Section 11 Discussion
Introduction

Bladder cancer occurs more frequently in men and those over 60 years of age. In 2013 there were 2555 new cases of bladder cancer in Australia, approximately 75% of these were men; the median age was 76.3 years. There were 1040 deaths from bladder cancer in Australia in 2014, approximately 70% were men, the median age for both sexes was 82.0 years. The five year survival during the period 2009-2013 is 53% (55.5% men and 46.1% for women), the one year prevalence at the end of 2012 was 2131 (78.4% men and 21.6% women), the 5-year prevalence was 7204 (78.3% men and 21.7% women).

There was a decrease in 5 year survival from 68% in 1982 – 1987, to 53% in 2009-2013, the reasons for this are not clear and cannot be explained by an increase in age at diagnosis which has only modestly increased in this time period. However, there was a decrease in age-standardised mortality rate from 5.4 per 100,000 in 1982 to 3.8 per 100,000 in 2017, this is due to a reduction of overall incidence.

Symptoms and risk factors

Risk factors for bladder cancer include smoking, workplace exposure in the textile dyeing, petrochemical and rubber industries, diabetes, the chemotherapy drug cyclophosphamide, family history, and chronic inflammation of the bladder. The most common symptom is haematuria, other less common symptoms include problems emptying bladder, dysuria, polyuria and abdominal or back pain.

There are higher age standardised mortality rates from bladder cancer for in those living in very remote areas of Australia compared with those living in the most advantaged cities, likewise, those in the most disadvantaged areas have higher age standardised incidence and mortality compared with those living in the most advantaged areas. Migrants have a higher risk than Australian born and Indigenous Australians have the same risk as other Australians.

Histological types

The most common type of bladder cancers are transitional cell carcinomas, accounting for more than 90% of cases. The remainder of bladder cancers are squamous cell carcinomas, adenocarcinomas and small cell carcinomas.

Stages of bladder cancer

Stage 0 bladder cancer is confined to the bladder lining, stage I has spread into the connective tissue, stage II is in the muscle of the bladder. Stage III has spread through the bladder and into the surrounding fat and may have spread to nearby organs and stage IV has spread throughout the body.

There are conflicting reports about the differences in the stage of presentation of the disease between men and women, some report no differences for men and women, while others report that women present with more advanced disease. Women are more likely to die from the disease than men, one study reports that this only occurs in those older than 70, the younger patients have the same disease specific survival.

Recurrence and progression

Bladder cancer recurrence typically occurs within a year of definitive treatment. Depending on type and stage of disease, recurrence occurs in approximately 50 to 70% cases, and will progress in 7-40% of cases.

Diagnosis

There are inconsistencies in diagnostic pathways with many patients experiencing delays in diagnosis, and there are no Australian evidence-based guidelines for haematuria presentation. The UK National Institute for Health and Care Excellence recommend investigating suspected bladder cancer in patients aged 45 and over with unexplained visible haematuria and in patients aged 60 and over who have unexplained non visible haematuria and either dysuria and raised white cell count. The American Urology Association recommend cystoscopic evaluation for all patients with visible haematuria and aged 35 or older, and high risk patients over the age of 40 presenting with microscopic haematuria. A patient cohort in an Australian hospital reported that the probability of bladder cancer in patients presenting with haematuria was less than 1% for patients under 45 years, 13% at age 65 and 26% at age 80, based on this the authors recommended an approach similar to the UK guidelines.

