**The latest treatment options for bladder cancer**

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Short title: Treatment options for bladder cancer

**Abstract**

**Introduction:** Bladder cancer carries a high health care burden and a poor prognosis once distant metastatic spread has occurred.

**Sources of data:** We utilised a PubMed/MEDLINE literature search using the terms bladder cancer, chemotherapy, immunotherapy, intra-vesical therapy, surgery and radiotherapy, and current clinical management guidelines (Association of Cancer Physicians, British Association of Urological Surgeons, National Institute for Health and Care Excellence, European Association of Urology).

**Areas of agreement:** Optimal bladder cancer management requires a multi-modal approach incorporating surgery, radiotherapy, chemotherapy and immunotherapy.

**Areas of controversy:** Selection criteria for radical surgery, or radiotherapy as a bladder sparing option, and their relative efficacy, remains poorly defined.

**Growing points:** Palliative immunotherapy has been recently established for advanced bladder cancer after prior chemotherapy. Earlier use is under investigation.

**Areas timely for developing research:** Validated predictive biomarkers, potentially from easily repeatable sites (‘liquid biopsies’), will be required to optimise use of molecularly targeted treatment options.

**Key words:** bladder cancer, urothelial cancer, chemotherapy, immunotherapy, intra-vesical, radiotherapy

**Introduction**

Bladder cancer is diagnosed in approximately 10,000 patients, and results in 5,300 deaths per annum in the UK where it is the 10th most common cancer.1 There is a male preponderance with a ratio of approximately 3:1. It is a disease primarily affecting older people, with 55% being over 75 years at diagnosis, and more common in areas of higher social deprivation. The most important, and avoidable, risk factor is smoking which accounts for over a third of cases. Other risk factors including occupational exposure to aromatic amines (in dyes, rubber, textiles and pesticides), ionising radiation, spinal cord injury (linked to infection and urinary catheterisation) and schistosomiasis infection in regions where this is prevalent.1,2 A heritable genetic link is not normally apparent, however polymorphisms in N-acetyltransferase 2 (NAT2), glutathione S-transferase-μ1 (GSTM1) and a number of other single nucleotide polymorphisms do confer modest increased risks.2

Over 90% of bladder cancers are pure, or partly, transitional cell carcinoma of the urothelial tract. Adenocarcinoma, squamous cell carcinoma, small cell carcinoma, sarcomas and secondary metastases are seen infrequently. In addition, these urothelial malignancies may occur anywhere from the renal pelvis to the urethra. Common presenting symptoms include haematuria, dysuria and pelvic discomfort or the symptomatic effects of distant metastatic disease.

Bladder cancer is divided at diagnosis according to two important disease states based on histology and staging that determines its subsequent management and prognosis. Non-muscle invasive bladder cancer (NMIBC, <T2 stage) is confined to the mucosal/sub-mucosal inner lining of the bladder. By contrast, muscle invasive bladder cancer (MIBC, T2-4 stage) has spread through to the detrusor muscle lining of the bladder and potentially beyond, and as a result, carries a high risk of current or future distant metastatic spread (Figure 1). T2 cancer is confined to the inner (T2a) or outer (T2b) muscle layer of the bladder wall. T3 cancer invades beyond the bladder wall muscle layer to invade peri-vesical fat either microscopically (T3a) or macroscopically (T3b). T4 cancers invade directly to prostate, uterus or vagina (T4a), bowel or pelvic or abdominal wall (T4b).

