Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study

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Summary

Background Little is known about the health-related quality of life (HRQOL) of men living with advanced prostate cancer. We report population-wide functional outcomes and HRQOL in men with all stages of prostate cancer and identify implications for health-care delivery.

Methods For this population-based study, men in the UK living 18–42 months after diagnosis of prostate cancer were identified through cancer registration data. A postal survey was administered, which contained validated measures to assess functional outcomes (urinary incontinence, urinary irritation and obstruction, bowel, sexual, and vitality and hormonal function), measured with the Expanded Prostate Cancer Index Composite short form (EPIC-26), plus questions about use of interventions for sexual dysfunction) and generic HRQOL (assessed with the 5-level EuroQol five dimensions questionnaire [EQ-5D-5L] measuring mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, plus a rating of self-assessed health). Log-linear and binary logistic regression models were used to compare functional outcomes and HRQOL across diagnostic stages and self-reported treatment groups. Each model included adjustment for age, socioeconomic deprivation, and number of other long-term conditions.

Findings 35 823 (60·8%) of 58 930 men responded to the survey. Disease stage was known for 30 733 (85·8%) of 35 823 men; 19 599 (63·8%) had stage I or II, 7209 (23·4%) stage III, and 3925 (12·8%) stage IV disease. Mean adjusted EPIC-26 domain scores were high, indicating good function, except for sexual function, for which scores were much lower. Compared with men who did not receive androgen deprivation therapy, more men who received the therapy reported moderate to big problems with hot flushes (30·7% [95% CI 29·8–31·6] *vs* 5·4% [5·0–5·8]), low energy (29·4% [95% CI 28·6–30·3] *vs* 14·7% [14·2–15·3]), and weight gain (22·5%, 21·7–23·3) *vs* 6·9% [6·5–7·3]). Poor sexual function was common (81·0%; 95% CI 80·6–81·5), regardless of stage, and more than half of men (n=18 782 [55·8%]) were not offered any intervention to help with this condition. Overall, self-assessed health was similar in men with stage I–III disease, and although slightly reduced in those with stage IV cancer, 23·5% of men with metastatic disease reported no problems on any EQ-5D dimension.

Interpretation Men diagnosed with advanced disease do not report substantially different HRQOL outcomes to those diagnosed with localised disease, although considerable problems with hormonal function and fatigue are reported in men treated with androgen deprivation therapy. Sexual dysfunction is common and most men are not offered helpful intervention or support. Service improvements around sexual rehabilitation and measures to reduce the effects of androgen deprivation therapy are required.

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Introduction

The number of men surviving after being diagnosed with prostate cancer has increased rapidly in high-income countries. According to population-based cancer registry data, 10-year survival has tripled in the past 40 years in the UK.[1] In England, there are an estimated 325 000 men alive who were diagnosed with prostate cancer between 1995 and 2015.[2] A principal challenge for health care is to understand the needs of this increasing group of men, in particular the problems and challenges faced by those living with advanced disease (30% of men with distant metastases now survive for at least 5 years[3]). The quality of survival experienced, with definition of the specific effects of the disease and its treatment, must be robustly measured to facilitate appropriate care provision.[4]

Substantial sexual, urinary, and bowel morbidities have been identified following treatment of localised prostate cancer, with the pattern and severity of morbidity varying according to the type and intensity of treatment received.[5–8] Most existing knowledge originates from randomised controlled trials and observational studies of specific cohorts, often reporting outcomes following surgery compared with radiotherapy and surveillance in men with localised prostate cancer.[9] Evidence for the UK has not been generated for an unselected population. Additionally, few studies have reported outcomes in men

Research in context

Evidence before this study

We searched Ovid databases (MEDLINE, Embase, and PsychINFO) for articles relating to health-related quality of life (HRQOL) using the terms "health-related quality of life", "localised", "advanced", "metastatic", "stage" and "prostate cancer" or "prostatic neoplasms" published between June 1, 1996, and June 1, 2018. Studies were excluded if they had no measure of HRQOL and were included if they included men with either early, late, or combined stages of prostate cancer. Most articles were about men with localised disease, with good quality evidence collected in clinical trials and observational studies of specific cohorts. Few studies have focused on those men with locally advanced or metastatic prostate cancer. In the few studies separating results by stage, poorer HRQOL has been associated with later stages of disease. However, sample sizes tend to be small. Therefore, little is known about the effects of metastatic prostate cancer in men living with and after a diagnosis of advanced disease, especially compared with men with non-metastatic disease.

Added value of the study

To our knowledge, this is first study to compare, at scale, the HRQOL and functional outcomes of men living with localised and advanced metastatic prostate cancer. Data were collected for 35 823 men, with diagnostic stage information available for 30 733, of whom 23·4% had stage III disease and 12·8% stage IV disease. The population-based approach can be used to investigate the quality of survival of the increasingly prevalent group of men living with and beyond a diagnosis of prostate cancer. We identified that men with stage III and IV disease reported more problems, including those generic to health and those related to treatment, particularly androgen deprivation therapy (ADT) than did those with early stage disease. Poor sexual function was reported by most men, regardless of stage, and more than half of men reported not being offered any intervention or support for this problem. Despite specific functional morbidities, many men with prostate cancer self-reported their overall health to be similar to men in general population studies and a substantial proportion of men with stage IV disease (23·5%) reported no problems on any dimension of the EuroQol five dimensions (EQ-5D) questionnaire. These results highlight areas of unmet need and will be crucial in helping men make informed decisions about their treatment.

Implications of all the available evidence

Most men living 18–42 months after a diagnosis of prostate cancer can expect to experience similar HRQOL to men in the general population, including those with stage III disease and many of those with stage IV disease. Although sexual morbidity is common, most men are not offered helpful interventions or support. The evidence suggests that there are subgroups of men who would benefit from service improvements around sexual rehabilitation and measures to minimise the use of ADT. These measures could include wider use of intermittent ADT (rather than continuous use), the avoidance of unnecessary ADT (ie, for non-metastatic disease), and the use of shorter courses of neoadjuvant treatment (reduced from 3 years to 1 year). We collected data from men living up to 42 months after diagnosis. Men with stage IV disease are likely to experience deterioration in their HRQOL at some point following this period. Further evidence is needed to inform appropriate service provision for such patients in these later years.

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with locally advanced or metastatic disease. Such studies tend to be small and are mostly clinical trials comparing specific treatment types.[10–12]

The Life After Prostate Cancer Diagnosis (LAPCD) study adopts an established approach to the measurement of health-related quality of life (HRQOL) at the population level, previously used in a national population of colorectal cancer survivors,[13] and extends this approach to men living with all stages of prostate cancer 18–42 months after diagnosis. This timeframe was chosen because it represents the period when initial treatment is complete and side-effects and HRQOL have begun to stabilise.[5] In men with advanced disease, treatment with androgen deprivation therapy (ADT) starts at diagnosis and therefore any ADT-related effects would be captured. An internationally recommended series of outcome measures has been used to facilitate comparison and interpretation, specifically regarding the effect of interventions offered for sexual dysfunction.[14]

In this report, we quantify and compare functional outcomes (urinary, bowel, sexual, vitality and hormonal) and HRQOL of men with prostate cancer across all disease stages and treatment groups, and identify implications for health-care delivery.

