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Title: Comparison of complications after transrectal and transperineal prostate biopsy: a national population-based study.

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Abstract

Objectives:

To assess the complications of transrectal (TR) compared to transperineal prostate (TP) biopsies.

Patients and Methods:

Men diagnosed with prostate cancer between 1st April 2014 and 2017 in England were identified by the National Prostate Cancer Audit. Administrative hospital data were then used to categorise the type of prostate biopsy and subsequent complications requiring hospital admission.

Administrative hospital data were used to identify patients staying overnight immediately after biopsy and those readmitted separately for hospital admissions because of sepsis, urinary retention or haematuria. Procedure related mortality and total length of hospital stay within 30 days was also recorded. Generalised linear models were used to calculate adjusted risk differences (aRD).

Results:

73,630 men undergoing prostate biopsy were identified. Those having TP biopsy (n=13,723) were more likely to have an overnight hospital stay (12.3% vs 2.4%; aRD 9.7%: 95% CI 7.1% to 12.3%), were less likely to be readmitted because of sepsis (1.0% vs 1.4%; aRD -0.4%: CI -0.6% to -0.2%), and were more likely to be readmitted with urinary retention (1.9% vs 1.0%; aRD 1.1%: CI 0.7% to 1.4%) than those undergoing a TR biopsy (n=59,907). There were no significant differences in the risk of haematuria or mortality.

Conclusions:

TP biopsy has a lower risk of readmission for sepsis but a higher risk of readmission for urinary retention than TR biopsy. Use of the TP route would prevent one readmission for sepsis in 278 men at the cost of three additional men readmitted for urinary retention.

Introduction

Most men diagnosed with prostate cancer have a prostate biopsy (1). The transrectal (TR) route is currently the most common technique in most countries but transperineal biopsy (TP) is used increasingly (1).

TP biopsies are reported to have a lower risk of sepsis than TR biopsies but the most recent systematic review reported only seven small studies comparing the safety of both routes directly (2). This review, which included a total of 1618 patients, is too small to allow precise estimates of the difference in the risk of sepsis, urinary retention and haematuria. It is therefore unclear whether the risk of complications is significantly different between TP to TR biopsies (3-5), something which is reflected in the uncertainty of national and international guidelines

We compared the risk of sepsis, urinary retention and haemorrhage after TR and TP prostate biopsies in all men included in the National Prostate Cancer Audit (1) who were diagnosed with prostate cancer between 1st April 2014 and 31st March 2017 in

the English National Health Service (NHS), using cancer registry and administrative hospital data linked at patient level.

Patients and Methods

Data sources and patient population

All patients newly diagnosed with prostate cancer between 1st April 2014 and 31st March 2017 and included in the National Prostate Cancer Audit were identified from the English cancer registry using the ICD 10 diagnosis code C61 and the date of cancer diagnosis (6).

The data set was linked at patient-level to Hospital Episode Statistics (HES), which also included mortality data derived from the Office for National Statistics. HES is an administrative database of all hospital outpatient appointments and inpatient admissions in England.

OPCS-4 procedure codes were used to identify men undergoing a TR (M70.3) and/or a TP biopsy (M70.2) (6). To account for the time interval between patient biopsy and date of diagnosis, all biopsies carried out from 1st January 2014 were identified to ensure biopsy data was available for all patients who received a cancer diagnosis from the 1st April 2014. For each patient, only the biopsy with a date closest to the date of diagnosis was taken to ensure that only a single biopsy session per patient was included.

118,526 men were identified with a prostate cancer diagnosis date between 1st April 2014 and 31st March 2017 (Fig 1). Of these, 75,464 (63.7%) had a prostate biopsy identified in the HES database. 1008 men were excluded because they had their biopsy at a private hospital, 11 because the hospital where they had their biopsy was unknown and 815 men because the biopsy route was not documented. Overall, data from 73,630 men was available for analysis.

Outcome variables

Readmissions for sepsis, urinary retention or haematuria were identified using the ICD-10 and OPCS-4 codes as described elsewhere (7) (Appendix). Consequently, complications were only identified if they were severe enough to require a hospital admission, which aligns with the Clavien-Dindo classification of a severe surgical complication (grade 3)(8). Previous studies of prostate biopsy complications have also used these outcomes to measure complications following this procedure. (2, 7, 9, 10).

