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ORIGINAL ARTICLE

Retrospective audit on the management of newly diagnosed non-muscle-invasive bladder cancer patients and their oncological outcomes

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Background

Non-muscle-invasive bladder cancer (NMIBC) is a heterogenous subclassification of urothelial carcinoma with variation in risk of recurrence and progression. The aim of this audit was to assess whether the clinical management of NMIBC was being carried out according to the recommendations provided by the European Association of Urology (EAU) guidelines.

Method

154 patients who were newly diagnosed with NMIBC were selected. Details about presentation, risk factors and clinical management were collected for analysis. The clinical standard of care used was the EAU Non-muscle-invasive Bladder Cancer Guidelines 2020. Oncological outcomes for this patient group was also documented. The European Organisation for Research and Treatment of Cancer (EORTIC) risk table was used to predict recurrence and progression in NMIBC. The risk group stratification table in the EAU guidelines (2020) was used to classify tumours according to their characteristics. SPSS and Kaplan Meier curves were used to analyse the results.

Results

TURBT was carried out in 52.9% of indicated patients; intravesical therapy in 14.1% of indicated patients; CT-IVU follow up according to guidelines in 64.3%; urine cytology follow up according to guidelines in 66.9% patients. Cystoscopy carried out after 3 months showed a recurrence rate of 12.3%

Conclusion

The clinical management of NMIBC has an important bearing on the progression of the cancer. Stricter adherence to the guidelines will enable the clinician to strike a balance between cost cutting and reduced tumour progression.

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Bladder cancer is the 7th most common cancer in males and the 17th in females worldwide.[1] In Malta bladder cancer is the 6th most common cancer, having accounted for 6.1% of all cancers diagnosed in 2020.[2]

Around 75% of cases present with non-muscle-invasive disease.[1] This group of patients represents a heterogeneous population with variable risk of recurrence and progression. This risk assessment is based on morphological and histopathological variables and stratifies non-muscle-invasive bladder cancer (NMIBC) into low risk, intermediate risk, high risk and very high risk groups.

Recurrence rates range from 31% to 78% and progression rates range from 0.8% to 45% at 5 years.[3] This implies that NMIBC will often require lifelong follow ups. Different grades of carcinoma exhibit differences in behaviour, aggressiveness and prognosis. Low-risk tumours are usually characterized by a relatively benign behaviour but often do recur although disease progression is rare, intermediate risk tumours have a higher recurrence rate but a low progression rate while high risk tumours have both a high recurrence and progression rate. These differences will require specific follow up strategies and treatment methods.

In this audit we looked into the clinical management of NMIBC including Trans-urethral removal of bladder tumour (TURBT), intravesical therapy, cystoscopy, CT intravenous urogram (CT-IVU) and urine cytology and assessed if it was carried out according to the recommendations provided by the European Association of Urology (EAU) guidelines.

MATERIALS AND METHODS

Patients who were newly diagnosed with NMIBC between January 2015 and December 2017 were selected from biopsy results obtained from the pathology department at Mater Dei Hospital (MDH). This excluded patients with muscle invasive bladder cancer, de novo metastatic disease, as well as patients with recurrent NMIBC diagnosed before 2015.

Distinction between new onset and recurrent NMIBC as well as details about presentation, risk factors and clinical management were obtained from the patient dashboard, MDH electronic database and the patients' medical notes. The primary outcome measured was the use of intravesical therapy in patients with NMIBC and their follow up. The clinical standard of care used as gold standard was the EAU Non-muscle invasive Bladder Cancer Guidelines 2020.[4] on intravesical therapy. Secondary outcomes measured included diagnostic and therapeutic interventions performed as well as oncological outcomes using Kaplan Meier curves.

The European Organization for Research and Treatment of Cancer (EORTC) risk table was then used to predict the recurrence and progression in stage Ta and T1 bladder cancer patients. The risk group stratification table in the EAU guidelines\(2020\) was used to classify the tumours into low, intermediate, high and very high risk according to their characteristics. Statistical Package for the Social Sciences (SPSS) was used to analyse the results and Kaplan Meier curves were used for survival analysis.

RESULTS

The cohort consisted of 154 patients who were newly diagnosed with NMIBC between 3rd January 2015 and 18th December 2017. Patient age ranged from 39 to 93 years. 129 patients (83.8%) were male while 25 patients (16.2%) were female.

