ARTICLE

Clinical Research

Comparison of the treatment of men with prostate cancer between the US and England: an international population-based study

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INTRODUCTION: The treatment of prostate cancer varies between the United States (US) and England, however this has not been well characterised using recent data. We therefore investigated the extent of the differences between US and English patients with respect to initial treatment.

METHODS: We used the Surveillance, Epidemiology, and End Results (SEER) database to identify men diagnosed with prostate cancer in the US and the treatments they received. We also used the National Prostate Cancer Audit (NPCA) database for the same purposes among men diagnosed with prostate cancer in England. Next, we used multivariable regression to estimate the adjusted risk ratio (aRR) of receiving radical local treatment for men with non-metastatic prostate cancer according to the country of diagnosis (US vs. England). The five-tiered Cambridge Prognostic Group (CPG) classification was included as an interaction term.

RESULTS: We identified 109,697 patients from the SEER database, and 74,393 patients from the NPCA database, who were newly diagnosed with non-metastatic prostate cancer between April 1st 2014 and December 31st 2016 with sufficient information for risk stratification according to the CPG classification. Men in the US were more likely to receive radical local treatment across all prognostic groups compared to men in England (% radical treatment US vs. England, CPG1: 38.1% vs. 14.3% – aRR 2.57, 95% CI 2.47–2.68; CPG2: 68.6% vs. 52.6% – aRR 1.27, 95% CI 1.25–1.29; CPG3: 76.7% vs. 67.1% – aRR 1.12, 95% CI 1.10–1.13; CPG4: 82.6% vs. 72.4% – aRR 1.09, 95% CI 1.08–1.10; CPG5: 78.2% vs. 71.7% – aRR 1.06, 95% CI 1.04–1.07)

CONCLUSIONS: Treatment rates were higher in the US compared to England raising potential over-treatment concerns for low-risk disease (CPG1) in the US and under-treatment of clinically significant disease (CPG3-5) in England.

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INTRODUCTION

Prostate cancer is the second most common non-skin male cancer in the world [1]. Despite this, the diagnosis and management of prostate cancer varies across Western societies due to differences in screening practices and healthcare systems. Differences between the fee-for-service, insurance-based healthcare system in the US and the publicly-funded UK system has the potential to influence management decisions of men newly diagnosed with prostate cancer towards both over- and under-treatment [2].

The National Prostate Cancer Audit (NPCA) in England and Wales is a national clinical audit assessing the quality of services and care provided to all men diagnosed with prostate cancer since 2014 [3]. The NPCA uses explicitly defined performance indicators, including initial treatment, to report on variation between hospitals. For example, the NPCA reports yearly on the proportion of men with low-risk localised and locally advanced prostate cancer who undergo radical local treatment providing insights into potential over- and under-treatment trends, respectively.

In the US, the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute collects cancer incidence data from population-based cancer registries covering ~35% of the US population irrespective of insurance coverage. While the US does not have a dedicated national programme to specifically assess prostate cancer services and care, the registry data are often coupled with administrative insurance claims to provide insights into national quality of prostate cancer care.

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Box 1. Cambridge Prognostic Groups (CPG) applied to both National Prostate Cancer Audit (NPCA) and Surveillance, Epidemiology, and End Results program (SEER) databases

Cambridge Prognostic Groups (CPG)

1. ISUP grade group 1 *AND* PSA < 10 ng/ml *AND* stages T1-T2*
2. ISUP grade group 2 *OR* PSA 10–20 ng/ml *AND* stages T1-T2
3. ISUP grade group 2 *AND* PSA 10–20 ng/ml *AND* stages T1-T2
   OR ISUP grade group 3 *AND* stages T1-T2
4. One of: ISUP grade group 4 *OR* PSA > 20 ng/ml *OR* stage T3
5. Any combination of ISUP grade group 4, PSA > 20 ng/ml or stage T3
   OR ISUP grade group 5
   OR Stage T4