The underlying molecular biology of NMIBC and MIBC is, to a degree, distinct. In muscle invasive disease, emerging data has defined distinct molecular subtypes that appear likely to hold differing response characteristics to conventional treatments such as chemotherapy and immunotherapy. They may also open up avenues to testing experimental treatment options in defined subtypes.3,4 Basal and luminal subtypes are consistently demonstrated in gene expression analyses. In addition, in the most recent TCGA update, the luminal subset divided in to three distinct subtypes (luminal, luminal infiltrated, luminal papillary) and neuronal and basal squamous groups.4

Approximately 70-80% of bladder cancer patients are diagnosed initially with NMIBC. NMIBC frequently recurs, in 50-70%, and infrequently progresses to MIBC, in 10-15%.5 MIBC, the potentially lethal form of the disease, accounts for the remaining disease presentations in addition to some progressions from NMIBC. Organ confined or locally advanced MIBC has a high risk of subsequent relapse and distant metastatic spread which occurs in approximately 50% overall.6-10 Once distant metastatic disease has developed, then bladder cancer is conventionally viewed as incurable and has a median overall survival of 12-18 months.11-13

**Non-Muscle Invasive Bladder Cancer**

NMIBC is commonly graded, using the world health organisation (WHO) 1973 criteria, as well (G1), moderately (G2) or poorly (G3) differentiated but more recently pathologists are adopting the new WHO 2004 classification which uses the descriptions of papillary urothelial neoplasia of low malignant potential (PUNLMP), low-grade tumours or high-grade tumours. In addition, there is a flat tumour with a velvet appearance called carcinoma in situ (CIS) that has poorly differentiated cells and is associated with an increased risk of progression to MIBC. There are several scoring systems such as the EORTC risk calculator (based upon 7 published trials) that uses number of tumours, size of tumour, grade of tumour, number of recurrences, depth of invasion and presence of CIS to predict the risk of recurrence and progression.14

NMIBC is divided into low, intermediate and high-risk groups based upon their histological characteristics and recurrence rates. Low risk tumours are almost uniformly non-fatal and their main impact relates to morbidity to patients and the high economic health care costs associated with repeat cystoscopies and intra-vesical therapies. The impact from intermediate risk tumours is similar to that of low risk tumours but they are more likely to progress to high risk disease. High risk disease has a significant chance of progression to potentially lethal MIBC. High grade disease, including CIS, is a precursor to muscle invasive disease and if left untreated will inevitably progress. Moreover, these poorly differentiated tumours lack cell to cell adhesion and some authors have reported metastatic disease in up to 15% of patients with high risk NMIBC.15

The difference in behaviour between low and high risk NMIBC is supported at the genetic level with observed mutations in the fibroblast growth factor receptor 3 (FGFR3) occurring frequently with low risk NMIBC whereas with high risk NMIBC the predominant genomic event is in loss of function of the tumour suppressor gene p53, as it is with MIBC. This picture is evolving with the genomic classification of MIBC and when the same technique is applied to NMIBC further insights into tumour biology are eagerly expected.

It is essential to make an accurate assessment of the stage of bladder cancer at the earliest opportunity and a marker of quality of the trans-urethral resection of bladder tumour (TURBT) is the presence of muscle in the specimen. If no muscle is present then an early re-resection should be undertaken in patients with high risk features.16 Recurrences can occur anywhere within the bladder and there are two main theories as to why this occurs. The field change, or oligo-clonal theory, implies that the whole urothelium has suffered a carcinogenic insult and as a result the whole urothelium acquires genomic instability resulting in a risk of spontaneous malignant transformation.17 The monoclonal theory postulates that a tumour arises from a single transformed cell and recurrences are a result of re-implantation of scattered tumour cells released at the time of resection.18 It is likely that both theories are relevant and not mutually exclusive. There is evidence that multiple tumours harvested from the same bladder or urinary tract may share identical clonal origins or conversely that oligo-clonal tumours may exist within the same bladder.19

To try and avoid the re-implantation risk the approach of ‘en-bloc’ resection is gaining popularity. This technique endeavours to remove the tumour whole and with removal via a cystoscope and as such reduce the risk of scattering tumour cells. This technique is only really appropriate for up to 4 tumours that are less than 2-3 cm. Tumours larger than this are difficult to remove whole. Three series of en-bloc resection, with up to 221 patients, have been published with promising results. The two-year recurrence rates were as low as 0-22% (Table 1).20-22

