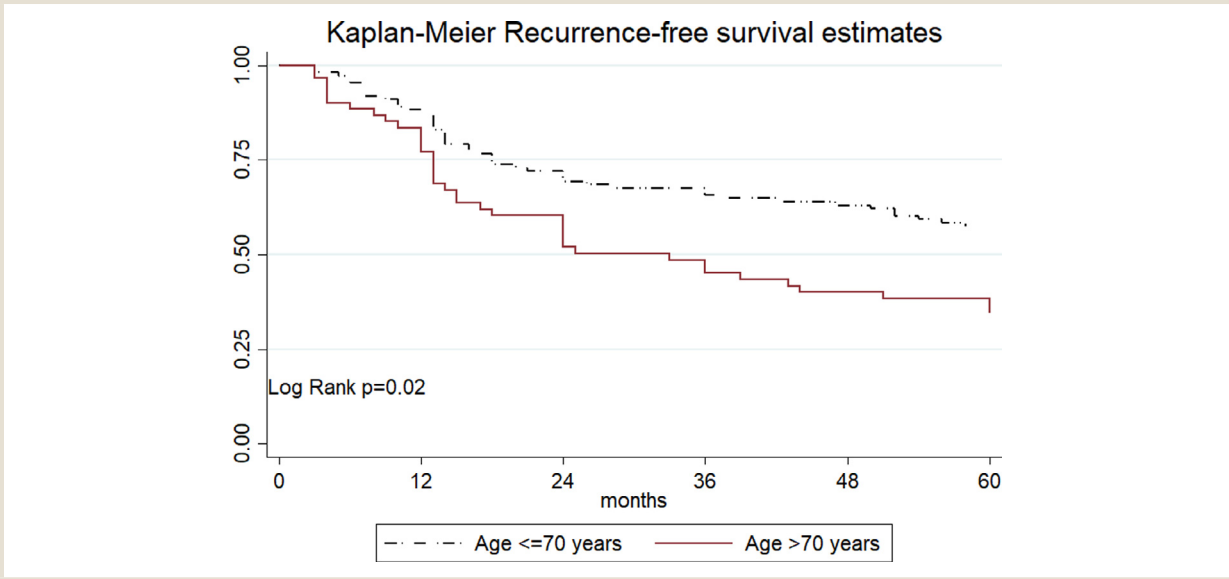
It was reported that, without any treatment, more than half of patients with CIS progress to muscle-invasive disease.[6] Even more, there are no valid prognostic factors that can be reliably used in clinical decision making, as many prognostic factors are based on retrospective analyses which hardly permit to draw useful conclusions. Several studies have reported a worse prognosis in concurrent CIS and T1 tumors compared to primary CIS[7] or extended CIS.[7,8]

Surveillance of NMIBC, including CIS, is recommended to follow a risk-adapted approach, with a combination of cystoscopy, cytology, and upper tract imaging. This management is necessary in order to minimize the high recurrence and progression rates.[9] Management of CIS has at least 3 problematic issues which comprehend detection, prediction of behavior, and treatment beyond Bacillus Calmette-Guerin (BCG), which is widely accepted as first-line therapy for CIS.[10] However, the high risk of progression, and in the absence of an alternative second-line intravesical therapy radical cystectomy (RC) is recommended as second-line therapy in case of BCG failure.[11] BCG activity requires a competent immune system, particularly cell-mediated immunity. On the contrary, older patients who may need it the most could be less able to respond to BCG therapy as the immune system wanes with age.[12]

Aging of the world population, has an impact also on the incidence of BC, as this disease is often reported in this group, as a consequence we should adapt treatment and management strategies according to their age and comorbidities.[13]

The aim of this multicenter study was to investigate the role of age (cut-off 70 years) at diagnosis in predicting oncologic behavior of pure carcinoma in situ of the bladder.

Figure 1 Kaplan-Meier recurrence-free survival estimates.



