Surrogate endpoints for prostate cancer-specific mortality after radiotherapy and androgen suppression therapy in men with localised or locally advanced prostate cancer: an analysis of two randomised trials

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Summary

Background **Androgen suppression therapy and radiotherapy are used to treat locally advanced prostate cancer. 3 years of androgen suppression confers a small survival benefit compared with 6 months of therapy in this setting, but is associated with more toxic effects. Early identification of men in whom radiotherapy and 6 months of androgen suppression is insufficient for cure is important. Thus, we assessed whether prostate-specific antigen (PSA) values can act as an early surrogate for prostate cancer-specific mortality (PCSM).**

Methods **We systematically reviewed randomised controlled trials that showed improved overall and prostate cancer-specific survival with radiotherapy and 6 months of androgen suppression compared with radiotherapy alone and measured lowest PSA concentrations (PSA nadir) and those immediately after treatment (PSA end). We assessed a cohort of 734 men with localised or locally advanced prostate cancer from two eligible trials in the USA and Australasia that randomly allocated participants between Feb 2, 1996, and Dec 27, 2001. We used Prentice criteria to assess whether reported PSA nadir or PSA end concentrations of more than 0·5 ng/mL were surrogates for PCSM.**

Findings **Men treated with radiotherapy and 6 months of androgen suppression in both trials were significantly less likely to have PSA end and PSA nadir values of more than 0·5 ng/mL than were those treated with radiotherapy alone ($p<0·0001$). Presence of candidate surrogates (ie, PSA end and PSA nadir values >0·5 ng/mL) alone and when assessed in conjunction with the randomised treatment group increased risk of PCSM in the US trial (PSA nadir $p=0·0016$; PSA end $p=0·017$) and Australasian trial (PSA nadir $p<0·0001$; PSA end $p=0·0012$). In both trials, the randomised treatment group was no longer associated with PCSM ($p\geq0·20$) when the candidate surrogates were included in the model. Therefore, both PSA metrics satisfied Prentice criteria for surrogacy.**

Interpretation **After radiotherapy and 6 months of androgen suppression, men with PSA end values exceeding 0·5 ng/mL should be considered for long-term androgen suppression and those with localised or locally advanced prostate cancer with PSA nadir values exceeding 0·5 ng/mL should be considered for inclusion in randomised trials investigating the use of drugs that have extended survival in castration-resistant metastatic prostate cancer.**

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Introduction

Randomised controlled trials[1,2] have shown a benefit in prostate cancer-specific survival and overall survival benefit in men with localised[1,2] or locally advanced[2] prostate cancer when 6 months of androgen suppression therapy is added to radiotherapy. In addition to the known prognostic value and clinical significance[3] of prostate-specific antigen (PSA) concentration, Gleason score,[4] and American Joint Commission on Cancer tumour category[5] based on digital rectal examination, post-treatment factors such as PSA nadir,[6] time to PSA failure,[7] and PSA doubling time[7,8] have been shown to have prognostic and clinical significance for men undergoing radiotherapy with or without androgen suppression. Prentice criteria[9] can be used to assess whether a prognostic factor can act as a surrogate for prostate cancer-specific mortality (PCSM). To identify a surrogate marker, individual patients' data are needed from a randomised controlled trial in which a cancer-specific survival benefit was observed and all four criteria were satisfied. First, men who achieved the surrogate need to be significantly more likely to have been randomised to the inferior treatment group. Second, the surrogate needs to be a prognostic factor. Third, the surrogate needs to remain prognostic for PCSM when included in a competing risk regression model in which the randomised treatment group is included as a covariate. Fourth, in the model that includes the surrogate the superior treatment must no longer be associated significantly with a reduction in the risk of PCSM.

A time to PSA failure of less than 1·5 years and the rate at which PSA is rising at the time of failure (characterised by a doubling time of less than 12 months) are surrogates for PCSM when comparing radiotherapy with or without 6 months of androgen suppression.[7] However, PSA nadir and concentration after completion of therapy (PSA end), which are assessable before PSA failure, have not been

assessed as possible surrogates. Because 3 years of androgen suppression confers a modest survival benefit in men treated with radiotherapy for locally advanced prostate cancer[10] compared with 6 months of androgen suppression (from 81·0% to 84·8% at 5 years), but is associated with increased toxic effects, identification of men in whom 6 months of androgen suppression is insufficient for cure is important. This aim would be achievable if the PSA concentration taken immediately after radiotherapy and 6 months of androgen suppression acted as a surrogate for PCSM in men undergoing this treatment course. Furthermore, an early endpoint such as PSA nadir after radiotherapy and at least 6 months of androgen suppression could identify men who are good candidates for future trials of additions of proven systemic therapies (ie, one that extends survival in men with castration-resistant metastatic prostate cancer).

