



Original Article

Net survival of men with localized prostate cancer after LDR brachytherapy

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ABSTRACT

OBJECTIVES: To compare survival of patients who received LDR prostate brachytherapy relative to that of peers in the general population of England, UK.

PATIENTS AND METHODS: Net survival was estimated for 2472 cases treated between 2002 and 2016 using population-based analysis guidelines. Life tables adjusted for social deprivation in England from the Office for National Statistics were used to match patients by affluence based on their postcode.

RESULTS: The median (range) age at time of brachytherapy was 66 (55–84) years, 84% resided in Southeast England, 51% under an index of deprivation quintile 5 (most affluent), 55% were clinical stage T1 and the remainder T2. Death from any cause occurred in 270 patients at a median (range) of 7 (1–17) years postimplant.

Five and 10-year estimates (95% CI) of overall survival were 96% (95–97) and 90% (89–92), and net survival 103% (102–104) and 109% (107–110) respectively. The net survival remained above 100% in all age-at-treatment and clinical stage groups.

CONCLUSION: Net survival above 100% indicates patients survive longer than the matched general population. The study shows for the first time the net survival of patients treated with a radical therapy for localized prostate cancer in England. The impact of treatment choice on the long-term net survival advantage requires further investigation. © 2024 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

Prostate cancer; Low dose rate; LDR; Brachytherapy; Net survival

Introduction

Survival analyses provide key measures of cancer control. To further monitor the effectiveness of our prostate brachytherapy program (1) we set out to estimate the net survival of our patients relative to that of peers in the general population. Previous studies have shown patients diagnosed with localized prostate cancer survive longer than

their matched counterparts in the general population (2–6) and that social demography factors influence the excess survival (7–9), implying that routine access to health care and screening and healthier lifestyles promote detection at an early stage.

The long-term impact of treatment options on net survival of prostate cancer patients relative to the general population remains largely unexplored (4,10), and for early prostate cancer, a benefit of radical treatment over treatment-related harm is often questioned. Herewith we show the net survival of patients with early-stage prostate cancer after treatment with LDR brachytherapy using modern life tables adjusted for social deprivation in England, UK.

Methods

The net survival approach followed guidelines from the UK and Ireland Association of Cancer Registries (UKI-

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ACR) (11) using the Pohar-Perme estimator and smoothed life tables for England issued in 2019 by the Office for National Statistics (ONS). These tables provide age-specific mortality rates by period, sex, regions of England, and quintiles of the English Index of Multiple Deprivation (EIMD 2019) (12). All statistical analyses were performed in R (13). The complete approach was used and survival estimates derived with the "relsurv" (14) and "survival" (15) packages.

Patients were selected from a recent internal survival audit (1) if treated between 2002 and 2016 (corresponding to periods in the ONS life tables) and who resided in England with a known postcode and thus their EIMD could be assessed. As per analysis protocol, patients grouped by age-at-treatment (55–64, 65–74, and 75–84) and clinical stage (T1,T2) require presence of at least 10 death events for valid calculations to be performed (Fig. 1).

The net expected sample size across age-at-treatment and clinical stage groups at 10 years ranged from 53 patients in the oldest to 579 in the youngest age groups, and the minimum expected remaining lifetime of the selected cases was 11 years (Table S1). Relapse-risk groups were defined by criteria from NICE guidelines (16).

Results

From 2472 cases selected (Fig. 1) the median (range) age at therapy was 66 (55–84) years (Table 1). Age-at-treatment group stratification showed 41%, 50%, and 8% were 55 to 64, 65 to 74, and 75 to 84 years old at treatment respectively. The majority of cases resided in Southeast England (84%) and 51% under an EIMD quintile 5 (most affluent). Clinical stage T1 was diagnosed in 55% of men and the remainder stage T2. Men with stage T3 diagnoses were excluded because of insufficient numbers of death events (see Fig. 1). The prostate cancer risk stratification using NICE criteria for low, intermediate and high risk was 33%, 56%, and 11% of men respectively.

In 67% of patients, brachytherapy was delivered as monotherapy, 19% of patients received a short course of androgen deprivation therapy (ADT), and in 13% of cases brachytherapy was part of trimodal treatment with ADT and external beam radiotherapy (EBRT). The median (range) post treatment follow-up time was 9 (1–18) years. Death from any cause occurred in 270 patients at a median (range) of 7 (1–17) years postimplant (Table 1).