84 patients (54.5%) presented with visible haematuria; 8 patients (5.2%) presented with microscopic haematuria; 6 patients (3.9%) presented with lower urinary tract symptoms (LUTS); 4 patients (2.6%) had pelvic pain while 1 patient (0.6%) presented with an upper tract obstruction. 22 patients (14.3%) were found incidentally while in 29 (18.8%) cases, the data was not available.

From our cohort of patients, 83 (53.9%) were classified as low risk; 21 (13.6%) were intermediate risk; 35 (22.7%) were high risk while 15 (9.7%) were classified as very high risk.

2nd look TURBT was indicated in 51 cases (33.1%) and performed in only 27 cases (52.9%).

Peri operative single dose mitomycin was administered in 36 patients (23.4%).

Intravesical therapy after primary diagnosis was indicated in 71 patients (46.1%) (intermediate, high and very high risk) but was only given in 10 patients (14.1%).

In the intermediate risk group 9.5% were given intravesical therapy. In the high risk group 5.7% of patients were given intravesical bacillus Calmette-Guerin (BCG) for 6 weeks; 5.7% were given intravesical BCG for 6 weeks with 2 years' maintenance while 8.6% were given intravesical BCG for 6 weeks with 3 years' maintenance. 80% of high risk cases were not given any form of intravesical

therapy. In the very high risk group 93.3% of patients were not given any form of intravesical therapy.

Cystoscopy was carried out after 3 months in 81 patients (52.6%). 10 of these patients (12.3%) had a recurrence. 3.6% of low risk cases had a recurrence; 14.3% of recurrences were in the intermediate risk group; 5.7% were in the high risk group while 13.3% were in the very high risk category.

CT-IVU follow up was carried out according to guideline in 99 cases (64.3%) while in 55 cases (35.7%) CT-IVU was not performed as recommended by EAU guideline. In the high risk group, 25.7% underwent CT-IVU as per EAU guidelines. In the very high risk group, 26.7% underwent CT-IVU.

In 103 cases (66.9%), urine cytology follow up was according to guideline while in 51 cases (33.1%) urine cytology was not performed according to the EAU guidelines. In the high risk category 11.4% underwent urine cytology according to the EAU guidelines. However none of the very high risk cases had urine cytology follow up carried out.

In 137 patients (89.0%), detrusor muscle was absent. Of these only 5 (3.6%) had a 2nd look TURBT performed.

Recurrence on follow up was noted in 31 out of 83 (37.3%) low risk cases, 15 of 21 (71.4%) intermediate risk cases, 21 of 35 (60%) high risk cases and 11 of 15 (73.3%) of very high risk cases. Average time to 1st recurrence was noted to be 491.2 days in low risk cases, 431.9 days in intermediate risk cases, 414.1 days in high risk cases and 266.1 days in very high risk cases.

In terms of prognosis, 61 of 83 patients (73.5%) with low risk NMIBC were found to be alive and disease free while 7 of 83 (8.4%) died of cancer. 10 of 21 patients (47.6%) with intermediate risk NMIBC were disease free while 2 of 21 (9.5%) died of cancer. 27 of 35 patients (77.1%) with high risk NMIBC were disease free while 5 of 27 (18.5%) died of cancer. 6 of 15 patients (40%) with very high risk NMIBC were found to be disease free while 9 of 15 (60%) died of cancer.

The Kaplan Meier curves in **Figure 1** and **Figure 2** highlight the cancer specific survival and the overall survival for the patient cohort respectively. Patients at very high risk had the worst prognosis in both overall and cancer specific survival (**Figures 3, 4**). Low risk patients had better cancer specific survival rates compared to high risk patients (**Figure 3**). However the overall survival rates in low risk patients was

