An Overview of the Management of Non-Muscle Invasive Bladder Cancer (NMIBC)

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Bladder cancer is the 10th most common cancer globally and carries the 13th highest cancer related mortality.[1] Bladder cancer is the 4th most commonly diagnosed cancer in men and the 10th most commonly diagnosed cancer in women in the US.[2] Bladder cancer is four times more common in men than women. The risk factors for bladder cancer can be separated into unavoidable and avoidable. Unavoidable risk factors include aforementioned gender, age and genetics. Bladder cancer is predominantly a disease of older adults, with 90% of cases diagnosed over 55 and 80% over 65 in the United States (US). Cancer syndromes like Lynch syndrome and Cowden's syndrome can predispose to bladder cancer. Mutations in growth factor receptor FGFR and p53 are also implicated in bladder cancer carcinogenesis.[1]

Smoking is the most significant and avoidable risk factor for bladder cancer accounting for 50-65% of new cases each year.[3] One study found that smoking cessation reduced the risk of bladder cancer by approximately 40% within 1-4 years, with a complete return to baseline by 20 years.[4] The importance of smoking cessation is highlighted in an Irish review on the incidence of bladder cancer. This retrospective review found the cases per 100,000 drop from approximately 24 and 9 to 13 and 4 in men and women respectively, from the year 1996-2015, in line with trends in smoking cessation.[5] The second most common avoidable risk factor for bladder cancer is occupational exposure, which accounts for about 18% of bladder cancer cases. One meta-analysis found red meat and processed meat to increase bladder cancer risk by 17% and 10%, respectively, while another meta-analysis found a 22% increase for processed meats and no statistically significant increase for red meat.[6, 7] Pre-obesity and obesity increased the risk of bladder cancer in one meta-analysis by 7% and 10%, respectively.[8]

With regards to survival rates from bladder cancer, according to the American cancer society, there is a 96% 5-year survival for in situ disease, 69% for localised disease (confined to the bladder), 37% for regional disease (spread to nearby structures or lymph nodes) and 6% for metastatic disease.[9] These figures highlight the importance of early detection and management.

The main presentation of bladder cancer is haematuria (blood in the urine). Haematuria is classified as visible (VH) or non-visible (NVH), while NVH is further classified as symptomatic NVH and asymptomatic NVH. The investigation of haematuria is risk stratified- patients with VH >45 years or patients with persistent NVH >60 years being deemed high risk. Haematuria investigation includes flexible cystoscopy for direct bladder visualisation, upper tract imaging with renal ultrasound or CT and urine for cytology. [10]

The Model of Care for Urology document recommended haematuria should have a direct access pathway through one-stop haematuria clinics.[11] These clinics could potentially be led by advanced nurse practitioners.[12]

At flexible cystoscopy, any abnormality within the bladder can be pictured, and if this abnormality looks suspicious for urothelial cancer, the patient is booked for an urgent transurethral resection of bladder tumour (TURBT). The principle of this procedure is to get a tissue sample that gives an accurate representation of the layers of the bladder, including the urothelium, lamina propria and muscularis propria (muscle). TURBT can be diagnostic but also therapeutic. Getting a good tissue sample ensures the histopathologist can demarcate whether the sample of tissue is in situ – stage pTis (confined to urothelium- but flat), pTa: non-invasive (confined to urothelium but often papillary growing in finger-like projections toward the hollow centre of the bladder), pT1 (invading lamina propria), pT2 (invading muscle), pT3 (invading peri-vesical fat) or pT4 (invading surrounding structures like prostate, uterus or vagina). The majority (95%) of the specimens will be transitional cell carcinomas (TCC).[2] Bladder cancer is then categorised as non-muscle invasive (up to 80%) and muscle invasive based on depth of invasion. These should also be reported with grades 1-3, with grade 1 being the least anaplastic, grade 3 being the most and grade 2 being somewhere in the middle. The patient's risk of disease progression can be calculated as low, intermediate, high or very high using the EAU non-muscle invasive bladder cancer (NMIBC) Risk calculator https://www.nmibc.net/. This calculator also gives the patient's probability of progression and 95% confidence interval at 1, 5 and 10 years. This risk is calculated based upon tumor size, grade, multifocality, presence of carcinoma in situ (CIS), age of patient and whether it is a primary or recurrent tumor.

Management of low-risk bladder cancer

If a bladder cancer is suspected or known to be low or intermediate risk, a patient should receive a single postoperative instillation of intravesical chemotherapy, e.g., mitomycin C, within 24 hours of TURBT. The patient should then be enrolled in standard low-grade flexible cystoscopy follow-up, including a check flexible cystoscopy at 3 & 12 months postoperatively and annually thereafter until five years. Urine for cytology is not recommended for low-risk bladder cancer follow-up. At the 5-year mark, recurrence is unlikely and follow up can be decided between clinician and patient, but some patients like to continue surveillance for peace of mind. If the patient has a recurrence during follow-up, a repeat TURBT should be carried out and their risk of progression re-calculated. If there is a low volume, low-grade

recurrence, this patient should maintain in the low-risk category, provided recurrence was not in less than one year; however, if there is a high-volume, low-grade recurrence, this patient would be switched to the intermediate-risk group.