Length of hospital stay following readmission within 30 days after biopsy was measured as a continuous outcome variable. HES records only report admission and discharge dates and therefore length of hospital stay was reported in days. For all patients readmitted, length of stay was calculated as the number of overnight stays plus one.

Patient characteristics

The HES database was used to identify patient age, comorbidities, socioeconomic deprivation and ethnicity. The cancer registry was used to identify patient ethnicity in instances where HES records were incomplete.

The Royal College of Surgeons (RCS) Charlson score was used to identify co-morbid conditions captured in the HES record within one year prior to each patient's prostate biopsy (11). Socioeconomic deprivation status was determined for patients from the English 2012 Index of Multiple Deprivation (IMD) based on their area of residence and divided according to quintiles of the national distribution (12). For ethnicity, men were categorised into four groups (white, asian, black and other).

Statistical analysis

Generalised linear models were used to estimate the adjusted risk differences between men who had a TR and TP biopsy. These models assumed a binomial distribution for the outcomes and used an identity link function. Multivariable linear regression was used to estimate the adjusted difference in the mean length of hospital stay following readmission within 30 days of biopsy.

Analyses were adjusted for the year of biopsy, patient age, ethnicity, comorbidity, and socioeconomic deprivation. It also took into account that patients were clustered within hospitals (13). Missing values for ethnicity (n=4987, 6.7%) were imputed using multiple imputation by chained equations. 20 data sets were created and Rubin's rules were used to combine estimates. Wald tests were used to calculate p values. The level for statistical significance was set at 0.05.

Results

Of the 73,630 men included in the analysis, 59,907 (81.4%) underwent a TR biopsy and 13,723 (18.6%) a TP biopsy. Men undergoing a TP biopsy tended to have their biopsy more recently (51.4% vs 42.4% in the two most recent years of the inclusion period), were younger on average (62.9% vs 51. 5% younger than 70) and were more likely to have at least one co-morbid condition (28.3% vs 22.0%) than men undergoing TR biopsy (Table 1).

TP biopsy patients were more likely to have an overnight stay immediately following the biopsy than those having TR biopsy (12.3% vs 2.4%; adjusted risk difference 9.7%; 95% CI 7.1% to 12.3%) (Table 2).

Men who had a TP biopsy were less likely to be readmitted because of sepsis (1.0% vs 1.4%; adjusted risk difference -0.4%; 95% CI -0.6% to -0.2%) but were more likely to be readmitted because of urinary retention (1.9% vs 1.0%; adjusted risk difference 1.1%; 95% CI 0.7% to 1.4%) (Table 2). 155 of the 59,907 men who underwent a TR (0.2%) and 38 of the 13,723 who underwent a TP biopsy (0.3%) had both sepsis and urinary retention.

We found that the mean length of hospital stay after a readmission due to sepsis was shorter in those who had a TP biopsy than in those who had a TR biopsy (5.1 vs 6.5 days; adjusted mean difference -1.1 days; 95% CI -1.8 to -0.4). The mean length of hospital stay after readmissions for urinary retention was also shorter than for TP

biopsy (2.6 vs 3.9 days; adjusted mean difference -1.3 days; 95% CI -2.0 to -0.7). No statistically significant difference was seen in length of stay for readmissions due to haematuria (3.1 vs 3.9 days; adjusted mean difference -0.7 days; 95% CI -2.0 to 0.63).

Discussion

Summary

This is the largest study comparing the risk of complications following TP and TR prostate biopsies to date. Our results indicate that patients who underwent a TP biopsy between 1st April 2014 to 31st March 2017 were less likely to be readmitted to hospital because of sepsis but were more likely to be readmitted because of urinary retention than patients who had a TR biopsy.

Comparison with other studies

Two systematic reviews have recently compared complications after TR and TP biopsies. One review, published in 2017, found that four studies, including 971 patients, reported on sepsis, four studies, including 710 patients, reported on urinary retention, and six studies, including 1327 patients, reported on haematuria. (9). This review concluded that there were no statistically significant differences in the risk of these complications after TR or TP biopsy.