Methods

Study design and participants

The methods used in the LAPCD study have previously been reported in full[15] but are outlined briefly here. All UK National Health Service (NHS) hospital trusts and boards treating patients with prostate cancer in the UK were approached. Men who were alive 18–42 months after a diagnosis of prostate cancer (International Classification of Diseases-10[16] C61) in participating trusts and boards were identified from national population-based cancer registries in England, Northern Ireland, and Wales. In Scotland, because of privacy restrictions, men were identified through hospital activity data and verified through the cancer registry. There was no age limit for inclusion. The study received ethics and governance approvals from the following organisations: Newcastle and North Tyneside 1 Research Ethics Committee (15/NE/0036), Confidentiality Advisory Group (15/CAG/0110), NHS Scotland Public Benefit and

For the **LAPCD study protocol** see https://bmjopen.bmj.com/content/6/12/e013555

Privacy Panel (0516-0364), and NHS Research and Development approval from Wales, Scotland, and Northern Ireland. These approvals allowed men to be contacted using details held within cancer registration and hospital activity data.

Procedures

See Online for appendix

Men were sent a postal survey (appendix pp 2–21) on behalf of their treating NHS trust or board. Men consented by returning completed surveys and declined by not returning them, returning them unanswered, or opting out via a freephone helpline. Up to two reminders were sent to non-responders (approximately 3 weeks apart). The data collection period differed by nation: for England from Oct 16, 2015, to April 21, 2016; for Northern Ireland from June 14, 2016, to Oct 18, 2016; for Scotland from July 20, 2016, to Nov 11, 2016; and for Wales from July 28, 2016, to Nov 9, 2016. The survey included a range of validated measures, including those defined in the International Consortium on Health Outcome Measurement (ICHOM) minimum outcome dataset:[14] the Expanded Prostate Cancer Index Composite short form (EPIC-26);[17] individual items on use of interventions to improve sexual function; and the 5-level EuroQol five dimensions questionnaire (EQ-5D-5L).[18] The survey also included questions relating to sociodemographics and treatments received.

Stage at diagnosis was obtained from national cancer registration records. Stages I and II were combined into a localised disease group and compared with stages III and IV separately. A measure of socioeconomic deprivation based on location (split into quintiles) was derived using postcode of residence.[19–22] Age, presence of other long-term conditions, and treatments received were derived from the survey response data. Age was categorised as younger than 55 years, 55–64 years, 65–74 years, 75–84 years, and 85 years or older. When missing, age at time of survey was supplemented by cancer registration data (accounting for the lag between diagnosis and survey). Other long-term conditions (appendix p 20, question 84) were counted and categorised as none, one, two, three, or four or more. Treatments (appendix pp 5–6, question 8) were categorised into single therapies (eg, surgery alone or external beam radiotherapy [EBRT] alone), or combination therapies (eg, EBRT and ADT) (appendix p 22).

A user advisory group, including six survivors of prostate cancer, was chaired by HB (co-investigator and also a survivor of prostate cancer). The group was involved in all stages of the study, from design through to interpretation and dissemination of results.

Outcomes

For functional outcomes, EPIC-26 measures function across five domains (urinary incontinence, urinary irritation and obstruction, bowel, sexual, and vitality and hormonal function) using 26 items. Domain scores range from 0 to 100, with 100 representing best possible function. We calculated mean domain scores and 95% CIs. If one item in a domain was missing, this item was substituted with the mean of the available items, as per the scoring guidance.[23] In addition to mean scores, individual item responses were used to derive the proportion of men reporting a moderate or big problem (or equivalent), as per Watson and colleagues.[24]

The ICHOM dataset includes two items assessing use of medications and devices for erectile dysfunction.[25] These questions were amended to avoid mentioning branded drug names (appendix p 12, questions 25 and 26). An extra item about use of specialist services to help with sex life was also included (appendix p 13, question 27). The possible response categories to the use of interventions were grouped as not offered, offered but did not want or try it, offered but did not help, and offered and it helped.

EQ-5D-5L records information about five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), plus a rating of self-assessed health based on how good the patient's health was on the day of survey completion (scored on a scale of 0–100, where 100 represents best possible health). The proportion of respondents reporting any problem, regardless of severity, in each dimension separately and across all five dimensions was derived. Mean EQ-5D self-assessed health ratings and 95% CIs were calculated.

Statistical analysis

All men who completed questionnaires were included in analyses. However, because not all men completed every item, records with missing responses were excluded on a question-by-question basis; therefore, results refer to the men who responded to that question. Log-linear regression was used to model the continuous outcomes (mean EPIC-26 domain scores and mean EQ-5D self-assessed health scores) because this approach provided a better fit to the data than a linear one. Binary logistic regression models were developed for each individual EPIC-26 item (with moderate or big problems, or equivalent, as the outcome) and each EQ-5D dimension (with reporting of any problem as the outcome). For each outcome, results were generated by disease stage and treatment group, by adding these variables separately to the models. Each model included adjustment for age (as a linear term), socioeconomic deprivation, and number of other long-term conditions. Subgroup analyses by age group were adjusted for socioeconomic deprivation and other long-term conditions. Resulting model coefficients were used to predict the adjusted mean scores (for the EPIC-26 domains and self-assessed health) and adjusted proportions of patients reporting problems (for the individual EPIC-26 items and EQ-5D dimensions) along with 95% CIs for each stage and treatment group. Analysis of the use of interventions for sexual dysfunction was based on the raw survey responses to reflect real-world provision of sexual support to men with

	All men	Stage I or II	Stage III	Stage IV	Stage unknown
Total	35 823 (100%)	19 599 (54·7%)	7209 (20·1%)	3925 (11·0%)	5090 (14·2%)
Treatment					
Active surveillance	2928 (8·2%)	2320 (11·8%)	0	0	457 (9·0%)
Watchful waiting	2292 (6·4%)	1666 (8·5%)	182 (2·5%)	164 (4·2%)	993 (19·5%)
Brachytherapy alone	1208 (3·4%)	940 (4·8%)	62 (0·9%)	13 (0·3%)	294 (5·8%)
Surgery alone	7054 (19·7%)	4606 (23·5%)	1323 (18·4%)	132 (3·4%)	193 (3·8%)
Surgery and EBRT or ADT	2349 (6·6%)	853 (4·4%)	801 (11·1%)	339 (8·6%)	548 (10·8%)
EBRT alone	2536 (7·1%)	1533 (7·8%)	573 (7·9%)	136 (3·5%)	431 (8·5%)
EBRT and ADT	7488 (20·9%)	3688 (18·8%)	2359 (32·7%)	658 (16·8%)	783 (15·4%)
ADT alone	3116 (8·7%)	965 (4·9%)	487 (6·8%)	1116 (28·4%)	356 (7·0%)
Systemic and ADT	630 (1·8%)	71 (0·4%)	37 (0·5%)	450 (11·5%)	72 (1·4%)
Systemic and EBRT (with or without ADT)	513 (1·4%)	84 (0·4%)	128 (1·8%)	237 (6·0%)	64 (1·3%)
Other treatment	5709 (15·9%)	2873 (14·7%)	1257 (17·4%)	680 (17·3%)	899 (17·7%)
Age at survey (years)					
<55	661 (1·8%)	447 (2·3%)	92 (1·3%)	45 (1·1%)	77 (1·5%)
55–64	5594 (15·6%)	3366 (17·2%)	1026 (14·2%)	473 (12·1%)	729 (14·3%)
65–74	16 638 (46·4%)	9420 (48·1%)	3406 (47·2%)	1712 (43·6%)	2100 (41·3%)
75–84	11 082 (30·9%)	5670 (28·9%)	2391 (33·2%)	1326 (33·8%)	1695 (33·3%)
≥85	1842 (5·1%)	696 (3·6%)	294 (4·1%)	369 (9·4%)	483 (9·5%)
Unknown	6 (0·02%)	0	0	0	6 (0·1%)
Socioeconomic deprivation quintile					
1 (least deprived)	9408 (26·3%)	5128 (26·2%)	1802 (25·0%)	962 (24·5%)	1516 (29·8%)
2	9289 (25·9%)	5186 (26·5%)	1889 (26·2%)	1000 (25·5%)	1241 (24·4%)
3	7381 (20·6%)	4082 (20·8%)	1504 (20·9%)	869 (22·1%)	926 (18·2%)
4	5266 (14·7%)	2846 (14·5%)	1084 (15·0%)	596 (15·2%)	740 (14·5%)
5 (most deprived)	3620 (10·1%)	1955 (10·0%)	786 (10·9%)	421 (10·7%)	458 (9·0%)
Unknown	859 (2·4%)	402 (2·1%)	144 (2·0%)	77 (2·0%)	236 (4·6%)
Other long-term conditions					
None	10 405 (29·0%)	5740 (29·3%)	2087 (28·9%)	1131 (28·8%)	1447 (28·4%)
One	12 527 (35·0%)	6910 (35·3%)	2594 (36·0%)	1316 (33·5%)	1707 (33·5%)
Two	7154 (20·0%)	3827 (19·5%)	1432 (19·9%)	807 (20·6%)	1088 (21·4%)
Three	3174 (8·9%)	1708 (8·7%)	605 (8·4%)	391 (10·0%)	470 (9·2%)
Four or more	2563 (7·2%)	1414 (7·2%)	491 (6·8%)	280 (7·1%)	378 (7·4%)