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Material and Methods

Patient Selection and Data Collection

Institutional-review-board approval was obtained at each institution, prior to the initiation of the study. Inclusion criteria were: patients with pure CIS confirmed and that followed intravesical BCG treatment. Pure CIS was defined at any CIS not associated with another urothelial cancer. Exclusion criteria were: any CIS associated with invasive urothelial carcinoma. A total of 172 with pure CIS treated between January1, 2002 and December 31, 2012 at 8 academic institutions met the inclusion criteria. The maintenance schedule was generally according to the EAU guidelines at the time.[14]

Management and Follow-up

All patients had a standard TURB with curative intent followed by BCG treatment and none discontinued BCG. Informed consent was obtained from each patient. Complete resection of all CIS lesions was a condition for BCG therapy in concordance with the EAU guidelines. The pathologic evaluation was carried out according to the TNM system of the Union for International Cancer Control (UICC) and to the 1973 or 2004 World Health Organization (WHO) grading classification. Patients were treated with 6 weeks course of intravesical BCG induction followed by a standard maintenance scheme, which consisted of intravesical BCG every week for 3 weeks given at 3, 6, 12, 18, 24, 30, and 36 months from initiation of therapy. All patients were followed according to guidelines recommendations with cystoscopy and voiding urine cytology every 3-4 months for the first 2 years, every 6 months for the third and fourth year, and annually thereafter. Diagnostic imaging of the abdomen and pelvis was performed at least annually or when clinically indicated. Demographical, clinical, pathologic, and outcomes data were collected and entered in a computerized database, based on data available at our institutions regarding the follow-up of the patients. Data integrity, completeness and quality were ensured through internal and external revisions.

Endpoints

Recurrence was defined as any tumor detection on follow-up while progression was defined as muscle-invasive disease on follow-up. Endpoints were time to recurrence-free survival (RFS) and progression-free survival (PFS).

Statistical Analysis

We divided patients into 2 groups according to age (cut-off 70 years) as previously suggested for NMIBC.[15,16] Association of age with categorical variables was assessed using $\chi 2$ tests; differences in continuous variables were analyzed using Mann-Whitney *U* test. Kaplan–Meier method was used to estimate RFS and PFS; log-rank tests were applied for pairwise comparison of survival. Univariable and multivariable Cox regression models addressed associations with RFS and PFSb adjusting for the effects of clinico-pathologic features (gender, age, smoking status, physical activity, hypertension, Type II diabetes, size, multifocality and primary tumor). All *P* values were 2-sided, and statistical significance was defined as a $P < .05$. Statistical analyses were performed using Stata 11.0 statistical software (Stata Corp., College Station, TX).

Results

Baseline Clinico-Pathologic Features

A total of 99 (57.6%) patients had an age > 70 years prior to TURBT. There was no difference between clinico-pathologic features among groups (group 1, age ≤ 70 years and group 2, age > 70 years), except that patients aged ≤ 70 years presented a larger size of CIS (35.6% vs. 21.2%), $P = .02$ (Table 1).

Disease Recurrence in Pure Carcinoma In Situ of the Bladder

Within a median follow-up of 53 months (IQR 14-120), 90 patients experienced disease recurrence (52.3%), among which 32 (43.8%) in group 1, and 58 (58.6%) patients in group 2. Five-year RFS was 41.7% (95%CI: 31.8-51.3) in patients with age > 70, compared to 60% (95%CI: 47.8-70.3) in patients with age ≤ 70, $P = .02$ (Figure 1). Among elderly patients, 17.17% reported a non–muscle invasive tumor at 1 year ($n = 17$), in comparison, 6 (8.2%) out of 73 in the under 70 years group.

In univariable Cox regression analyses, age > 70 years (HR 1.64, 95%CI 1.06-2.52, $P = .02$), multifocality (HR 1.73, 95%CI 1.13-2.64, $P = .01$), and the recurrent tumor state (HR 2.24, 65%CI 1.41-3.54, $P = .001$) were significantly associated with worse RFS. In multivariable Cox regression analyses, the same clinico-pathologic factors (age, multifocality, and recurrent tumor state) were independently associated with worse RFS. Harrell's C-index was 65.75 (Table 2).

