

## Research Article

# Clinicopathological Features and Therapeutic Outcomes of Bladder Cancer in Younger Adults

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### Abstract

**Objectives:** To evaluate the clinicopathological features, recurrence and survival in patients up to 50 years of age diagnosed with primary bladder-cancer.

**Methods:** During a 14-year period (1997-2011), 71 patients aged  $\leq 50$  years with bladder-cancer were analyzed in a single institution. Survival probabilities and associations were calculated using Kaplan-Meier, log-rank and Chi-squared-tests.

**Results:** Median age at diagnosis was 43.4 years (inter quartile-range [IQR] 39-47); median follow-up was 60.9 months (2.1-168.3). Non-muscle-invasive (NMI; pTa-pT1) bladder-cancer was commoner than muscle-invasive (MI; pT2-pT4) bladder-cancer (89% [n=63] versus 11% [n=8], respectively). Nineteen patients (27%) were  $\leq 40$  years and 52 (73%) were 41-50 years. MI bladder-cancer was commoner in 41-50-year group (13% [n=7/52]) than  $\leq 40$ -year group (5% [n=1/19]; p=0.03), as was high-grade disease (23% [n=12/52] versus 16% [n=3/19], respectively; p=0.04). Twenty-one patients (30%) developed recurrence (29% [n=6/21]  $\leq 40$ -years versus 72% [n=15/21] 41-50-years; p=0.12), with progression occurring only in 41-50-year group (19% [n=4/21]). A higher proportion of patients underwent cystectomy in the 41-50-year group (89% [n=8/9]) compared to those in the  $\leq 40$ -year group (11% [n=1/9]; p=0.03). Five-year overall survival and cancer-specific survival were both 100% in  $\leq 40$ -year group, and 84% and 86% in 41-50-year group, respectively. Among patients aged 41-50 years, those with MI bladder-cancer had particularly lower survival rates.

**Conclusion:** Bladder-cancer in younger adults is generally characterized by less aggressive disease with a favorable outcome. However, there is an increase in tumors incidence, muscle invasion, recurrence and progression after 40 years of age. Higher cystectomy and lower survival rates are also observed in this age group.

**Keywords:** Bladder-Cancer; Natural History; Cystectomy; Prognosis; Younger Adults.

### Introduction

Bladder cancer is typically a disease of older individuals with a peak incidence in the sixth decade. It is uncommon below the age of 40 years with a reported incidence of less than 1% occurring in this age group [1,2]. In the UK, there were 10,373 newly-diagnosed primary bladder cancers in 2008. Among these, only 64 (<1%) cases were found in patients aged below 40 years and 266 (3%) in patients aged less than 50 years [3]

Among younger patients, there is debate and uncertainty in the literature regarding the clinicopathological characteristics and prognosis of the disease. Some groups have observed similar patterns of clinical behavior and prognosis between younger and old-

er patients [4,5] while others have reported lower rates of disease recurrence and progression with higher survival rates in younger counterparts [6,7]. This uncertainty of the natural history of bladder cancer in younger patients can have important implications for both healthcare providers and patients, particularly in the selection of appropriate diagnostic and surveillance modalities and for choosing suitable treatment strategies. Furthermore, although no consistent age criteria have been used to define 'younger' groups of patients, the majority of studies on bladder cancer in younger adults have assumed this to be patients aged 40 years or less. In addition, most previous series have used sample sizes that are too small for meaningful interpretation of the prognosis in younger patients.

The primary aim of this study was to evaluate the clinicopathological characteristics, disease recurrence, overall survival

(OS) and cancer-specific survival (CSS) in patients up to 50 years of age diagnosed with primary bladder cancer in a large tertiary referral centre between 1997 and 2011.