Management of Intermediate risk bladder cancer

One option for these patients is intravesical chemotherapy which has fewer side effects than BCG therapy. The optimal dosing schedule and duration for intravesical chemotherapy is still unknown.[13] These patients can also be offered an induction course of Bacillus Calmette-Guerin (BCG). Induction BCG is a six successive weekly course of 1 hour BCG instillations. If patients do not respond to this, they can be offered a re-induction. If the patient responds to either of these inductions, they can be enrolled in maintenance BCG for one year, which comprises BCG given once a week for three successive weeks at 3-, 6- and 12-months post-induction. After this, they can continue surveillance according to the high-grade, flexible cystoscopy follow up schedule, which is every three months for two years, then every six months for three years and annually thereafter. As these patients are intermediate risk there may be more leniency with this schedule. Urine for cytology should be checked at each flexible cystoscopy, similar to high-risk patients. If an intermediate-risk bladder cancer does not respond to 2 inductions of BCG or maintenance BCG, they should be offered a radical cystectomy, if fit. If patients are unfit, they should be enrolled in a clinical trial; if no trial is available, they should have intravesical chemotherapy if none has already been given. If an intermediate-risk patient recurs in less than a year after one-year maintenance BCG, they are deemed BCG refractory and they should be offered cystectomy; if they recur over a year after one-year maintenance BCG, they may be offered a re-induction of BCG. If a patient recurs after chemotherapy, they may still be offered BCG therapy as intravesical chemotherapy has no effect on BCG instillations.[14]

Management of high-risk bladder cancer

Patients with pT1 and high-grade pTa tumours should have a re-resection within six weeks of initial TURBT. Patients with pT1 tumours, any high-grade tumour or CIS are deemed high risk for progression. If a patient is pT1, high risk according to the EAU risk calculator and do not respond to induction BCG; they should be offered radical cystectomy. If they are unfit, they should be enrolled in a clinical trial and intravesical chemotherapy if unavailable. Other high-risk patients at a lower stage than pT1 may be offered a trial of re-induction before progressing in the same manner. If high-risk patients respond to induction or re-induction BCG, they may be enrolled in maintenance BCG for three years.[15]

Management of very high risk bladder cancer

A subset of patients with NMIBC are deemed very high risk- These patients include very high-risk pT1 disease, lymphovascular invasion & variant histology, e.g., plasmacytoid. These patients should be considered for up front radical cystectomy.

Intravesical immunotherapy with BCG

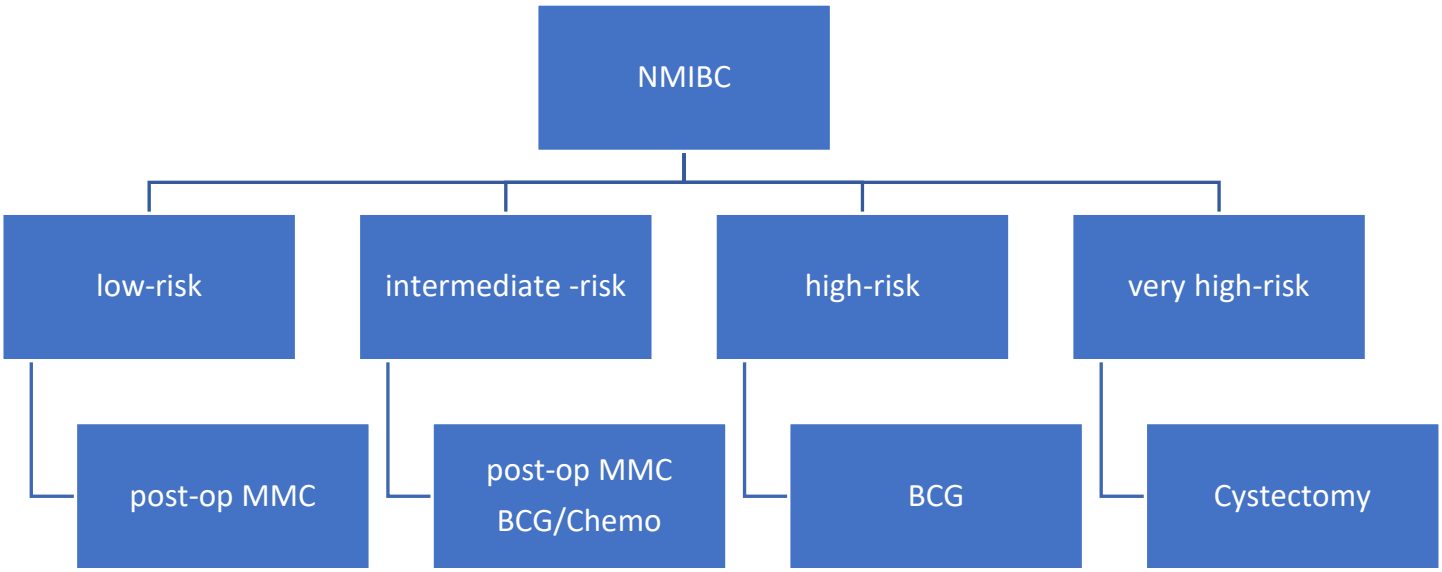
BCG is the gold standard bladder instillation for reducing the risk of recurrence and progression in bladder cancer. Simply put, BCG works by three steps: 1. Infection of the urothelium, 2. Induction of an immune response and 3. Inducing an anti-neoplastic effect. Infection of the urothelium promotes immune response by both TH1-cytokines (cell-mediated acquired immune response) and TH2-cytokines (humoral immune response) which synergistically provide anti-neoplastic activity.[16]