Disease Progression in Pure Carcinoma In Situ of the Bladder

Within a median follow-up of 120 months (IQR 52-120), 41 (23.8%) patients experienced disease progression, among which 11 (15.1%) in group 1, and 30 (30.3%) patients in group 2. Five-year PFS was 68.3% (95%CI: 57.85-76.7) in patients with age > 70, compared to 86.04% (95%CI: 75.6-92.2) in patients with age ≤ 70, $P = .01$ (Figure 2). Among elderly patients, 6 (6%) had progression to T2 at 12 months versus 1 (1.3%) out of 73 in the under 70 years group.

In univariable Cox regression analyses, age>70 years (HR 2.37, 95%CI 1.19-4.74, $P = .01$), and multifocality (HR 3.22, 95%CI 1.74-5.97, $P < .001$) were significantly associated with worse PFS. In multivariable Cox regression analyses in addition to age ($P = .006$) and multifocality ($P < .001$) also BMI ($P = .04$) was independently associated with worse PFS. Harrell's C-index was 74.71(Table 3).

Discussion

The role of advanced age in BC is well known. The median age at diagnosis is 69 years for men and 71 years for women, with 10-fold higher incidence for patients > 85 years.[17] In addition, the overall probability to develop invasive disease linearly increase with age, rising from 0.01% to 0.02% per year before 40 years to 1.2%-3.7% per year up to 70 years.[18,19] Consistent with literature, in our study, we demonstrated that age represent a strong and independent risk factor for development of recurrence and progression of BC, reporting, for elderly patients, a RFS of 41.7% versus 60% while PFS was 69.3% versus 86.04%. Herr showed, indeed, on a cohort of

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Table 1 Association of Clinic and Pathologic Features With Age (cut-off 70 years) in Patients With Carcinoma In Situ Bladder Cancer

	All cohort	Age ≤ 70 y.	Age > 70 y	*P* value
Total, n (%)	172	73 (42.4)	99 (57.6)	
Gender, n (%)				
Male	134 (77.9)	58 (79.5)	76 (76.8)	.67
Female	38 (22.1)	15 (20.5)	23 (23.2)	
BMI, mean (SD)	24.75 (2.96)	24.44 (2.64)	24.98 (3.18)	.88
Physical Activity, n (%)				
No	144 (83.7)	57 (78.1)	87 (87.9)	.08
Yes	28 (16.3)	16 (21.9)	12 (12.1)	
Hypertension, n (%)				
No	64 (37.2)	29 (39.7)	35 (35.4)	.55
Yes	108 (62.8)	44 (60.3)	64 (64.6)	
Diabetes, n (%)				
No	130 (75.6)	55 (75.3)	75 (75.8)	.95
Yes	42 (24.4)	18 (24.7)	24 (24.2)	
Smoker, n (%)				
No	43 (25)	15 (20.6)	28 (28.3)	.51
Yes	29 (16.9)	13 (17.8)	16 (16.1)	
Former	100 (58.1)	45 (61.6)	55 (55.6)	
Multifocality, n (%)				
Single	120 (69.8)	52 (71.2)	68 (68.7)	.71
Multiple	52 (30.2)	21 (28.8)	31 (31.3)	
Size, n (%)				
< 3cm	125 (72.7)	47 (64.4)	78 (78.8)	.03
≥ 3 cm	47 (27.3)	26 (35.6)	21 (21.2)	
Primary tumor, n (%)				
No	38 (22.1)	12 (16.4)	26 (26.3)	.12
Yes	134 (77.9)	61 (83.6)	73 (73.7)	

Table 2 Univariable and Multivariable Cox Regression Analyses Predicting Disease Recurrence of 172 Patients With Pure CIS Bladder Cancer Treated With BCG. Values in bold are statistically significant (<0.05)