Five and 10-year overall survival (95% CI) was 96% (95–97) and 90% (89–92) and net survival was 103% (102–104) and 109% (107–110), respectively (Fig. 2 and Table 2). Five and 10-year net survival in patients with T1 clinical stage was 103% (102–104) and 108% (106–110) and with T2 clinical stage 102% (100–103) and 109% (106–112] respectively (Table 2; T1 vs T2 log-rank p value=0.8). Net survival increased with age at treatment in T1 or T2 patients (Fig. 3 and Table 2), or in relapse risk groups (Table S2).

Discussion

This is the first study to show the net survival of men with early-stage prostate cancer treated by LDR brachytherapy. Their survival exceeds that of peers in England matched by their age, year of treatment, and social deprivation level. A net survival of 100% indicates patients have equal chance of surviving relative to the general population and have reached statistical cure. The 5- and 10-year net survival in our brachytherapy cohort was above that of the general population in patients diagnosed with T1 or T2 clinical stage. Estimates from the most recent national report for England showed five-year net survival of 101% in T1 and T2 stage cases (17) similar to our estimates of 103% in T1 and 102% in T2 patients. The national report did not assess longer-term survival by stage. Ten-year estimates were reported however for the East of England and showed net survival of 101.4% in T1 and 86.5% for T2 cases (18) whereas we obtained 108% for T1 and 109% for T2 patients. Given that we followed analysis guidelines used by these national reports (i.e., the Pohar-Perme estimator and most up to date national life tables adjusted for social deprivation) these differences would be due to factors other than age or affluence. Further investigation that allows for additional adjustments is needed to confirm the significance of these differences in the long-term net survival. It would be important to assess the influence of the method of cancer detection (be it symptomatic patients or those asymptomatic screen detected), the weight of clinical stage subdivisions (T2b–T2c) or imaging-assisted staging, and the types of treatment delivered. Our small sample size might limit the interpretation when stratifying by relapse risk and age-at-treatment groups.

The results echo previous observations of excess survival in localized prostate cancer from further afield. Brenner et al. in 2005 reported age-dependent excess survival of grade 1 and 2 prostate cancer from 180,605 cases in the SEER program (2). Mathers et al. in 2011 showed excess survival of stage I and II patients in 2,121 histologically confirmed cases in Germany (3). Roder et al. in 2013 demonstrated excess survival of 1,350 non-PSA-screened prostatectomy patients in Denmark (4). Matthes et al. in 2017 observed in a Swiss registry of 1,541 cases an excess survival for grade 1 prostate cancer only and no excess when stratifying by age or treatment types (5). Orrason et al. in 2021 reported age-dependent survival excess in patients with low or intermediate-risk disease from 168,793 cases in Sweden (6). Collectively these studies show that excess net survival is a feature of localized disease and is age-dependent and that there is very little evidence on the impact of treatment choice.

The indolent nature of localized prostate cancer, and advanced age, do increase the likelihood of death from other causes thereby increasing the net survival in the longer-term. Interestingly, excess survival from non-cancer causes

