Update on bladder cancer diagnosis and management

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Although the basis of the diagnosis and management of urothelial bladder cancer has remained unchanged for two decades or more, there have been some subtle but important changes in several components of these pathways over the past five to ten years, as outlined in this review.

In the western world, bladder cancer is the fourth most common cancer in men and ninth most common cancer in women, with a rising global incidence. In the UK, the disease accounts for approximately 10,000 new cases and 5,000 deaths per year (Cancer Research UK).

The cardinal symptom of urothelial bladder cancer (UBC) is painless visible haematuria, occurring in more than 80 per cent of patients at presentation, and requiring prompt investigation, most often in a ‘haematuria clinic’ setting. A small but significant proportion of patients present with irritative, urinary tract infection (UTI)-like symptoms in the absence of visible haematuria, and this is often associated with a delay in the diagnosis of UBC. Further investigation of patients suspected of having UBC requires multiple diagnostic procedures, including imaging of the upper urinary tract, urine cytology and cystoscopy, and in most cases the diagnosis is subsequently confirmed following transurethral resection of a bladder tumour (TURBT). At presentation, 75–80 per cent of patients will be diagnosed with non-muscle-invasive tumours (NMIBC: stages Ta, T1 and Tcis), with the remainder diagnosed with muscle-invasive bladder cancer (MIBC, stages T2–4), and with a male:female preponderance of at least 3:1.

Go to the Trends website (www.trendsinurology.com) to see Rik Bryan discussing the diagnosis and management of bladder cancer.

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Aside from providing grading and local staging, TURBT represents the principal treatment for NMIBC. Further treatment may be required in the form of intravesical therapy, most often with mitomycin C (MMC) or Bacillus Calmette-Guerin (BCG). NMIBC is typified by a high rate of recurrence (15–61 per cent at one year, depending upon risk category) and so long-term, even lifelong, surveillance with outpatient flexible cystoscopy is the mainstay of subsequent management. Progression to MIBC is also a concern for high-risk NMIBC patients, occurring in up to 17 per cent of patients at one year, and so long-term, even lifelong, surveillance with outpatient flexible cystoscopy is the mainstay of subsequent management.

Systematic reviews of the management of NMIBC and MIBC are regularly undertaken by the European Association of Urology (EAU), whose guidelines direct the management of UBC in Europe and the UK. The 2013 updates to the EAU guidelines are available online at www.uroweb.org.

**DIAGNOSIS OF BLADDER CANCER**

**Haematuria clinic**

Haematuria clinics represent a one- or two-stop infrastructure for the investigation of patients referred with visible or non-visible haematuria. Patients undergo history and examination, imaging of the upper urinary tract, urinalysis (including urine cytology) and flexible cystoscopy. In the UK, there is no standardised protocol for this series of haematuria clinic investigations and multiple permutations are practised (ultrasound, intravenous urography, CT, etc.), although urine cytology and flexible cystoscopy are currently considered essential components. More recently, CT urography (CTU) has demonstrated improved detection rates for upper tract urothelial cancers, renal cancers and stones, and may allow for the more streamlined management of these patients as well as those diagnosed with UBC (Figure 1). There is thus a school of thought suggesting that CTU should become the standard imaging investigation for haematuria (although costs and capacity may be issues for some units), even permitting certain patients to be listed for TURBT without the need for prior flexible cystoscopy.

Around 19 per cent of patients presenting with visible haematuria will be diagnosed with a urinary tract malignancy, compared with around 5 per cent presenting with non-visible haematuria. Importantly, a diagnosis of UBC should also be considered in those patients with irritative or UTI-like symptoms in the absence of a UTI, especially in female patients, or in those whose symptoms have not responded to a course of antibiotics.

**Urinary biomarkers**

Since 75–80 per cent of patients present with NMIBC, where recurrence and progression are significant issues, current guidelines recommend long-term surveillance with regular outpatient flexible cystoscopy. Consequently, bladder cancer is one of the most expensive malignancies to manage on a per-patient basis from diagnosis to death, and this has led to over a decade of diagnostic urinary biomarker research in an attempt to overcome the cost and invasive nature of NMIBC surveillance.