Higher risk disease is frequently associated with CIS that can be hard to see under traditional white light cystoscopy. Emergent techniques to address this include ‘blue light’ cystoscopy, which instils the photosensitive agent hexaminolevulinate (HEXVIX) into the bladder that binds with the tumour cells causing them to fluoresce red under blue light, and an optical image enhancement technology called ‘narrow band’ imaging. Centres that routinely use these techniques are reporting superior recurrence free survivals.23

As a result of the wide spectrum of disease characteristics in NMIBC, there are specific treatment options for each risk category. At the first TURBT there is level 1 evidence for the intra-vesical administration of the anti-tumour antibiotic mitomicin-C (MMC). This reduces the risk of recurrence by 38% and reduces the 5-year recurrence rates from 58.8% to 44.8% but does increase the morbidity of the resection.24 Lower risk tumours benefit the most; however, as these tumours are by their nature the least troublesome for patients some clinicians would still debate the benefit to risk ratio of its administration. Patients who develop numerous recurrences are often classified as intermediate risk and an option for these patients is to receive a 6-week course of weekly MMC intra-vesical installations or intra-vesical Bacillus Calmette–Guérin (BCG) vaccine. High risk disease has the worst prognosis both in terms of recurrences and progression to lethal disease. As such additional or alternative treatments are recommended in the majority of cases. Patients with this form of bladder cancer will be offered disease modifying intra-vesical treatment or early radical cystectomy.

Intra-vesical BCG is an immunotherapy that reduces the risk of recurrence and progression by 70% and 27% respectively and has been used for bladder cancer for over 40 years.25 The procedure is generally well tolerated but can be associated with significant dysuria and flu-like symptoms that are generally self-limiting and resolve within 1 to 2 days. Very occasionally patients can become systemically unwell with ‘BCG-osis’ which may require hospitalisation and anti-tuberculosis therapies. If a patient tolerates a 6-week induction course, and is seen to be responding, then a maintenance schedule for either 1 or 3 years is undertaken. For those who recur then radical cystectomy should be considered. When patients still wish to try and avoid cystectomy then differing methods (described below) of delivering intra-vesical therapies have been developed.

Electro-motive drug administration (EMDA) ionises MMC dissolved in either water or saline. By passing a low current between a special catheter, with an incorporated electrode, and metallic pads, coupled to the lower abdominal wall via electro gel, better tissue absorption of the MMC is achieved into the detrusor muscle and hence efficacy is improved.26 The most popular approach to this is the Di-Stasi regimen, although some have found it hard to recreate their results. This alternates traditional BCG installations (to induce inflammation) with EMDA installations of MMC in a ratio of 1:2 for a 9 week induction period followed by maintenance for 9 months.27

Hyperthermic BCG or MMC has also been shown to have success in patients who have failed traditional BCG regimes. This involves the active warming of BCG or MMC with constant infusion through the bladder at 43°C. Again this approach appears promising and we await the results of the HIVEC 2 study which has recently completed recruitment in the UK.

**Muscle Invasive Bladder Cancer – Radical Therapy**

MIBC that has not yet spread to distant sites is a curable but high risk disease that requires multimodality treatment that may include chemotherapy, surgery and radiotherapy. Patients should have a management plan delivered through a specialist bladder cancer multi-disciplinary team (<https://www.nice.org.uk/guidance/ng2>). There has been little improvement in survival in this stage of the disease over the last 40 years with 5-year overall survival sitting stubbornly at around 50%.28

Surgery by radical cystectomy has been the mainstay of curative treatment providing a 5-year recurrence free survival of 58% and a bladder cancer specific survival of 66%.29 The surgical steps have been optimised over time however it remains a morbid, life changing procedure with an associated peri-operative mortality rate of 2-4%. Extent and completeness of lymph node dissection are used, by some, as a surrogate of surgical quality and it is hypothesised that this may impact on survival rates. The SWOG S1011 trial is testing this through comparison of extended versus standard pelvic lymphadenectomy.

