Determinants of variation in radical local treatment for men with high-risk localised or locally advanced prostate cancer in England.

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ABSTRACT

Background: Many factors are implicated in the potential 'under-treatment' of prostate cancer but little is known about the between-hospital variation.

Methods: The National Prostate Cancer Audit (NPCA) database was used to identify high-risk localised or locally advanced prostate cancer patients in England, between January 2014 and December 2017, and the treatments received. Hospital-level variation in radical local treatment was explored visually using funnel plots. The intra-class correlation coefficient (ICC) quantified the between-hospital variation in a random-intercept multivariable logistic regression model.

Results: 53,888 men, from 128 hospitals, were included and 35,034 (65.0%) received radical local treatment. The likelihood of receiving radical local treatment was increased in men who were younger (the strongest predictor), more affluent, those with fewer comorbidities, and in those with a non-Black ethnic background. There was more between-hospital variation ($P<0.001$) for patients aged ≥80 years (ICC: 0.235) compared to patients aged 75-79 years (ICC: 0.070), 70-74 years (ICC: 0.041), and <70 years (ICC: 0.048). Comorbidity and socioeconomic deprivation did not influence the between-hospital variation.

Conclusions: Radical local treatment of high-risk localised or locally advanced prostate cancer depended strongly on age and comorbidity, but also on socioeconomic deprivation and ethnicity, with the between-hospital variation being highest in older patients.

BACKGROUND:

Recent figures from the National Prostate Cancer Audit (NPCA) show that in 2017 over 47,000 men were diagnosed with prostate cancer in England and that 41% of these had high-risk or locally advanced disease (1). International guidelines advise that radical local treatment, with either surgery or radiotherapy, should be used for these cases. It is also generally accepted that watchful waiting, where treatment is only recommended for symptomatic progression, should be reserved for men whose life expectancy is under 10 years (2). However, the proportion of men with high-risk localised or locally advanced disease who do not receive radical local treatment (potential 'under-treatment') is on average 32% across England and this is thought to be a consequence of a number of factors.

Previous studies from the US have shown that age, comorbidities, Black ethnicity and socioeconomic status are all associated with under-treatment in prostate cancer (3-6). It has also been shown that radical local treatment rates vary from 44% to 85% of patients (i.e. 66% to 15% potentially under-treated) between hospitals across England and Wales (1). This said, radical local treatment for high-risk or locally advanced prostate cancer is not always appropriate, particularly in the old and frail, and therefore the term 'under-treatment' is not always valid. Management decisions in this setting are often complex and require a balance between estimated life expectancy, co-morbidities, the side-effect profile of treatments, and patient choice.

In this study, we explore the determinants of receiving treatment for high-risk or locally advanced prostate cancer in the English National Health Service (NHS) and the between-hospital variation in the radical local treatment rates.

METHODS:

Patient population

As this study used registry and routine data, there were no a priori sample size calculations. All men newly diagnosed with high-risk or locally advanced prostate cancer between 1st January 2014 and 31st December 2017 were identified from the English Cancer Registry using the ICD-10 diagnosis code C61 (10). This database was linked at patient level with two routine databases. Hospital Episode Statistics (HES) is a database of all hospital admissions in the English NHS which is a source of surgery-specific information about operation type and date (7). The National Radiotherapy Data Set (RTDS) is a national

database that contains standardised data from all NHS providers of radiotherapy services in England (8).

Prostate cancer risk was based on TNM stage (9), Gleason score, and PSA level (hereafter referred to as 'cancer characteristics'), according to a modified D'Amico risk stratification algorithm developed previously by the NPCA (10). Men were excluded if they had advanced disease (n = 23,292, 14.7%), intermediate-risk disease (n = 53,225, 33.5%), low-risk disease (n = 12,893, 8.1%), or if prostate cancer risk was unknown (n = 15,104, 9.5%). 540 men from 19 hospitals were excluded if they had fewer than 10 men in any of the strata of age (<70 years, 70-74 years, 75-79 years, and ≥80 years), comorbidity (men with no comorbidities and at least one comorbidity), socioeconomic deprivation (less deprived and more deprived men) and ethnicity (Black and non-Black). The definitions for these baseline characteristics are described below. The final cohort for analysis included 53,888 men with high-risk or locally advanced prostate cancer diagnosed at 128 English hospitals **(Figure 1)**.