Data are n (%). Systemic therapy includes chemotherapy, abiraterone, and enzalutamide. EBRT=external beam radiotherapy. ADT=androgen deprivation therapy.

Table 1: **Characteristics of men who completed surveys by stage**

prostate cancer. Because of the large number of men included in the study, statistical significance can be achieved with only small differences in outcomes, and these differences might not be clinically relevant. Therefore, to aid interpretation, results are presented alongside previously estimated minimally important differences, where available.[26–28] Analyses were done with Stata (version 15.0).

Role of the funding source

The funder of the study had no role in the design of the study, data collection, data analysis, data interpretation, or writing of the report. Anonymised study data were available to AD and SW. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In England, 111 (82%) of 136 trusts participated; 21 (15%) declined and four (3%) were excluded because they were involved in overlapping studies. All NHS providers in Northern Ireland (n=5), Scotland (n=14), and Wales (n=6) participated. Approximately 82% of eligible men with prostate cancer across the UK were invited to participate. 59 990 men were identified; 1060 (1·8%) died during the study period, giving a final sample of 58 930 men. Of these men, 35 823 (60·8%) returned completed questionnaires (appendix p 23, 29). Men younger than 55 years (51·8% of whom responded) or older than 85 years (36·9%), from non-white ethnic groups (38·0%), and those living in the most socioeconomically deprived areas (48·3%) were the least likely to participate (appendix p 23). By stage, response rates were highest in the men diagnosed with stage III

	EPIC-26 domain (adjusted mean score, 95% CI)*					EQ-5D-5L dimension (adjusted %, 95% CI)*†					Overall HRQOL*†	
	Urinary incontinence (n=31 827)	Urinary irritation (n=29 274)	Bowel function (n=30 861)	Hormonal function (n=31 746)	Sexual function (n=32 525)	Mobility (n=35 411)	Self-care (n=35 470)	Usual activities (n=35 416)	Pain or discomfort (n=35 349)	Anxiety or depression (n=35 310)	Men reporting ≥1 problem (%, 95% CI; n=34 769)	Mean SAH rating (95% CI; n=35 003)
All men	82·6 (82·4–82·9)	85·9 (85·7–86·1)	88·9 (88·8–89·1)	79·9 (79·7–80·1)	24·0 (23·6–24·2)	33·8% (33·2–34·3)	11·5% (11·1–11·9)	36·5% (35·9–37·0)	41·7% (41·1–42·2)	33·0% (32·5–33·5)	63·2% (62·6–63·7)	76·3 (76·1–76·5)
Prostate cancer stage												
I or II	82·9 (82·6–83·3)	86·0 (85·8–86·3)	89·6 (89·4–89·8)	83·6 (83·3–83·8)	28·5 (28·1–28·9)	29·7% (29·0–30·3)	9·8% (9·4–10·2)	32·0% (31·3–32·7)	38·9% (38·1–39·6)	31·0% (30·3–31·7)	59·8% (59·1–60·1)	77·4 (77·2–77·7)
III	81·2 (80·7–81·8)	86·2 (85·8–86·5)	87·4 (87·0–87·8)	75·3 (74·8–75·9)	16·4 (15·9–16·9)	34·8% (33·6–36·0)	11·6% (10·8–12·2)	38·5% (37·3–39·6)	42·3% (41·1–43·5)	33·9% (32·8–35·0)	64·7% (63·6–65·9)	76·3 (75·9–76·7)
IV	83·2 (82·5–83·9)	84·7 (84·1–85·2)	88·1 (87·5–88·7)	68·0 (67·3–68·7)	11·9 (11·4–12·4)	49·8% (48·0–51·6)	18·9% (17·6–20·2)	53·3% (51·6–55·0)	54·6% (53·0–56·3)	43·0% (41·4–44·6)	76·5% (75·2–77·9)	71·7 (71·1–72·3)
Treatment												
Active surveillance	87·6 (87·0–88·3)	83·0 (82·3–83·6)	93·1 (92·6–93·6)	90·0 (89·5–90·5)	44·6 (43·6–45·7)	24·3% (22·6–26·0)	7·4% (6·4–8·3)	23·9% (22·2–25·5)	34·5% (32·6–36·3)	30·8% (29·0–32·5)	57·3% (55·4–59·2)	78·7 (78·2–79·3)
Watchful waiting	87·1 (86·3–87·9)	85·2 (84·6–85·9)	93·1 (92·6–93·7)	88·0 (87·4–88·5)	41·3 (40·0–42·6)	31·6% (29·6–33·5)	10·4% (9·3–11·6)	31·6% (29·7–33·4)	36·7% (34·8–38·7)	30·9% (29·0–32·8)	59·0% (56·9–61·0)	77·2 (76·5–77·8)
Brachytherapy alone	89·2 (88·3–90·1)	84·1 (83·1–85·0)	88·8 (87·9–89·7)	89·3 (88·4–90·1)	37·6 (36·2–39·0)	20·7% (18·1–23·2)	5·9% (4·5–7·3)	22·9% (20·3–25·5)	36·4% (33·5–39·3)	25·2% (22·7–27·7)	52·6% (49·6–55·6)	79·6 (78·9–80·4)
Surgery alone	73·5 (72·8–74·1)	90·0 (89·7–90·4)	93·4 (93·1–93·7)	89·6 (89·2–89·9)	22·1 (21·5–22·6)	23·9% (22·8–25·0)	7·6% (7·0–8·2)	29·1% (27·9–30·2)	33·5% (32·3–34·7)	27·3% (26·2–28·4)	54·6% (53·3–55·8)	79·5 (79·2–79·9)
Surgery and EBRT or ADT	73·1 (71·9–74·2)	86·1 (85·3–86·8)	86·2 (85·5–87·0)	76·9 (76·0–77·8)	14·9 (14·1–15·7)	34·0% (32·0–36·0)	11·6% (10·3–12·8)	40·0% (37·9–42·1)	42·9% (40·1–45·0)	35·5% (33·5–37·4)	66·1% (64·1–68·1)	76·0 (75·4–76·7)
EBRT alone	86·7 (85·9–87·5)	86·1 (85·4–86·8)	86·2 (85·4–87·0)	80·7 (79·9–81·5)	25·6 (24·5–26·7)	32·8% (30·9–34·7)	10·2% (9·1–11·3)	33·4% (31·5–35·3)	41·2% (39·3–43·2)	28·4% (26·6–30·2)	59·7% (57·6–61·7)	77·6 (76·9–78·2)
EBRT and ADT	86·8 (86·4–87·3)	85·5 (85·1–85·8)	84·4 (84·0–84·9)	72·2 (71·7–72·7)	19·1 (18·5–19·6)	34·4% (33·3–35·6)	10·7% (10·0–11·4)	38·0% (36·8–39·2)	44·6% (43·4–45·7)	34·3% (33·2–35·4)	64·8% (63·7–66·0)	76·2 (75·8–76·5)
ADT alone	86·4 (85·7–87·2)	84·6 (83·9–85·2)	90·9 (90·3–91·5)	69·3 (68·5–70·1)	15·3 (14·6–16·1)	43·0% (41·0–45·0)	15·9% (14·6–17·2)	47·6% (45·6–49·6)	46·5% (44·5–48·4)	41·0% (39·1–42·9)	74·3% (72·5–76·0)	72·0 (71·3–72·7)
Systemic therapy‡ and ADT	86·2 (84·5–87·9)	84·6 (83·3–86·0)	90·7 (89·6–91·9)	66·9 (65·2–68·5)	11·5 (10·4–12·7)	55·1% (50·7–59·5)	19·5% (16·2–22·8)	59·3% (55·1–63·5)	57·2% (53·1–61·2)	46·4% (42·4–50·5)	81·8% (78·7–84·8)	70·4 (68·9–71·9)
Systemic therapy‡ and EBRT	85·1 (83·3–86·9)	83·4 (81·7–85·0)	83·8 (82·1–85·5)	66·2 (64·3–68·1)	12·4 (11·1–13·8)	59·5% (54·8–64·3)	25·5% (21·2–29·7)	62·2% (57·7–66·8)	61·7% (57·3–66·1)	45·6% (41·1–50·1)	82·4% (79·0–85·7)	68·3 (66·5–70·0)