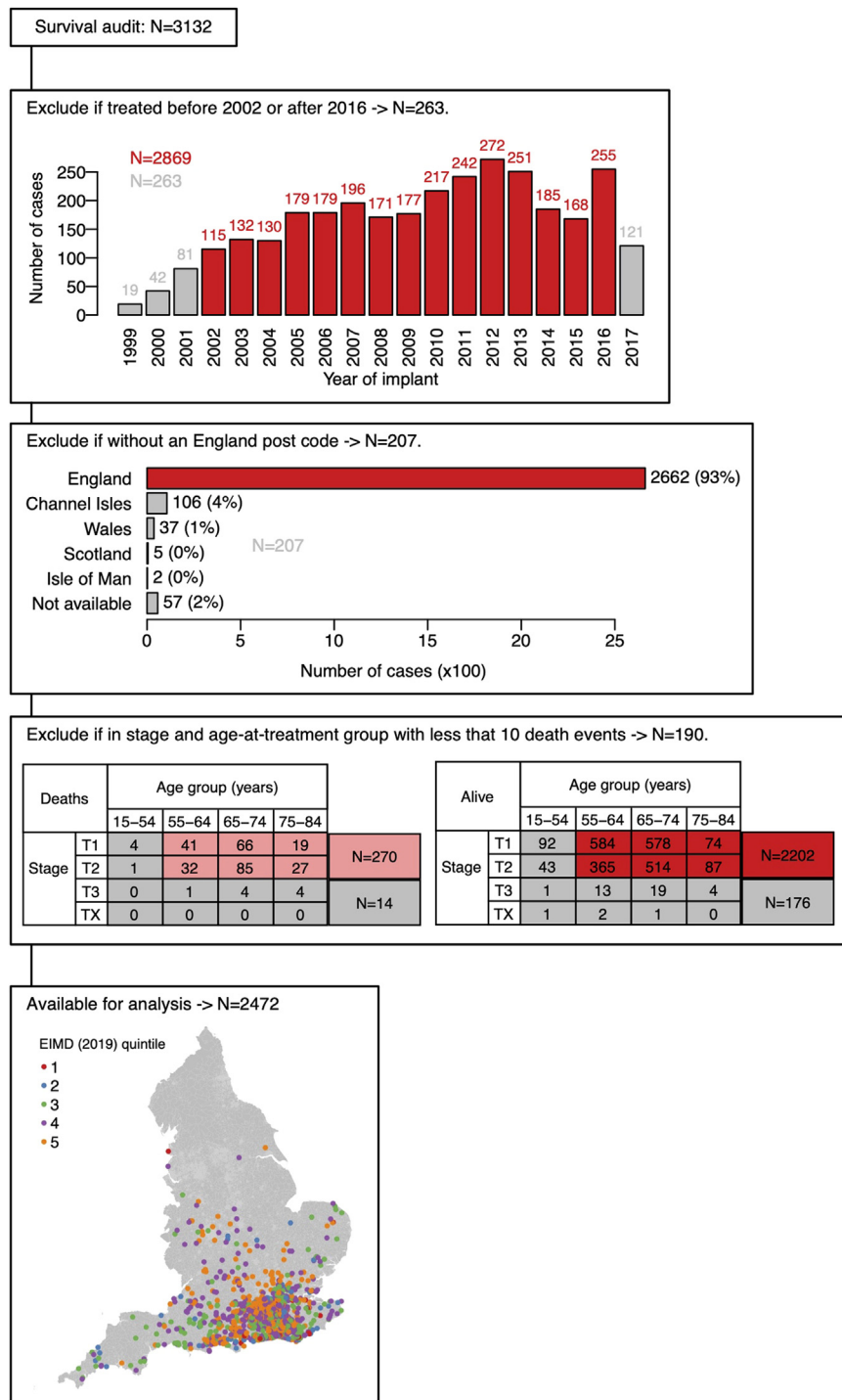


Fig. 1. Consort diagram of case selection. Patients were selected from a recent audit on cause-specific survival if treated between 2002 and 2016 to correspond to periods in the smoothed life tables (12), if a post code in England (and thus an EIMD quintile) was available, and if in stage and age-at-treatment groups with at least 10 death events. Of 2472 cases available for analysis 84% resided in the Southeast of England, and 51% under an EIMD quintile 5 (most affluent) (see Table 1A).

relative to the general population is also expected of patients diagnosed with localized prostate cancer (7). The survival advantage of an early-stage diagnosis has been attributed to biased access to screening and health care by

men with healthier lifestyles. In the absence of a screening program, early detection of clinically significant disease (19,20) would be more frequent in the affluent and health-conscious men. These biases are minimized in our

Table 1

Demography summary.

		All	Alive	Deceased
Number of cases		2472	2202	270
		Median (range) or <i>N</i> (%)		
Age at therapy		66 (55–84)	66 (55–84)	68 (55–81)
Age at therapy group	55–64	1022 (41)	949 (43)	73 (27)
	65–74	1243 (50)	1092 (50)	151 (56)
	75–84	207 (8)	161 (7)	46 (17)
Region of England	Southeast	2083 (84)	1872 (85)	211 (78)
	Southwest	175 (7)	142 (6)	33 (12)
	London	108 (4)	93 (4)	15 (6)
	East of England	64 (3)	59 (3)	5 (2)
	West Midlands	24 (1)	20 (1)	4 (1)
	East Midlands	13 (1)	11 (0.5)	2 (1)
	Northwest	3 (0.1)	3 (0.1)	0 (0)
	Yorkshire and the Humber	2 (0.1)	2 (0.1)	0 (0)
	Northeast	0 (0)	0 (0)	0 (0)
EIMD 2019 quintile	1—most deprived	32 (1)	28 (1)	4 (1)
	2	140 (6)	123 (6)	17 (6)
	3	397 (16)	343 (16)	54 (20)
	4	646 (26)	573 (26)	73 (27)
	5—most affluent	1257 (51)	1135 (52)	122 (45)
Clinical stage	T1	1362 (55)	1236 (56)	126 (47)
	T2	1110 (45)	966 (44)	144 (53)
Relapse risk (NICE)	Low	809 (33)	737 (33)	72 (27)
	Intermediate	1391 (56)	1228 (56)	163 (60)
	High	272 (11)	237 (11)	35 (13)
Treatment	LDR-PB	1665 (67)	1503 (68)	162 (60)
	ADT+LDR-PB	477 (19)	407 (18)	70 (26)
	ADT+EBRT+LDR-PB	330 (13)	292 (13)	38 (14)
Years follow-up		9 (1–18)	9 (3–18)	7 (1–17)

N=Number, EIMD=English Index of Multiple Deprivation, NICE=National Institute for Healthcare and Excellence, LDR-PB=Low Dose Rate Prostate Brachytherapy, ADT=Androgen Deprivation Therapy, EBRT=External Beam Radiotherapy.