A systematic review and meta-analysis by Chou et al. from 2017 concluded that while several forms of intravesical therapy decreased the risk of recurrence versus TURBT alone, BCG was the only therapy to decrease the risk of progression versus TURBT alone. This review also found that BCG maintenance regimens were associated with a decreased risk of recurrence vs intravesical chemotherapy; the strength of evidence was low. The rate of adverse events was higher with BCG vs intravesical chemotherapy, including haematuria, granulomatous cystitis, dysuria and fever; strength of evidence was low.[17]

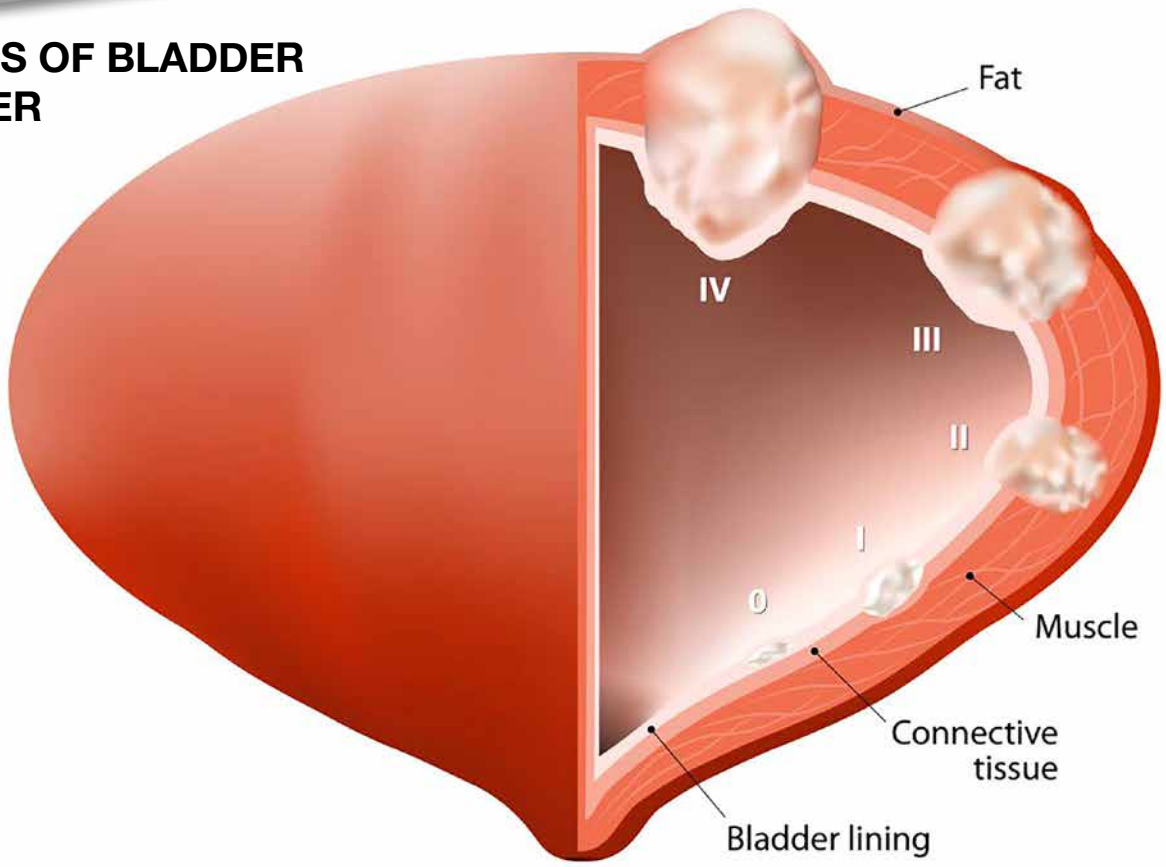
Intravesical chemotherapy

The most common form of intravesical chemotherapy used in Ireland is Mitomycin C (MMC). Other examples of intravesical chemotherapy include gemcitabine, epirubicin, valrubicin, doxorubicin, thiotepa, interferon, apaziquone, paclitaxel and docetaxel. Different chemotherapy agents have different mechanisms of action, benefits and risks. For example, an alkylating agent, MMC, has a low molecular weight, meaning better bladder wall penetration with increased risk of allergic skin reaction and possible systemic absorption. In contrast, the anthracyclines, e.g., epirubicin and doxorubicin, have high molecular weight and lower systemic absorption.[18] All chemotherapy agents have the general risks of haematuria, dysuria and frequency, but to a lesser extent than BCG. The role of these, as mentioned previously,

Figure 1. Flow diagram of NMIBC with most common interventions in each risk group



STAGES OF BLADDER CANCER



is to be used either as a single dose postoperatively in low and intermediate-risk bladder cancer, as possible adjuvant treatment in intermediate-risk bladder cancer and when BCG fails.

Patients with BCG unresponsive tumours who are not radical cystectomy candidates

This subgroup of patients should be enrolled in a clinical trial if available. If no trial is available, they may be offered intra-vesical chemotherapy. A Recent randomised controlled trial looked at the effect of MMC with radiofrequency-induced thermo-chemotherapy effect (RITE). Patients who recurred after at least one induction course of BCG patients were randomised to MMC with RITE vs control second line therapy- BCG, MMC & MMC and electromotive drug administration. This study found higher disease-free survival for MMC with RITE in non-CIS papillary tumours (53% vs 24%), suggesting patients with papillary tumours may benefit from this.[19] A 2021 phase 2 clinical trial in the Lancet examined the effect of pembrolizumab monotherapy (200mg intravenously every 3 weeks for up to 24 months) in high risk NMIBC patients unresponsive to BCG. This initially showed promising results with 39 (41%) of 96 patients showing complete response at 3 months. However, only 11% of the initial cohort remained in remission. This means pembrolizumab monotherapy delayed cystectomy in a small number of patients. Given 95% of this patient population were eligible for, but declined cystectomy, it was not considered a sensible treatment option, but may be beneficial for patients who are unfit for cystectomy.[20]