For EPIC-26 scores and SAH ratings, 100 is equal to best possible function or health. Because the large number of men included in the study, statistical significance can be achieved with only small differences in outcomes, and these differences might not be clinically relevant. Results should be considered alongside previously estimated minimally important differences. For EPIC-26, these differences are: urinary incontinence, 6–9 points; urinary irritation or obstruction, 5–7 points; bowel function, 4–6 points; vitality and hormonal function, 4–6 points; sexual function, 10–12 points. For EQ-5D self-assessed health, the previously estimated minimally important difference is 7 points. EPIC-26=Expanded Prostate Cancer Index Composite short form. EQ-5D-5L=5-level EuroQol 5D questionnaire. HRQOL=health-related quality of life. SAH=self-assessed health. EBRT=external beam radiotherapy. ADT=androgen deprivation therapy. *Adjusted for age at survey, socioeconomic deprivation, and number of other long-term conditions. †Adjusted percentage reporting any level of problem. ‡Systemic therapy includes chemotherapy, abiraterone, and enzalutamide.

Table 2: **Functional and HRQOL outcomes**

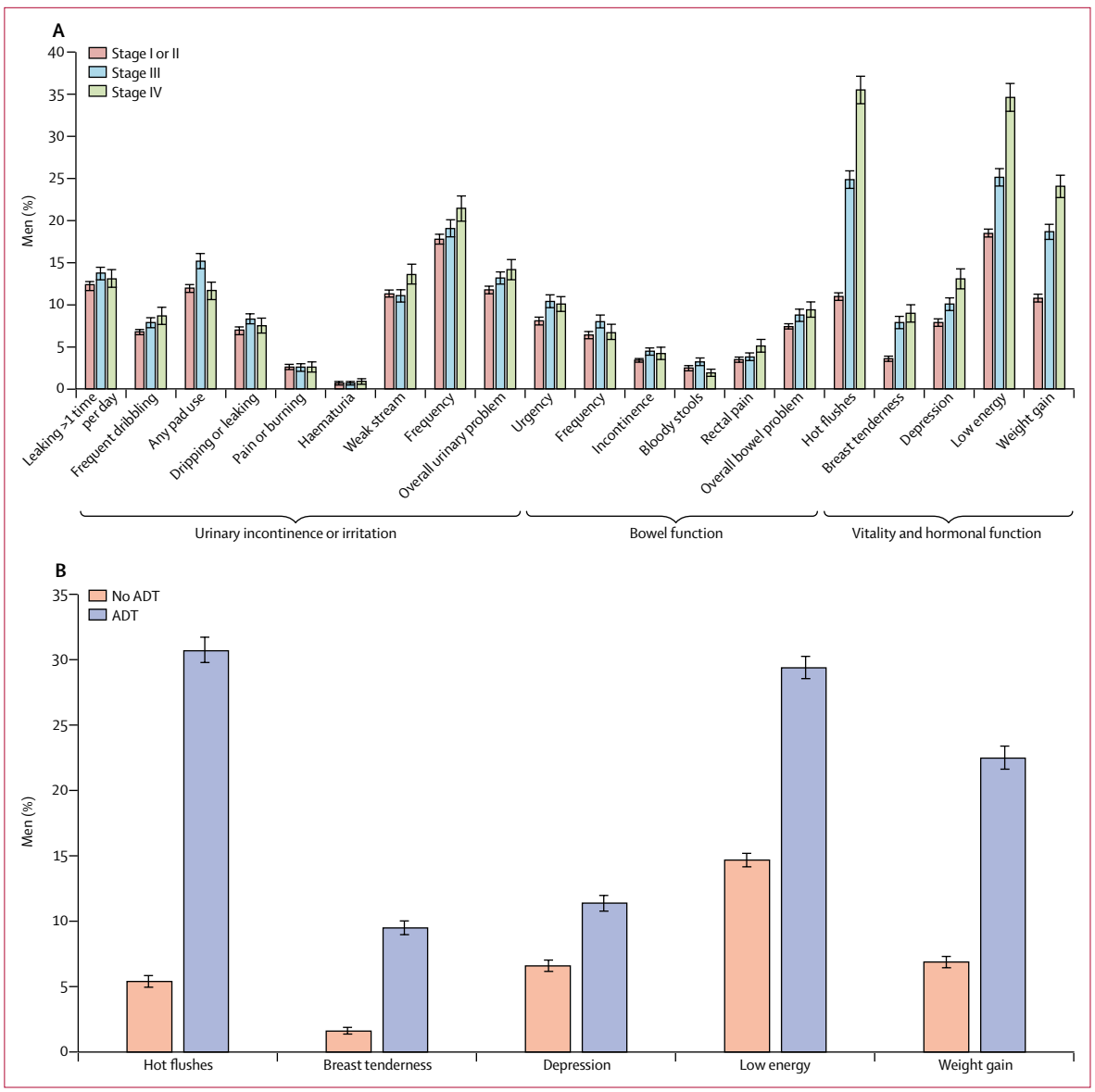

Figure 1: **Urinary, bowel, and vitality and hormonal function measured using EPIC-26**
(A) Moderate or big problems with urinary, bowel, and vitality and hormonal function by stage. (B) Moderate or big problems with vitality and hormonal function by ADT use. Proportions adjusted for age, socioeconomic deprivation, and number of other long-term conditions. ADT=androgen deprivation therapy. EPIC-26=Expanded Prostate Cancer Index Composite short form.

cancer (65·7%) and lowest in those diagnosed with stage IV disease (58·1%). Within the completed questionnaires, levels of missing data were generally low (eg, <3% missing for EQ-5D [appendix p 24]). EPIC-26 items were the least well completed and domain scores could not be calculated in 9–18% of cases. EPIC-26 completion was highest for the sexual function domain and lowest for the urinary irritation or obstruction domain (appendix p 24).