In this PEEK study, participants were asked to describe the symptoms that actually led to their diagnosis, as opposed to all the symptoms that they could recall. The most common symptom leading to a diagnosis of bladder cancer was blood in the urine followed by
frequent urination and more than half the participants were diagnosed within 2 months of noticing symptoms. Early detection for bladder cancer is important, delayed diagnosis is associated with poor outcomes, investigations for patients with suspected bladder cancer include blood and urine tests, imaging studies and referral for urology review, and cystoscopy.28,19,21

A worldwide systematic review of the haematuria assessment described that women compared with men had a longer wait for urology review, were referred to urology less often, had fewer imaging studies and fewer cystoscopy.27 In addition, despite greater risk of disease, smokers had less comprehensive assessments compared to non-smokers.27 Delays in diagnosis and treatment of bladder cancer are associated with poorer outcomes.22,23 Patients with macroscopic haematuria are more likely to be referred to urology sooner than those with microscopic haematuria, and are diagnosed sooner.25 However, between 15 and 20% of patients presenting with haematuria will have bladder cancer,17,26 general practitioners may not want to over-investigate the cause of haematuria for an unlikely cancer diagnosis, this may be a factor in the delays that patients have in referral to urology.17

A hundred participants that had visual haematuria and had subsequently been diagnosed with bladder cancer in Western Australia described the waiting times to diagnosis and treatment.27 The median time from haematuria to surgery in this cohort was 69.5 days.27 Delays commonly occurred due to lack of public awareness of symptoms of bladder cancer, patient fear and anxiety, delayed and non-referral from primary care, administrative delays and resource limitations.27

Biomarkers

Biomarkers may be used to detect bladder cancer or recurrences.28 The protein nuclear matrix protein 22 (NMP22) has lower specificity to detect bladder cancer compared to cytology, however, the presence of NMP22 was associated with recurrence.29,30 UroVysion uses fluorescence in situ hybridisation (FISH) to detect chromosomal abnormalities, it is approved in USA to aid diagnosis and to monitor tumour recurrence.28 Other methods of detection under investigation include analysis of microRNA, epigenetic changes and next generation sequencing.28 There are some mutations that may be of prognostic value, FGFR3 in NMIBC was shown to be associated with recurrence in a large study,31 however, two other studies found no association.32,33 Next generation sequencing techniques have highlighted that TP53 mutations and CDKN2A mutations may have worse outcomes and PIK3CA and or PI3K/Akt mutations may be associated with better disease specific outcomes.34,35

There are no routine biomarker tests currently recommended by the Royal College of Pathologists of Australasia, most bladder cancers can be identified by histological examination, immunohistochemistry may be useful in distinguishing between tumour types.36

Treatment

Treatment decisions are based on tumour grade and stage. Treatment may include surgery, chemotherapy, radiotherapy or a combination of these.14, a multidisciplinary approach improves the use of multimodal treatment.17 Tumour recurrence frequently occurs within the first year of definitive treatment, and more than half of high grade tumours recur.38,39 The majority of participants had surgery to treat bladder cancer, almost half the participants had Bacillus Calmette-Guérin (BCG) treatment, 20 participants had chemotherapy, and three participants had radiotherapy.

Surgery

Early bladder cancer are treated by Trans Urethral Removal of Bladder Tumour (TURCH). High risk early bladder cancer, invasive bladder cancer and locally advanced bladder cancer, the tumours are treated by cystectomy, urinary function is restored by procedures such as an ileal conduit, continent urinary diversion, or bladder reconstruction (neobladder).40 There is growing evidence of better outcomes for patients who undergo radical cystectomies in high volume hospitals. Following implementation of volume guidelines in the UK, there was a decrease in 30 and 90 day mortality.41 In Australia, a review of radical cystectomy in Victoria reports of increased in-hospital mortality and prolonged intensive care unit admission in patients who had a radical cystectomy in a low volume hospital (less than 4 radical cystectomies per year) compared with those in a high volume hospital (more than 10 radical cystectomies per year).42 A review of NSW RCs reported that high volume centres (more than 6 radical cystectomies per year) had better disease specific survival than low volume centres (less than 3 radical cystectomies per year).43 A registry of radical cystectomies performed could be beneficial, it could detect quality improvements (Udovicich 2017). In addition, the number of RC performed by surgeon and hospital to ensure that...
bladder cancer patients are treated in medium to high volume centres. In Sweden a prospective database of radical cystectomies identified risk factors for complications\textsuperscript{44}.