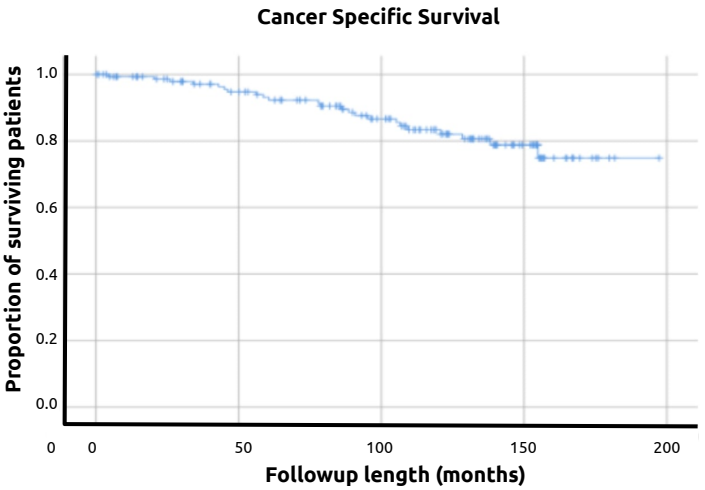

Figure 1 *Kaplan Meier Curve showing Cancer Specific Survival for whole cohort*

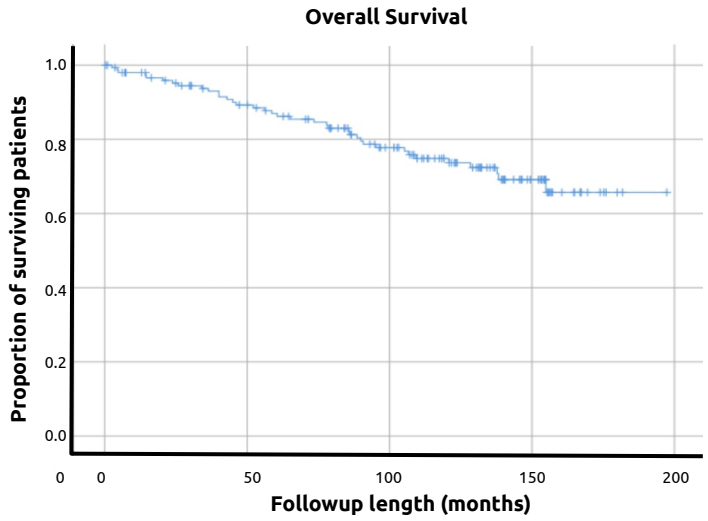

Figure 2 *Kaplan Meier Curve showing overall survival for the whole cohort*

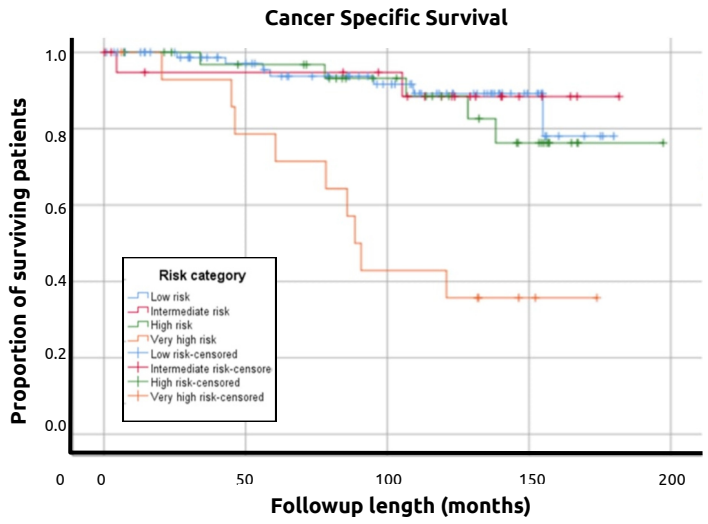

Figure 3 *Kaplan Meier curve showing cancer specific survival stratified by risk group*