Of the 35 823 men who completed questionnaires, 16 638 (46·4%) were aged 65–74 years at the time of survey (table 1); the median age of all participants who completed questionnaires was 71 years (IQR 67–77). 9408 (26·3%) of men lived in the least socioeconomically deprived areas and 3620 (10·1%) lived in the most deprived areas. Most men (25 418 [71·0%]) reported at least one other long-term condition, with 2563 (7·2%) reporting four or more (table 1).

Stage at diagnosis was known for 30 733 (85·8%) of 35 823 respondents, of whom 19 599 (63·8%) had stage I or II disease, 7209 (23·4%) stage III, and 3925 (12·8%) stage IV. Table 1 shows the characteristics of each stage group, including those with unknown stage disease. The men diagnosed with stage IV disease (median age

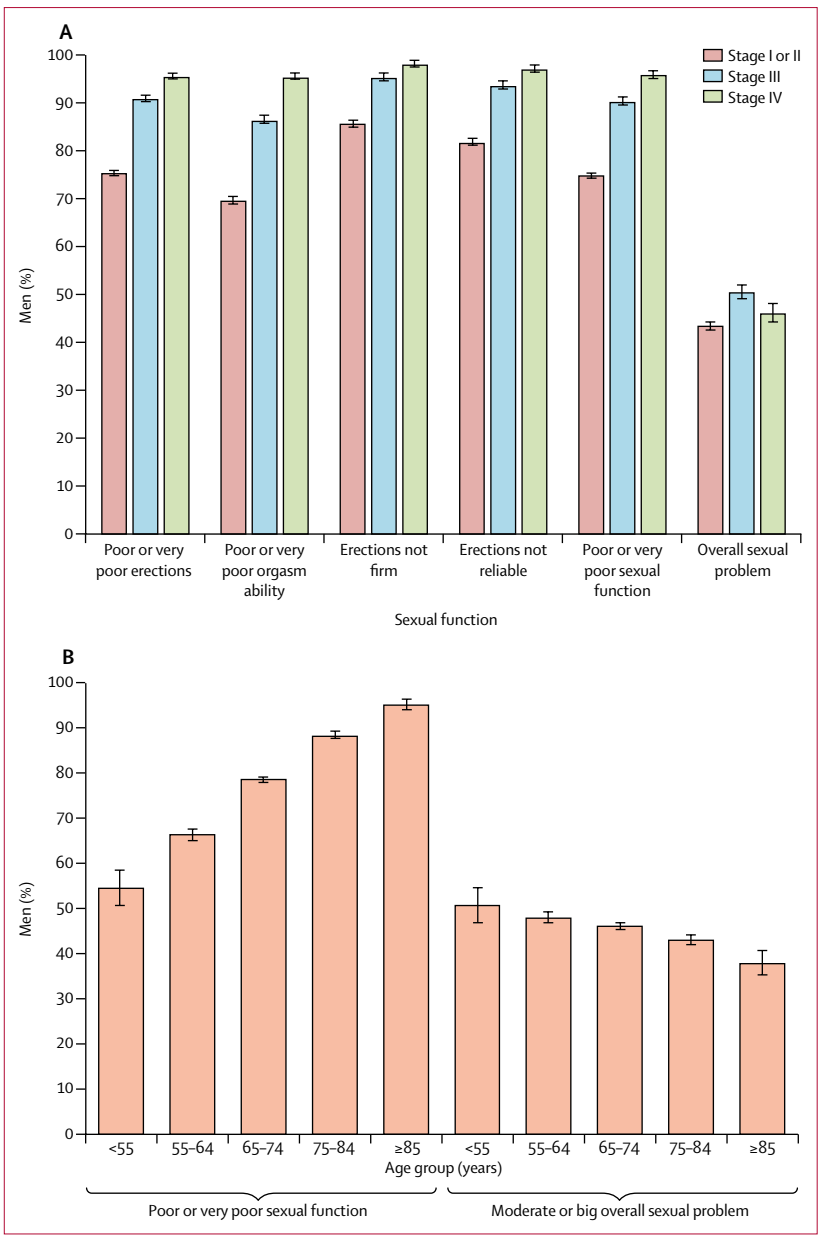

***Figure 2*: Sexual function measured using EPIC-26**

(A) Moderate or big problems with sexual function by stage. Proportions adjusted for age, socioeconomic deprivation, and number of other long-term conditions. (B) Sexual function and severity of overall sexual problem by age. Proportions adjusted for socioeconomic deprivation and number of other long-term conditions. Error bars are 95% CI. EPIC-26=Expanded Prostate Cancer Index Composite short form.

73 years [IQR 68–79]) were older than those with stage I or II disease (71 years [66–76]). The median age of those with stage III disease was 72 years (62–77). The median age of the group with unknown stage disease was 73 years (IQR 67–79). The socioeconomic deprivation and long-term condition profiles were similar across the known stage groups (table 1), and a higher proportion of the group with unknown stage lived in the least socio-economically deprived areas compared with those with known stage (29·8% *vs* 25·7%).

Across the whole cohort, 7488 (20·9%) men reported receiving combined EBRT and ADT, with a further 7054 (19·7%) reporting having surgery alone (table 1). Of the 19 599 men diagnosed with stage I or II disease, 3986 (20·3%) reported being on a monitoring regime (active surveillance or watchful waiting) and 4606 (23·5%) reported having surgery alone. Most men diagnosed with stage IV cancer were receiving ADT at the time of survey, either alone (1116 [28·4%] of 3925) or in combination with EBRT (658 [16·8%]), or other systemic therapy (chemotherapy, abiraterone, and enzalutamide; 450 [11·5%]).

Mean adjusted EPIC-26 domain scores were high in all men, indicating good function, except for sexual function, for which scores were much lower (24·0, 95% CI 23·6–24·2; table 2). Urinary and bowel function were similar across all disease stages (<3-point difference across disease stages within each domain), whereas scores for vitality and hormonal, and sexual function were substantially reduced in men with stage III and IV prostate cancer compared with those with localised disease (8–16-point difference for hormone function and 12–17-point difference for sexual function; table 2). Men treated surgically reported more urinary incontinence than did those who did not have surgery, and those on ADT reported worse hormonal and sexual function than did those not on ADT (table 2).

The need to urinate frequently was the most common urinary symptom (adjusted proportion 18·6% [95% CI 18·1–19·0] reported a moderate or big problem), followed by leaking at least once per day (12·7% [12·3–13·0]) (appendix p 25). There were only small differences in the reporting of urinary symptoms by stage (figure 1A). Men who had surgery reported high levels of urinary incontinence (23·4%, 95% CI 22·3–24·5) leaked at least once per day, and 31·4% (30·2–32·6) used one or more pads per day in the surgery alone group (appendix p 25). Problems with urinary frequency and weak stream or incomplete emptying were less frequent in the surgery alone group than in other treatment groups (appendix p 25).

Problems with bowel function were relatively infrequent compared with other EPIC-26 domains and varied little by stage of disease (figure 1A). Bowel urgency was the most common bowel problem (adjusted proportion 8·8% [95% CI 8·5–9·2] reported a moderate or big problem; appendix p 26). Bowel problems were more frequent after EBRT, alone or in combination with other treatments. For example, 11·4% (10·2–12·7) of the EBRT alone group reported moderate or big problems with bowel urgency compared with 4·4% (3·9–4·9) in the surgery alone group (appendix p 25).