Several biomarkers are commercially available and are FDA-approved, but no single marker has sufficient sensitivity and specificity to replace cystoscopy. However, the latest generation of...
experimental platforms shows significant promise in the field of urinary biomarker discovery, identifying protein-, DNA- and RNA-based biomarkers with potential clinical utility.\textsuperscript{20,21} A number of studies are ongoing, although for the foreseeable future it is likely that these biomarkers will only reduce the frequency of cystoscopic surveillance and not replace cystoscopy altogether, especially for high-risk NMIBC. However, we are hopeful that the future will see the development of a multi-biomarker urinary test with utility for both the diagnosis and surveillance of UBC.

**GRADING AND STAGING**

**Grading**

The 1973 WHO system classifies tumours according to three grades of increasingly aggressive behaviour, grades 1, 2 and 3, whereas the 2004 system classifies tumours as papillary urothelial neoplasm of low malignant potential, low-grade urothelial carcinoma and high-grade urothelial carcinoma.\textsuperscript{22} Controversy exists as to the more accurate system for prognostication, although more recent evidence supports use of the 1973 system \textsuperscript{22,24} and those trials in set-up may generate absolute quantitation of the benefits of UBC stage. Ta (UBC confined to the lamina propria) and Tis (carcinoma \textit{in situ} – abnormal flat urothelium, but highly aggressive) are now termed NMIBC by the Union for International Cancer Control (UICC) and the International Union Against Cancer.\textsuperscript{7} Over the past 10–15 years there has been significant interest in the use of cystoscopic image enhancement technologies that can improve the thoroughness of resection at TURBT, or that can improve the detection of carcinoma \textit{in situ} and recurrent tumours.\textsuperscript{73}

**TREATMENT OF NMIBC**

**Transurethral resection of a bladder tumour**

As well as confirming the diagnosis, and providing pathological specimens for tumour grading and staging, TURBT is considered the principal management of NMIBC.\textsuperscript{7} Over the past 10–15 years there has been significant interest in the use of cystoscopic image enhancement technologies that can improve the thoroughness of resection at TURBT, or that can improve the detection of carcinoma \textit{in situ} and recurrent tumours.\textsuperscript{73} Photodynamic diagnosis (PDD, also known as ‘blue light cystoscopy’, and utilising the intravesical photosensitising agent hexaminolevulinate or Hexvix) and narrow-band imaging (NBI, an Olympus technology that narrows the bandwidth of light to 415nm and 540nm) have come to the fore,\textsuperscript{24} and are being used almost routinely in some units (Figure 2). However, trial and meta-analysis data in support of PDD are conflicting, and the NBI data are less mature; for both technologies, absolute quantitation of the benefits to demonstrate cost-effectiveness remains elusive, although ongoing trials and those trials in set-up may generate these data. This is particularly pertinent for PDD, where the cost of Hexvix is £375 per instillation.

**Adjuvant therapy**

The use of adjuvant intravesical chemotherapy (most commonly MMC in the UK) and immunotherapy (BCG) to prevent recurrence are long established in urological practice.\textsuperscript{7} Where there are no contraindications, a single dose of intravesical MMC should be administered immediately after TURBT.\textsuperscript{7} Subsequent courses of intravesical therapy are determined by the patient’s risk category (based on clinical and pathological factors\textsuperscript{7}), with courses of MMC or BCG recommended for intermediate-risk patients and BCG recommended for high-risk patients.\textsuperscript{7} Given the not insignificant side-effects related to intravesical BCG therapy (as well as cost), debate continues as to whether patients should receive one or three years of maintenance treatment following induction.\textsuperscript{25} ‘Waiting in the wings’ as potential alternatives to conventional (passive diffusion) MMC and BCG are device-assisted intravesical therapies utilising electromotive drug administration (EMDA) and heated/hyperthermic agents (chemohyperthermia, CHT). Prospective randomised controlled trial data are awaited for both EMDA and CHT, but they are likely to become important options for adjuvant therapy for NMIBC in the future.