Baseline characteristics

English Cancer Registry data was used to identify the diagnosing hospital, the date of diagnosis, cancer characteristics, ethnicity and age at diagnosis for each man. Cancer characteristics were used for stratifying disease status but also to provide baseline information (11). Men were categorised into ethnic groups comprising White, Asian, Black and Other as defined in the 2001 Census in England and Wales (12). The Royal College of Surgeons (RCS) Charlson score was used to identify any comorbid conditions captured in the HES record within one year before diagnosis (13). 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 (14). Less deprived men and most deprived men were defined as the lowest two and highest three quintiles of IMD respectively.

Outcome variable

The OPCS Classification of Interventions and Procedures (OPCS-4) code 'M61' in the HES database was used to identify men who underwent a radical prostatectomy and their operation date (15). The RTDS data item 'treatment modality' was used to select men

undergoing radiotherapy and/or brachytherapy and their treatment date. Brachytherapy information was also supplemented from HES records with the following OPCS-4 codes: 'X653 - Delivery of a fraction of interstitial radiotherapy' + 'M706 - Radioactive seed implantation into prostate' or 'M712 - Implantation of radioactive substance into prostate'.

Statistical analysis

Multilevel multivariable random-effects logistic regression was used to estimate associations between receiving radical local treatment and patient characteristics, including age, comorbidities, socioeconomic deprivation, and ethnicity (16). The regression model was also adjusted for all cancer characteristics. A random intercept was modelled for each hospital to adjust for clustering of outcomes within hospitals (17). Separate regression models were used which included interaction terms between age groups and a number of baseline characteristics (presence of comorbid conditions, socioeconomic deprivation and ethnicity). Wald tests were performed to test the statistical significance of the interaction terms. Missing data for ethnicity (4.6%), T stage (3.0%), N stage (10.2%), Gleason score (9.6%) and PSA (27.1%) were imputed with statistical imputation using chained equations, which created ten data sets. Rubin's rules were then used to combine the adjusted odds ratios (aOR) across all ten data sets (18).

Hospital-level variation in use of radical local treatment was explored visually using funnel plots to establish whether the between-hospital variation in the proportion of patients receiving radical local treatment was greater than expected by chance alone (19).

The intra-class correlation coefficient (ICC) was used to quantify the between-hospital variation in a random-intercept logistic regression model adjusted for patient characteristics. The ICC is an index, ranging from 0 to 1, expressing the variance in the treatment rates between hospitals as a proportion of the total variance (which is the sum of the within and between-hospital variance). A larger ICC represents a greater degree of between-hospital variation.

To identify sources of between-hospital variation, the ICC was estimated in four strata of age (<70 years, 70-74 years, 75-79 years, and ≥80 years), two strata of comorbidity (men with no comorbidities and men with at least one comorbidity) and two strata of socioeconomic deprivation (IMD 1-2 and IMD 3-5). Ethnicity was not explored in this way due to low patient numbers in the minority ethnic group strata. One risk-adjustment model

was estimated for all patients and used to estimate the ICC for each stratum of these three patient characteristics. We compared the ICC between strata using an independent *t*-test to calculate two-tailed *P* values, using 0.05 as the significance level.

RESULTS:

Determinants of treatment

Of the 53,888 men with high-risk or locally advanced prostate cancer, 35,034 men (65.0%) were identified as having received radical local treatment (**Table 1**). Between the ages of 70 and 80 years there was a decline in treatment rates as shown in **Figure 2**. The age below which at least 50% of men with no comorbidities received radical local treatment was 79 years, as opposed to 78 years for men with one comorbidity and 76 years for men with at least two comorbidities. Younger age was the strongest predictor of radical local treatment after adjustment for all other factors. 81.1% of patients aged younger than 70 years received radical local treatment compared to 73.6% of those aged 70-74 years (adjusted OR 0.65, 95% confidence interval 0.61-0.70), 59.6% of those aged 75-79 years (aOR 0.34, 95% CI 0.31-0.37), and 16.3% of those aged 80 years and older (aOR 0.04, 95% CI 0.04-0.05).