With respect to vitality and hormonal function, problems with low energy, hot flushes, and weight gain were most commonly reported. There were much larger differences in the reporting of these symptoms by stage than was seen for urinary and bowel function (figure 1A); however,

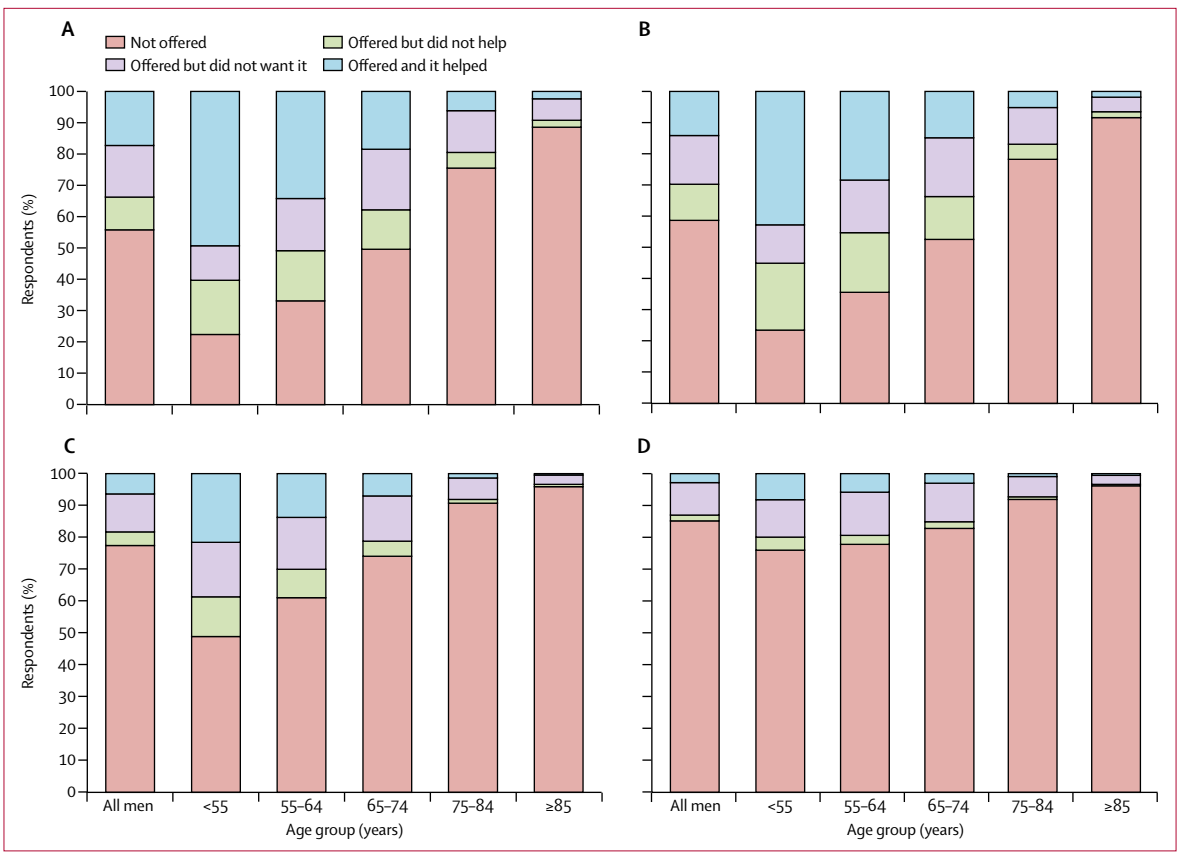

Figure 3: **Use of interventions to improve sexual function**
(A) Any intervention (medications, devices, or services). (B) Medications to aid or improve erections. (C) Devices to aid or improve erections. (D) Specialist services to improve sex life. Error bars are 95% CI.

this difference varied greatly according to the type of treatment received. Men treated with ADT, either alone or in combination with other therapy, reported much higher rates of problems with hormonal function and fatigue than did those not treated with ADT. For example, 30·7% (95% CI 29·8–31·6) of men treated with ADT reported moderate or big problems with hot flushes (compared with 5·4% [5·0–5·8] in the no-ADT group), 29·4% (28·6–30·3) of men treated with ADT reported problems with low energy (compared with 14·7% [14·2–15·3] in the no-ADT group), and 22·5% (21·7–23·3) of men treated with ADT reported problems with weight gain (compared with 6·9% [6·5–7·3] in the no-ADT group, figure 1B, appendix p 27). There was a smaller difference in the reporting of depression between the ADT groups (11·4% [10·8–12·0]) reporting moderate to big problems) and no-ADT groups (6·6% [6·2–7·0], appendix p 27).

Across the whole cohort problems with sexual function were more common than issues in other domains, including poor or very poor erections (81·5% [95% CI 81·1–82·0]), poor or very poor ability to reach orgasm (76·6% [76·1–77·1]), and poor or very poor overall sexual function (81·0%, 80·6–81·5; appendix p 26). In men with localised disease, 75·0% (74·3–75·6) reported poor or very poor sexual function, as did 90·4% (89·7–91·1) of men with stage III and 96·0% (95·3–96·6) of men with stage IV cancer (figure 2A). By treatment, just over half of men on active surveillance (51·1% [49·1–53·1]) reported poor or very poor overall sexual function, increasing to 83·7% (82·8–84·6) of men who had surgery alone and 93·6% (92·4–94·7) receiving ADT alone (appendix p 26). Just over half (54·5% [50·7–58·4]) of men aged younger than 55 years reported poor or very poor sexual function and this proportion increased sharply with age (figure 2B). A substantial proportion of all men (45·2% [44·7–45·8]) perceived their poor sexual function to be a moderate or big problem; however, this proportion decreased slightly with age (figure 2B).

Across the cohort, 13 972 (41·4%) of 33 777 men reported being offered medications to aid or improve erections, 7621 (22·6%) of 33 737 were offered devices to aid erections and 4984 (14·8%) of 33 653 were offered specialist services to help with their sex lives (appendix p 28). 18 782 (55·8%) of 33 674 were not offered any of these interventions. More of the younger men reported having been offered an intervention than did the older men; however, even in the youngest age group (men aged <55 years), 153 (23·5%) were not offered medications, 320 (48·9%) were not