Therefore, we aimed to assess whether two metrics of PSA (nadir and end) can act as surrogates for PCSM. Cutoff values were chosen on the basis of reports that a PSA nadir of more than 0·5 ng/mL after radiotherapy and short-course androgen suppression is associated with an increased risk of recurrence[6,11,12] and, since there is no precedent for what PSA end concentration to assess, the same cutoff was selected for PSA end analysis.

Methods

Study design and participants

We assessed individual patients' data from two randomised controlled trials—the Dana Farber Cancer Institute (DFCI) trial[1] and the Trans-Tasman Radiation Oncology Group (TROG)[2] trial—that showed a statistically and clinically significant reduction in PCSM when 6 months of androgen suppression was added to radiotherapy versus radiotherapy alone. We identified these studies on the basis of a systematic review of randomised controlled trials that reported better overall and prostate cancer-specific survival with radiotherapy and 6 months of androgen suppression than with radiotherapy alone. 734 men from the USA and Australasia with localised or locally advanced prostate cancer were enrolled into these studies[1,2] between Feb 2, 1996, and Dec 27, 2001 (webappendix p 1). We obtained permission from respective institutional review boards or ethics boards to reuse patients' data.

See Online for webappendix

Procedures

Androgen suppression was defined as use of a luteinising-hormone-releasing hormone agonist and an anti-androgen. Radiotherapy doses were 70 Gy in 1·8–2·0 Gy fractions in the DFCI trial[1] and delivered during months 3 and 4 of androgen suppression and 66 Gy in 2·0 Gy fractions in the TROG trial[2] and initiated at the start of month 6 of androgen suppression.

In both studies, a physical examination including a digital rectal examination was done at every follow-up and PSA concentrations were obtained before the visit. Patients were followed up every 3 months for 2 years, every 4–6 months up to 5 years, and once a year thereafter, permitting a rigorous assessment of the lowest PSA value achieved (ie, PSA nadir) after completion of treatment. Specifically, participants had 14–20 measurements during the first 5 years of follow-up and all men had eight concentrations available for analysis during the first 2 years. Follow-up data were available until January, 2008, for the DFCI trial[1] and August, 2010, for the TROG trial.[2] These data are an update of the results of the previously reported TROG data.[2] Salvage androgen suppression therapy after PSA failure was luteinising-hormone-releasing hormone agonist that was recommended to be initiated at a PSA concentration of 10 ng/mL in DFCI[1] and 20 ng/mL in TROG.[2] To be defined as a prostate cancer-specific death, participants needed to have documented castration-resistant and metastatic prostate cancer and a rising PSA at the time of last follow-up before death. We excluded five men in DFCI and seven men in TROG because of missing data that would have been needed to calculate one or both of the candidate surrogates.

Statistical analysis

We used descriptive statistics to characterise the distribution of prognostic factors at randomisation, stratified by the randomised treatment group for each trial. We used the Mantel-Haenszel χ^2 test[13] to compare the distribution of categorical variables and the Wilcoxon two-sample test[14] to compare medians (IQRs) for continuous variables between randomised treatment groups. We used logistic regression[14] to assess whether, compared with radiotherapy alone, treatment with radiotherapy and 6 months of androgen suppression was significantly associated with the occurrence of the surrogates in both trials.

With univariable Fine and Gray competing risks regression,[15] we ascertained whether addition of the two candidate surrogates in the randomised treatment groups were significantly associated with the risk of PCSM in each trial. We also included treatment and proposed surrogate in a single multivariable Fine and Gray model.[15] We assessed both candidate surrogates as time-dependent covariates.[15] For all analyses, time 0 was defined as the date of randomisation. We calculated unadjusted odds ratios (ORs) and unadjusted and adjusted hazard ratios (HRs) with associated 95% CIs and p values for every covariate assessed in the regression analyses.

To assess performance characteristics of the surrogate endpoints in PCSM, we calculated point estimates (with 95% CIs) of the proportion of the treatment effect (PTE)[16] explained by the surrogate and the partial proportion of the variation explained by treatment (pPVE).[17] A perfect surrogate occurs when all of the treatment effect can be explained by the surrogate (ie, PTE for the surrogate is 1) and when no additional information is provided when treatment is added to the multivariable model in which the surrogate is included (ie, pPVE for treatment is 0).