Variables	Recurrence					
	Univariable			Multivariable		
	HR	95%CI	*P*	HR	95%CI	*P*
Age cat.	1.64	1.06-2.52	**.02**	1.68	1.07-2.64	**.02**
Gender (male vs. female)	0.94	0.43-1.59	.58	1.34	0.79-2.29	.27
No Smoking	**Ref.**					
Current	1.46	0.76-2.79	.24	1.07	0.53-2.14	.84
Former	1.26	0.75-2.11	.37	1.21	0.71-2.06	.61
Physical Activity (no vs. yes)	1.36	0.8-2.31	.24	1.26	0.71-2.24	.42
BMI cont.	1.03	0.96-1.11	.36	1.02	0.95-1.1	.52
Hypertension (no vs. yes)	1.26	0.81-1.94	.29	1.24	0.79-1.94	.34
Type 2 Diabetes (no vs. yes)	0.72	0.43-1.2	.21	0.64	0.36-1.14	.13
Multifocality (single vs. multiple)	1.73	1.13-2.64	**.01**	1.7	1.06-2.71	**.02**
Size (<3 vs. ≥ 3) cm	0.84	0.53-1.35	.48	1.02	0.6-1.74	.93
Primary (no vs. yes)	2.24	1.41-3.54	**.001**	1.8	1.07-3.03	**.02**
Harrell's C Index	65.75					

BCG = Bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio; *P* = *P* value; CIS = carcinoma in situ.

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Figure 2 Kaplan-Meier progression-free survival estimates.

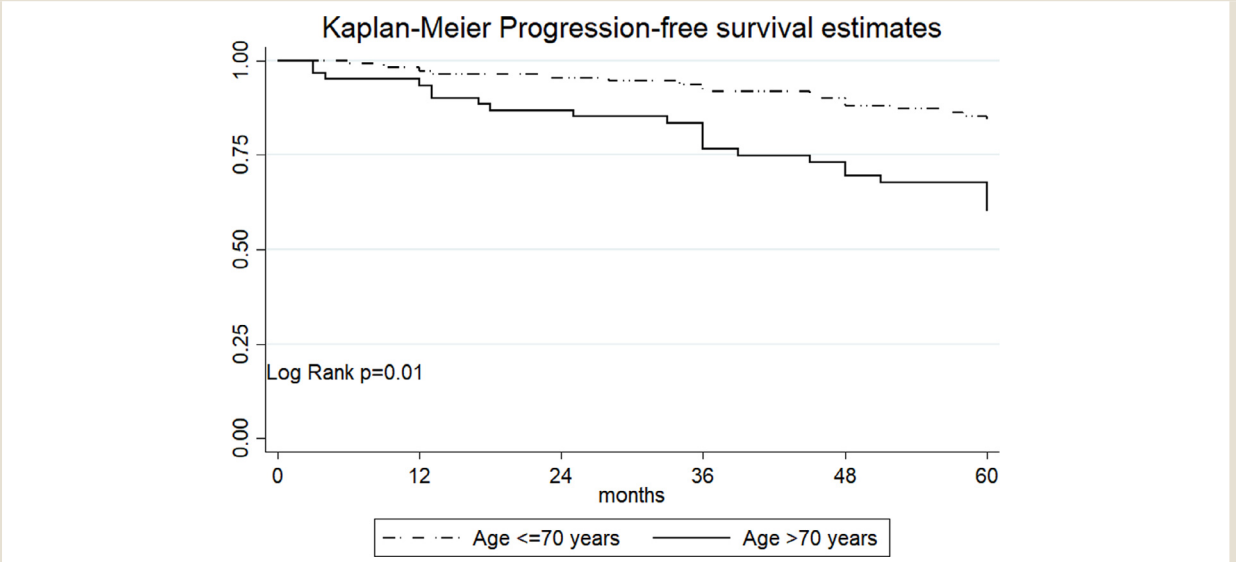

Table 3 Univariable and Multivariable Cox Regression Analyses Predicting Disease Progression of 172 Patients With Pure CIS Bladder Cancer Treated With BCG. Values in bold are statistically significant (<0.05)