Urine can be diverted in various ways following cystectomy. The most common technique is to utilise a small length of distal ileum to create an ileal conduit (urostomy). This is the simplest ‘plumbing’ solution with the lowest peri-operative complication rate but leaves a permanent stoma. Some patients opt for a continent reservoir, generally made out of a de-tubulised length of small or large bowel. These are often known as neo-bladders and if they reside in the pelvis and re-connected to the urethra they are called orthotopic or if not reconnected to the urethra and lie away from the original bladder position they are called heterotopic neo-bladders with a catheterisable cutaneous channel. These solutions utilise longer lengths of bowel and as such may lead to malabsorption and therefore post-operative vitamin B12, bicarbonate and folate levels need to be monitored. Neo-bladders require more patient input for the first few months as they are initially of a low volume and need to be gradually stretched. While this is happening continence is poor but as the pressure in the reservoir reduces continence improves. The best results are in men who also have a nerve sparing procedure to preserve erectile function. In this scenario 80% of men are dry during the day but still only 50% are completely dry at night. Interestingly some studies report very similar quality of life scores when comparing neo-bladder to ileal conduit.30

The most morbid part of radical cystectomy is the risk of post-operative ileus and reducing this incidence has a knock-on effect of reducing other complications and length of stay. Traditionally, radical cystectomy was associated with peri-operative transfusion rates of 25-30% and lengths of stay of over 14 days.31 However, centres with a well-developed and properly resourced enhanced recovery program (ERP) will experience lengths of stay of closer to 6-7 days.32 In addition, high volume centres typically experience reduced transfusion rates of less than 10% and lower complication rates. The key elements of an ERP includes no bowel preparation, carbohydrate and protein supplementation pre-operatively, a personalised anaesthetic, reduced use of opiate analgesia, use of rectus sheath catheters, avoidance of naso-gastric tubes, early feeding (small volume as appropriate), chewing gum to aid the gastro-colic reflex, early mobilisation and a dedicated enhanced recovery nurse. Perhaps the most important of these is a dedicated enhanced recovery nurse to ensure that each of the potential ‘marginal gains’ is achieved.32

Robotic cystectomy is becoming used more commonly. Potential advantages include smaller incisions translating into reduced post-operative pain, better visualisation thanks to the high definition 3D optics and less blood loss and ileus due to a reduction in bowel mobilisation. High level evidence for these gains remains to be established however. Other potential advantages include reducing surgeon fatigue and physical injury through a more ergonomic surgical position.

Radical radiotherapy may be offered as an organ sparing approach in suitable selected patients. There has been no definitive randomised comparison between radical surgery and radiotherapy and uncontrolled historical comparisons are potentially confounded making clear statements on relative efficacy challenging.33 Certain contraindications to the use of radiotherapy (some of which are relative rather than absolute) exist including widespread CIS, adenocarcinoma or squamous carcinoma histology, inflammatory bowel disease, bilateral hip replacements, poor response to prior chemotherapy, ureteric obstruction, bulky tumour volume, high post-micturition residual volume (which increases the irradiated volume) and a bladder diverticulum (increasing day to day target volume errors).

For those managed with an organ sparing approach, there are data indicating that there is a superior loco-regional control, and a non-statistically significant trend towards superior overall survival, if radiotherapy is augmented with mitomycin and 5-flourouracil as radio-sensitising agents.34 Similar efficacy improvements over radiotherapy alone are seen with tumour hypoxia modification through inhaled carbogen (2% CO2 and 98% O2) before and during radiotherapy and concomitant oral nicotinamide.35 Gemcitabine is also used for radio-sensitisation in some UK centres.36 Most centres will utilise a ‘tri-modal’ approach if an organ sparing approach is followed using maximal TURBT, radiotherapy and a radio-sensitizing agent.33 The key side effects relating to an organ sparing, radical radiotherapy approach are gastrointestinal, urinary and sexual dysfunction. In addition, some patients (11.4% in the chemo-radiotherapy arm of the BC2001 trial) will require subsequent cystectomy for relapse within the bladder or occasionally the late effects of radiotherapy.34-36

