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Review Article

# New Technologies for Diagnosis of Non-Muscle-Invasive Bladder Cancer (NMIBC) and its Management

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## Abstract

Bladder carcinoma is one of the commonest cancers in Australia and accounts for 2% of all cancers in Australia. According to the European Association of Urology (EAU) Guidelines, macroscopic Transurethral Resection (TUR) is the standard therapy for Ta and T1 papillary bladder tumours. The majority of bladder tumours are Non-Muscle Invasive (NMIBC) and are usually curable by endo-resection. However, despite the use of currently available equipment, the recurrence rate for bladder tumours remained very high.

Our aim is to highlight the new technologies available for the diagnosis and management of NMIBC. A review of the literature was performed using a PubMed search.

We conclude that new modalities in detection (Photodynamic Diagnosis (PDD) and Narrow Band Imaging (NBI)) and management (bipolar transurethral resection and en bloc resection) of bladder tumours might play a vital role in reducing the recurrence rate of bladder tumours.

**Keywords:** Bladder carcinoma; Non-muscle-invasive; Narrow-band imaging; Photodynamic diagnosis

## Introduction

Bladder carcinoma is one of the commonest types of cancer in Australia and accounted for 2.0 percent of the total incidence of cancer in 2009. There were 2316 incident cases of bladder carcinoma diagnosed in 2009 with 73.2% (1695 cases) male patients and 26.8% (621 cases) female patients. The age-standardised incidence rate of bladder cancer was 9.7 per 100,000 person years with a higher risk in men (16.0 per 100,000 person years). By the age of 75, 1 in 113 men will have been diagnosed with bladder cancer, rising to 1 in 43 men by the age of 85. For the female population, 1 in 403 female will develop bladder cancer by 75 which further increases to 1 in 148 by the age of 85. There were a total of 1031 deaths (44.5%) from bladder carcinoma in 2010 with a mortality rate of 4.1 per 100,000 person years accounting for 2.4% of all cancer deaths in Australia [1].

The majority of patients diagnosed with bladder cancer have histologically Non-Muscle-Invasive Bladder Carcinoma (NMIBC) that is potentially curable via endo-resection thus avoiding more invasive surgery. At present, however, the recurrence rates for bladder cancer remain high despite management with standard contemporary treatment.

The number of patients that present with symptoms requiring investigation, treatment and subsequent surveillance continues to have a significant impact on the Australian health system. Presently, there are new technologies that could potentially improve the detection and treatment of NMIBC and therefore reduce the recurrence rates.

## Diagnosis

### Flexible cystoscopy

Flexible cystoscopy has been the gold standard to investigate patients with symptoms suggestive of bladder carcinoma [2,3]. This can be performed easily by administering local anaesthetic gel into the urethra rather than general anaesthesia being used for patients undergoing rigid cystoscopy, saving both time as well as cost. Sterile disposable sheath was also introduced for flexible cystoscopes and showed that this method is safe to use and able to prevent cross contamination without sterilizing the equipment [4]. Kimuli and Lloyd concluded that patients preferred out-patient than day case attendance and thus freeing up theatre day or endoscopy theatre time [5].

However, in cases where cytology is positive and no lesions were found in the bladder radiologically, rigid cystoscopy was preferred allowing for evaluation of the upper urinary tracts with retrograde pyelograms and therefore, not all hospitals practice flexible cystoscopy as an initial investigation [6].

### Photodynamic Diagnosis (PDD)

Photodynamic Diagnosis (PDD), also known as fluorescence cystoscopy, assists in detecting NMIBC in comparison to the conventional method of white light cystoscopy. The fluorescence guided technique with photosensitising agents such as, 5-Aminolaevulinic Acid (5-ALA) or in its ester form Hexaminolaevulinate (HAL) are administered intravesically prior to cystoscopy procedure to induce exogenous fluorescence. This results in enhancing contrast of pathologic tissue from the normal lining of the bladder. This improves the visualisation of bladder tumour especially small papillary tumour (Ta/T1) or Carcinoma In Situ (CIS) [7]. Rink et al. has shown that 13 randomised studies reported to have recurrence-free survival rates

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between 3-24 months with 8 studies found to have significantly lesser recurrence. This proves that PDD has an impact on reducing disease recurrence and benefits patients with NMIBC. Several studies also showed that there are increased detection rates of bladder cancer with PDD in comparison with white light cystoscopy. However, the main limitation of PDD includes a false positive detection but this reduces with experience of using the PDD method. Other limitations such as benign inflammatory lesions or cystitis cystic which may show fluorescence by PDD could lead to a potential false positive [2,8].

### Narrow Band Imaging (NBI)

White Light Imaging (WLI) has been used for every flexible or rigid cystoscopy for a long time and up to now. However, despite careful resection under WLI, there is still a high recurrence rate of NMIBC [9]. Narrow band imaging cystoscopy was later introduced to complement detecting bladder tumour when performing cystoscopy. Under NBI visualization, the white light is filtered into 2 discreet centre wavelengths of blue (415 nm) and green (540nm) colour and it is strongly absorbed by haemoglobin on the bladder surface. Therefore, this enhances visibility of capillaries and gives out a contrast of pathologic tissue from the normal tissue [10].