Table 2

Summary of net survival by age-at-treatment and clinical stage groups. Shown for each group are the number (*N*) of cases and death events throughout the follow-up, and the number of patients at risk and censored (cen.) at the 5- and 10-year postimplant timepoints with corresponding estimates of survival and 95% confidence interval (CI).

Group		Throughout		5-year				10-year			
Stage	Age	<i>N</i> cases	<i>N</i> events	<i>N</i> at risk	<i>N</i> cen.	OS (95% CI)	Net (95% CI)	<i>N</i> at risk	<i>N</i> cen.	OS (95% CI)	Net (95% CI)
All	All	2472	270	2065	312	96 (95–97)	103 (102–104)	1027	942	90 (89–92)	109 (107–110)
T1	All	1362	126	1142	181	97 (96–98)	103 (102–104)	547	544	91 (90–93)	108 (106–110)
	55–64	625	41	546	69	98 (97–99)	101 (100–102)	296	232	94 (92–96)	102 (100–104)
	65–74	644	66	527	98	97 (95–98)	105 (103–106)	235	266	90 (87–93)	112 (108–116)
	75–84	93	19	69	14	88 (82–95)	108 (100–116)	16	46	74 (62–88)	132 (112–155)
T2	All	1110	144	923	131	95 (93–96)	102 (100–103)	480	398	89 (87–91)	109 (106–112)
	55–64	397	32	354	33	98 (97–99)	100 (99–102)	238	106	94 (92–96)	102 (99–105)
	65–74	599	85	486	83	97 (95–98)	102 (100–104)	220	238	90 (87–93)	110 (106–114)
	75–84	114	27	83	15	88 (82–95)	104 (96–113)	22	54	74 (62–88)	139 (124–157]

study given the universal access to healthcare in England and lifestyle healthiness accounted for by the use of life tables adjusted for social deprivation.

The relative survival method is unaffected by differences in mortality from other causes enabling a fair comparison between populations according to time periods, geography, or other characteristics (21–23,10). However, the choice of life tables that most accurately represents the populations of interest needs careful consideration. This

is particularly relevant to prostate cancer (9,6) where use of life tables corrected for social deprivation bring net survival estimates closer to those obtained with a cause-specific approach, and this held true in our analyses (Fig. S1). Therefore, survival from localized prostate cancer can be substantially influenced by socio-economic factors. The same does not hold true for survival from advanced disease (6). The current view in England that prostate cancer mortality is not dependent on social deprivation (24) does not

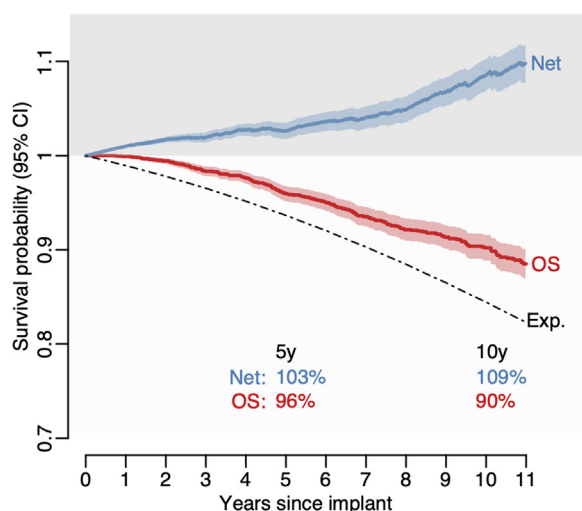


Fig. 2. Net survival is the average ratio between overall (OS) and expected (Exp.) survival. The expected survival is derived from mortality rates in the general population matched for age at therapy, year of therapy, England region, and the English index of multiple deprivation.

consider the prominent effect of tumor stage at diagnosis on survival (8).