**Outcomes**

The European Organisation for Research and Treatment of Cancer (EORTC) risk tables were published in 2006\textsuperscript{86} and give absolute values for recurrence and progression rates at one, three and five years based upon a risk score, which is calculated from a number of clinical and pathological factors; they are also available online as the EORTC ‘Bladder cancer calculator’. Although very useful as an indicator of the behaviour of low-, intermediate- and high-risk NMIBC, they have not been thoroughly validated in large independent cohorts and the absolute values for recurrence and progression that are generated may not be accurate in light of modern urological practice. However, to date, there is no
better risk categorisation tool, although large-scale genomic and epigenomic analyses of UBCs in the near future may lead to improved prognostication. For 2013, NMIBC risk categorisation has actually been simplified in the EAU guidelines.

TREATMENT OF MIBC

Until recently, neoadjuvant chemotherapy followed by radical cystectomy has been considered the ‘gold standard’ in the UK, EU and USA for the treatment of organ-confined MIBC, with up to 50 per cent five-year survival reported. However, historically the UK has always treated a significant proportion of MIBC patients (up to 50 per cent) with external beam radiotherapy for curative intent. Recent data suggest that chemotherapy–radiotherapy regimens can achieve long-term outcomes that rival those achieved with neoadjuvant chemotherapy and radical cystectomy. Chemoradiotherapy is thus a viable alternative to neoadjuvant chemotherapy–radiotherapy, and this is particularly relevant for the rapidly growing proportion of over 80-year-old patients diagnosed with MIBC, for whom the 90-day mortality rates for radical cystectomy are significantly greater than those for younger patients. In reality, data demonstrate that the majority of over 80-year-old patients diagnosed with MIBC in the UK are treated with radiotherapy, although experts consider that cystectomy in this group is safe when carried out in selected patients in specialist high-volume units, and utilising enhanced recovery programmes.

The precise details of the chemoradiotherapy regimens and the techniques of radical cystectomy are beyond the scope of this review, but can be found in recent publications and the EAU guidelines. However, the choice of surgical approach for radical cystectomy is now between a conventional open approach, laparoscopic, or robot-assisted laparoscopic, depending upon the expertise of individual units and surgeons. The extent of the cystectomy will be determined by disease involvement of the prostate and urethra and the type of reconstruction proposed (urinary diversion/ileal conduit or neobladder/orthotopic bladder substitution). Radical cystectomy also involves removal of the regional lymph nodes, and an extended lymph node dissection is now recommended by the 2013 EAU guidelines.

Although neoadjuvant chemotherapy has a clear evidence base to support its use (UK regimens most commonly utilise gemcitabine and cisplatin), the case for the routine use of adjuvant chemotherapy administered after cystectomy is weak. However, adjuvant chemotherapy may be an individualised recommendation for locally advanced disease or for those with positive lymph nodes, although further trial data are needed; the 2013 EAU guidelines advise that adjuvant chemotherapy should be given only within the setting of a clinical trial.

METASTATIC DISEASE

When patients present with metastatic disease, treatment focuses around systemic chemotherapy. Gemcitabine–cisplatin are most commonly used initially, with MVAC also utilised in this setting (methotrexate, vinblastine, adriamycin or doxorubicin, and cisplatin). Subsequent regimens may utilise MVAC, gemcitabine-cisplatin, gemcitabine–carboplatin, paclitaxel–carboplatin or vinflunine. For metastatic bone disease, the 2013 EAU guidelines recommend zoledronic acid or denosumab, and external beam radiotherapy may be utilised to treat isolated symptomatic bone lesions.

DISCUSSION

The basis of the diagnosis and management of UBC has remained unchanged for two decades or more, and as a result outcomes have not improved significantly during this period. In addition, there has been a lack of research funding into the disease, especially when compared with other malignancies, even malignancies with a lower incidence and prevalence. We hope that the subtle but important changes in various components of patient management that we have outlined here may translate into improved long-term outcomes for UBC patients, as well as improved health-related quality of life. However, it is imperative that research funding improves, and that innovation and refinement of treatments continue.

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