In addition to radical local therapy with either surgery or radiotherapy, there is level 1 evidence to support the addition of neoadjuvant cisplatin based chemotherapy. This approach, in those that are fit to receive it, provides an absolute survival advantage of 5-6% based on two clinical trials testing either the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or CMV (cisplatin, methotrexate and vinblastine) combination regimens and a subsequent meta-analysis.7,8,10 In the UK most clinicians will utilise cisplatin with gemcitabine based on extrapolation from data in advanced disease and indirect evidence for equivalence to MVAC in the likelihood of achieving pathological complete response at subsequent cystectomy.37 Not all patients are suitably fit for this form of chemotherapy based, most commonly, based on performance status or renal function.

Following curative therapy, patients require close monitoring for risk of relapse although the evidence base for how this should be undertaken is limited. National Institute for Health and Care Excellence (NICE) guidelines (<https://www.nice.org.uk/guidance/ng2>) propose regular cross sectional imaging for 2 years for local and distant recurrence, imaging of the upper urinary tract and determination of glomerular filtration rate at least annually, monitoring for metabolic acidosis and B12 and folate deficiency at least annually following cystectomy, and, for men with a defunctioned urethra, urethral washing for cytology and/or urethroscopy annually for 5 years and regular cystoscopy for at least 4 years following radiotherapy.

**Advanced Bladder Cancer**

Patients with advanced metastatic bladder cancer are normally treated with systemic therapy using chemotherapy or immunotherapy. A survival advantage exists for the use of combination cisplatin based chemotherapy in the first line setting for patients with incurable disease. Generally either a doublet with gemcitabine, which is relatively well tolerated, or an accelerated MVAC regimen utilising granulocyte colony stimulating factors to facilitate dose intensification and improved tolerability, are used.12,13,38 Median overall survival in the range of 14 months is possible, compared to under 1 year without treatment, but with few long term survivors and only 15% alive at 5 years.13 Median time to progressive disease is in the order of 7 months.12 Factors shown to adversely affect overall survival following chemotherapy include poor performance status, distant metastatic versus locally advanced disease, high blood alkaline phosphatase levels, increasing number of sites of metastatic disease and the presence of visceral metastases.13,39 Toxicity from combination cisplatin based chemotherapy includes myelosuppression, infection, nausea, vomiting, alopecia, rash, stomatitis, peripheral sensory neuropathy and ototoxicity.7,9,12

Of note, 40-50% of patients who present with, or develop, incurable bladder cancer are not suitably fit for cisplatin based chemotherapy. International consensus criteria to define ‘cisplatin ineligible’ patients includes one or more of an Eastern Cooperative Oncology Group performance status of 2 or more, a creatinine-clearance below 60 mL/min (because cisplatin requires adequate renal clearance for safe administration and is nephrotoxic), Common Toxicity Criteria for Adverse Events (CTCAE) grade 2 or worse audiometric hearing loss (because cisplatin is ototoxic), CTCAE grade 2 or worse neuropathy (because cisplatin is neurotoxic) or NYHA Class III heart failure (as significant IV hydration is required for cisplatin administration).40 Chemotherapy for patients who are cisplatin ineligible most commonly comprises a carboplatin/gemcitabine doublet which is generally a better tolerated treatment.11

For patients that have disease progression following first line chemotherapy there are generally rather less good outcomes to subsequent chemotherapy and no demonstration of a survival advantage over supportive care alone. However, useful palliative benefit can be achieved in well selected patients with agents such as paclitaxel, docetaxel and vinflunine.41-43