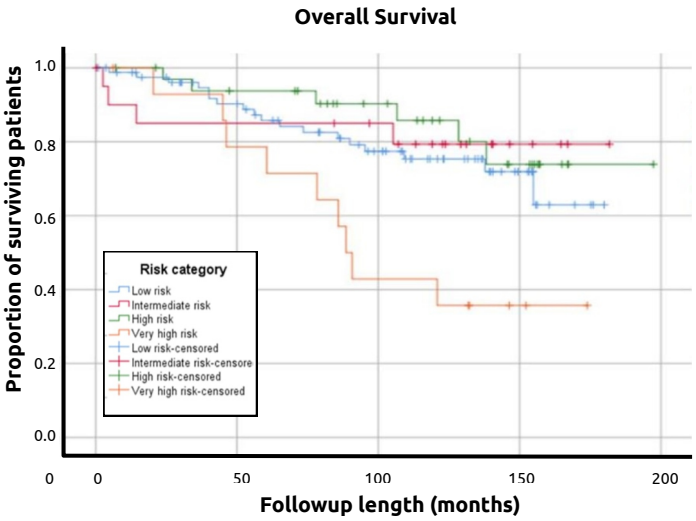

Figure 4 *Kaplan Meier curve showing overall survival stratified by risk group.*

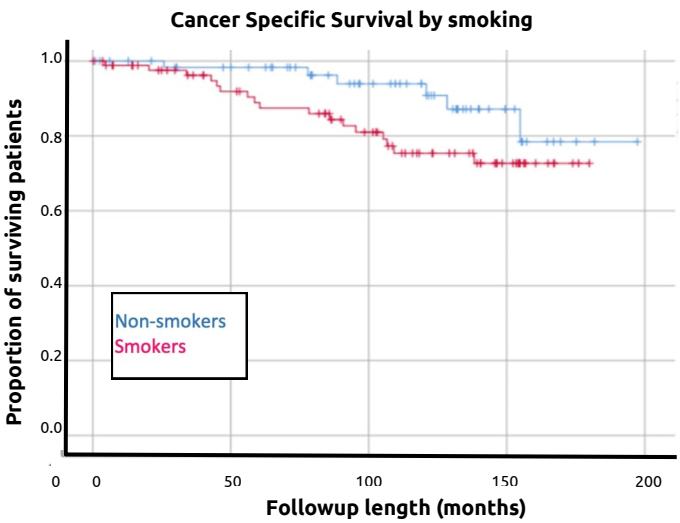

Figure 5 *Kaplan Meier curve showing cancer specific survival stratified by risk group*

lower than that of high risk patients (Figure 4). Non-smokers had better cancer specific survival than smokers (Figure 5).

DISCUSSION

The natural history of NMIBC is characterized by a high probability of recurrence, as well as by progression to muscle-invasive cancer in the presence of high-grade tumours. This mandates a follow-up strategy designed to identify recurrences and grade/stage progression in the bladder early in its evolution in order to facilitate timely intervention and ablation [5]

The EAU guidelines emphasize the importance of a focused patient history when diagnosing NMIBC In our study, we focused on age, gender, smoking status (smoker; ex-smoker; non smoker) as well as the patients' presentation.

Our cohort of patients consisted of a significantly higher number of males (83.8%) than females (16.23%). Studies show that the incidence and mortality for urothelial bladder cancer (UBC) are higher in men, whereas cancer specific mortality to incidence ratio is significantly lower for men than for women. This phenomenon could be partially explained by differences in exposure to bladder cancer carcinogens. Studies also show that female gender is associated with a higher stage at presentation.[6] In our study, 48% of females were diagnosed with NMIBC of a stage higher than pTaG1 no CIS compared to 43% of males.

Tobacco smoking is the most important risk factor for bladder cancer, accounting for approximately 50% of cases.[7,8].In our study, 57% of patients were smokers. Quitting smoking decreases the risk of developing bladder cancer by more than 30% after 1–4 years and by more than 60% after 25 years, but the risk never returns to the level enjoyed by non-smokers [9,10] However an association between tobacco consumption and progression or death resulting from bladder cancer has never been found.[9]

Haematuria is the most common finding in NMIBC[4] In our study, 54.5% of patients presented with visible haematuria. In addition, visible haematuria was found to be associated with higher stage disease compared to non-visible haematuria.[11]

Intravesical therapy after primary diagnosis was only given to 14.1% of eligible patients according to the EAU guidelines. The main reason can be attributed to a logistical restraint caused by the global shortage of intravesical therapy at present. The clinician has to therefore prioritize the allocation of the treatment to higher risk cases.

Patients who are on maintenance doses of intravesical therapy would have a survival advantage over those who only receive the 6-week induction doses.[12] In such cases where there is shortage of intravesical therapy, Frankhauser et al recommend splitting each dose of intravesical therapy into three separate doses.[13] while Mayor et al suggest that upfront cystectomy may be the most sensible option in high risk NMIBC [14]

The EAU guideline recommends that cystoscopy should be performed in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or by any other non-invasive test. Patients with haematuria and/or urinary tract symptoms should undergo CT-IVU and/or renal and

bladder ultrasound.[4] From our cohort of patients, only 15% had a CT-IVU Urine cytology was performed in 5.8% of patients.