Another review, published in 2019, summarised seven studies, including 1618 patients (2). This review found that sepsis was less likely after a TP biopsy but it did not find significant differences for urinary retention or haematuria. This systematic

review failed to include four studies that were previously included in the systematic review published in 2017 (9). The range of methods used to assess complication rates in the studies that were included in these reviews and the overall low statistical power are likely to explain the differences with the results reported in our study.

One population-based study, conducted in New York State, comparing TR versus TP biopsy complications, was not included in the two systematic reviews mentioned above (10). This study included 9893 men and reported that sepsis was more common after a TR biopsy than after a TP biopsy (adjusted odds ratio 3.48; 95 CI 1.27-9.54; *P*=0.02). It did not find statistically significant differences for urinary retention and haematuria. However, only 421 men (4.3% of the total study population) had a TP biopsy. This study was therefore inadequately powered to detect a meaningful difference in urinary retention rates.

Clinical interpretation

Our study highlights the dilemma in choosing between TR or TP biopsy as a means of reducing or avoiding biopsy-related complications. There is clearly a trade-off between the risk of sepsis and acute urinary retention. In this context, it is also important to note that the average length of stay due to sepsis or urinary retention is shorter in men who had a TP biopsy than in those who had a TR biopsy. These differences in hospital length of stay suggest that the complications that occur after a TP biopsy may be less severe than those after a TR biopsy.

Sepsis remains the most serious complication related to prostate biopsy. However, the adjusted risk difference for sepsis requiring subsequent hospital admission

between TR and TP biopsy was relatively small. Based on our results, it can be estimated that the use of TP rather than TR biopsies would prevent one readmission for sepsis in 278 men (= 1 / 0.36%) at the cost of three additional men (= 1.06% / 0.36%) readmitted for urinary retention.

The higher risk of developing urinary retention requiring hospital readmission following a TP biopsy may in part be associated with the use of a general anaesthetic and the larger number of cores taken with a TP biopsy. It is important to note that there is a gradual shift in clinical practice towards carrying out TP biopsies under local anaesthetic and taking fewer but more targeted tissue cores (1, 14, 15). It is likely that most of this change in practice has occurred after the study period. Such a practice change may help to reduce the subsequent retention and infection rate and the need for an overnight stay immediately following TP biopsy. However, this hypothesis needs to be tested in further studies.

Another factor which might affect changes in infectious complication risk after prostate biopsy and thereby influence the decision to use TP over TR biopsy is the decreasing effectiveness of antibiotic prophylaxis (16). These trends suggest that over time the trade-off between sepsis and retention risk may become more favourable for TP biopsies, given that the higher risk associated with TR biopsies (sepsis) may increase and the higher risk associated with TP biopsies (urinary retention) is likely to decrease with newer, modified sampling methods.

To address this question, we undertook a sensitivity analysis of our results for each year of the inclusion period (2014 -2017) to assess whether the risk of urinary

retention and sepsis changed over time. We did not find evidence for a time trend in the risk for either complication. For each year the study was undertaken, the increased risk of urinary retention observed in the TP group and the increased risk of sepsis observed in the TR group remained significant.

Strengths and limitations

Key strengths of this report, which is part of the National Prostate Cancer Audit, include the high number of men studied using data that represent contemporary clinical practice, and the relatively high proportion of TP biopsies (18.6%). Comorbidity was more prevalent in men who had a TP biopsy. For example, a more detailed analysis of specific comorbidities (results not reported) found that the prevalence of diabetes, which is an important risk factor for the development of complications, was higher in men who had a TP biopsy (11.2%) than in men who had a TR biopsy (8.8%) (11). However, all comparisons were adjusted for comorbidity. Our findings therefore represent current real-world practice within the English NHS, which covers more than 90% of the prostate biopsies carried out in England (1, 17).

Our coding framework was developed to identify severe complications that require a hospital admission. This method ensured that we only considered complications at a specific severity level. However, in doing so we were unable to capture complications including minor infections, haematospermia, rectal bleeding and pain, most often treated by general practitioners in primary care or in outpatient clinics or emergency departments of NHS hospitals. These complications would rarely be considered severe enough to require hospital admission.