Recently we have seen data to support the use of an alternative treatment approach for bladder cancer through immunotherapy with agents targeting the programmed cell death protein 1 (PD-1) receptor. PD-1 is expressed on the cell surface of T and pro-B lymphocytes and is a component of a complex system for regulating self-tolerance within the immune system. It is an ‘immune checkpoint’ and thus a guard against pathological auto-immunity. It is activated by two ligands, PD-L1 and PD-L2. PD-L1 is highly expressed by a range of malignancies as a mechanism of immune evasion. This is now therapeutically targetable through monoclonal antibodies against either PD-1 or PD-L1. In bladder cancer, a series of early phase clinical trials have shown responses to such agents in a proportion of patients. Subsequently, a randomised phase III trial of pembrolizumab, a highly selective, humanized monoclonal IgG4κ isotype antibody against PD-1, demonstrated a survival advantage compared to an investigator’s choice of chemotherapy options (docetaxel, paclitaxel or vinflunine) in patients with progressive metastatic urothelial cancer (bladder or elsewhere in the urinary tract) following prior platinum containing chemotherapy. Median survival for pembrolizumab treated patients was 10.3 months compared with 7.4 months for chemotherapy (hazard ratio (HR) for death, 0.73; 95% confidence interval (CI) 0.59 to 0.91; p=0.002).44 Furthermore, immunotherapy was moderately better tolerated than chemotherapy. Common side effects that were considered treatment related, and severe, occurred in 15% receiving immunotherapy compared to 49% with chemotherapy and included fatigue, nausea, pneumonitis, colitis, nephritis, adrenal insufficiency and skin reactions. Investigation of a patient subset with a high percentage of PD-L1–expressing tumour and infiltrating immune cells (10% or more) did not indicate significant between-group differences, indicating that this is not a predictive biomarker for treatment benefit in this setting.44 Subsequently, a similar, second line, phase III trial testing the PD-L1 inhibitor atezolizumab did not show a survival advantage compared to chemotherapy. A potential explanation for this discordant outcome relates to methodological differences in the atezolizumab trial which was predicated on an initial analysis of a subset of patients with high PD-L1 expression on tumour-infiltrating immune cells assessed in archival samples.45 Further phase II data exist for the use of immunotherapy in the first line cisplatin ineligible setting based on encouraging durable response rates, survival and tolerability.46

Recent presentation of data for second line therapy with the angiogenesis inhibitor ramucirumab in combination with docetaxel has shown a modest improvement in progression free survival compared to docetaxel alone (median 4·07 months vs 2·76 months; HR 0·757, 95% CI 0·607–0·943; p=0·0118).47 Data on overall survival outcomes are awaited to determine if this is a benefit that would warrant routine use.

**Future Directions**

Bladder cancer has existed as a Cinderella disease, without any practice changing advance in systemic therapy (aside from UK led developments in chemo-radiotherapy options34-36) for decades. This has changed in the last year with the emergence of immunotherapy as an established second line palliative therapy.44 Whether first line cisplatin eligible patients would be better served with immunotherapy, or if cure rates in localised MIBC can be improved through incorporation of immunotherapy, is the focus of multiple ongoing trials. There are also ongoing efforts to test the addition of immunotherapy based approaches in NMIBC, both as a systemic therapy and through intra-vesical administration.

One of the key limitations for systemic therapy for this disease lies in our failure, so far, to validate predictive biomarkers for a precision medicine approach to patient selection for available treatment options. We know that some patients derive major benefit, but others none, from both chemotherapy and immunotherapy, but we are unable to reliably and prospectively identify them. Immunotherapy trials have investigated PD-L1 expression on tumour and/or infiltrating immune cells, using diverse methodologies, but to date this does not seem to be likely to allow selection of which patient subsets to treat.44,45 In a single arm phase II study of the PD-1 inhibitor nivolumab, higher values of a 25-gene interferon γ signature was associated with higher rates of treatment response, as was a basal urothelial cancer subtype based on gene expression analysis. Whether these more complex biomarkers, based on multiplexed RNA based gene expression signatures, will allow for selection for immunotherapy, or if they will simply mark for different prognostic outcomes, requires prospective validation.