The impact of comorbidity on net survival of men with localized prostate cancer is unclear. Population-level estimates show the prevalence of comorbidity in prostate cancer patients is low; from SEER data the prevalence was the same as that in non-cancer patients and ranged from 20% to 40% increasing with age (7), and similarly estimates for England suggest a prevalence of comorbidity of 20% (25) with regional variations and interaction with social deprivation (26). The relative good health of men with early

prostate cancer likely underlies the survival advantage over men in the general population. Moreover prostate cancer management guidelines (27,28,16) suggest that only men with a life expectancy of 10 years should undergo PSA testing and treatment having considered frailty and comorbidity, an approach that further selects for men deemed healthy and suitable for radical treatment. Whether radical treatments for management of localized prostate cancer contribute to the survival advantage is unclear. Studies designed to directly compare net survival after treatment for prostate cancer are needed to determine if this is the case.

Finally, given that net survival is particularly suited to comparison of outcomes between different time points, we were able to compare patients treated with implant techniques that we have delivered in two eras. In the initial 10 years of our LDR brachytherapy program, a two-stage (2S) technique was used. From 2009, the 4D Brachytherapy technique, a one-stage real-time approach, was adopted providing improved dosimetry and reduced morbidity (29). Net survival was significantly greater with 4D Brachytherapy compared to the 2S technique (Fig. S2) in agreement with the improved biochemical control recently reported (29).

Prostate cancer is the most common cancer in men and a leading cause of mortality. Tens of thousands of men are newly diagnosed with early prostate cancer each year in England and the number suitable for radical treatment continues to increase. As such, these men are interested in their likely clinical outcome and overall survival compared to their peers. This paper suggests that their long-term survival is likely to be greater than that of men in the general population who are suitable and treated by LDR Brachytherapy. Concerns that use of hormone therapy or

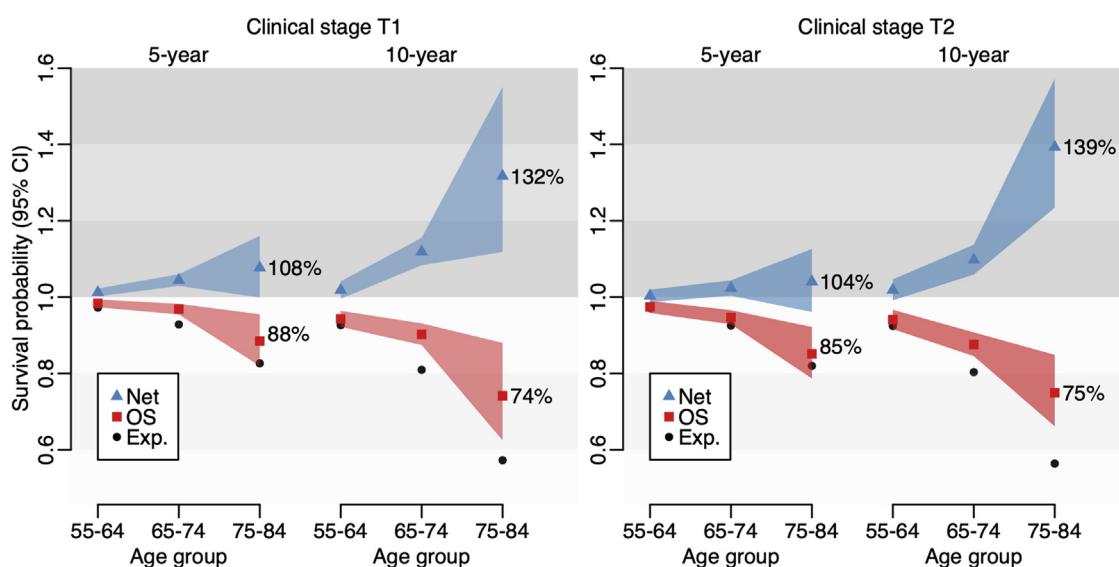


Fig. 3. Five and 10-year survival by clinical stage and age-at-treatment groups. Only values for the oldest group are shown to avoid clutter (please see complete summary in Table 2).

pelvic irradiation might have an adverse effect on their longevity seem unwarranted.

Conclusion

This longitudinal retrospective study is the first to compare men treated with LDR brachytherapy to their peers in England and complements the favorable long-term cause-specific outcomes recently reported (1). The value of treatment of early prostate cancer is often questioned as there has been little evidence that treated patients actually live longer than those in the general population. This is the first paper, using modern life tables with adjustment for social deprivation, to show that patients diagnosed with early prostate cancer who choose to be treated by LDR brachytherapy can expect to live longer than their matched peers in the general population of England. Further studies are needed to determine the extent to which treatment choice contributes to the long-term net survival.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.brachy.2024.02.006](https://doi.org/10.1016/j.brachy.2024.02.006).

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