## Materials and Methods

**Subjects:** This study was approved internally and informed consent was sought from all participants at time of surgery. During a 14-year period (between May 1997–March 2011), all consecutive patients aged  $\leq 50$  years diagnosed and managed with primary bladder cancer were analyzed using a prospectively maintained database. The study was undertaken in a single tertiary institution (University Hospital Southampton NHS Foundation Trust). Patients diagnosed with non-primary bladder cancer and those aged over 50 years were excluded. Thus, 71 patients were considered to be suitable for inclusion in the study. Demographic data, presenting symptoms, initial transurethral resection pathology and primary treatment were obtained using medical records. Disease recurrence, progression, and final patient status were also recorded.

**Tumor Classification And Outcome Measurement:** Histological staging and grading of bladder cancer was performed by a dedicated histopathologist using the tumor-node-metastasis (TNM) [8] and the World Health Organization classification [9]. Non-muscle-invasive (NMI) tumors were categorized as carcinoma in situ (CIS), pTa and pT1 tumors, and muscle-invasive (MI) tumors included pT2, pT3 and pT4 tumors. Additionally, grade I and II tumors were considered low grade, while grade III high grade. Disease progression was defined as the transition, on pathological examination, of NMI to MI bladder cancer. Survival was defined as the time from initial presentation to the study endpoint. Death due to bladder cancer was defined when bladder cancer was the main attributable disease on the death certificate or suggested from case notes (e.g., palliative treatment for metastasis prior to death). For patients who were lost to follow-up, the general practitioner was contacted in order to clarify the patient's survival status.

**Statistical Analysis:** Results were entered into a database and analyzed using Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago). Data are presented as numbers and percentages of patients. Associations between groups were analyzed using the Chi-squared test. Five year OS, CSS and recurrence-free survival (RFS) probabilities were plotted using the Kaplan-Meier method, with statistical significance calculated using the log-rank test. A  $p$  value of  $<0.05$  was considered statistically significant.

## Results

**Demographics:** The median age at diagnosis of primary bladder cancer was 44.3 years (inter quartile-range 39-47). The male-to-female ratio was 5.5:1 (60 males, 11 females). The median follow-up period was 60.9 months (2.1–168.3). Visible haematuria was the presenting symptom in 52 (72%) patients. Other presenting symptoms included lower urinary tract symptoms ( $n=11$ ; 16%),

microscopic haematuria ( $n=6$ ; 9%) and urinary tract infection ( $n=2$ , 3%). Twenty-eight (39%) patients were current tobacco smokers and a further 11 (16%) were ex-smokers. Thirty (42%) patients were non-smokers and smoking status in 2 (3%) patients was unknown.

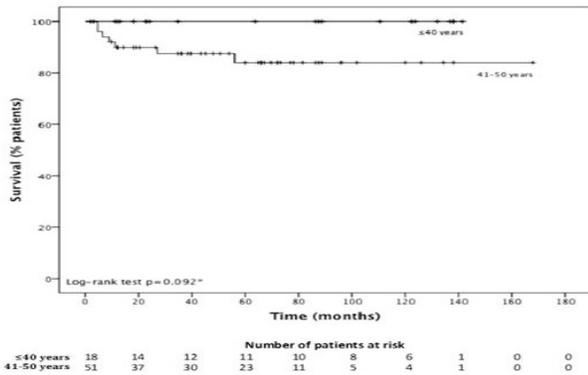
**Tumor Stage and Grade:** All patients underwent cystoscopy with biopsy for histological staging and grading of tumors. Tumor pathology was transitional cell carcinoma (TCC) in all cases. Primary histopathology was NMI TCC in 63 (89%) patients and MI TCC in eight (11%) patients. There were 56 (79%) low-grade and 15 (21%) high-grade tumors.

