Closing the Gender Gap: Can We Improve Bladder Cancer Survival in Women? – A Systematic Review of Diagnosis, Treatment and Outcomes

Introduction

In most cancers, female gender offers a survival advantage; however, this does not appear to extend to bladder cancer [1]. This is not a newly recognized phenomenon. Yet, despite this, there still exists a gender disparity in cancer-specific mortality [2].

The cause for the discrepancy is multifactorial and, over recent years, studies have attempted to determine the impact of differences in referral patterns, clinicopathological characteristics, treatment variations and tumor biology on outcome.

In this article, we will review the literature surrounding bladder cancer diagnosis and treatment with reference to gender differences. Our intention is to identify factors in which a change of practice could lead to a change in outcome.

Methods

A systematic search of MEDLINE was conducted from inception to December 2015 to identify studies comparing gender differences in referral pattern and diagnosis, treatment and survival of bladder cancer. Search terms included the following: exp urinary bladder neoplasms AND sex factors OR gender identity OR women ...
AND survival OR mortality. A second search was conducted using the following terms: exp urinary bladder neoplasms AND sex factors OR gender identity OR women AND hematuria OR referral and consultation OR diagnosis or delayed diagnosis. The following restrictions were placed on the studies: human, English language and adults >19 years.

One hundred thirty-seven studies were identified and were screened and excluded on the basis of title of the article and abstract. Of these, 40 full text articles were screened. Bibliographies of the included articles were reviewed to ensure inclusion was as complete as possible. Fifteen studies were included from other sources.

Are There Gender Differences in Referral Patterns?

Patient Presentation

Patient factors may result in delayed presentation to a healthcare provider. These may include poor recognition of the significance of symptoms (for example, an inaccurate acceptance of symptoms as an inevitability of ageing) or psychosocial issues such as fear or embarrassment.

This is evidenced by the Public Health England ‘Blood in Pee’ campaign which found that only 27% of patients were able to spontaneously list hematuria as a sign of cancer despite it being the most common symptom [3] and a failure of some women to recognize abnormal pelvic bleeding as a sign of a potentially sinister condition [4].

Two European studies based on health systems that allow for direct self-referral to a specialist Urology service found that 78 versus 55% [5] and 84.0 versus 66.7% [6] of men and women, respectively, self-referred. This raises the possibility of a gender difference not only in terms of appreciation of significance of symptoms but also different attitudes toward accessing specialist healthcare that is in contrast to the traditional view of men displaying more risk-taking behavior and an aversion to seeking medical attention.

Referral from Primary Healthcare Provider

A number of studies demonstrate a difference in referral patterns from primary care providers to an Urologist. These studies are limited by being largely retrospective in nature and reliant upon patients’ recall. Others use surrogate markers of symptoms and delay such as claim for hematuria and number of consultations, investigations or treatment for other conditions before diagnosis of bladder cancer. The majority of studies do not differentiate between visible and non-visible hematuria.

One Surveillance, Epidemiology and End Results (SEER) review of the Medicare database found that male patients with increased age and comorbidities experienced the greatest delay to diagnosis [7]. Results from a single institution in North America did not demonstrate any significant difference in duration between symptom and diagnosis or diagnosis to cystectomy and symptom to cystectomy [8]. Most studies, however, indicate that men are referred more promptly than women.

Hematuria is the commonest initial symptom in bladder cancer affecting >80% men and >70% women with bladder cancer [9]. Despite this, the same Danish study found that women with hematuria had a greater delay to diagnosis. Johnson et al. [10] also found that male patients presenting exclusively with hematuria were referred after fewer episodes of hematuria than their female counterparts. This difference was most pronounced in the high-risk patients >60 years. In this group, men were twice as likely to be referred within a month of their hematuria compared to women (36 vs. 17%). A retrospective review of MarketScan databases for hematuria also demonstrated a significant delay to diagnosis in women who were more likely to experience a delay greater than 6 months (17.3 vs. 14.1%, p < 0.001) [11].

Similarly, the study by Lyratzopoulos et al. [12] about referral in an English primary care setting indicated that despite 71% of women presenting with hematuria, only 51% were referred after the first consultation. Women were significantly more likely to require 3 or more pre-referral appointments (27 vs. 11%, p < 0.001) and had a longer interval before secondary care review.