We used the cumulative incidence method[18] to estimate and characterise PCSM stratified by randomised treatment

	DFCI trial[1]			TROG trial[2]		
	Radiotherapy alone	Radiotherapy and androgen suppression	p value	Radiotherapy alone	Radiotherapy and androgen suppression	p value
Participants randomly allocated (n)	104	102	NA	270	267	NA
Assessable participants PSA end (n)	102	99	NA	267*	263*	NA
Assessable participants PSA nadir (n)	104	100	NA	267*	263*	NA
Median follow-up (years)	8·17 (6·77–9·78)	8·17 (6·77–9·78)	NA	11·52 (10·89–12·30)	11·52 (10·89–12·30)	NA
Prostate cancer deaths	14	4	NA	70	32	NA
Non-prostate cancer deaths	30	26	NA	63	52	NA
Median age (years)	73·21 (68·90–76·30)	71·99 (68·91–74·70)	0·13	67·51 (63·23–72·07)	68·47 (63·06–72·18)	0·64
Median PSA (ng/mL)	11·00 (7·52–16·35)	11·00 (7·52–15·72)	0·74	16·40 (10·00–28·00)	14·60 (9·00–25·10)	0·12
Gleason score[4]			0·62			0·62
≤6	27 (26%)	29 (29%)		112 (42%)	121 (46%)	
7	61 (59%)	57 (57%)		114 (43%)	99 (38%)	
8–10	16 (15%)	14 (14%)		41 (15%)	43 (16%)	
1992 AJCC tumour category[5]			0·10			0·93
T1b	2 (2%)	2 (2%)		..	..	
T1c	41 (39%)	52 (52%)		..	..	
T2a	26 (25%)	20 (20%)		..	..	
T2b	35 (34%)	26 (26%)		72 (27%)	67 (25%)	
T2c	..	..		89 (33%)	94 (36%)	
T3 or T4	..	..		106 (40%)	102 (39%)	
Median PSA end (ng/mL)	1·46 (0·82–2·80)	0·10 (0·10–0·11)	<0·0001	2·10 (1·10–4·40)	0·23 (0·10–0·52)	<0·0001
PSA end >0·5 ng/mL	90 (88%)	6 (6%)	<0·0001	247 (93%)	66 (25%)	<0·0001
PSA end ≤0·5 ng/mL	12 (12%)	93 (94%)	<0·0001	20 (7%)	197 (75%)	<0·0001
Median PSA nadir (ng/mL)	0·71 (0·40–1·32)	0·10 (0·08–0·10)	<0·0001	1·10 (0·50–2·30)	0·20 (0·10–0·40)	<0·0001
PSA nadir >0·5 ng/mL	64 (62%)	5 (5%)	<0·0001	200 (75%)	39 (15%)	<0·0001
PSA nadir ≤0·5 ng/mL	40 (38%)	95 (95%)	<0·0001	67 (25%)	224 (85%)	<0·0001
Median time to PSA end (months)†	3·88 (3·42–4·47)	0·59 (0·23–1·48)	<0·0001	6·90 (5·71–9·30)	1·97 (1·51–4·11)	<0·0001
Median time to PSA nadir (months)†	15·33 (8·57–33·10)	0·69 (0·20–4·37)	<0·0001	14·82 (9·36–22·87)	4·24 (1·74–9·26)	<0·0001

Data are median (IQR) or n (%) unless otherwise stated. PSA end was concentration after radiotherapy or radiotherapy plus 6 months of androgen suppression. DFCI=Dana Farber Cancer Institute. TROG=Trans-Tasman Radiation Oncology Group. NA=not applicable. PSA=prostate-specific antigen. AJCC=American Joint Commission on Cancer. *Missing data due to death of men before PSA assessment. †Time from end of treatment.

Table 1: **Comparison by treatment group of distribution at randomisation of prognostic factors for the USA and Australasia randomised trials**

group for each trial[1,2] and by PSA nadir or PSA end concentrations (>0·5 ng/mL *vs* ≤0·5 ng/mL). Time 0 was defined on the date of PSA end or the date of PSA nadir. We compared these estimates across randomised treatment groups and within cohorts, defined by whether the surrogate occurred or not, with a k-mean p value and illustrated them graphically. Because both surrogates were confirmed in both trials, we combined the data from the trials for clarity. A two-sided k-mean test p value of less than 0·0125 was regarded as significant after Bonferroni correction[19] for the four comparisons.

We used R version 2.12.1 for calculations of the Gray k-mean p value and a revised version of the Fortran codes from StatLib for Fine and Gray regressions with time-dependent covariates. We used SAS version 9.2 for all other analyses.

Role of the funding source

There was no funding source for this study. M-HC had full access to all the data in the study and AVD'A takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had final responsibility for the decision to submit for publication.

	DFCI trial[1]		TROG trial[2]	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
PSA end >0·5 ng/mL	0·01 (0·003–0·02)	<0·0001	0·03 (0·02–0·05)	<0·0001
PSA nadir >0·5 ng/mL	0·03 (0·01–0·05)	<0·0001	0·06 (0·04–0·09)	<0·0001

PSA end was concentration after radiotherapy or radiotherapy plus 6 months of androgen suppression. DFCI=Dana Farber Cancer Institute. TROG=Trans-Tasman Radiation Oncology Group. PSA=prostate-specific antigen.

