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Method of Presentation of Young Bladder Cancer Patients Under 50 Years

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ABSTRACT:

Background: Bladder cancer is the 11th most common cancer in the UK, making up 3% of all new cancer diagnoses each year [1]. Our understanding of this disease in younger patients is relatively scarce and contentious. Objective: The aims of the project were to examine how younger patients present to healthcare, considering symptoms, mode of presentation and the severity of pathology at diagnosis. This data could then be compared with the variety of literature available for older patients. Data sources: The Urology Pathology database of the North Bristol NHS Trust was searched back to 2016. Methods: Exclusion criteria identified 43 patients suitable for the study. Patient data was collected, anonymised and statistical analysis was then used. Results: The most common presenting symptom was visible haematuria at 81.4%. The most common mode of presentation was via the 2-Week-Wait referral system, with 67.4% of patients presenting following referral from their GP. 83.7% of patients presented with non-muscle –invasive bladder cancer.

Introduction and Method

In younger patients bladder cancer is relatively scarce, as increasing age is the greatest risk factor [2]. Some studies suggesting younger patients have similar disease to older adults [3]. However there is evidence of heterogeneity amongst younger patients; as while most present with less severe disease associated with better prognosis, a small subset present with aggressive disease with poorer outcomes [4]. The gap in the literature for the clinical experience of younger patients with this disease is intriguing, as often it is older patients whom we have a poorer understanding of [5]. An improved understanding of the presentation of younger bladder cancer patients could influence development of standardised evidence-based guidelines specific to this age group, as necessary.

The Urology Pathology database of the North Bristol NHS Trust was searched for patients under 50 with bladder cancer pathology from 2016-2020. Following updates to the North Bristol Trust database, 2016 was the earliest data available. This data was collected and anonymised, yielding 52 patients. Several patients (n=9) were subsequently excluded from the analysis: 7 patients due to missing data in 2 or more of the analysed categories; 1 patient had

benign histology; 1 patient was older than 50. Simple statistical analysis was then used to process the numerical data from the 43 patients presenting with bladder cancer under the age of 50 in the last 4 years. All data was anonymous and so ethical approval was not needed.

Results

There were 32 male patients and 11 female patients, giving a ratio of 2.91. The mean age of diagnosis was 39.3, with a range of 19-49 years. The mean age of diagnosis for men was 38.8, and 40.6 for women. 1 patient was younger than 20, 4 patients were aged 21-30, 16 were 31-40 and 22 were 41-50. The most common presenting symptom was visible haematuria (VH), with 81.4% (n=35) presenting with VH. Symptom presentation is summarised in table 1.

2 patients presented with a urinary tract infection (UTI) and this was always alongside VH or NVH. 2 patients did not present with any specific bladder cancer symptoms; cancer was found incidentally from a CT scan, and a flexible cystoscopy investigation for low sperm count.

Table 1: Symptoms at Presentation

| Symptom | Number of patients presenting with this symptom | Percentage of patients presenting with this symptom |
|-------------------------|---|---|
| Visible haematuria | 35 | 81.4 |
| Non-visible haematuria | 2 | 4.7 |
| Urinary Tract Infection | 2 | 4.7 |
| Abdominal pain | 1 | 2.3 |
| Loin pain | 1 | 2.3 |
| Ureteric obstruction | 1 | 2.3 |
| Unknown | 1 | 2.3 |
| No symptoms | 2 | 4.7 |

Table 2: Mode of Presentation

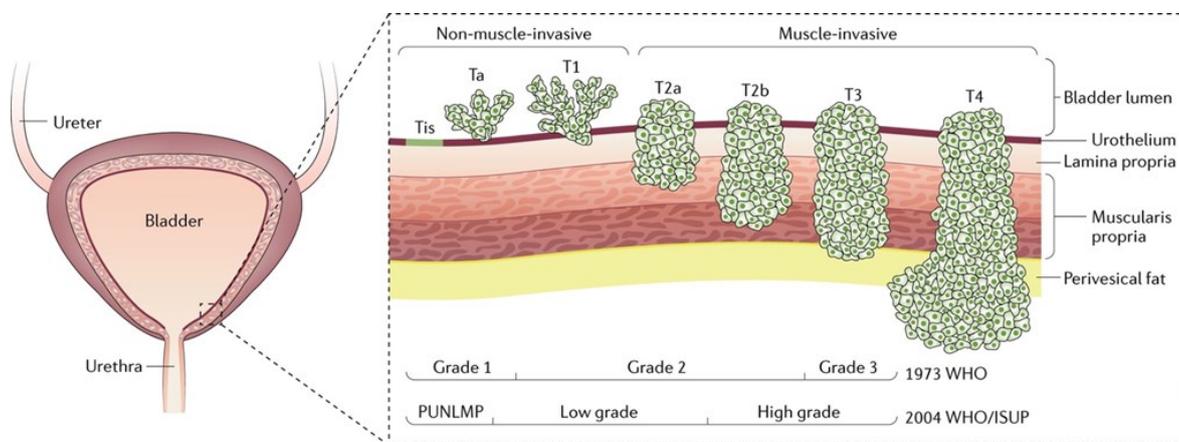
| Age category | Mode of Presentation | | | | |
|-----------------------|----------------------|-------|-----------|--------|---------|
| | 2WW | Other | Emergency | Urgent | Unknown |
| <20 | | | | | 1 |
| 21-30 | 3 | 1 | | | |
| 31-40 | 13 | 2 | | | 1 |
| 41-50 | 13 | 2 | 3 | 4 | |
| Total n | 29 | 5 | 3 | 4 | 2 |
| % Presentation | 67.4 | 11.6 | 7.0 | 9.3 | 4.7 |
| Average age | 38.5 | 40.2 | 45.3 | 46.3 | |