**Primary Treatment:** Forty-five (63.4%) patients with NMI bladder cancer underwent primary transurethral resection of bladder tumor (TURBT), of which four (6%) patients received additional Bacillus Calmette–Guérin injection. Fourteen (20%) patients with NMI tumors underwent biopsy and diathermy and the remaining four (6%) patients with NMI tumors underwent radical cystectomy due to high-grade disease. Fourteen (20%) patients had postoperative intravesical instillation therapy with mitomycin-C ( $n=12$ ) or epirubicin ( $n=2$ ). Among patients with MI bladder cancer, five (7%) underwent radical cystectomy, two (2.8%) underwent TURBT as the only treatment and one (1%) received palliative chemotherapy. Seven (10%) patients with MI bladder cancer received neo-adjuvant or adjuvant chemotherapy with cisplatin or gemcitabine.

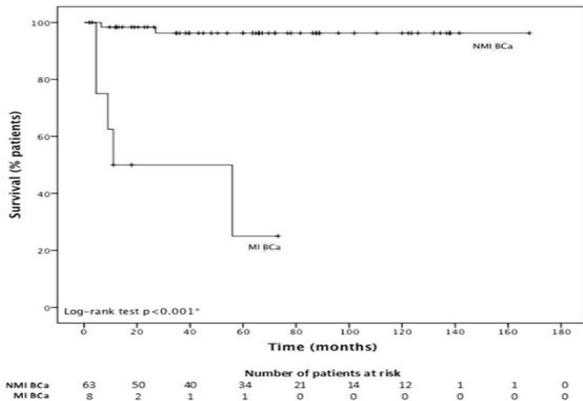
**Disease Recurrence:** During follow-up, a total of 21 (30%) patients developed recurrence, with a median time to first recurrence of 13 months (6.3–26). Of these, 13/21 (62%) were progression-free and 8/21 (38%) progressed to a higher stage (2/21 [10%] from NMI to MI). Three [14%] patients progressed to a higher grade (all upgraded to grade III).

**Comparison of age  $\leq 40$  years versus 41-50 years:** Nineteen (27%) patients were aged  $\leq 40$  years and 52 (73%) were 41-50 years. Muscle invasive bladder cancer was significantly commoner in the 41-50-year group (13% [ $n=7/52$ ]) than the  $\leq 40$ -year group (5% [ $n=1/19$ ];  $p=0.03$ ). Patients aged 41-50 years also had a higher grade of disease at presentation (23% [ $n=12/52$ ]) compared to those aged  $\leq 40$  years (16% [ $n=3/19$ ];  $p=0.04$ ). Of the 21 patients who developed tumor recurrence, 6/21 (29%) were in the  $\leq 40$ -year group compared to 15/21 (72%) in the 41-50-year group ( $p=0.12$ ). Tumor progression to MI disease occurred only in the 41-50-year group (19% [ $n=4/21$ ]).

**Os, Css and Rfs Probabilities:** Fifty-six (78%) patients were alive with no evidence of disease, one (1%) was alive with loco-regional disease and six (9%) were alive but lost to follow-up, seven (10%) patients died during the study period and six (9%) died as a direct result of the disease. Cancer-specific mortality was only observed in the 41-50-year group (12% [ $n=6/52$ ];  $p=0.19$ ). The 5-year OS (Figure 1).



**Figure 1:** Overall survival of young adults with primary bladder cancer by age group (\*two-tailed test).



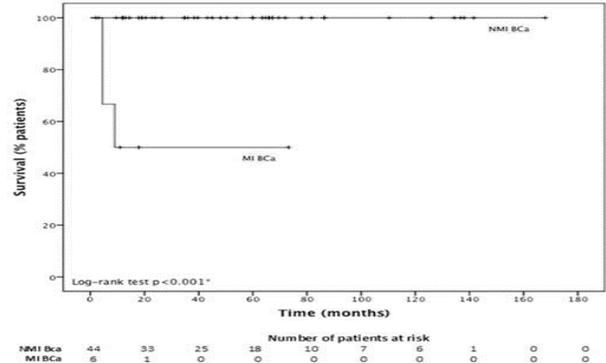
**Figure 2:** Overall survival of young adults aged 41-50 years with NMI versus MI BCa (NMI, non-muscle invasive; MI, muscle invasive; BCa, bladder cancer; \*two-tailed test).