A further limitation of our study is that we only included men diagnosed with prostate cancer who had a biopsy documented in the HES database. Thus, we were unable to report on biopsies carried out in men who had benign changes only. However, we do not envisage that biopsy type or the risk of complications would differ between men included in the study and those receiving a prostate biopsy but who did not subsequently have a confirmed cancer diagnosis. Indication for biopsy was also not identified, but the indication for most biopsies is likely to have been the suspicion of cancer.

Furthermore, the coding of the type of biopsy may not always be correct. However, a systematic review of coding accuracy for urological patients in HES found that about 90% of the procedure codes were correct (18). Also, coding errors in the type of biopsy are unlikely to be associated with biopsy complications which suggests that the misclassification is ‘non-differential’. Our results may therefore slightly underestimate the true differences in complication rates between men who had a TR or a TP biopsy.

We were also unable to determine the differences in the prophylactic antibiotic regimens between men who had a TR or TP biopsies. Previous studies have reported a potential benefit of TP over TR biopsies, which suggests that prophylactic antibiotic regimes are not required routinely.(19) However, the British Association of Urological Surgeons advocates the use of prophylactic antibiotics in both TR and TP biopsy and in practice prophylaxis is generally used in both groups (20, 21).

Finally, we do not have data on prostate size or volume, the number or locations of needle insertions, the experience of the practitioner undertaking the biopsies, whether a targeted or mapping biopsy method was employed, or whether a local or general anaesthetic was used. However, we feel that our comparison is an accurate report of the complications after TR and TP biopsies in contemporary practice within a publicly funded health system.

Conclusions

Our results represent real-world practice during a period when the use of TP was increasing. TP prostate biopsies are associated with a lower risk of readmission due to sepsis compared to TR biopsies. However, this lower risk of sepsis comes at the expense of a higher risk of readmission for urinary retention.

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Figure, Tables and Appendix Legends

Figure 1: Consort Diagram of Patient Selection.

Table 1: Patient characteristics according to prostate biopsy method for men diagnosed with prostate cancer between 1st April 2014 and 31st March 2017 in the English NHS.

Table 2: Risk of readmission and mean length of hospital stay in the first 30 days after transrectal (TR) and transperineal (TP) biopsy.

Appendix: Coding framework based on ICD-10 and OPCS-4 codes

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Figure 1. Consort Diagram of Patient Selection