Variables	Progression					
	Univariable			Multivariable		
	HR	95%CI	P	HR	95%CI	P
Age cat.	2.37	1.19-4.74	**0.01**	2.82	1.33-5.97	**0.006**
Gender (male vs. female)	2.25	0.88-5.74	0.08	2.12	0.81-5.52	0.12
No Smoking	**Ref.**					
Current	0.93	0.36-2.37	0.88	0.71	0.26-1.95	0.51
Former	0.77	0.38-1.57	0.48	0.84	0.4-1.73	0.63
Physical Activity (no vs. yes)	1.26	0.58-2.73	0.55	0.98	0.4-2.39	0.98
BMI cont.	1.09	0.98-1.21	0.09	1.13	1-1.28	**0.04**
Hypertension (no vs. yes)	0.6	0.32-1.1	0.1	0.65	0.34-1.24	0.19
Type 2 Diabetes (no vs. yes)	0.78	0.37-1.63	0.51	0.46	0.19-1.12	0.09
Multifocality (single vs. multiple)	3.22	1.74-5.97	**<0.001**	4.4	2.21-8.75	**<0.001**
Size (<3 vs. ≥ 3) cm	1.31	0.68-2.5	0.41	1.27	0.58-2.81	0.54
Primary (no vs. yes)	0.87	0.38-1.97	0.74	0.54	0.21-1.4	**0.21**
Harrell's C Index	74.7					

BCG = Bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio; *P* = *P* value; CIS = carcinoma in situ.

805 patients with multiple or recurrent high-grade Ta, T1, and/or carcinoma in situ BC treated with TURB plus BCG therapy, that 27% of patients older than 70 years were cancer free compared with 37% younger than 70 years ($P = .005$).[12] Similarly, Joudi et al. reported, in a cohort of 412 patients with superficial BC treated with TURB plus BCG therapy, a 22% of difference in cancer free survival (CFS) among patients < 70 years and > 80 years (61% vs. 39%, $P = .0002$), with the latter that also reported a persistently lower response rate to BCG therapy.[20] Analougously, Kohjimoto et al., reported on 491 patients with non–muscle invasive BC treated with TURB followed by BCG therapy, an higher incidence of multiple and higher grades tumors in > 70 patients and a lowest RFS (47.2%) and PFS (89.4%) at 2 year among > 80 years patients, with a recurrence and progression risk of 2.3 and 2.8 times respectively higher compared to < 70 years patients.[21] More recently, an European Organization for Research and Treatment of Cancer (EORTC) trial, demonstrated, in 822 Ta-T1 patients treated with BCG or epirubicin and followed for a median of 9.2 years, a shorter time to progression, overall, and cancer specific survival in patients >70 years, confirming the worse oncological outcomes

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in elderly patients.[15] Nevertheless, if age seems to be significantly associated with non–muscle invasive BC, its role in pure CIS is still controversial. As reported by Chade et al.in 155 patients with primary CIS treated with TURB followed by BCG therapy, 5-year cumulative incidence of progression to invasive disease was 45% (95% CI, 37%-55%) while to muscle-invasive disease was 17% (95% CI, 12%-25%); no association was however found with age or gender.[22] Analogously, Takenaka et al., did not report, in a cohort of 185 patients with CIS (of which 62 with primary CIS) followed by BCG instillations, a predictive value of age in PFS[8]; similar results were also reported by a multicenter study effected in a smaller cohort of 47 patients with CIS (median age 59,5 years, range 40-76 years) .[23] On the contrary, Hurle et al. showed a better progression free survival (PFS), with181 months (95% CI: 169-193 months) compared to 154 months (95% CI: 133-176 months), in CIS patients compared to non–pure CIS population ($P = .03$), reporting, in addition a significant association between pure CIS, and older age ($P = .02$) .[24] Similar conclusions were reported by Kim et al. which included, in a retrospective study,64 patients with primary CIS, treated with at least 6 cycles of BCG: patients with recurrence were indeed significantly older ($P = .044$) and a worse RFS was reported in patients > 60 years ($P = .015$) .[25]