*At least 2 complete variables required

Taken together, cancer registry data in each country can provide the basis for international comparisons given the improved accuracy of these data sources within the last decade [4, 5]. Importantly, new prostate cancer risk stratification systems are available to support contemporary international treatment comparisons in order to contextualise treatment trends and highlight potential opportunities to improve consistency and quality of care across nations. The Cambridge Prognostic Group (CPG) classification incorporates the five International Society of Urological Pathology (ISUP) grade groups and has been shown to be a better prognostic tool than traditional three-tiered classification systems used in prior international comparisons [6]. Most notably the CPG subdivides intermediate-risk disease into cases with favourable features (CPG2: one of ISUP grade group 2 or PSA 10–20) and unfavourable features (CPG3: ISUP grade group 3, or ISUP grade group 2 and PSA 10–20) helping to infer additional over- and under-treatment implications. We therefore aimed to investigate differences between the distinct US and England healthcare systems in how newly-diagnosed prostate cancer patients are managed with respect to a novel and improved prognostic group classification system.

MATERIALS AND METHODS

Study population

As this study used registry and routine data, there were no a priori sample size calculations. All patients newly diagnosed with prostate cancer between April 1st 2014 and December 31st 2016 were identified in the SEER and NPCA databases. The SEER database collates information from population-based cancer registries, covering 19 US geographic areas [7]. The NPCA database uses the English Cancer Registry which collects cancer-specific information on every new diagnosis of cancer in England [3].

The following data items from the SEER database were used for the purposes of this study: age at diagnosis, ethnic background, socioeconomic deprivation, TNM stage, ISUP grade group, and PSA at diagnosis. Hispanic ethnicity was derived by SEER from an algorithm based on the North American Association of Central Cancer Registries (NAACCR) Hispanic Identification Algorithm [8] to create the following ethnicity groups: non-Hispanic White (referred to as 'White'), non-Hispanic Black (referred to as 'Black'), non-Hispanic Asian (including Chinese) or Pacific Islander (referred to as 'Asian'), Hispanic and Other.

Socioeconomic deprivation status was based on the area of residence at diagnosis, at the census tract level (typical population size 4000–8000). The Yost Index is constructed by SEER using a factor analysis of seven socioeconomic variables (median household income, median house value, median rent, percent below 150% of poverty line, education index, percent working class, and percent unemployed) and grouped into quintiles of the national distribution [9].

Prior to January 1st 2016 cancer registries in the US collected information using Collaborative Stage, a unified data collection system designed to provide a common dataset [7]. TNM was collected within this system and derived according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 7th Edition [10]. From January 1st 2016 TNM stage was derived according to the UICC 7th Edition which corresponds to the AJCC Cancer Staging Manual 7th Edition. Both methods derived staging according to the AJCC and so we did not expect there to be any difference in how TNM was derived within the SEER database across the study period.

The NPCA database includes data from the English Cancer Registry which provides similar variables: age at diagnosis, ethnic background, socioeconomic deprivation, TNM stage, ISUP grade group and PSA. Men were categorised into ethnic groups comprising White, Black, Asian (including Chinese) and Other as defined in the 2001 Census in England and Wales [11]. Socioeconomic deprivation status was determined for patients from the English 2012 Index of Multiple Deprivation (IMD) based on their area of residence and grouped according to quintiles of the national distribution [12]. The IMD ranks 32,482 areas, and each area covers a mean population of around 1500 people or 400 households [13].

TNM was derived according to the UICC in both the NPCA and SEER databases. The five-tiered CPG classification was assigned according to Box 1 and imputation used for missing cancer stage based on clinical assumptions [14].

Outcome variables

Our primary outcome variable was whether any radical local treatment was received within 1 year of diagnosis. The SEER database collects information on the first course of therapy via information from the cancer registries (surgery, radiotherapy, and brachytherapy). As individuals initiate therapy at different times after diagnosis, cancer registries are updated with respect to treatment information as it becomes available [15]. Any treatment given after 1 year is regarded as a second course of therapy in the absence of a documented treatment plan or a standard of treatment [16]. Therefore, where there was no documented treatment within SEER we regarded these as men who did not receive radical local treatment within one year of diagnosis.

To identify which men received radical local treatment in England, the NPCA database was linked at patient level with two routine databases. Hospital Episode Statistics (HES) is an administrative database of all hospital admissions in the English National Health Service (NHS) and is a source of information about type and date of surgery [17]. The OPCS Classification of Interventions and Procedures (OPCS-4) code 'M61' was used to identify the men in the HES dataset who underwent a radical prostatectomy (RP) and the date of their operation [18]. The National Radiotherapy DataSet (RTDS) is a national database that contains standardised data from all NHS hospital providers of radiotherapy services in England [19]. The RTDS data item 'treatment modality' was used to select men who underwent external beam radiation therapy and/or brachytherapy and the date of this treatment. This allowed a consistent comparison to be made between the SEER and NPCA databases.