A recent Canadian study of cystectomy patients found that female patients had experienced a greater number of pre-referral visits and more than double the wait time to referral of male patients (56 vs. 23 days, p < 0.0001) [13].

Irritative urinary symptoms and urinary tract infections (UTIs) can also be symptoms of bladder cancer. NICE have developed guidelines for the investigation of these symptoms in men [14]. A study of British men found that the incidence of bladder cancer in these patients was low (0.9%) [15].

Until very recently, there were no such gender-specific guidelines for investigation of lower urinary tract symptoms or UTIs in women. This may be because previous studies have found a low yield of bladder cancer in older women investigated with cystoscopy for UTIs (∼1%) [16].

However, it is worth noting that cystitis may act as a confounding factor in the diagnosis of bladder cancer, lengthening delay to diagnosis [8]. Women are more like-
ly to have urinalysis and culture sent and more likely to be diagnosed with a UTI (33.1 vs. 17.6%, p < 0.001) [11] (61.1 vs. 20.0, p = 0.005) [6]. Cohn et al. [11] also found that women were more likely to receive 3 or more courses of antibiotics than male patients prior to their bladder cancer diagnosis (8.7 vs. 5.2%, p < 0.001). Having a diagnosis of UTI was found to be the most significant independent predictor of delay to bladder cancer diagnosis, approximately doubling the chance of a delay beyond 6 months.

The combination of cystitis and bladder cancer may be significant given the findings of a study in New South Wales indicating that a history of cystitis is associated with an increased hazards ratio (HR) of death from bladder cancer after cystectomy (HR 1.55, 95% CI 1.15–2.10 with cystitis and 0.99, 95% CI 0.57–1.70 for those without cystitis, p < 0.001) and highlights this symptom as one that may benefit from a guideline review in terms of investigation [17].

Recently, data from the English ‘Routes to Diagnosis’ project has demonstrated that a greater proportion of women with bladder cancer present as emergencies compared to men (OR 1.5, 95% CI 1.39–1.6) [18]. The authors speculate that a relative difficulty in diagnosing women leads to a greater time between presentation and diagnosis with the emergency attendance likely to reflect advanced stage at presentation. However, they acknowledge that the study lacks information on presenting symptom, previous healthcare interactions and stage and are therefore unable to draw definite conclusions.

**Does Delay in Diagnosis Affect Stage at Diagnosis or Cancer Mortality?**

There is concern that a delay in referral may lead to a higher stage cancer at presentation leading to adverse outcomes.

Hollenbeck et al. [7] found that delays did not appear to result in any significant difference in tumor stage at diagnosis (p = 0.66) but was associated with an increased cancer-specific mortality if the delay was greater than 9 months (HR 1.38, 95% CI 1.17–1.63).

The Danish study by Mommersen et al. [9] demonstrated no difference in survival between delay groups presenting with T3/T4 disease but a shorter delay was related to better survival in T1/t2 tumors.

Both male and female cystectomy patients in the Canadian study had poorer survival if they were ‘indirectly’ referred (>5 pre-referral visits). No comment was made regarding the stage of cancer at diagnosis [13].

**Does the Stage of Cancer Differ at Diagnosis?**

Two small European studies have shown a non-significant trend toward men having more muscle invasive disease at diagnosis [19, 20].

Most large studies refute this, however, with evidence that women not only present with more advanced tumors than their male counterparts [8, 21–26], but are also more likely to have nodal involvement at diagnosis [8, 23, 27].

**Does Histological Type Explain Differing Mortality?**

Non-urothelial cancer of the bladder (UCB) is rare but has a poorer prognosis than UCB. Women are more likely to have a non–UCB than men (approximately 10–12% in women vs. 5–7% in men) [17, 20, 22, 23].

In addition, women with non–UCB appear to present with more advanced disease. Results from the Netherlands Cancer Registry indicate 26.4% of non–UCB present with superficial disease in men compared with 12.1% in women. Incidence of T2 disease was equal but T3 and T4 disease were more common in women than in men: 21.7 versus 14.4% and 11.0 versus 8.4% for pT3 and pT4 disease, respectively [23].

The UK National Cancer Intelligence Network 2012 statistics report a high proportion of non–UCB in women of approximately 25%. The report also notes that treatment for non–UCB differs from treatment of UCB with only 47% of patients having surgery (inclusive of transurethral resection of bladder tumor [TURBT]) compared to 82% of UCB. As with UCB, women’s survival is poorer than their male counterparts with 5-year survival 16.9 versus 26.5% [28].