1 patient had no information for their original ‘Other’ modes; 4 were incidental findings of bladder presentation, as their original diagnosis was outside of the time period the data was collected, and was under monitoring with cystoscopies.

The most common mode of presentation was via the 2-Week-Wait referral system, with 67.4% [n=29] of patients presenting following referral from their GP. 9.3% [n=4] were Urgent presentations and 7.0% [n=3] were Emergency. 5 patients presented via

‘Other’ modes; 4 were incidental findings of bladder cancer from other investigations and 1 was a referral for an ultrasound scan that identified a mass, as shown in table 2.

The pathological staging of the tumours at diagnosis, summarised in table 3, used the 2017 TNM classification published by the UICC. A summary of the ‘T’ [tumour] element of this classification is shown in figure 1.



Nature Reviews | Disease Primers

Figure 1: TNM Classification- tumour staging

Sanli, O., Dobruch, J., Knowles, M., Burger, M., Alemozaffar, M., Nielsen, M. and Lotan, Y., 2017. Bladder cancer. Nature Reviews Disease Primers, 3.

Table 3: TNM Classification of Tumour at Diagnosis

| Age | Tumour Classification | | | | | | |
|-----------------------|-----------------------|-----|------|----------|----------|----------|--------------------|
| | Ta | T1 | T2 | Ta + TIS | T1 + TIS | T2 + TIS | Metastatic deposit |
| <20 | 1 | | | | | | |
| 21-30 | 3 | | | 1 | | | |
| 31-40 | 14 | 1 | 1 | | | | |
| 41-50 | 14 | 1 | 4 | | 1 | 1 | 1 |
| Total n | 32 | 2 | 5 | 1 | 1 | 1 | 1 |
| % Presentation | 74.4 | 4.7 | 11.6 | 2.3 | 2.3 | 2.3 | 2.3 |

Table 4: Grading of Pathology at Diagnosis

| Age | Grade | | | |
|----------------------|-------|------|------|--------------------|
| | G1 | G2 | G3 | Metastatic deposit |
| <20 | | 1 | | |
| 21-30 | | 3 | 1 | |
| 31-40 | 3 | 11 | 2 | |
| 41-50 | 3 | 11 | 7 | 1 |
| Total n | 6 | 26 | 10 | 1 |
| % of Patients | 14.0 | 60.5 | 23.3 | 2.3 |

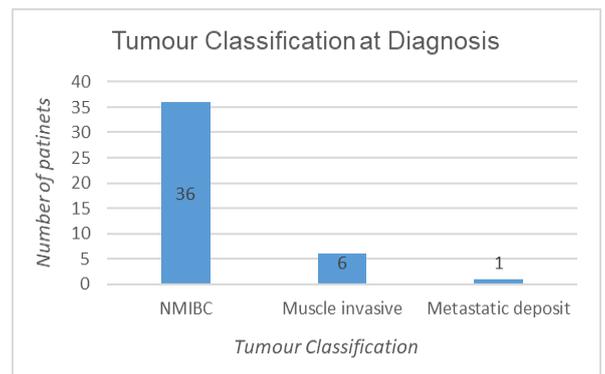


Figure 2: NMIBC Tumour classification at Diagnosis

At diagnosis, 83.7% of patients presented with non-muscle-invasive bladder cancer [NMIBC], as shown in figure 2. 11.6% of patients presented with muscle invasive bladder cancer. The average age of diagnosis with NMIBC was 38.4; the average age of diagnosis with muscle invasive bladder cancer was 44.3. 3 patients had more than 1 tumour type; 1 patient had Ta with TIS; 1 had T1 and TIS and one patient had T2 and TIS. One tumour was a metastatic deposit from a gastric adenocarcinoma.

Tumours were graded according to the 1973 WHO Grading system. Where the tumour grade was on a boundary the less severe grading was used. For example, "G2/3pTa" was classed as Grade 2 cancer for the analysis. The grading is summarised in table 4. One tumour was a metastatic deposit from a gastric adenocarcinoma hence why it was not graded.