Statistical analysis

Multivariable Poisson regression, with robust standard errors, was used to estimate the adjusted risk ratio (aRR), with the 95% confidence interval (CI), of receiving radical local treatment comparing men in the US with men in England. CPG was included as an interaction term to provide aRRs according to each CPG. A Wald test was performed to test for interaction. All regression models were adjusted for age at diagnosis, ethnicity, socioeconomic deprivation status, year of diagnosis, T-stage, ISUP grade group and PSA value [20].

Missing data across both countries for ethnicity (4.8%), socioeconomic deprivation status (3.7%), T-stage (0.7%), ISUP grade group (3.4%) and PSA (16.4%) were imputed with a statistical imputation method using chained equations to create ten datasets prior to running the regression models. Rubin's rules were used to combine the risk ratios across all ten datasets [21].

RESULTS

We identified 137,655 newly-diagnosed patients from the SEER database and 108,747 patients from the NPCA database. We excluded 13,084 men (9.5%) from the SEER dataset, and 11,381 men (10.5%) from the NPCA dataset, as there was insufficient information available for risk stratification. We also excluded 30,645 men (12.4%) with distant metastases and 7202 men (2.9%) with nodal metastases.

Men diagnosed in the US were younger, were diagnosed at an earlier stage, and had a lower PSA and ISUP grade group at

Table 1. Patient and tumour characteristics of men with prostate cancer according to whether they were diagnosed in England or the US.

	England (n = 74,393)		US (n = 109,697)		All men (N = 184,090)	
	N	%	*N*	%	*N*	%
Diagnosis year						
2014	19,402	26.1	28,388	25.9	47,790	26.0
2015	27,499	37	40,702	37.1	68,201	37.0
2016	27,492	37	40,607	37.0	68,099	37.0
Age group (years)						
<60	10,623	14.3	25,462	23.2	36,085	19.6
60–69	28,883	38.8	49,214	44.9	78,097	42.4
70–79	28,179	37.9	28,513	26.0	56,692	30.8
≥80	6708	9.0	6508	5.9	13,216	7.2
Ethnicity						
White	63,871	92.7	72,940	68.5	136,811	78.0
Black	2530	3.7	17,362	16.3	19,892	11.3
Asian	1465	2.1	5146	4.8	6611	3.8
Hispanic	0	0	10,283	9.7	10,283	5.9
Other	1067	1.5	674	0.6	1741	1.0
Missing	5460		3292		8752	
Socioeconomic deprivation status (quintiles of national distribution)						
1 (least deprived)	18,019	24.2	25,105	24.4	43,124	24.3
2	18,504	24.9	22,531	21.9	41,035	23.2
3	15,605	21.0	20,705	20.1	36,310	20.5
4	12,487	16.8	18,223	17.7	30,710	17.3
5 (most deprived)	9778	13.1	16,269	15.8	26,047	14.7
Missing	0		6864		6864	
T-stage						
1	16,696	22.6	50,335	46.3	67,031	36.7
2	35,978	48.6	44,774	41.2	80,752	44.2
3	20,570	27.8	13,214	12.1	33,784	18.5
4	749	1.0	454	0.4	1203	0.7
Missing	400		920		1320	
ISUP grade group						
1	19,134	27.0	41,629	38.9	60,763	34.2
2	25,610	36.2	30,903	28.9	56,513	31.8
3	12,668	17.9	15,346	14.3	28,014	15.8
4	5962	8.4	11,187	10.5	17,149	9.6
5	7406	10.5	7915	7.4	15,321	8.6
Missing	3613		2717		6330	
Serum PSA (ng/ml)						
<10	32,766	57.4	71,875	74.3	104,641	68.0
10-20	15,165	26.6	16,967	17.5	32,132	20.9
>20	9123	16.0	7927	8.2	17,050	11.1
Missing	17,339		12,928		30,267	
Cambridge prognostic group						
CPG1	13,749	18.5	12,712	11.6	26,461	14.4
CPG2	16,354	22.0	18,892	17.2	35,246	19.1
CPG3	10,503	14.1	15,088	13.8	25,591	13.9
CPG4	17,872	24.0	26,365	24.0	44,237	24.0
CPG5	15,915	21.4	36,640	33.4	52,555	28.5