Men were more likely to receive radical local treatment if they were from a less deprived socioeconomic background, had fewer comorbidities, and were of non-Black ethnicity (all $P<0.001$). The overall proportion of Black men who received radical local treatment was 60.8% compared to 65.1% of White men (aOR 0.75 95% CI 0.65-0.85, **Table 1**). Similar patterns were observed when the analysis was restricted to men younger than 70 years.

A further analysis was carried out to investigate if there was any interaction of Charlson score, deprivation status and Black versus non-Black ethnicity on the relationship between age and the use of radical local treatment (**Table 2**). A downward trend in the proportion of men receiving radical local treatment was observed with increasing age for each factor and regression modelling did not demonstrate any statistically significant interaction (Wald test *P* values all >0.05).

Variation between hospitals

Use of radical local treatment among men with high-risk or locally advanced prostate cancer varied substantially between the 128 diagnosing hospitals with the proportion of

men undergoing radical local treatment ranging from 35.5% to 81.9%. For men aged 80 years and older, this proportion ranged from 0% to 51.9%. In comparison, it ranged from 13.6% to 94.8% for men aged 75-79 years, from 16.9% to 93.8% for men aged 70-74 years, and from 50.3% to 94.2% for men aged younger than 70 years (**Figure 3a to 3e)**.

The ICC, which quantifies between-hospital variation, was 0.235 (95% CI 0.179-0.302) for patients aged 80 years and older, compared to 0.070 (95% CI 0.052-0.095) for patients aged 75-79 years, 0.041 (95% CI 0.028-0.058) for patients aged 70-74 years, and 0.048 (95% CI 0.035-0.064) for patients younger than 70 years. Between-hospital variation for older patients (aged 80 years and older) was significantly larger compared to patients younger than 70 years ($P<0.01$). Differences in ICCs by comorbidity and socioeconomic deprivation were not statistically significant, indicating that these patient characteristics did not affect the between-hospital variation.

DISCUSSION:

This study of over 50,000 men has shown that 35% of men with high-risk localised or locally advanced prostate cancer did not receive radical local treatment and that there is significant variation between hospitals in the use of radical local treatment in the English NHS. There was relatively little between-hospital variation across the country in how the prostate cancer of men younger than 80 years was managed. However, there was significantly greater between-hospital variation for men aged 80 years and above, suggesting there is more uncertainty of treatment efficacy across the country in elderly patients.

Determinants of treatment

In line with findings in other studies we have shown that men who are older, have more co-morbidities, are socioeconomically deprived or are of Black ethnicity are less likely to receive radical local treatment (3-6). Variation in the treatment of prostate cancer with respect to ethnicity and socioeconomic deprivation has been shown previously within the US health system but not within the publicly-funded English NHS (5). It is unclear how or why this treatment variation occurs. Factors such as the quality of the local healthcare environment, the resources available, the knowledge and skills of the professionals

involved, patient understanding, and patient choice have all been indicated as factors that may explain the variation in treatment rates according to these criteria (20).

As expected, age was found to be a major determinant of radical local treatment in men with high-risk or locally advanced prostate cancer (21). However, this effect of age cannot be fully explained by the presence of comorbidities. For example, we found that the number of comorbidities only had a relatively small effect on the age below which at least 50% of men received radical local treatment. This suggests that age, rather than life expectancy, is an important factor determining whether men with high-risk or locally advanced disease receive radical local treatment. This is in contrast to widely accepted guidelines that indicate that men with prostate cancer aged 75 years and older should be managed according to their individual health status and not according to age (22). Evidence for this has been shown in a US prospective cohort study of 3183 men where 71% of men aged 75 years or older at the time of their prostate cancer diagnosis, with at least three comorbid conditions, died from a cause other than prostate cancer within 10 years (23). Predictive modelling, incorporating these factors has been shown to facilitate an individualised approach for counselling patients regarding prostate cancer management (24). Furthermore, self-reported health status is strongly associated with other-cause mortality and can also further support informed decision-making (25).

Variation between hospitals

The observation that the between-hospital variation in radical local treatment use was increased in patients aged 80 years is likely to reflect the professional uncertainty and the paucity of data about whether or not radical local treatment is beneficial in this age group (26). A similar effect of age on the between-hospital variation of treatment has been shown for other cancers, for example with respect to the use of adjuvant chemotherapy for Stage III colon cancer in England (27). Also, use of major surgery for bowel cancer varies between countries most strongly for older patients (28). It is important to note that we did not find an impact of comorbidity on the between-hospital variation whilst both age and comorbidity do have an impact on life expectancy.