Discussion

The male risk of bladder cancer is 3-4 times greater than the female risk, which has historically been attributed to increased relative carcinogen exposure through smoking and occupational hazards [6, 7]. However, there is evidence that this gender disparity exists even when controlling for this increased carcinogen exposure [8]. The 2.91 ratio of male to female patients was slightly lower than the average ratio of 3-4 times, and a reduced gender ratio in younger patients has also been found by other studies [4, 9, 10]. It is unclear why a greater proportion of

younger patients are female if this is not due to varying carcinogen exposure. Studies have found women are diagnosed later than men, in these results by an average of 1.8 years, and have been found to have worse outcomes [11]. In younger patients this could be magnified by the increased proportion of female patients, if later diagnosis is contributing to poorer outcomes. To suggest all younger patients should be managed conservatively, as some studies have concluded, [18] owing to an increased presentation of low-grade and low-stage cancers, is inappropriate as it could prevent quicker diagnosis of more severe cancers.

The age range of the patients included was large, at 19-49 years, and incidence increased with age with the majority of patients [51%] aged 41-50 years. Other studies have excluded patients over 40 years, [12] however to do so here would have given too small a sample of 21 patients. The increase in incidence with age was to be expected as age is the most significant risk factor.

Other studies have also found similar rates of VH as the presenting symptom, at approximately 80% in younger patients [13]. The second most common symptom we found was NVH, and UTIs with haematuria, while in the average population irritative voiding symptoms, such as dysuria and urgency, are the second most common symptom [14]. Interestingly no patients presented with this set of symptoms as their primary complaint.

In the average population it is unusual to have symptoms such as abdominal pain without accompanying VH or NVH, [14] but in these results 5 patients presented in this way. As this was a small group of patients it is not possible to draw firm conclusions, yet it suggests that younger patients may present with more 'atypical' symptoms or no symptoms at all relative to the average bladder cancer patient.

67.4% of patients presented following referral from their GP via the 2WW, a higher rate than found by Ellis-Brookes et al and Blick et al [15, 16] who found rates of 30% and 42% respectively for the average bladder cancer population. It has been shown that the proportion of cancers diagnosed after a 2WW referral decreases with age, and although this was across all cancers [15], this trend could explain the higher than average proportion of patients presenting via 2WW referral. Patients presenting via the 2WW were on average younger than Emergency and Urgent modes of presentation. Emergency presentations were associated with the worst outcomes, as all 3 patients who presented this way died, with 2 patients offered palliative care on diagnosis. All 3 of these patients were aged 41-50; however owing to these small numbers it is not possible to conclude their age contributed to this worse prognosis.

Most tumours were Ta and 83.7% of patients had NMIBC, higher than the 75% proportion for the average bladder cancer population [2]. Of the patients (n=6) diagnosed with muscle invasive bladder cancer, 5 were aged 41-50 and 1 was 31-40, suggesting an association between more advanced cancer and age.

Amongst the 21 patients aged under 40 in our study only 14.3% presented with G1 cancer, with the majority G2 (60.5%, n=26). Overall only 14.0% of tumours were G1, an unusually high grade presentation for younger patients, who typically present with low grade tumours. Gunlusoy et al [17] found that 82.4% of tumours in patients under 40 were G1 and other studies have reported similar low grade presentation in younger patients [4, 6, 10, 13, 18]. It is unclear why the grading was higher for this group at presentation than found by others, particularly as it could be even higher as tumours on the boundary of grades were classed as the less severe grade.

Limitations

This retrospective analysis was limited by missing data that led to patients being excluded. It was not possible to examine some questions such as if it took longer to diagnose younger patients, as other studies have found [13] since this data could not be collected. The database for the North Bristol Trust changed in 2016 meaning results were constricted by the time frame of 4 years, with 21 patients identified in the range of 19-40 years. The 30 year age range of the patients examined is large, and due to the increasing incidence of bladder cancer with age, 51% of patients were aged 41-50. Other studies in 'younger' patients have often had a cut-off of 40 years and so these results show the characteristics of slightly older patients than typically examined [12].

It was not always possible to compare grading with other studies which used the 2004/2016 WHO grading system as it does not directly translate to the 1973 system for comparison. Ambiguity in the grading of some of the tumours was due to

the 1973 system used, which is recommended by the EAU as it has not been shown to be outperformed by the 2004/2016 system but does mean some tumours are considered to be on the boundary [19].

Conclusions

Bladder cancer presents differently in younger patients, with an increased proportion of female patients and less typical symptoms of presentation than for older patients. More patients present via the 2WW than older patients, following the trend seen in other cancers. There is no consensus on the severity of presentation, as although more patients present with NMIBC than average, there is not enough evidence to show that all younger patients present with less aggressive disease. The patients in this analysis presented with higher grade cancers than others have found. More research is required to determine if there is a delay in diagnosing younger patients, particularly women, and if this is contributing to poorer outcomes. As one of the most expensive cancers to treat due to its chronic nature, and with one of the lowest patient satisfaction ratings, [2, 20], further research could warrant the development of age-specific guidelines.

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