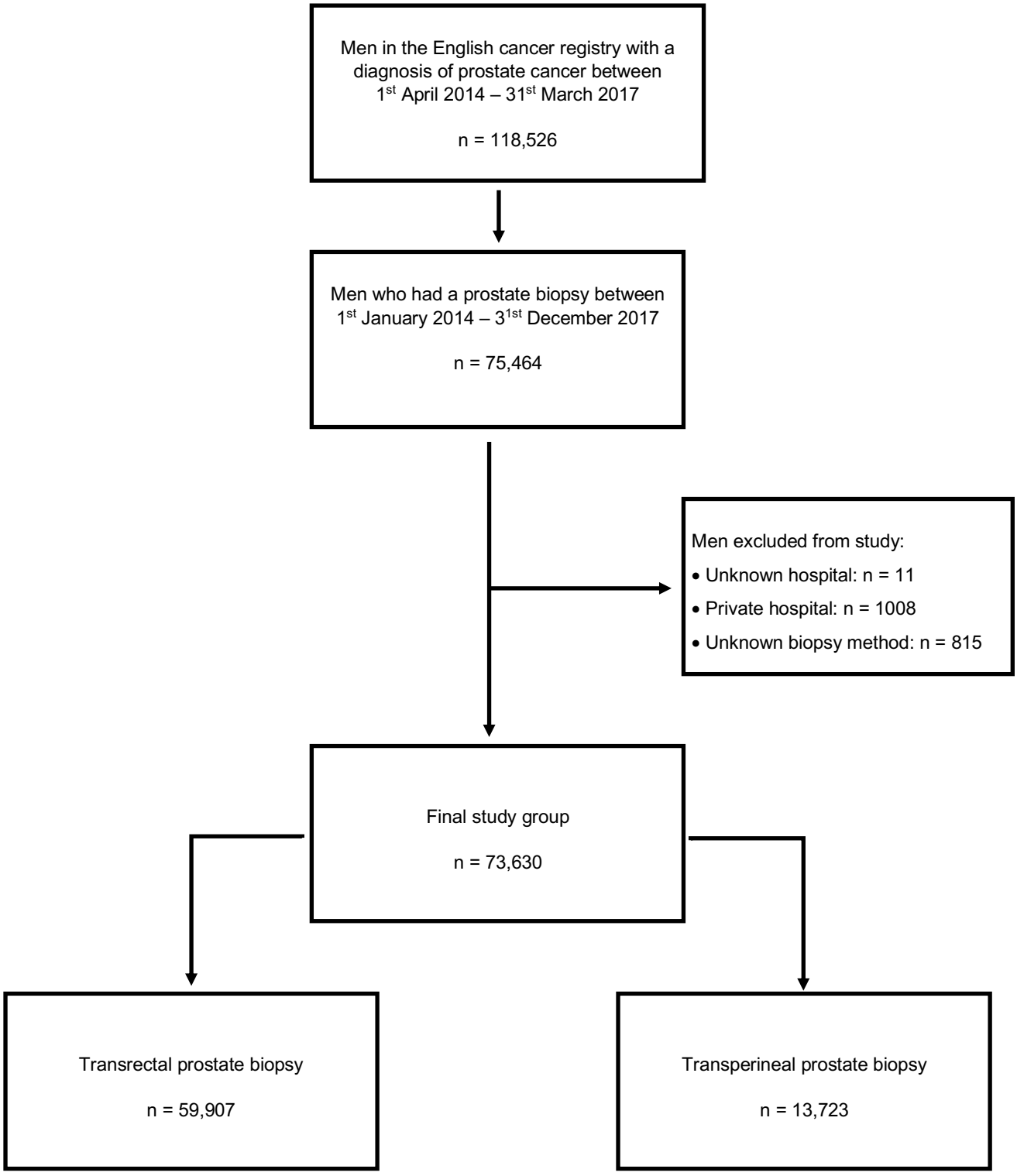

Table 1. Patient characteristics according to prostate biopsy method for men diagnosed with prostate cancer between 1st April 2014 and 31st March 2017 in the English NHS.

	Transrectal biopsy		**Transperineal biopsy**		**Total**	
	No.	%	No.	%	No.	%
Total	59,907	81.4	13,723	18.6	73,630	100
Biopsy year						
2014	14,744	24.6	2,340	17.1	17,084	23.2
2015	19,750	33.0	4,334	31.6	24,084	32.7
2016	19,875	33.2	5,162	37.6	25,037	34.0
2017	5,538	9.2	1,887	13.8	7,425	10.1
Age group (years)						
< 60	7,941	13.3	2,534	18.5	10,475	14.2
60-69	22,898	38.2	6,090	44.4	28,988	39.4
70-79	24,113	40.3	4,676	34.1	28,789	39.1
≥ 80	4,955	8.3	423	3.1	5,378	7.3
Comorbidity according to RCS Charlson co-morbidity score						
0	46,744	78.0	9,841	71.7	56,585	76.9
1	9,152	15.3	2,952	21.5	12,104	16.4
≥2	4,011	6.7	930	6.8	4,941	6.7
Socioeconomic deprivation status (quintiles of the national distribution)						
1 (least deprived)	14,169	22.7	4319	25.6	18,488	23.3
2	14,593	23.4	3874	23.0	18,467	23.3
3	13,453	21.5	3544	21.0	16,997	21.4
4	10,976	17.6	2883	17.1	13,859	17.5
5 (most deprived)	9286	14.9	2230	13.2	11,516	14.5
Ethnicity						
White	52,599	93.6	11,752	90.2	64,351	92.9
Asian	959	1.7	274	2.1	1,233	1.8
Black	1,896	3.4	708	5.4	2,604	3.8
Other	765	1.4	292	2.2	1,057	1.5
Missing	*3,688*		*697*		*4,385*	

Abbreviation: RCS = Royal College of Surgeons

Table 2 Risk of readmission and mean length of hospital stay in the first 30 days after transrectal (TR) and transperineal (TP) biopsy.