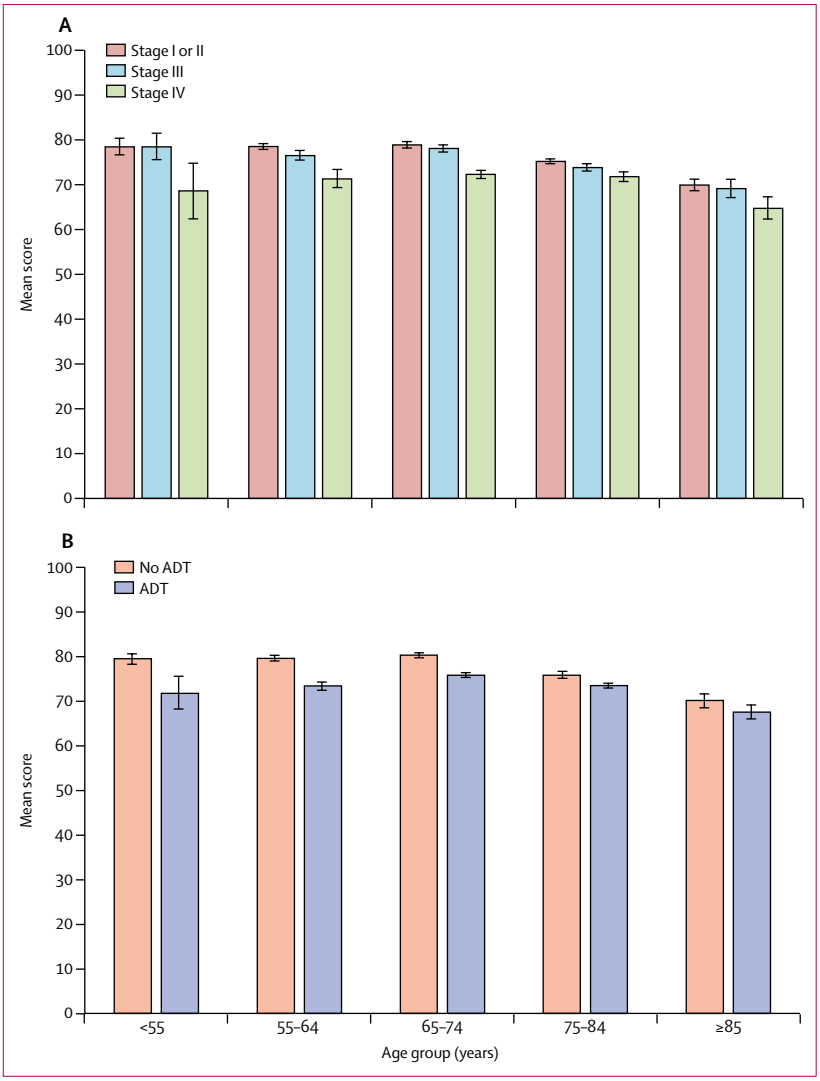

Figure 4: **Self-assessed health ratings using EQ-5D-5L**
(A) Mean self-assessed health rating by stage and age group. (B) Mean self-assessed health rating by ADT use and age group. Mean scores are adjusted for socioeconomic deprivation and number of other long-term conditions. Results should be considered alongside the previously estimated minimally important difference for EQ-5D self-assessed health (7 points). Error bars are 95% CI. ADT=androgen deprivation therapy. EQ-5D-5L=5-level EuroQol 5D questionnaire.

	Men (n)	Mean SAH score (SD)
Life After Prostate Cancer Diagnosis cohort		
Stage I or II	18055	77·8 (17·4)
Stage III	6792	76·6 (17·8)
Stage IV	3759	71·7 (19·8)
Overall	33370	76·5
General population		
Northern Ireland, 2016[29]	2597	77·2 (19·1)
Health Survey for England, 2012[30]	1016	74·2 (19·6)

SAH=self-assessed health.

Table 3: **Self-assessed health ratings of men aged ≥60 years**

offered devices, and 493 (76·0%) were not offered access to specialist services (figure 3). Similar proportions of men with stage I or II (n=8678, 46·7%) and stage III (n=3247, 47·7%) disease were offered any of the interventions, compared with 957 (26·9%) with stage IV prostate cancer. The proportion of men being offered interventions varied greatly according to the type of treatment received. For example, 5567 (80·9%) of 6883 men who had surgery alone, 735 (62·9%) of 1168 men who had brachytherapy alone, 812 (34·5%) of 2354 men who had EBRT alone, and 523 (18·8%) of 2783 men who had ADT alone were offered one of the three interventions (data not shown).

Among the 14892 men who were offered any of the three interventions, 5534 (37·2%) did not want them or did not try them, 3546 (23·8%) found they did not help, and 5812 (39·0%) reported at least one of them being helpful (appendix p 28). Of the 13972 men offered medications, 4774 (34·2%) reported them being helpful. Of the 7621 men offered devices, 2154 (28·3%) reported them as helpful. For those offered specialist services, 943 (18·9%) of 4984 found them helpful.

For the EQ-5D dimensions, men reported the most problems (of any level) with pain or discomfort (41·7% [95% CI 41·1–42·2]) and fewest problems with self-care (11·5% [11·1–11·9]; table 2). Men with stage IV cancer reported the most problems in each dimension, and this proportion was highest for pain or discomfort (54·6% [53·0–56·3]) and carrying out usual activities (53·3% [51·6–55·0]). 76·5% (75·2–77·9) of men with stage IV prostate cancer reported one or more problems on the EQ-5D, compared with 59·8% (59·1–60·1) of men with stage I or II disease and 64·7% (63·6–65·9) of men with stage III disease. 23·5% (22·1–24–8) of men with stage IV disease reported no problems on any EQ-5D dimension.

The overall mean adjusted self-assessed health score was 76·3 (95% CI 76·1–76·5; table 2). Self-assessed health was 5·7 points lower in men with stage IV disease (71·7, 95% CI 71·1–72·3) than in men with localised (ie, stage I or II) cancer (77·4, 77·2–77·7). Men with stage III disease reported a mean adjusted self-assessed health score of 76·3 (95% CI 75·9–76·7). The difference in self-assessed health between stage I–II and stage IV prostate cancer was greater in younger men than in older men (figure 4A). A similar pattern was seen for the effect of ADT use by age (figure 4B). Self-assessed health scores were generally similar in men with prostate cancer compared with men in the general population (table 3).

Discussion

To our knowledge, this study is the largest population-based, patient-reported outcomes study of men with prostate cancer to date. Our study includes 11000 men living with locally advanced or metastatic disease (stage III or IV disease), an increasingly prevalent cohort of cancer survivors, who are often excluded from quality-of-life studies. Most men living 18–42 months after a diagnosis of prostate cancer can expect to experience as good

HRQOL as men in the general population, including those with stage III disease and many of those with stage IV disease. However, sexual morbidity is high, irrespective of stage of disease, with more than half of men reporting they had not been offered any intervention to help with this condition. More so than other treatments, men treated with ADT reported poorer outcomes, particularly for sexual, and vitality and hormonal function.

More than 80% of the men in this cohort reported poor or very poor sexual function and this figure was consistently high across the disease stages. A previous study of men aged 60 years and over in the general population found that 48% reported poor sexual function.[29] In the current study, 51% of men on active surveillance reported poor sexual function, which is unlikely to be related to the diagnosis or treatment of prostate cancer because these men had not received any active treatment. Therefore, although sexual dysfunction is common in the general population, the levels reported by men receiving active treatment for prostate cancer are substantially higher. Sexual dysfunction increased with age and is probably partly explained by the normal ageing process. However, the data show that older men are less concerned with their lack of sexual function than are younger men. In those younger than 55 years, around 50% reported poor sexual function and the same proportion reported the dysfunction to be a problem. In men aged 75 years and older, more than 80% reported poor function but they were less likely to view this dysfunction as a major problem. Overall, 56% of all men reported not being offered access to medications, devices, or specialist services to improve sexual function, and only 39% of those offered help found it to be beneficial. Access to these interventions varied by age and by treatment received. Further analysis of these data is needed to look at this variation in more detail and to understand which groups of men find the interventions helpful. However, to our knowledge, this extent of failure to receive support has not previously been described. Our data suggest that clinical services need to proactively address this problem and ensure that support to improve sexual function is routinely offered to all men, while acknowledging that not all men view their lack of sexual function as a problem and some will not want to use interventions to address this.