Elderly patients experience higher complication rates, higher hospital readmissions and higher perioperative rates following radical cystectomy\textsuperscript{45}. Alternatives need to be considered and more data is needed to determine which elderly patients will benefit from radical cystectomy in terms of complications, quality of life and survival\textsuperscript{46}.

**Other treatments**

Following the surgical removal of the tumor, non-invasive high grade tumours can be treated with BCG immunotherapy for prevention or delaying of recurrence\textsuperscript{46-48}. This is given weekly for six weeks once the bladder has healed from surgery, maintenance schedules with BCG are not well defined\textsuperscript{47,49}. Non-invasive low-grade tumours have a poor response to BCG\textsuperscript{48}.

Muscle invasive tumours and BCG failures should be treated with cystectomy with urinary diversion. Neoadjuvant chemotherapy may be used with large tumours to assist with resection, there is a 5% advantage at five years, however, those that do not respond have a worse outcome due to delaying surgery. Adjuvant chemotherapy should be administered for lymph node positive tumours and or for tumours that invade muscle or surrounding organs\textsuperscript{49}.

Advanced non-curable cases may be treated with palliative cystectomy and urostomy diversion\textsuperscript{46}. Palliative radiotherapy may relieve symptoms\textsuperscript{46}. Radiation may be given in place of cystectomy in those that are elderly or those with poor performance status\textsuperscript{46}.

Post surgical follow up of bladder cancer patients usually consists of urine cytology, repeat CT and regular check cystoscopies. Recurrence usually occurs within 12 months and over 50% of high grade tumours recur\textsuperscript{14}.

**Clinical trial overview**

In this PEEK study, 84% of all participants described not being spoken to about clinical trials. A search of the ANZCTR clinical trials registry for bladder cancer trials that have been open to recruitment in the past five years identified 26 clinical trials (ANZCTR website accessed 10/10/2017). Three of these were observational, including two diagnostic tests and an evaluation of patient reported symptoms. There were 23 interventional clinical trials including 20 drug clinical trials, two radiotherapy trials and one patient information delivery trial.

Seven studies were conducted in single sites, the remaining 19 multi-centre studies were conducted in between two and 45 centres across Australia. The majority of trials were conducted in New South Wales and Victoria, with 26 studies were conducted in centres in NSW, and 18 in centres in Victoria. Fewer studies were conducted across the rest of Australia with 11 in Western Australia, ten in Queensland, seven in South Australia, four in Tasmania, and one in the Australian Capital Territory. No studies were conducted in the Northern Territory.

**Quality of life**

In relation to quality of life, participants in this PEEK study spoke about the need to plan life around treatment, and this included managing work and their care schedules. They also spoke about having to slow down and not do as much as they may want to, this was particularly in relation to the physical changes that are associated with bladder cancer. In addition, participants commonly noted the need to monitor or manage continence issues, including staying close to the bathroom and needing to manage their stoma.

Early stage bladder cancer, though curative, has an impact on quality of life. A qualitative study of the experience of NMIBC reported three important aspects for patients, side effects and symptoms of treatment, functioning outcomes, and experience of care\textsuperscript{51}. The main side effects and symptoms of treatment that patients reported were urinary problems, pain and sensations in bladder, pelvic and abdominal areas, gastrointestinal problems mostly associated with chemotherapy, fatigue and general malaise were commonly especially associated with disrupted sleep from urinary problems. Changes to physical, sexual, emotional, cognitive and social function were reported. Body stiffness and pain affected physical function. Anxiety about leakage and sexual ability were common aspects of sexual function. Anxiety about repeated treatment, disease progression, urinary leakage were common, as well as embarrassment while receiving some treatments. Participants reported difficulty in remembering things. Social participation and enjoyment was hampered by urinary function and need to be near toilets. The need to organise life around treatments, recovery time,
extended hospitalisation, not being able to drive following treatment, and time taken to resume normal activities of life were described as greatest burdens from treatment. Those that had the same nurse throughout treatment expressed greatest satisfaction with care. Satisfaction with care from clinicians were improved by perceived competency, information, advice and support given, and when clinicians were reassuring, appeared interested and responded to patient needs.