TURBT is a crucial procedure in the management of bladder cancer. It is used to make the correct diagnosis and completely remove all visible lesions. TURBT eradicates all visible tumours and provides tissue for pathological analysis and determination of histological type, grade and depth of invasion.[15] The quality of the initial TURBT specimen is extremely important.[16]

Detrusor muscle should be included in the specimen to rule out T2 disease and minimize the risk of under-staging. According to the EAU guidelines, 2nd look TURBT should be carried out when detrusor muscle is lacking in the specimen, if there is residual tumour at first resection, in pT1 as well as G3 tumours. In our case, 137 patients had absent detrusor muscle. Of these only 5 (3.6%) had a 2nd look TURBT performed. High grade tumours lacking detrusor muscle in the initial resection specimen are subsequently associated with residual tumour or muscle invasive disease in up to 50% of cases.[17,18]

Although TURBT alone can be effective method to treat TaT1 tumours, these tumours can recur or even progress to MIBC The high variability in the 3-month recurrence rate may be due to an incomplete TURBT, the implantation and growth of a circulating tumour cell at the time of TURBT or the presence of a very aggressive neoplasm.[19] Adjuvant therapy should be considered in all patients.

Following TURBT, immediate single instillation (SI) of chemotherapy significantly reduces the recurrence rate compared to TURBT alone.[20,21] Peri operative single dose mitomycin was administered in 36 patients (23.4%).

The prognosis of each tumour determines the need for additional adjuvant intravesical therapy. Patients with low risk tumours do not require further intravesical therapy.[20] In patients with intermediate, high and very high risk tumours, a single instillation is considered an incomplete treatment. 71 patients required further intravesical therapy. However this was only carried out in 14.1% of cases.

The EAU guidelines treatment recommendations in TaT1 tumours suggest that intermediate risk tumours should receive one-year full dose BCG treatment. Whereas high and very high risk tumours should receive full dose BCG instillations for 1 to 3 years. From our results, it is clear that guidelines were not followed especially in the high risk cases.

SUMMARY BOX

- The EAU guidelines emphasize the importance of a focused patient history when diagnosing NMIBC Age gender, smoking status and patients' presentation should all be considered.
- NMIBC is characterized by a high probability of recurrence and progression to muscle-invasive cancer in the presence of high-grade tumours.
- A follow-up strategy designed to identify recurrences and grade/stage progression in the bladder early in its evolution is needed in order to facilitate timely intervention.
- This audit showed that there must be stricter adherence to the EAU guidelines in the clinical management of newly diagnosed NMIBC

According to the EAU Guidelines it is recommended that the first control cystoscopy be performed 3 months after TURBT of the bladder tumour. This is a very important prognostic factor for recurrence and progression.[22,23] In our study, only 52.6% of patients underwent cystoscopy at 3 months. 12.3% of these patients had a recurrence. From our results we can note that the highest risk of recurrence was in the intermediate risk group (14.3% of recurrences), however this might not represent the true recurrence risk in view of low number of patients in the high and very high risk category.

Since the intermediate risk group is heterogenous (as seen in the Kaplan Meier curves), Kamat et al propose that this group be divided into three categories; one closely resembling low-risk tumours, another one resembling high-risk tumours in behaviour, and another category in between the two, based on a management algorithm for intermediate risk proposed by the International Bladder Cancer Group (IBCG).[24]

The Kaplan Meier curves in this study show that cancer specific survival is directly related to the cancer risk group. This compares well with international cancer specific survival rates where patients with high risk NMIBC and tumour progression have a poor prognosis.[25]

CONCLUSION

Leal et al looked at the economic costs of bladder cancer across the European Union (EU). These were €4.9 billion in 2012, of which health care costs were €2.9 billion (59%), productivity loss €1.1 billion (23%) and informal care costs €0.9 billion (18%).[26] From this audit we can conclude that the clinical management of NMIBC was carried out in accordance to the EAU guidelines in a minority of cases. Stricter adherence to the guidelines will enable the clinician to strike a balance between cost cutting (by reducing the number of unnecessary follow ups) and reduced tumour progression.

ABBREVIATIONS

NMIBC	Non-muscle-invasive bladder cancer
TURBT	Trans urethral removal of bladder tumour
CT-IVU	CT Intravenous Urogram
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
BCG	Bacillus Calmette-Guerin
SI	single instillation
IBCG	International Bladder Cancer Group
EU	European Union
SPSS	Statistical Package for the Social Sciences

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