Overall levels of urinary and bowel problems in men with prostate cancer are quite low; however, some subgroups of men have increased levels of dysfunction. For example, men treated surgically reported higher levels of urinary incontinence than did those who did not have surgery, with 30% reporting using pads daily, a finding which supports previous research.[5,8] These men are between 18 and 42 months post-diagnosis and there might be some recovery in function with longer follow-up.[5]

Generally, men with stage III and IV disease reported a higher level of problems than those with localised disease, but in many cases these differences were small and were less than previously estimated minimally important differences for urinary and bowel function.[28] Larger negative effects on sexual function, hormonal function, fatigue, and depression were seen in men with stage III and IV disease than in those with stage I and II disease, and will most likely be driven, in part, by treatment with ADT. Most men with stage III or IV prostate cancer will be on long-term or indefinite ADT. There might be some recovery in vitality and hormonal function in those who stop ADT, with a corresponding reduction in symptoms, but testosterone concentrations might never recover to pre-treatment levels. Long-term follow-up of men would be required to assess recovery of sexual function, levels of fatigue, and other ADT-related effects. The results suggest that clinicians should pursue treatment approaches that preserve testosterone function when possible and minimise ADT use. Steps to reduce ADT-related morbidity might include wider use of intermittent ADT (rather than continuous use), the avoidance of unnecessary ADT (ie, for non-metastatic disease), and the use of reduced neoadjuvant courses (ie, reduction in length from 3 years to 1 year).

Despite the problems with sexual dysfunction, urinary difficulties, and hormonal issues in some groups, this cohort of men living with the diagnosis of prostate cancer report similar self-assessed health to men in the general population.[29,30] Differences in self-assessed health among the overall cohort of men living with prostate cancer and general population samples are small—fewer than 3 points—with minimally important differences in EQ-5D self-assessed health ratings having previously been estimated at 7 points.[26,27] This apparent resilience of men with prostate cancer might be accounted for by the gap hypothesis of quality of life, with the diagnosis of a life-threatening illness and subsequent experience of undergoing treatment leading to recalibration of expectations and values.[31]

Overall the self-assessed health of men with stage III disease is not substantially different from those with localised (stage I or II) disease or surveys of the UK general population. Although scores from those with stage IV disease are 6 points lower than for those with localised disease, this difference might not be clinically meaningful. A quarter of men with stage IV prostate cancer reported no problems in any EQ-5D domain. Not all men with stage IV prostate cancer experience similar clinical trajectories, with some living for prolonged periods and others living for substantially shorter periods after diagnosis. Subgroups of men, such as those with oligometastatic disease, might have few problems whereas others experience diminished HRQOL. This study did not capture the detailed clinical information needed to investigate subtypes of disease. The absence of other large scale, population-level studies of the outcomes of men living with stage III and IV disease prevent comparisons of our results with those of other studies. Further investigation into the outcomes of men living with metastatic disease is required, especially over a

longer period, since many patients will only develop symptoms several years after diagnosis.

Since our study used whole population sampling, potential bias relating to recruitment or clinical trial intervention has been avoided. Additionally, all disease stages and treatments have been included, adding important new data about men living with diagnoses of advanced disease who have been largely omitted from previous quality-of-life outcome studies. Use of a standardised set of accepted outcome measures enables future international benchmarking. Data collection on this scale, from all centres in Northern Ireland, Scotland, and Wales, and 111 of 136 hospital trusts in England, has allowed us to produce reports for individual participating providers. These reports are available through the secure NHS network, via a platform hosted by Public Health England, and allow providers to see how their patients responded. To support wider dissemination of the findings, the Movember Foundation are developing a public-facing online tool, to be released within the next 12 months, which will provide an information resource for men and their families.

Four hospital trusts in England were excluded from the study because they were participating in an overlapping programme.[32] A further 21 trusts did not participate. Several of these declined because they were already participating in other local studies of patient-reported outcomes studies and were concerned about questionnaire fatigue. The remaining trusts did not respond to the multiple invitations to take part. The effect of these trusts and their patients not being included in the study is unclear.

The response rate of 61% is similar to that of a survey of colorectal cancer survivors in England (63%).[13] Comparison of response rates with other prostate cancer trials and cohort studies is difficult because of the different identification and recruitment methods used. Our response rate is reported without exclusion or screening of eligible individuals. Compared with responders, non-respondents were more likely to be older; black, Asian, or other ethnic minority; and to live in more socioeconomically deprived areas. These groups might be expected to potentially report poorer HRQOL in some areas of function;[33] however, because of the small proportion of ethnic minorities in this study, the effect on the results of the lower response rate from these groups is likely to be small. The underrepresentation of prostate cancer survivors from socioeconomically deprived areas might, however, result in a slight underestimation of functional difficulties. Variation in response rate by stage was identified; those with stage III disease had the highest response rates and those with stage IV disease at diagnosis had the lowest. We do not know whether or not patients with worse health status were less likely to respond than those with better health. A further limitation of the study is that records with missing data were excluded from analysis, which assumes that those who did not respond to the question had similar outcomes to those who did, an assumption that cannot be validated using the available data. However, data completeness was high for most questions. Completeness of questions on sexual function was higher than for other domains, which might indicate that sexual function is of particular concern to prostate cancer survivors who otherwise feel healthy.

Staging information was taken from national cancer registration data at diagnosis and was available for 86% of respondents. The national cancer registry uses a variety of data sources, including pathology reports and treatment databases, to capture stage information. Some groups of men are less likely to appear in a treatment or pathology dataset near the time of diagnosis (for example, those on watchful waiting are the least likely to have undergone a biopsy). At the time when men in this study were diagnosed, there was less access to multidisciplinary team systems to capture staging information than there is now. To measure socioeconomic deprivation, cancer registries routinely derive a location-based measure of socioeconomic deprivation using patient postcode and completeness of this measure is high (only 2% missing in our study). Therefore, we used this measure rather than add additional items to an already long questionnaire. Treatment information was self-reported, because of insufficient data in cancer registries about types of monitoring and difficulties in capturing hormone therapies administered through primary care prescriptions (Hounsome L, personal communication). However, some respondents had difficulty reporting the treatments that they had received (eg, distinguishing between types of radiotherapy) and these groups had to be excluded from some analyses (appendix p 22).

Overall, our findings show that most men living 18–42 months after diagnosis of prostate cancer can expect to have similar HRQOL to men in the general population. Those diagnosed with locally advanced and metastatic prostate cancer do not report substantially different HRQOL outcomes to those diagnosed with localised disease, although notable problems with hormonal function and fatigue are reported as a result of ADT. However, this study covers a limited window of time, and HRQOL in those with metastatic disease might deteriorate over a longer period. Sexual dysfunction is common across all disease stages, with notably poor provision of sexual support in the UK. Our results suggest that there are subgroups of men who would benefit from service improvements around sexual rehabilitation and measures to reduce the effects of ADT. Findings from this study show that outcomes for men with prostate cancer are more strongly linked with the treatments received than with disease stage itself, although the two are clearly intertwined. Overall, these results allow clinicians to present a positive outcome for quality of life in men 18–42 months after a diagnosis of prostate cancer, including for a substantial proportion of men with metastatic disease.

Contributors

AG and AWG are co-principal investigators and designed the study together with co-investigators AD, PW, LH, PS, EW, RW, PK, and HB. RM, MA, TK, and OM managed the study and data collection. AD and SW analysed the data. JWFC, WC, MM, LS, DW, EM, GV, and DWH are members of the Clinical and Scientific Advisory Group (chaired by PS), which provided study oversight and advised on interpretation of the data. DD, DHB, EM, and DWH advised on study design, data collection, and interpretation of data from the devolved nations. AD wrote the initial draft of the paper. All authors contributed to revising the paper and approved the final version.

Declaration of interests

AWG reports grants from Candlelighters, Macmillan Cancer Support, NIHR, and Yorkshire Cancer Research, outside the submitted work. JWFC reports personal fees from Steba Biotech (advisory board), outside the submitted work. GV reports grants from NIHR, Yorkshire Cancer Research, and Cancer Research UK; personal fees from Roche and Novartis; and personal fees and non-financial support from Eisai, outside the submitted work. MM reports personal fees from Janssen and Endocyte, outside the submitted work. All other authors declare no competing interests.

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