A mixed methods study of NMIBC patients that had recently had a TURBT procedure reported that half had problems emptying their bladder and a third had emotional concerns about the future. The main symptoms reported were urinary problems, these caused sleep difficulties. Those that were employed at the time of the TURBT procedure had more anxiety for the future, and in some cases, pain delayed return to work following the procedure.

BCG-treated NMIBC cancer patients found it difficult to cope with their diagnosis, and quality of life during this period was poor.

**Urinary diversions**

Three systematic reviews of quality of life following neobladder or ileal conduct diversion suggests that those with a neobladder had a quality of life advantage over other methods of urinary diversions.

A meta-analysis of post-operative quality of life following continent and incontinent diversion showed no overall difference in overall quality of life, mental health and social health. However, those that had incontinent diversion displayed improvements in physical health compared to continent diversions. Those that had a neobladder had better emotional function and body image compared to incontinent diversion. The long-term quality of life following continent or incontinent diversion was not clear.

A mixed methods study of cancer and non-cancer ostomy patients described the most common symptoms that influenced daily life, these were fatigue and/or sleep problems, leakages, pain, bladder or bowel complaints, physical activity, usual daily activities such as work, clothing, diet and relationships/sexual intimacy.

A qualitative study of people that had undergone urinary diversion described that resumption of normal daily activities with no or limited restrictions on social and personal life, older age, and lower complications were associated with a better quality of life. Those that had difficulty in the management of the ostomy, and those that had only a partial resumption of normal activities were more likely to have poorer quality of life.

**Health professional communication/decision-making**

Treatment decision making in oncology requires a balance between efficacy and side effects in order to maintain QoL.

Dutch participants with NMIBC expressed that verbal and non-verbal communication was important to them, participants were less likely to ask questions if the medical professionals appeared to be busy, they preferred information that was clear and concise otherwise they worried. An organised hospital implied to the participants professionalism and was confidence building. One study described women including family in decision making whereas male participants were more likely to describe family in a non-supportive role.

**Care coordination**

There is limited information about care coordination in Australia as there are very few bladder cancer-specific care coordinators. In this PEEK study however, the entire cohort had scores in the highest quintile for quality of care global measure, indicating very good care. The scores for navigation, and care coordination global measure were in the second highest quintile, indicating good incomes, however the scores for communication, and the total score, were in the middle of the scales.

In the USA, a study that included thirty participants with MBIC discussed their unmet needs, medical needs were lacking during the post-operative period, pain, bowel dysfunction and support for stoma and catheters were most frequent unmet needs. Approximately half of the participants had support from a visiting nurse during post-operative period, among the third that were unhappy with the support received from the nurse, the most common reason was lack of specific training about stoma care. During the survivorship period (6 to 72 months post-operatively) participants most frequently needed ongoing support to adjust to functions of daily living.
Support at diagnosis is particularly important. In this PEEK study participants were asked whether they felt supported at the time of diagnosis. Only a minority of participants felt that they had enough support between testing and diagnosis from healthcare professionals, however the majority had no support at all. There is a particular need to build a community-based support system for bladder cancer patients where specific and timely support and information is provided.

Bladder Cancer Awareness Australia was established in 2014. It is a Facebook group and is the first bladder cancer awareness group in Australia that aims to advance awareness, further education, support research and promote the prevention of Bladder Cancer in Australia. Bladder Cancer Australia Charity Foundation was established in 2016 aiming to increase public awareness and campaign for improved bladder cancer screening. Bladder Cancer Australia Charity Foundation at the time of this report had produced a bladder cancer information booklet that costs $5.00 for patients to access or they must register their details to obtain a copy of the information booklet. In early 2018, a new bladder cancer – BEAT bladder cancer was also established and at the time of this report had yet to implement any significant programs.