A systematic review of NBI detecting bladder cancer was conducted by Zheng et al. [11]. Eight studies were selected for meta-analysis that included 1022 patients. The end result of the study showed high sensitivity and therefore improving detection rate but a lower specificity with the possible reasons due to patients with recurrent disease were enrolled and similar to PDD, leading to high false positive rate. Overall, there is moderate to strong evidence that shows NBI can detect lesions more effectively in comparison to WLI [12].

## Management

### Mono polar vs. bipolar transurethral resection

The standard management for NMIBC involves macroscopic Transurethral Resection of The Bladder Tumours (TURBT) as well as part of the underlying muscle [13]. Mono polar diathermy involves electric current via tissue contact from active electrode on the instrument through the body and exiting via return electrode place on the skin. In comparison, bipolar transurethral resection is performed using current that travels through the loop and any tissue contact but not through the patient's body [12].

Accurate resection of NMIBC can be determined via both correct surgical technique as well as thorough pathologic investigation. However, there are many flaws that could impair a proper diagnosis [14]. Although mono polar resection has been the common method of resecting NMIBC, it carries a risk of destroying the histologic findings due to the carbonizing effects on the tissues [15]. Several studies have been conducted to compare the outcome between resection of non-muscle invasive bladder cancer using bipolar and mono polar resection to observe if there are possibilities to obtain the tissue without much thermal artefacts [14,15]. Yang et al. stated that there is no difference in complications and duration in hospital, but shorter duration of catheterization and reduced blood loss with bipolar resection [16]. They also reported no statistical difference between mono polar and bipolar in level of thermal damage in tissues. Wang et al. reported that there was no significant pathologic difference between specimens obtained by mono polar and bipolar resection [14].

The potential complications of bladder tumour resection include intra/post-operative bleeding and bladder wall perforation. Bladder perforation may result from deep resection or accidentally from the triggering of the obturator nerve reflex. Stimulation of the obturator nerve causes sudden adduction of the leg. Pu et al. reported on the long-term results of using bipolar energy for the resection of superficial bladder tumours [17]. They reported a complication prevalence of 13.2%, which included 2.5% of patients who required blood transfusion secondary to haematuria, bladder perforation (1.7%) and urethral strictures (4.1%). Adductor contractions were reported in 4.9% of cases and no cases of transurethral resection (TUR) syndrome was noted [17]. Gupta et al. reported on using bipolar at two different energy levels. They reported that at lower voltage no obturator nerve reflex occurred. With the higher voltage there was an obturator reflex triggered in 30% of the cases [18].

Geavlete et al. noted that a cleaner tissue cut is achieved when a bipolar TURBT procedure was done, therefore having a more accurate and precise tumour resection. They also suggested that bipolar TURBT is useful during the resection of the thinned tumoral bed area, especially tumours on lateral or posterior bladder walls with high risk of bladder perforation [9].

### Local anaesthetic

A prospective pilot study was conducted by Brausi et al. to investigate the safety and feasibility of complete transurethral resection of bladder tumours or bladder mapping by using local anaesthesia via endoinjector [19]. The N-DO injector, a 5F catheter needle is used together with cystoscope via working channel. In the beginning of the procedure, it is similar to cystoscopy where lidocaine based gel is inserted into urethra and followed by N-DO injector injecting local anaesthetic into the bladder neck under cystoscopy guidance. Injection was necessary for each biopsy when bladder mapping is performed.

The outcomes showed that 60% (24 out of 40) had no or mild pain and required no further analgesia or anaesthesia. 30% (12 out of 40) of patients had moderate pain and required light analgesia or sedation. Only 10% (4 out of 40) had severe pain requiring further anaesthesia. Patients with mild to moderate pain stayed an average of 6 hours in hospital, while those with severe pain stayed 1.5 days on average.

Brausi et al. reported no major complications [19]. There were only 4 patients (10%) with minor complications of haematuria that was managed with an indwelling catheter and continuous bladder irrigation. Of these 4 patients with haematuria, only 1 was readmitted overnight while the others were discharged after a few hours from the Emergency department. No blood transfusion was required.

They also reported an approximately 50% reduction in the cost of each Physion procedure when compared to the same procedure done according to standard practice (1185.20 euros vs. 2282.27 euros)

### En bloc resection

En bloc resection of bladder tumours is indicated in small tumours less than 1 cm. Geavlete et al. reported using simple loop TUR as a safe and effective tool for resection of these small tumours [9]. It can be also be used in the en bloc resection of tumours between 1 and 3 cm and those tumours with a narrow pedicle. However, en bloc resection is not indicated in tumours more than 3 cm or tumours with a wide base. The advantage of using en bloc resection is that it prevents the scattering of tumoral cells as the tumour is resected as a single whole specimen.

## Conclusion

The high rate of bladder cancer recurrence despite current

management continues to be a major concern in modern day urology. The use of Photodynamic Diagnosis (PDD) and Narrow Band Imaging (NBI) has been shown to increase the detection rates of bladder tumours when compared to standard White Light Imaging (WLI). In the surgical management of bladder tumours the use of bipolar TUR has been shown to have more precise resection of these tumours with less surgical complications. En bloc resection has also been shown to be a safe and effective modality in the surgical management of small bladder tumours. These new modalities in detection and management of bladder tumours may play a vital role in reducing the recurrence rate of bladder tumours.

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