However, studies of outcomes following cystectomy for UCB continue to demonstrate poorer survival in women indicating that, although histological subtype may contribute, it does not fully explain the gender discrepancy in bladder cancer mortality [17, 29].

**Does Type of Treatment Received Differ between Genders?**

The SEER review by Konety and Joslyn [30] demonstrated a regional difference in utilization of different radical therapy for MIBC, and Chamie et al. [31] demonstrated a difference in guideline adherence for treatment of high-risk NMIBC between academic cancer centers...
and non-academic non-cancer centers. These studies suggest the influence of healthcare providers on a patient’s treatment. However, a patient’s decision will also be influenced by comorbidities, experience, proximity to healthcare provider and willingness to attend for follow-up as well as psycho-socio-sexual issues regarding body image that is likely to vary between the genders. These factors are practically impossible to elucidate from retrospective databases. The small amount of information available is conflicting; treatment for all bladder cancer as recorded in the SEER database stratified into intravesical, systemic therapy or cystectomy has shown no difference by gender [32] and an English study of high-risk NMIBC noted that men and women were equally likely to receive Bacillus Calmette-Guérin (BCG) [33]. However, comparison of treatment of superficial cancers in a Spanish study found female patients were almost 5 times more likely to receive intravesical therapies after transurethral resection (TUR) compared with their male counterparts despite there being a greater proportion of men with G3pT1 tumors than women [20] (the difference was not explained by men opting for immediate cystectomy), and 2 American studies have indicated that a higher proportion of female patients receive radiotherapy for MIBC [22, 31].

As well as being less likely to have a radical cystectomy for MIBC [34], women historically were less likely to receive continent urinary diversion (3 vs. 49% of men) [35]. More recently, the proportion of women having cystectomy has significantly increased, approaching that of men: 18% in 1989–1996 to 44.4% in 2003–2008 as reported by May et al. [37]. Women are also more likely to have good functional results when having cystectomy has significantly increased, approaching that of men: 18% in 1989–1996 to 44.4% in 2003–2008 as reported by May et al. [37]. Women are also more likely to have good functional results when having cystectomy, and 2 American studies have indicated that a higher proportion of female patients receive radiotherapy for MIBC [22, 31].

As well as being less likely to have a radical cystectomy for MIBC [34], women historically were less likely to receive continent urinary diversion (3 vs. 49% of men) [35]. More recently, the proportion of women having cystectomy has significantly increased, approaching that of men: 18% in 1989–1996 to 44.4% in 2003–2008 as reported by May et al. [37]. Women are also more likely to have good functional results when having cystectomy, and 2 American studies have indicated that a higher proportion of female patients receive radiotherapy for MIBC [22, 31].

**Does Response to Treatment Differ between Genders? – What Is the Evidence?**

Gender outcomes following cystectomy have been widely reported but there is a lack of information regarding other treatment modalities.

Women receiving endoscopic treatment (resection or destruction of tumor) in the New South Wales study had worse cancer-specific mortality than their male counterparts (HR 1.18, 95% CI 1.03–1.34) [17].

There are a number of studies that have compared sex-related outcomes for bladder sparing treatment of high-risk NMIBC. Increased risk of progression and bladder cancer death have been found in a SEER review of Medicare claims [39] (HR 1.23, 95% CI 1.12–1.36 and HR 1.55, 95% CI 1.34–1.81 for progression and bladder cancer death, respectively), and at a single English institution (HR 1.37, 95% CI 1.03–1.83, p = 0.03) for progression [40] and 5 years cancer-specific mortality 32% women versus 22% men, p < 0.001 [32]. A retrospective analysis of Spanish patients by Palou et al. [41] following single TUR and induction BCG found a non-significant trend toward increased risk of progression in women (HR 2.41, 95% CI 0.96–6.04, p = 0.06) an increased cancer-specific mortality rate (p = 0.004, HR 3.53) as well as a significant association with a shorter time to recurrence (HR 2.30, 95% CI 1.25–4.22, p = 0.008). Whereas the study of 916 patients in 7 tertiary referral centers by Kluth et al. [42] diagnosed with T1 high-grade transitional cell carcinoma and found that female gender was associated with increased risk of recurrence but not progression nor increased mortality (HR 1.359, 95% CI 1.071–1.724, p = 0.012). Treatment for high-risk NMIBC has been found to be inconsistent, with poor adherence to treatment guidelines and may explain the variation in findings to an extent [31, 40, 42].