**Summary: Characterisation of the study population**

Before diagnosis, the participants in this cohort commonly experienced symptoms of having blood in urine and problems emptying the bladder. More than half the participants were diagnosed within 2 months of noticing symptoms, however there were still some participants that had more than a year from noticing symptoms until diagnosis. Support at diagnosis was lacking with the majority of participants having no support at all. The main treatments being discussed were cystectomy and BCG and participants reported that clinical trials were not commonly spoken about. Participants most commonly included their partner or spouse (or close family member) in consultations with their clinician or the advice of their clinician only when making decisions about treatment. The participants in this study most commonly accessed information via the internet, however their preference for information was to talk to someone, often in conjunction with online information. Care and support was primarily received by family and friends, as well as the healthcare team. In relation to quality of life, participants in this PEEK study spoke about the need to plan life around treatment, and this included managing work and their care schedules. They also spoke about

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**Information and Education**

The readability and quality of information was assessed for 62 bladder or kidney cancer websites\(^63\). The websites were hosted by universities, foundations, pharmaceutical/commercial organisations, charities and non-university education providers\(^63\). The quality of the information varied, however no difference in quality was found by type of organisation hosting the websites. Readability was frequently above the public readability level\(^63\).

In this PEEK study, knowledge and confidence for managing health was measured and overall, the participants scored in the top quintile for Knowledge, Recognition and Management of Symptoms, and Adherence to Treatment, indicating very good outcomes for these scales. The scores for Coping, and Total Score, were in the second highest quintile also indicating good outcomes.

Thirty participants in USA with MBIC discussed their unmet information needs. At diagnosis, participants had unmet informational needs about urinary diversion options and side effects, self-care, the recovery process, and financial concerns including health insurance\(^62\). A third of the participants obtained additional information about treatment options and side effects from the internet, support groups or online discussion groups\(^62\). During the post-operative period, there was a lack of information about recovery and post-information self care\(^62\). In this PEEK study, gaps in information provision were also identified, providing the first Australian data on this issue. Information about treatment options, disease cause, and disease management were most frequently given to participants by healthcare professionals, information about complementary therapies, hereditary, genes and biomarkers and clinical trials were given least often. The largest gaps in information, where information was neither given to patients nor searched for independently were hereditary, genes and biomarkers, clinical trials and complementary therapies.

**Support available**

Support for bladder cancer patients their families and carers is available from the Cancer Council Australia and from each state Cancer Council. Support includes information about bladder cancer, access to telephone or email help, links to support groups, legal and financial help and advice, healthy living advice. Some states offer help with transportation to treatment, help with stomas, and holiday breaks for patients and their carers and families.
having to slow down and not do as much as they may want to, this was particularly in relation to the physical changes that are associated with bladder cancer. In addition, participants commonly noted the need to monitor or manage continence issues, including staying close to the bathroom and needing to manage their stoma.

In the future, this cohort of patients would like to see treatments that are less invasive and the ability to have more choice in relation to treatment. They would like information that supports early detection and awareness, as well as information that is specific to bladder cancer types and information that is readily available. In relation to communication from health professionals, this patient group expects that communication is clear, understood by patients, comprehensive and delivered with compassion. The care and support that this patient group would like to have is via access to a health professional or telephone service that specialises in bladder cancer to help them know what to expect, what is available to them and to ask questions between and also being able to access peer support specific to bladder cancer. Finally, the message that this patient group would like to send to those that make decisions about the treatment and care that patients with bladder cancer receive is, that there is a need for timely and equitable access to services and treatment and the need for clinicians to provide comprehensive information that patients can understand.
References


27. McCombie SP, Bangash HK, Kuan M, Thyer I, Lee F, Hayne D. Delays in the diagnosis and initial treatment of bladder cancer in Western Australia. *BJU Int* 2017; **120 Suppl 3**: 28-34.