diagnosis compared to men diagnosed in England (Table 1). The majority of the men diagnosed were of White ethnicity (US: 68.5% and England: 92.7%) with more Black men diagnosed in the US (16.3%) compared to England (3.7%). One in ten US men (9.7%) were of Hispanic ethnicity. Similar distributions of these variables were observed when sub-stratified by CPG. Overall, we found a significant interaction of CPG on the association between country of diagnosis and the receipt of radical local treatment ($P < 0.001$). Significantly more men received radical local treatment if they were diagnosed in the US compared to England, irrespective of CPG, with the difference in treatment rates being largest for CPG1 and smallest for CPG5.

Of the 36,640 men diagnosed with CPG1 prostate cancer in the US, 13,951 (38.1%) received radical local treatment within one year of diagnosis (16.1% and 22.0% received radiotherapy and surgery, respectively; Fig. 1), compared to 2283 of the 15,915 men (14.3%) in England (8.0% and 6.4% received radiotherapy and surgery, respectively) – aRR 2.57, 95% CI 2.47–2.68 (Table 2). However, treatment rates declined over the 3 years of the study from 42.0 to 34.8% in the US, and from 18.5 to 10.4% in England.

Of the 26,365 men diagnosed with CPG2 prostate cancer in the US, 18,088 (68.6%) received radical local treatment within 1 year of diagnosis (33.0% and 35.6% received radiotherapy and surgery, respectively; Fig. 1), compared to 18,088 of the 26,365 men (52.6%) in England (26.9% and 25.7% received radiotherapy and surgery, respectively) – aRR 1.27, 95% CI 1.25–1.29 (Table 2).

Of the 15,088 men diagnosed with CPG3 prostate cancer in the US, 11,567 (76.7%) received radical local treatment within 1 year of diagnosis (45.9% and 30.8% received radiotherapy and surgery, respectively; Fig. 1), compared to 7048 of the 10,503 men (67.1%) in England (41.3% and 25.9% received radiotherapy and surgery, respectively) – aRR 1.12, 95% CI 1.10–1.13 (Table 2).

Of the 18,892 men diagnosed with CPG4 prostate cancer in the US, 15,604 (82.6%) received radical local treatment within 1 year of diagnosis (28.0% and 54.6% received radiotherapy and surgery, respectively; Fig. 1), compared to 11,842 of the 16,354 men (72.4%) in England (43.7% and 28.7% received radiotherapy and surgery, respectively) – aRR 1.09, 95% CI 1.08–1.10 (Table 2).

Of the 12,712 men diagnosed with CPG5 prostate cancer in the US, 9944 (78.2%) received radical local treatment within 1 year of diagnosis (35.5% and 42.7% received radiotherapy and surgery, respectively; Fig. 1), compared to 9863 of the 13,749 men (71.7%) in England (57.1% and 14.7% received radiotherapy and surgery, respectively) – aRR 1.06, 95% CI 1.04–1.07 (Table 2). The proportion of men receiving radical local treatment for CPG5 disease increased over the 3 years of the study from 76.0 to 79.8% in the US and from 69.9 to 73.5% in England.

DISCUSSION

Although differences in treatment rates of men with prostate cancer between the US and England were expected, this study has provided evidence for the size of these differences. Radical local treatment is much more frequently used for men with prostate cancer in the US compared to England, particularly for CPG1 disease where 38% of US men received treatment compared to 14% of English men. Given prostate cancer-specific mortality is so low for active surveillance of this patient group, over a twofold higher treatment rate in the US compared to England raises concerns about over-treatment. Equally, 77–83% of US men receive radical local treatment for clinically significant prostate cancer (CPG3–5) compared to 67–72% of English men, indicating potential under-treatment in England. While we found improvement trends across both nations, opportunities likely still exist to address both over- and under-treatment of men with newly-diagnosed prostate cancer.