Determining a patient's physical fitness and life expectancy is challenging and it is likely that inconsistencies in how these are assessed goes some way to explaining why there was an observed increase in variation for patients aged 80 years and older. For future

practice it may be useful to consider adopting structured geriatric assessments, such as the International Society of Geriatric Oncology, to assess and optimise fitness for active cancer treatment. It is critically important that men are stratified according to their fitness for treatment and not their age alone (22).

It has been shown that the recommendations that clinicians give to their patients are strong determinants of why older patients accept or decline cancer treatment (29). This highlights the importance of shared decision making in elderly patients with multi-disciplinary team discussions (involving both urology and oncology) and, where appropriate, the involvement of care of the elderly specialists. Ultimately, a randomised trial is required in order to guide whether the radical treatment of elderly patients is efficacious (in terms of both oncological outcomes and toxicity), and this would help to reduce the treatment variation observed across England.

Strengths and Limitations

The main strengths of this population-based study are the high number of patients included and the generalisability of the findings nationally, given that about 95% of men with prostate cancer are diagnosed in English NHS hospitals (30). The accuracy of the routine data that we used has also been shown to be consistently high, which ensures that any misclassification of whether a man received radical local treatment or not is low (31).

Limitations include the fact that prostate cancer risk was not available for 9.5% of men. However, additional analysis showed that the percentage of men who received radical local treatment did not vary according to whether prostate cancer risk was available or missing. We also excluded 19 hospitals because of low patient numbers to ensure that strata of important baseline characteristics (age, comorbidity, socioeconomic deprivation and ethnicity) included at least 10 men. However, a sensitivity analysis showed that being diagnosed at one of these hospitals did not affect whether treatment was received or not.

Finally, there are several potential determinants of treatment that were not available in our data sources, including patient preferences, family history, marital and carer status and frailty, but it is unlikely that these factors would vary substantially between hospitals and in turn, it is unlikely that these factors would affect our findings.

Conclusions

The proportion of men with high-risk or locally advanced prostate cancer who received radical local treatment declined sharply in older men. The between-hospital variation was highest in older patients which suggests uncertainty of treatment efficacy in this patient group. The use of radical local treatment was also lower in men who were from more deprived socioeconomic backgrounds, in men with comorbidities, and in men of Black ethnicity. These findings demonstrate the need for a detailed review of how treatment decisions are being made at a local level to reduce the risk of under-treatment related to age, socioeconomic deprivation and ethnicity.

ADDITIONAL INFORMATION:

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Author's Contributions

Designed the work: M.G.P., J.v.d.M., H.P., N.W.C.

Analysed and interpreted data: M.G.P., J.M.B, J.v.d.M., H.P., N.W.C.

Drafted article: M.G.P., J.v.d.M., H.P., N.W.C.

Provided critical revision: All authors.

Approved final version to be published: All authors.

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.

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.

Conflicts of Interest

J.v.d.M. reports a contract with the Healthcare Quality Improvement Partnership for the provision of the National Prostate Cancer Audit (www.npca.org,uk) funded by the Healthcare Quality Improvement Partnership (www.hqip.org.uk).

H.P. has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Ipsen, Ferring, Sandoz, and Novartis.

N.W.C. has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Bayer, Janssen, Sanofi Aventis, Takeda, Ipsen and Ferring.

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Table 1. Distribution of patient characteristics and their effect on receipt of radical local treatment.