Although the precise reason for adverse oncological outcomes of BC in elderly is unclear, several potential explanations have been proposed, including the advanced stage at the diagnosis, a longer exposure to carcinogens and a longer time permitting the development and the accumulation of cellular alterations leading, ultimately, to neoplastic transformations.[26] Moreover, a deteriorated innate, and adaptive immune system in elderly has been hypothesized to impair the efficacy of BCG therapy.[27] The efficacy of BCG for CIS has been well determined in the SWOG 8507 trial which compared induction therapy only with induction plus maintenance in a prospective and randomized fashion. The complete response (CR) rate at 3 months (after induction therapy) was 57% and 55% in the induction-only and the maintenance arms of the trial, respectively while the CR rate after 6 months increased to 68% in the induction-only arm, and to 84% in the maintenance arm ($P = .004$).[28] As reported by this trial, BCG is a real game-changer in the management of CIS. Therefore, a potential alteration of its efficacy in older patients could be highly detrimental. However, despite the well-known hypotheses on the lower efficacy of BCG therapy in elderly (that could have explained the worse oncological outcomes in this subset of patients), a recent study by Calò et al. reported similar benefit and adverse reactions between patients over and under 75 years.[29] A similar result was also reported in a previous study by Yuge et al. .[30] Consistently with reported literature, we found no statistical significance regarding BCG side effects between groups, except regarding cystitis, which was more frequently reported in group 1 (age < 70 years). Recently, when including molecular subtypes of CIS, age together with smoking status were the only risk factors for worse outcomes.[31] To our knowledge, no previous study has reported a significant association of age with pure CIS.

Furthermore, BMI, and multifocality were also independent predictive factors for worse outcomes in patients with pure CIS. BMI was investigated in many studies[32] and in the most recent meta-analysis was demonstrated that obese individuals were at higher risk for disease progression (HR 1.88, 95% CI: 1.41, 2.50, $n = 3$) and recurrence (HR 1.60, 95% CI: 1.06, 2.40, $n = 7$) compared to normal BMI patients.[33] Multifocality is a well-known predictive factor for NMIBC,[34] and its role is even more important in case of CIS. In our cohort, CIS increased both the risk of recurrence, and progression.

The result of our study should be interpreted in the light of some limitations due to its retrospective nature, the variability among the centers participating in the study, and number of patients included from each center. However, despite the intrinsic variability among the centers participating in the study, the management, and the follow up of bladder cancer was always performed according to the EAU guidelines at that time. In addition, the longer follow-up, multi-center design, and the size of patients involved are among the strength of our study. Considering the insidious nature of CIS and its harmfulness in progress to muscle-invasive disease, present findings are particularly important for counselling, and treatment of older patients. In addition to standard TURB and BCG therapy, a strict follow-up is required in elderly, in order to intercept and promptly treat recurrence and progression in those patients.

Conclusion

Aging appears to be associated with an increased risk of recurrence and progression of pure carcinoma in situ of the bladder. Elderly patients might fail to respond to BCG therapy. Due to the scarcity of data reported in the literature, further studies are required to evaluate, in addition to the role of age, the influence of other variables as BMI, multifocality, and origin of CIS (primary/secondary) in disease recurrence and progression.

Clinical Practice Points

Bladder cancer represents the fourth most common cancer in the USA and the 12th most common cancer worldwide. Up to 75% of patients has a disease confined to the bladder mucosa. Carcinoma in situ (CIS) is a flat, high-grade tumor confined to the mucosa which presents an increased risk of progression to muscle-invasive disease, although a proper therapy that includes transurethral resection, and adjuvant immunotherapy with intravesical instillations of Bacillus Calmette-Guerin (BCG). In order to achieve the best results, BCG requires a competent immune system which could be weakened in older patients. As results, older patients with CIS (> 70 years) report worse oncological outcomes in terms of recurrence-free survival (RFS), and progression-free survival (PFS) compared to younger patients. It is therefore of the uttermost importance provide a strict follow-up in elderly in order to avoid a rapid worsening of the disease, preserving the bladder, and thus the quality of life.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper

Disclosure

Protocol development: Ferro; Data collection: Musi, Lucarelli, Del Giudice, Hurle, Damiano, Cantiello, Mari, Minervini,

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