Review
Recent advances in diagnosis and treatment of transitional cell carcinoma of the bladder

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ABSTRACT
The management of transitional cell carcinoma of the bladder (TCCB) presents a challenge to urological surgeons due to the diversity of patient factors, stage at presentation and propensity for disease recurrence and progression. Advances in the last decade have seen an evolution in techniques for diagnosis, treatment and ongoing surveillance. A good understanding of our patients, the disease and the available diagnostic and therapeutic options is essential for the management of this condition. We review the current literature focusing on the merits of recent advances in this field. Given the breadth of the subject, we have deliberately selected only the most relevant and recent advances already in clinical use.

TCCB remains a therapeutically challenging pathology. In this review, we present the most relevant recent advances in the field. We deliberately focus on those advances in current practice; a discussion on experimental and evolving technology is beyond the scope of this review. References were sourced from a MEDLINE review on the selected topics.

1. Introduction

Transitional cell carcinoma of the bladder (TCCB) remains the second commonest urological malignancy after prostate cancer. Management of the disease and its sequelae represent significant associated morbidity, mortality, and global healthcare costs.1 Incidence rates are highest in the elderly with a 3:1 ratio of male preponderance.2 TCCB is the most prevalent histological subtype of bladder cancer (90%), with squamous cell (5%) and adenocarcinomas (<2%) much less common.2,3 Of these, approximately 80% are non-muscle invasive at the time of diagnosis.4 The European Organisation for Research and Treatment of Cancer (EORTC) published disease recurrence rates for non-muscle invasive bladder cancer (NMIBC) ranging from 15 to 61% at one year, increasing to 31–78% at five years, compared with progression rate calculations of <1–17% and 1–45% at one and five years respectively.5(Table 1)

The diversity of patient factors, stage at presentation, pathological grade and subsequent recurrence is reflected in the wide range of treatment options. This diversity also mandates individually tailored long-term surveillance programs after initial management.

2. Diagnosis and surveillance

2.1. Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) is a cytogenetic test allowing for the identification of aberrations on chromosomes 3, 7, 9 and 17 in shedded urothelial cells in a urine specimen.6–8 FISH may be of clinical use in confirming the presence of urothelial cancer in equivocal or suspicious urine cytology,9 predicting recurrence in cases of established disease in response to treatment.7,8

In a study of 280 urine specimens of patients with known urothelial carcinoma, FISH was shown to be significantly more sensitive than urine cytology across all tumour grades (81% vs 58%, p = 0.001). There was no difference in the specificity (98% vs 96%, p = 0.564).6

A recent single-centre, prospective study of 126 patients identified the potential value of FISH analysis in predicting subsequent disease recurrence in relation to immunomodulatory treatment of non-invasive bladder cancer with bacillus Calmette-Guérin (BCG)
therapy. The group cited an increased recurrence risk of 3–5 times (p < 0.01) in FISH positive samples at two year follow up, following interval testing. There is currently limited evidence to suggest FISH can predict progression in TCCB.8

2.2. Photodynamic diagnosis

Photodynamic diagnosis (PDD), also known as ‘fluorescence’ or ‘blue-light’ cystoscopy, has been shown to be more sensitive than white-light cystoscopy at detecting papillary bladder tumours and carcinoma in situ (CIS) lesions.10 Intravesical instillation of photosensitizing agents: 5-aminolevulinic acid (5-ALA) or its more lipophilic hexyl ester; hexaminolevulinate (HAL) (Hexvi) causes accumulation of photoactive porphyrin in hypermetabolic tissues/rapidly proliferating cells. This results in selective fluorescence emission from cancer cells.11 Normal tissue appears blue and suspicious tissue appears red under blue light. HAL has a higher formation capacity of photoactive porphyrin at lower pro-drug concentrations and deeper urothelial penetration compared to 5-ALA.11 This translates into shorter instillation times and brighter fluorescence for HAL.12

CIS is often not visible, or distinguishable, from an area of inflammation under white-light cystoscopy. Numerous studies have shown HAL-guided fluorescence cystoscopy is superior at detection of CIS than white-light cystoscopy,12,13,38 especially when used in conjunction with urine cytology testing.12 A European multicentre study by Jocham D et al., demonstrated 96% of all tumours detected by HAL-PDD compared to 76% using white-light cystoscopy. This study led to improved treatment for 17% of patients (p < 0.0001).13 A meta-analysis of 12 prospective trials showed an additional detection rate of 20% for PDD (range: 5–49%). In CIS patients, the additional detection rate with PDD was 39% (range: 17–78%).15