There are no studies directly comparing the treatment of MIBC with curative intent. However, one recent study comparing outcomes of TURBT combined with either chemo-radiotherapy or radiotherapy for bladder cancer with intention to cure found female gender to be an independent risk factor for poorer outcome regardless of treatment modality (CSS HR 2.4, 95% CI 1.52–3.80) [43].

Worse outcomes for women following radical cystectomy are well documented [18, 29, 35–37, 44, 45] but these findings are refuted by Mitra et al. [8]. Having intensively matched 414 female and male cystectomy patients for demographic, tumor and treatment characteristics, no significant difference in recurrence-free survival, cancer-specific survival or overall survival was found (p = 0.45, p = 0.34, p = 0.71, respectively). Only when subsequently compared to an unmatched cohort of male patients are the results of previous studies replicated. The authors offer the following as possible explanation of their findings – women presenting with more advanced disease or unbalanced study design affecting power calculations.
Conclusion/Discussion

Although progress continues to be made in understanding genetic and hormonal contributions to the development, prognosis and treatment of bladder cancer, clinical applications are still lacking. We have identified evidence of poor recognition of the symptoms and signs of bladder cancer, a difference in referral patterns between genders and a possible difference in treatment stratagems.

We would therefore recommend that these areas are targeted to rebalance gender inequality in bladder cancer outcomes.

Education

We would recommend public awareness is improved with campaigns similar to the Public Health England ‘Blood in Pee’ campaign, which increased both patients’ knowledge of bladder cancer symptoms and bladder cancer diagnoses: 62% of those questioned spontaneously offered hematuria as a sign of bladder cancer as compared with 31% pre campaign; confidence in signs and symptoms of bladder and kidney cancer showed a significant increase from 29 to 43% in women and the number of bladder cancer diagnoses increased by 8.2% [3].

Referrals and Investigation

There are well-publicized guidelines for the investigation of hematuria and in the majority of Urology units in England, these patients are assessed in a ‘one stop’ clinic where urological, radiological and cystoscopic evaluations are performed in a single attendance. To prevent a delay in investigation and diagnosis of patients presenting with symptoms other than hematuria, a similar process would be beneficial.

However, establishing referral criteria for such clinics is difficult as the evidence for investigation in patients without hematuria is poor: the yield of bladder cancer in patients having cystoscopy for recurrent infection [16, 46, 47] or irritative symptoms is low, there is no apparent association between severity of symptoms and risk of cancer [48] and cancer may be present in the absence of hematuria [49, 50].

The newly updated NICE guidance [51] will hopefully reduce delays to diagnosis in this group of patients. Investigation for bladder cancer is recommended in patients:

- >45 years with visible hematuria persisting after successful treatment of UTI (urgent referral),
- >60 years with unexplained NVH and either dysuria or raised white cell count on a blood test (urgent referral),
- >60 years with recurrent or persistent unexplained UTI (non-urgent referral).

Adjuncts such as cytology do not improve detection of bladder cancer in patients with irritative lower urinary tract symptoms [52, 53] and neither is it helpful in the investigation of patients with recurrent UTIs as its sensitivity is reduced in the presence of cystitis. Although there are currently no tumor markers superior to cytology [54], there is an opportunity for research in this group of patients as it may be possible to improve the yield of cystoscopy with either a marker or simple imaging.

Treatment

Allowing for patient preference, bladder cancers in both genders should be treated according to current guidelines. When assessing the risk of progression or recurrence in new patients with bladder cancer, female gender should probably be included as a relevant prognostic factor.

Current evidence suggests variable treatment of NMIBC. Improved adherence to treatment and surveillance protocols for high-risk NMIBC may reduce progression to MIBC.

The fact that fewer than half of patients with non-UCB are treated with surgery (inclusive of TUR) is surprising. This most likely reflects an elderly group of patients, many with advanced disease at presentation, but does suggest a degree of under-treatment. A more aggressive operative approach in the treatment of non-UCB may be considered in this high-risk cancer.

References