Predictive biomarker development has also been pursued in relation to chemotherapy response. For example in analysis that has suggested that defined bladder cancer subtypes may have differential response rates to neoadjuvant chemotherapy.48 Prospective evaluation of this approach to determine who might be spared the toxicity of neoadjuvant chemotherapy is now warranted.

It is also becoming increasingly clear that systemic therapy interventions provide a Darwinian selection pressure towards clonal evolution of treatment resistant subtypes. For example, recent data has shown this with respect to cisplatin based chemotherapy in bladder cancer where treatment resistant sub-clones emerged at the point of disease progression.49,50 This implies that we will need to consider genomic analyses, through sequential tissue sampling at the point of each treatment intervention, if we are to optimise treatment selection choices. Most likely this will not be feasible through repeated direct tumour tissue biopsy on the grounds of safety and patient tolerance. One potential alternative would be through the use of blood or urine based ‘liquid biopsies’. Recent evidence, mirroring other cancers, suggests that bladder cancer circulating tumour DNA is frequently detectable in blood and urine samples, at least in the presence of metastatic disease, and may potentially be useful for determining likelihood of chemotherapy efficacy and identification of potential therapeutic targets through genomic alteration.51-53 Development of our understanding of genomic aberrations that underpin bladder cancer is allowing understanding of novel potential therapeutic targets. The most promising, beyond immunotherapeutic targets, include cell surface receptors (e.g., FGFR3, HER2), cell cycle regulators (e.g., the cyclin dependant kinases CDK4 and CDK6), epigenetic regulators (e.g., EZH2, BRD4) and intracellular signalling pathways (e.g., the PI3K/AKT/mTOR pathway).4,53

**Conclusions**

Bladder cancer is a challenging disease with a high health care burden and persisting poor prognosis for those who develop advanced metastatic spread. Optimal management requires a fully integrated multi-disciplinary approach that can incorporate surgery, radiotherapy and systematic chemotherapy and immunotherapy. We have seen important recent advances in our understanding of the underlying molecular biology that are providing novel therapeutic hypotheses to be tested. Probably the key unmet need at present is for the development of formally validated predictive biomarkers to allow targeting of treatments to subsets of patients most likely to benefit.

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|  | Recurrence rate - **Low risk** | Recurrence rate - **Intermediate risk** | Recurrence rate - **High risk** |
| TURBT(EORTC) | 1yr -15%5yr – 31% | 1yr – 24%5yr – 46% | 1yr – 61%5yr – 78% |
| En-bloc resection(amalgamation of papers) | 1yr – 2.5%2yr – 0% | 1yr – 11-12%2yr – 17% | 1yr - 18.5-24.5%2yr – 22% |

Table 1: Recurrence rates between traditional TURBT using European Organisation for Research and Treatment of Cancer (EORTC) table figures for risk groups and en-bloc resection.20-22



Figure 1: Schematic demonstrating the different T stages of bladder cancer with respect to bladder wall and extra-vesical invasion. TX Primary tumour cannot be assessed. T0 No evidence of primary tumour. Ta Non-invasive papillary carcinoma. Tis Carcinoma in situ ('flat tumour'). T1 Tumour invades subepithelial connective tissue. T2 cancer is confined to the inner (T2a) or outer (T2b) muscle layer of the bladder wall. T3 cancer invades beyond the bladder wall muscle layer to invade peri-vesical fat either microscopically (T3a) or macroscopically (T3b). T4 cancers invade directly to prostate, uterus or vagina (T4a), bowel or pelvic or abdominal wall (T4b). For the purpose of this illustration only invasion into the rectum is illustrated as an example.