PDD is associated with higher false positive results compared to white-light cystoscopy. One study reported a PDD false positive detection rate of 8.8%–62.5% vs 7.1%–47% for white-light cystoscopy.14 False positive fluorescence may be induced by inflammation, recent transurethral resection of bladder tumour (TURBT), recent BCG instillation or obscure illumination at the bladder neck.15 Mostafid H et al. conducted a multicentre prospective trial and reported only a 1% difference in HAL-PDD and white-light cystoscopy.16 The reduction in false positivity rates may be due to increasing PDD experience and equipment improvements.13

The meta-analysis reported PDD-TURBT recurrence-free survival was 15.8%–27% higher at 12 months and 12%–15% higher at 24 months than the white-light TURBT group.15 Similar 12-month recurrence rates have also been reported.8 Geavlete et al. showed significantly improved recurrence rates at 3, 12 and 24 months in the HAL-PDD group compared to the white-light cystoscopy group.11

The benefit of PDD is highest in CIS patients and has been clearly demonstrated in a number of studies. Despite a limited increase in false positive detection rates, PDD use is still recommended in view of its improved detection compared with white-light cystoscopy.16 The value of fluorescence cystoscopy in relation to bladder cancer progression rate or long-term survival has yet to be determined. European Association of Urology (EAU) 2011 guidelines state that PDD should be advocated in all patients suspected of having high-grade individual tumours or recurrences, (i.e. positive urine cytology, negative white-light cystoscopy) and especially known CIS and multifocal disease.18

2.3. Narrow band imaging

Narrow band imaging (NBI) represents a novel imaging modality, independent of fluorescent agents, aimed at improving the detection of non-muscle invasive bladder cancers (NMIBC). It filters white light into two narrow bandwidths of about 415 nm (blue light) and 540 nm (green light). These are strongly absorbed by haemoglobin, penetrating only the superficial layers of the tissue. This facilitates enhancement of the contrast between normal urothelium and well vascularised bladder tumours.18 NBI has improved detection rates compared with white-light cystoscopy for NMIBC. There is evidence supporting improved TCCB detection rates in flexible and rigid NBI-cystoscopy when compared with white-light cystoscopy.19 A NBI-TURBT group had a residual tumour rate of 15% compared to a matched white-light TURBT cohort of 30.5%.20 Herr H et al. found that follow up with NBI-cystoscopy was associated with lower incidence of tumour recurrence and longer recurrence-free survival time compared with white-light cystoscopy.24 A more recent study in which 148 subjects were included in a prospective randomised trial reported a one-year recurrence risk of 32.9% in the NBI-TURBT group compared to 51.4% in the white-light TURBT group.25 The study’s authors concluded that NBI-TURBT reduces the recurrence risk at one-year of NMIBC by at least 10%. Similar to PDD, NBI has a low specificity. One study reported a diagnostic specificity of 27.8%. The false positive rates can occur with inflammation, cystitis and trauma, which may resemble vascular changes in TCCB.26

3. Treatment

3.1. Electromotive drug administration (EMDA)

Electromotive drug administration (EMDA) is an emerging technique to enhance the delivery of intra-vesical mitomycin
(MMC) in the bladder. This works on the principle of electrophoresis, whereby an electrical current can accelerate the diffusion of a charged particle (MMC) through a membrane (bladder wall). This can be achieved in practice with activation of electrodes in the catheter and on the patient’s skin during instillation of MMC. In vitro and in vivo studies have demonstrated an increase concentration of MMC within the lamina propria and muscularis layers when compared with passive diffusion (PD) modes of administration.4–27

A prospective randomized trial has shown EMDA-MMC to be superior to PD-MMC regarding complete response at 6 months (58.3% vs 30.5%, p = 0.012) and equivalence with BCG for CIS patients with or without T1 tumours.4 The longer-term effects on recurrence and progression rates are yet to be determined.

3.2. EMDA and BCG combination therapy

This regimen involves combination therapy with intravesical BCG and EMDA-MMC for CIS and T1 tumours. Nine weekly instillations are given, with 6 instillations of BCG interspaced with 3 instillations of EMDA-MMC.28 Maintenance therapy is initiated if patient is disease-free at three months post-resection with once monthly MMC, MMC then BCG (i.e. three month cycles) for nine months after cystoscopy.29

In a landmark phase 3 randomised trial involving 212 patients with superficial high risk bladder cancer, combined BCG and EMDA-MMC was superior to BCG alone in disease-free interval (69 vs 21 months, p = 0.012), recurrence rates (41.9% vs 57.9%, p = 0.0012), progression rates (9.3% vs 21.9%, p = 0.004) and crucially disease-specific mortality (5.6% vs 16.2%, p = 0.01).28 Such remarkable results are yet to be validated by another centre.