In both the US and England we found a decline in the radical treatment of low-risk prostate cancer. Treatment rates of low-risk disease were reported as 61–72% in the US in 2014 [22], and 38% in England between 2004 and 2008 [23]. Despite considerable improvements over the last decade, a substantially higher proportion of men with CPG1 prostate cancer are still being

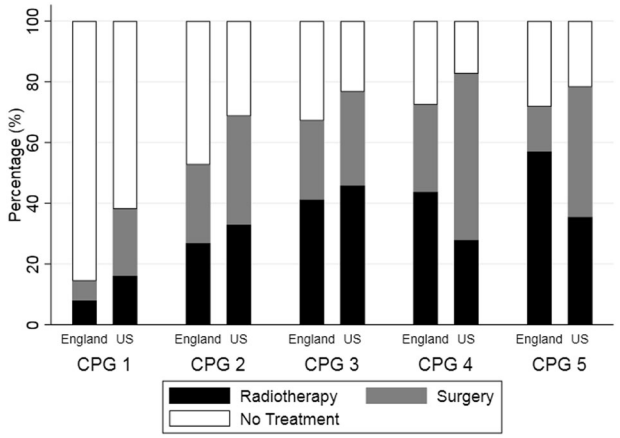

Fig. 1 Management of men with prostate cancer between 2014 and 2016, stratified by country (England vs. US) and Cambridge Prognostic Group (CPG). The CPG classification is a five-tiered risk stratification tool for non-metastatic prostate cancer which incorporates the five International Society of Urological Pathology (ISUP) grade groups.

Table 2. Adjusted risk ratios for the likelihood of receiving radical local treatment according to country of diagnosis, stratified by Cambridge Prognostic Group.

	N (%)	Adjusted RR	95% CI			*P*
Received radical local treatment (CPG1)						<0.001
England	14.3	1				
US	38.1	2.57	2.47	–	2.68	
Received radical local treatment (CPG2)						<0.001
England	52.6	1				
US	68.6	1.27	1.25	–	1.29	
Received radical local treatment (CPG3)						<0.001
England	67.1	1				
US	76.7	1.12	1.10	–	1.13	
Received radical local treatment (CPG4)						<0.001
England	72.4	1				
US	82.6	1.09	1.08	–	1.10	
Received radical local treatment (CPG5)						<0.001
England	71.7	1				
US	78.2	1.06	1.04	–	1.07	

treated in the US compared to England (38% vs. 14%). One potential cause for this is the fee-for-service, insurance-based healthcare system in the US compared to the nationally-funded NHS in England. Indeed, de-implementation of prostate cancer over-treatment is complex, involving stakeholders ranging from health systems, payers, policymakers, providers, patients and their families [24]. While continued progress is being made towards active surveillance in localised prostate cancer, multi-level improvement opportunities exist, particularly in the US.

The latest estimate from the NPCA for the treatment of low-risk disease is now only 4%, which corresponds to men diagnosed between April 2018 and March 2019 [3]. The availability of SEER data at the time of writing prevented the use of these, more contemporary, data. This is considerably lower than the 14% of men with CPG1 receiving treatment in England. The reason for this is that although both definitions required ISUP grade group 1, CPG1 includes T2 cases as well as T1 cases. This provides evidence that a substantial number of ISUP grade group 1 cases are being treated in England and likely dependent on T2b and T2c cases which are not considered to be 'low-risk' according to National Institute for Health and Care Excellence guidelines.

As with CPG1, the treatment rates of CPG2-5 in the US are higher than in England. The majority of CPG2 cases ('favourable' intermediate-risk) are being treated radically in both the US (69%) and England (53%). This brings into focus the lack of consensus within national guidelines regarding the management of these cases [25–27]. The adoption of active surveillance for 'favourable' intermediate-risk disease is beginning to become more accepted, but clearly this is not recognised universally, and in England there is evidence of significant regional variation in how these cases are managed [28, 29].

Treatment rates for high-risk localised prostate cancer have remained high in the US with estimates of 83–85% between 2004 and 2013 [23, 30, 31] which are consistent with our treatment rates for CPG4 (82%) and CPG5 (78%). Despite having lower treatment rates in England, a substantial increase has been observed over time for English cases. We report treatment rates of 72% for both CPG4 and CPG5, compared to 30% reported between 2004 and 2008 [23]. This is important to highlight given that historical data have already shown that prostate cancer-specific mortality for high-risk men is significantly lower in the US compared to England [23]. Nonetheless, a recent study also highlights potential under-treatment of high-risk disease among elderly men in the US [32]. Taken together, further work is required to fully understand the impact of the potential under-treatment of men with high-risk prostate cancer in both the US and England, and consideration of the increased toxicity implications that this would entail.