Risk of readmission in first 30 days after					
	TR	**TP**			
	number (%)	**number (%)**	**Adjusted risk difference* (%)**	**95% CI**	***P*- value**
Number of men	59,907	13,723			
Overnight stay immediately after biopsy*	1,415 (2.36)	1,681 (12.25)	9.70	7.12 to 12.27	<0.001
Sepsis	806 (1.35)	142 (1.03)	-0.36	-0.56 to -0.15	0.001
Urinary retention	571 (0.95)	265 (1.93)	1.06	0.71 to 1.41	<0.001
Haematuria	396 (0.66)	97 (0.71)	0.07	-0.15 to 0.28	0.546
Mortality**	59 (0.10)	9 (0.07)	-0.03	-0.07 to 0.01	0.197
Length of hospital stay					
	TR	**TP**			
	Mean (SD)	**Mean (SD)**	**Adjusted mean difference* (%)**	**95% CI**	***P*- value**
Number of men	806	142			
Readmission LOS (sepsis; days)	6.53 (8.88)	5.08 (3.95)	-1.10	-1.84 to -0.36	0.004
Number of men	571	265			
Readmission LOS (urinary retention; days)	3.87 (4.50)	2.58 (2.70)	-1.32	-1.97 to -0.66	<0.001
Number of men	396	97			
Readmission LOS (haematuria; days)	3.88 (5.78)	3.12 (3.55)	-0.70	-2.03 to 0.63	0.304

Abbreviations: LOS = length of hospital stay; **RCS = Royal College of Surgeons**;
*** Adjusted for biopsy year, age, ethnicity, RCS Charlson score and socioeconomic deprivation status**
**** Only adjusted for age.**

Appendix 1: Coding framework based on ICD-10 and OPCS-4 codes (6)	
Codes:	**Description of code**
Sepsis	
ICD-10 codes within the first 7 diagnostic fields	
N30.0	Acute cystitis
N39.0	Urinary tract infection, site not specified
N41.0	Acute prostatitis
N41.2	Abscess of prostate
N41.3	Prostatocystitis
N41.9	Inflammatory disease of the prostate, unspecified
N45.0	Orchitis, epididymitis and epididymo-orchitis with abscess
N45.9	Orchitis, epididymitis and epididymo-orchitis without abscess
N49	Inflammatory disorder male genital organs
R36	Urethral discharge
B96.1	Klebsiella pneumoniae as the cause of diseases classified to other chapters
B96.2	Escherichia coli as the cause of diseases classified to other chapters
B96.4	Proteus as the cause of diseases classified to other chapters
B96.5	Pseudomonas as the cause of diseases classified to other chapters
B96.8	Other specified bacterial agents as the cause of diseases classified to other chapters
A41.8	Other specified sepsis
A41.9	Sepsis, unspecified
A49.9	Bacterial infection, unspecified
ICD-10 codes within the first diagnostic field and as part of an emergency admission	
I48	Atrial fibrillation and flutter
N17.9	Acute renal failure, unspecified
Haematuria	
ICD-10 codes within the first 7 diagnostic fields	
R31	Unspecified haematuria
N42.1	Congestion and haemorrhage of prostate
OPCS-4 codes within the first 3 procedure fields and as part of an emergency admission	
M45.9	Unspecified diagnostic endoscopic examination of bladder
M45.8	Other specified diagnostic endoscopic examination of bladder
X33.9	Unspecified other blood transfusion
Urinary retention	
ICD-10 codes within the first seven diagnostic fields	
R33	Retention of urine
ICD-10 codes within the first 2 diagnostic fields and as part of an emergency admission	
Z46.6	Fitting and adjustment of urinary device

Additional information and conflict of interest statement

Ethics Approval:

All patient data used is fully anonymised and is therefore exempt from UK National Research Ethics Committee (NREC) approval.

Data and Materials:

The cancer registry data used for this study are based on information collected and quality assured by Public Health England's National Cancer Registration Service (www.ncras.nhs.uk). Access to the data was facilitated by the Public Health England's Office for Data Release. Hospital Episode Statistics were made available by the NHS Digital (www.digital.nhs.uk); all rights reserved). B.B. and M.G.P. had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Data are not available to other researchers as it uses a registry database of patients providing routinely collected data.

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