The 5-year RFS rate was also lower in patients with MI (50%) compared NMI (100%) bladder cancer in this age group ( $p<0.001$ ) as shown in (Figure 3).

patients with bladder cancer are crucial for adequate treatment and follow-up decisions. The majority of previous studies have reported on patients younger than 40 years of age. There is marginal data in the literature on the clinical behavior and outcomes of the disease in those aged 41-50 years.

There is still much debate regarding the clinicopathological behavior and outcomes of bladder cancer in younger patients (Table 1).

Authors	n	Age (yr)	NMI BCa (%)	MI BCa (%)	Recurrence (%)	Progression to MI BCa (%)	Mortality (%)
Present series	71	22-50	88.7	11.3	29.6	5.6	9.9
Fitzpatrick et al. (1986) [6]	50	15-40	100	0	28	6	?
Kurz et al. (1987) [4]	25	14-39	92	8	36	12	4
Wan et al. (1989) [2]	35	16-?	77.1	22.9	48.6	25.7	29
Erozenci et al. (1994) [7]	156	19-40	89.1	10.9	48.7	22.8	1.3
Perez et al. (1996) [13]	34	?-30	67.6	23.3	32	3.6	0
Aboutaieb et al. (1998) [11]	26	20-40	42.3	57.7	19.2	23.1	19.2



**Figure 3:** Recurrence-free survival of young adults aged 41-50 years with NMI versus MI BCa (NMI, non-muscle invasive; MI, muscle invasive; BCa, bladder cancer; \*two-tailed).

**Patients Treated With Cystectomy:** A total of nine (13%) patients ultimately treated with cystectomy. Primary histo-pathological staging was NMI bladder cancer in four (6%) patients and MI bladder cancer in five (7%) patients. This was revised to three (4%) NMI and six (9%) MI cases following cystectomy. One (1%) tumor was low-grade and eight (11%) were high-grade, which remained unchanged following cystectomy. A higher proportion of patients underwent cystectomy in the 41-50-year group (89% [n=8/9]) compared to those in the ≤40-year group (11% [n=1/9];  $p=0.03$ ). In addition, tumor recurrence and mortality following cystectomy only occurred in the 41-50-year group (44% [n=4/9]). Five-year OS rates were 100% in the ≤40-year group and 40% in the 41-50-year group ( $p=0.61$ ) whilst the corresponding CSS rates were 100% and 46%, respectively ( $p=0.70$ ).

## Discussion

In this retrospective, single centre study, we evaluated the clinicopathological characteristics and outcomes of bladder cancer in relatively large cohort of younger adult patients, a group we defined as being aged 50 years or less. Data on the outcome of young

Ozbey et al. (1999) [12]	25	19-39	64	36	20	12	28
Yossepowitch et al. (2002) [5]	74	16-40	83.4	16.6	38.7	16	2.7
Wen et al. (2005) [14]	30	22-40	76.6	23.4	43.3	8.3	6.7
Nomikos et al. (2011) [10]	31	21-39	90.3	9.7	32	3.2	0

**Table 1:** Comparative data of young patients with BCa from other series (NMI, non-muscle invasive; MI, muscle invasive; BCa, bladder cancer).

While some groups have reported less aggressive disease with favorable rates of recurrence, progression and survival [6,7,10] others have shown higher rates of invasiveness, recurrence and mortality similar to that seen in older patients [2,11,12]. Whilst treatment for bladder cancer should be instituted on the basis of the clinical stage and not age, this conflicting data on the outcomes in younger patients can create difficulties for clinicians when deciding on the most appropriate surveillance strategies for reassuring and following-up such patients.