The financial cost of bladder cancer

Bladder cancer is the most expensive cancer from a health economic perspective given the frequent surveillance schedules, the intravesical treatments and the reoperation rates due to risk of recurrence and progression. As a result, it is key to establish the risk category of the patient accurately at diagnosis and ensure they receive optimal treatment.[21]

Challenges in the management of bladder cancer

One of the biggest challenges faced with the management of bladder cancer is the lack of supply of BCG and the lack of resources to enrol patients in maintenance BCG. This problem started in 2017 when one of the two suppliers of BCG, Sanofi Pasteur, shut down production. Merck Millipore remains the sole producer of BCG for the US, Canada and 70 countries worldwide. This underproduction means that supply cannot keep up with demand despite production being increased by 100%. This BCG shortage encouraged the use of alternative treatments like intravesical chemotherapy, particularly in intermediate-risk bladder cancer, where there may be less of a distinction regarding inferiority vs BCG. The advice was also given during BCG shortage to curtail maintenance BCG if patients had already received it for a year or two. The priority for usage of BCG was to get high risk, first diagnosis patients, through their induction and 3-month doses of BCG.[22] It was also suggested that patients could be considered for early radical cystectomy which is a significant undertaking. While this shortage is not felt as strongly now, there were occasions over the preceding year or two where BCG was unavailable. This hold on the delivery of maintenance and sometimes induction BCG meant that the resources of staffing, hospital beds or outpatient rooms were redirected elsewhere in some hospitals. In a situation where BCG is now becoming again more accessible, this reorganisation to put in place effective BCG induction delivery is a challenge, with the delivery of maintenance BCG being a more significant challenge. Nonetheless, these efforts to re-establish BCG delivery are rightly well supported.

Conclusion

NMIBC is common. Patients often present with VH. Diagnosis is made by means of a cystoscopy and TURBT. From a urologist's perspective, the crucial part of NMIBC management is the risk stratification of patients. Once the risk is calculated, the next part of management is following the correct treatment algorithm for a patient based on risk category and to engage in multi-disciplinary decision making if necessary.

The wider hospital team can also help manage patients with bladder cancer; this may include aiding with resources for effective and timely BCG delivery.

Smoking is the key risk factor for bladder cancer that cannot be overlooked or disregarded, and in this regard, there is a duty on patients to manage NMIBC- to help prevent it from occurring or recurring.

References available on request