	Total		Received radical local treatment		*P* value	Adjusted odds ratios*	
	n = 53,888	%	n = 35,034	%	X^2	95% CI	*P* values
Age (years)					**<0.001**		**<0.001**
<70	23,051	42.8	18,685	81.1		1	
70-74	12,032	22.3	8,858	73.6		0.65 (0.61-0.70)	
75-79	10,217	19.0	6,091	59.6		0.34 (0.31-0.37)	
≥80	8,588	15.9	1,400	16.3		0.04 (0.04-0.05)	
RCS Charlson score (number of comorbid conditions)					**<0.001**		**<0.001**
0	39,842	73.9	27,232	68.3		1	
1	8,968	16.6	5,342	59.6		0.77 (0.72-0.82)	
2+	5,078	9.4	2,460	48.4		0.51 (0.47-0.55)	
Deprivation status (national quintiles)					**<0.001**		**<0.001**
1 (least deprived)	12,803	23.8	8,671	67.7		1	
2	13,465	25	8,909	66.2		0.96 (0.91-1.02)	
3	11,388	21.1	7,374	64.8		0.87 (0.81-0.94)	
4	9,179	17	5,805	63.2		0.82 (0.76-0.89)	
5 (most deprived)	7,053	13.1	4,275	60.6		0.69 (0.63-0.75)	
Ethnicity					**0.005**		**<0.001**
White	48,235	93.8	31,381	65.1		1	
Asian	1,018	2.0	679	66.7		1.06 (0.88-1.26)	
Black	1,479	2.9	899	60.8		0.75 (0.65-0.85)	
Other	696	1.4	455	65.4		0.91 (0.76-1.08)	
Missing	2,460		1,620				
T stage					**<0.001**		**<0.001**
1	2,257	4.3	939	41.6		1	
2	8,705	16.7	5,987	68.8		2.36 (2.05-2.73)	
3	38,429	73.5	26,796	69.7		2.30 (1.98-2.67)	
4	2,886	5.5	910	31.5		0.85 (0.72-1.02)	
Missing	1,611		402				
N stage					**<0.001**		**<0.001**
0	41,722	86.2	30,235	72.5		1	
1	6,652	13.8	3,339	50.2		0.38 (0.34-0.42)	
Missing	5,514		1,460				
Gleason score					**<0.001**		**<0.001**
6	1,777	3.6	933	52.5		1	
7	18,933	38.8	15,172	80.1		4.19 (3.57-4.91)	
≥8	28,027	57.5	18,309	65.3		3.24 (2.75-3.82)	
Missing	5,151		620				
PSA (ng/ml)					**<0.001**		**<0.001**
<10	13,852	35.3	11,017	79.5		1	
10-20	10,619	27.0	7,838	73.8		0.99 (0.92-1.06)	
>20	14,787	37.7	7,835	53		0.62 (0.57-0.66)	
Missing	14,630		8,344				

*Adjusted for age, RCS Charlson score, deprivation status, ethnicity, T stage, N stage, Gleason score and PSA.

Table 2. Proportion of patients receiving radical local treatment for high-risk/locally advanced disease according to comorbidities, socioeconomic deprivation status and ethnicity.

	<70 years			70-74 years			75-79 years			≥80 years		
	N	n (%)		N	n (%)		N	n (%)		N	n (%)	
RCS Charlson Score												
0	18,271	15,020	(82.2)	8,832	6,693	(75.8)	7,107	4,502	(63.3)	5,635	1,021	(18.1)
≥1	4,783	3,667	(76.7)	3,198	2,164	(67.7)	3,112	1,591	(51.1)	2,952	379	(12.8)
Deprivation status												
1-2	10,726	8,889	(82.9)	6,116	4,685	(76.6)	5,111	3,221	(63)	4,318	788	(18.2)
3-5	12,328	9,798	(79.5)	5,914	4,172	(70.5)	5,108	2,872	(56.2)	4,269	612	(14.3)
Ethnicity												
White/Asian/Other	20,900	17,107	(81.9)	11,271	8,351	(74.1)	9,603	5,731	(59.7)	8,176	1,329	(16.3)
Black	867	625	(72.1)	218	129	(59.2)	254	131	(51.6)	140	14	(10)
Missing	1,287	955	(74.2)	541	377	(69.7)	362	231	(63.8)	271	57	(21)

Figure 1. Flow chart showing inclusion of patients in study.

Figure 2. Graph showing percentage of men with high-risk/locally advanced prostate cancer who receive radical local treatment within 12 months according to age at diagnosis.

Figure 3. Funnel plots showing the proportion of men with high-risk/locally advanced disease who receive radical local treatment within 12 months of diagnosis at each hospital, adjusted for all patient factors in **Table 1**.
(a) All men; (b) Men aged ≥80 years; (c) Men aged between 75 and 79 years); (c) Men aged between 70 and 74 years); (c) Men aged <70 years.