With respect to the type of treatment received, the lower risk cancers (CPG1 and 2) received similar proportions of radiotherapy and surgery in both countries but approximately two-thirds of the treated CPG3 cases received radiotherapy, compared to one third receiving surgery. For more aggressive disease (CPG4 and 5), surgery was more commonly used in the US compared to radiotherapy in England, indicating that factors, such as healthcare organisation and funding, may be influencing treatment decisions. Treatment selection in both the US and England has been shown to be dependent on the services available [33, 34]. Mandatory multidisciplinary team (MDT) working for all newly-diagnosed patients with cancer and the use of joint urology/oncology clinics in England may affect patient selection and patient choice compared to the US. As with England, the primary clinician in the US is usually a urologist, but the lack of mandated MDT presentation in the US may influence onward referral and access to radiotherapy services [35].

Strengths and limitations

Strengths of this population-based study include the high volume of patients included. Data on all men newly-diagnosed with prostate cancer in England are collected by the National Cancer Registration and Analysis Service (NCRAS), which maximises the generalisability of the English cohort. The SEER database does not have national coverage and only represents 35% of the US population, including cancer registry data from 19 US geographic areas. However, these areas are representative of the demographics of the entire US and so we expect any selection bias to be minimal [7]. All new cancer diagnoses within these areas are included, irrespective of insurance coverage or age, and so we also expect the SEER database to be highly representative of all prostate cancer patients within the US.

A further strength of our study is the accuracy of the routinely collected English data used. These data have been shown to be

sufficiently high to support its use for research [36]. Misclassification of treatment allocation is more of an issue for the SEER database given that a reduced ascertainment of radiotherapy has been previously reported in 2012 [37, 38]. Any bias caused by this would only lead to larger differences in treatment rates between England and the US, and so we do not expect this to impact on the interpretation of our results.

Further limitations include the selection bias due to the exclusion of men with an unknown risk group (US: 7.2%; England: 8.2%). However, the amount of missing data was modest in relation to the overall study size, and comparable between countries, and so we feel that the findings remain representative. Furthermore, the diagnostic period of the study is slightly outdated (April 2014–December 2016) but we expect that our results are still representative of the differences between both countries.

A final limitation is that we could not adjust for some potential confounders, such as comorbidities and frailty, which could potentially impact on treatment decisions. Although a Charlson comorbidity score can be calculated using HES data [39] a comparable measure is not collected, or unable to be calculated, within the SEER registry without coupling to administrative claims such as Medicare data. Despite this, the risk of confounding is likely to be small given that male life expectancy is not dramatically different between countries (US: 76.4 year; England: 79.0 years) [40]. Equally, although we were able to adjust for socioeconomic deprivation the measures used were relative to each country, and so the lack of a consistent measure could potentially give misleading results [41]. Equally, in the US there were more men of Black and Asian ethnicity compared to England but, as ethnicity was also included within the adjustment model, we do not expect this to necessarily alter the interpretation of our findings.

CONCLUSIONS

Treatment rates of prostate cancer were higher in the US compared to England, which is likely a consequence of differences between the two national healthcare systems. This raises concerns of potential over-treatment of low-risk disease in the US. It will also be important to understand the factors contributing to the potential under-treatment of clinically significant disease in England in order to improve survival but limit treatment-related morbidity.

DATA AVAILABILITY

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. MGP 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 existing national datasets.

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AUTHOR CONTRIBUTIONS

Designed the work: MGP, JvdM, QT, HP, NWC. Analysed and interpreted data: MGP, JvdM, QT, HP, NWC. Drafted paper: MGP, JvdM, QT, HP, NWC. Provided critical revision: All authors. Approved final version to be published: All authors.

COMPETING INTERESTS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was exempt from NHS Research Ethics Committee approval because it involved analysis of pseudonymised linked data collated for the purpose of service evaluation as part of the National Prostate Cancer Audit.

ADDITIONAL INFORMATION

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