3.3. Pre-operative EMDA-MMC

Pre-operative EMDA-MMC is postulated to be effective in destroying tumour cells within the wall of the bladder before resection. This may be of benefit over PD-MMC given post-operatively which is effective at destroying free tumour cells in the bladder, but less so any residual tumour cells in the bladder wall.29 A randomized trial showed patients having pre-operative EMDA-MMC to have a longer disease-free interval than post-operative PD-MMC and TURBT alone (52, 16 and 12 months, p < 0.0001) and a lower recurrence rate (38%, 59% and 64%, p < 0.001). There were no significant differences in progression rates.29

3.4. Robot-assisted radical cystectomy

While open radical cystectomy (ORC) remains the gold standard treatment for muscle invasive bladder cancer (MIBC),7 advances and increasing experience in robotic surgery have led to robot-assisted radical cystectomy (RARC) becoming a mainstream alternative to open surgery.24–26 Until recently, urinary diversions have been performed extra-corporeally only. With increasing experience, a few centres are switching to intra-corporeal diversions.

In a standard RARC, the cystectomy and extended pelvic node dissection are completed robotically, with the ileal conduit or neobladder formed extra-corporeally through a small midline or transverse incision after undocking of the robot.

In a randomized trial of 41 patients, RARC was shown to have less blood loss (median 200 ml vs 600 ml, p < 0.0001), quicker return of bowel function (median 3 days vs 4 days, p = 0.0008) and lower analgesic requirements (median morphine equivalent 87.5 mg vs 121.5 mg, p = 0.0044). There was a shorter length of stay in the RARC group (median 4 days vs 6 days, p = 0.2387), but this did not reach statistical significance. There were no differences in Clavien graded complications.30 Direct comparison of complication rates across larger RARC and ORC series is difficult due to selection bias in RARC patients.30

Despite initial criticism, RARC has been shown to have equivalent short-term oncological outcomes in terms of positive margin rates and lymph node yield.30,32–35 Long-term oncological and functional outcomes in a limited cohort of patients reported by Khan et al. appear equivalent to that of ORC.30

3.5. Robotic-assisted intra-corporeal diversion

Further advances in robotic surgery have allowed for total intra-corporeal reconstruction of an ileal conduit or neobladder after RARC, with the potential for improved cosmesis, less analgesia and quicker return of bowel function.30

In the largest collaboration to date, the International Robotic Cystectomy Consortium (IRCC) reported a non-randomised series of RARC from 18 centres. A total of 167 patients who had intra-corporeal diversion (106 conduits, 61 neobladders) were compared with 768 patients who underwent extra-corporeal diversion (570 conduits, 198 neobladders). The operating time was equivalent in the two groups (414 min). The intra-corporeal group had a longer length of stay (median 9 days vs 8 days, p = 0.036) but experienced a lower 90-day complication rate (40% vs 50%, p = 0.019). Overall, the intra-corporeal group was 32% less likely to have a major complication. There was no difference in the re-operation rate between the two groups.37 To date, there are no randomized studies comparing intra and extra-corporeal reconstruction after RARC. As yet, there are no long-term follow up data on functional outcomes from intra-corporeal urinary diversion.

4. Conclusion

The last decade has seen several advances in the diagnosis and treatment of TCCB, which are now in clinical use. The technique of FISH helps solve the age-old problem of suspicious urine cytology in patients with suspected urothelial cancer and may have a role in predicting response to treatment. PDD and NBI techniques have increased detection of bladder cancer at cystoscopy and allowed for higher quality resection. EMDA has improved delivery of intra-vesical MMC and shows great promise in combination with BCG for superficial high-grade disease. Robotic techniques have revolutionized cystectomy allowing a less morbid procedure with equivalent oncological outcomes. These advances have the potential to improve the accuracy of our diagnosis, reduce recurrence and possibly progression, as well as reduce surgical morbidity. The downside is that new advances carry increased cost, limiting the technology to selected tertiary referral centres. We keenly await what the next decade will bring to the field.

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