In our cohort, the majority of patients (89%) were diagnosed with NMI bladder cancer, with only a small proportion of patients with MI tumors. In addition, nearly 80% of all cancers were of low grade. Whilst 30% of patients had a recurrence, over 90% of these were NMI tumors that had not progressed, suggesting that the majority of bladder cancer in patients aged 50 years or less is low-stage and low-grade for which current treatment is potentially curable. These findings are supported by Erozcenci et al. who published the largest series of bladder cancer in younger adults aged 40 years or less, documenting that 89% of patients had NMI disease, with recurrence and progression rates of 49% and 23%, respectively [7].

In a recent meta-analysis of bladder cancer in younger adult and paediatric patients, tumor recurrence and progression were infrequent in the first two decades and increased gradually in each successive decade, likely influenced by the increased proportion of higher grade and stage tumors [15]. Similarly, an important finding of our study was the differences in tumor characteristics between patients aged 40 years or less and 41-50 years. Patients in the younger group had a significantly lower rate of MI and high-grade disease compared to their older counterparts. Furthermore, in the younger cohort, all six patients who had a recurrence did not progress to MI disease. The only cases of tumor progression to MI bladder cancer occurred in the 41-50-year group who had a higher rate of recurrence. Some researchers have attributed differences in observed tumor behaviour between different age groups as being secondary to increasing mutations in a number of cell cycle regulators. Paner et al. reported bladder cancer occurring in younger patients to have a much lower incidence of aberrations in chromosome nine, fibroblast growth factor receptor three, p53 and microsatellite instability [15]. Our study would suggest 40 years of age to be a threshold above which a critical number of genetic alterations favoring the MI phenotype are significantly more likely.

Our findings also suggest that the prognosis for younger patients with bladder cancer is dependent on the patient age group and stage of the cancer. The 5-year CSS rate in our series was 100% and 86% in younger and older groups of patients, respectively. Moreover, patients aged 41-50 years with MI disease had significantly lower OS, CSS and RFS rates than those with NMI disease.

Notably, the one patient in the  $\leq 40$ -year group who underwent cystectomy for MI disease had a better survival outcome following cystectomy compared to the eight patients in the 41-50-year group undergoing cystectomy for MI disease. Although it is difficult to draw firm conclusions from this single case, it may be that at a younger age there is a tendency towards a better disease course in patients undergoing cystectomy [16]. reported similar findings in 75 patients undergoing cystectomy for primary bladder cancer; younger patients aged less than 31 years had a significantly better prognosis compared to those aged 31-40 years [16]. Additionally, 5-year survival rates post-cystectomy for those aged 41-50 years in our series were better in high-grade NMI bladder cancer than in high-grade MI bladder cancer, implying that the subset of younger patients with MI disease are particularly at higher risk of poor outcome following surgery. These differences in survival patterns following cystectomy may suggest the need for varied follow-up protocols for different groups of patients with targeted surveillance for high-risk groups.

We recognize that our study has limitations, particularly the relatively small number of patients aged 40 years or less which can limit survival analysis. Even though we reviewed our records over a 14-year period at a large tertiary referral centre, we recruited only 19 patients in this age category. This reflects the low incidence of primary bladder cancer in this age group. A solution to this low yield may be a national young bladder cancer registry. An additional limitation in this study is its retrospective nature and the consequences this has for the quality of data collection and medical documentation. Thus, larger prospective studies could confirm long-term progression and outcomes, particularly in younger adults undergoing cystectomy.

In conclusion, bladder cancer in younger patients up to 50 years of age is usually associated with low-grade, NMI tumors for which standard endoscopic treatment is potentially curative. However, our study suggests that after the age of 40 years there is an increase in tumor incidence, muscle invasion, recurrence and pro-

gression. Higher rates of cystectomy and lower survival rates are also observed in this age group. Prospective studies using larger samples of patients are needed to clarify the clinicopathological characteristics and outcomes in this group of patients. This would allow for the development and implementation of guidelines on how to best follow-up younger patients with bladder cancer.

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**Conflicts Of Interest:** We do not have any direct conflict of interest that we should disclose.

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