Table 2: **Odds ratios from logistic regression analyses for observation of the candidate surrogate in men randomised to radiotherapy and 6 months of androgen suppression compared with radiotherapy alone**

Results

We noted no significant differences (p≥0·10) in the distribution of prognostic factors in men treated in the DFCI and TROG trials between randomised treatments groups (table 1). In both trials, men who were randomly

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	DFCI trial[1]						TROG trial[2]					
	Men (n)	Events (n)	Univariable analysis		Multivariable analysis		Men (n)	Events (n)	Univariable analysis		Multivariable analysis	
			HR (95% CI)	p value	Adjusted HR (95% CI)	p value			HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Radiotherapy and androgen suppression	100	4	0·25 (0·085–0·75)	0·013	0·72 (0·25–2·12)	0·55	263	32	0·44 (0·29–0·67)	0·00014	1·22 (0·76–1·96)	0·42
Radiotherapy alone	104	14	1 (reference)	..	1 (reference)	..	267	70	1 (reference)	..	1 (reference)	..
PSA nadir >0·5 ng/mL*	69	13	6·51 (2·29–18·48)	0·0004	5·35 (1·89–15·13)	0·0016	313	82	5·50 (3·43–8·81)	<0·0001	6·17 (3·63–10·50)	<0·0001
PSA nadir ≤0·5 ng/mL*	135	5	1 (reference)	..	1 (reference)	..	217	20	1 (reference)	..	1 (reference)	..
Radiotherapy and androgen suppression	99	4	0·25 (0·083–0·74)	0·012	0·58 (0·25–1·33)	0·20	263	32	0·44 (0·29–0·67)	0·00014	0·79 (0·48–1·30)	0·35
Radiotherapy	102	14	1 (reference)	..	1 (reference)	..	267	70	1 (reference)	..	1 (reference)	..
PSA end >0·5 ng/mL*	96	14	4·35 (1·46–12·94)	0·0083	2·76 (1·20–6·31)	0·017	239	80	3·22 (1·92–5·41)	<0·0001	2·60 (1·46–4·63)	0·0012
PSA end ≤0·5 ng/mL*	105	4	1 (reference)	..	1 (reference)	..	291	22	1 (reference)	..	1 (reference)	..

PSA end was concentration after radiotherapy or radiotherapy plus 6 months of androgen suppression. DFCI=Dana Farber Cancer Institute. TROG=Trans-Tasman Radiation Oncology Group. HR=hazard ratio. PSA=prostate-specific antigen. *Time dependent.

Table 3: **Unadjusted and adjusted HRs from the competing risks regression analysis[15] showing risk of prostate cancer-specific mortality for treatment and the candidate surrogates**

	DFCI trial[1]		TROG trial[2]	
	PTE (95% CI)	pPVE (95% CI)	PTE (95% CI)	pPVE (95% CI)
PSA nadir >0·5 ng/mL	0·85 (0·53–1·35)	0·0010 (0–0·0166)	1·12 (0·83–1·53)	0·0012 (0–0·0106)
PSA end >0·5 ng/mL	0·75 (0·48–1·19)	0·0016 (0–0·0100)	0·81 (0·49–1·33)	0·0016 (0–0·0140)

PSA end was concentration after radiotherapy or radiotherapy plus 6 months of androgen suppression. DFCI=Dana Farber Cancer Institute. TROG=Trans-Tasman Radiation Oncology Group.

Table 4: **Proportion of treatment effect (PTE)[16] explained by the surrogate and the partial proportion of the variation explained (pPVE)[17] by treatment when the surrogate was included in the competing risks multivariable regression model[14]**

allocated to receive radiotherapy and 6 months of androgen suppression were less likely to have a PSA end or PSA nadir of more than 0·5 ng/mL than were those given radiotherapy alone (p<0·0001; table 2). Assessment of PSA end occurred at a median of 1·84 months (IQR 0·56–3·02) and PSA nadir at 2·43 months (0·72–7·92) after the completion of radiotherapy and 6 months of androgen suppression.

74 men died during a median follow-up of 8·17 years (IQR 6·77–9·78) in the DFCI trial; 18 deaths (24%) were from prostate cancer (median follow-up 11·52 years [IQR 10·89–12·30]). 102 (47%) of 217 deaths in the TROG study were from prostate cancer. The candidate surrogates alone and when assessed in conjunction with randomised treatment groups were significantly associated with an increased risk of PCSM in the DFCI and TROG trials (table 3). For both trials, the cumulative incidence estimates of PCSM after PSA end did not differ for men randomly allocated to androgen suppression and radiotherapy compared with radiotherapy alone on the basis of PSA end concentration (>0·5 ng/mL [p=0·20] and ≤0·5 ng/mL [p=0·38]) or PSA nadir concentration (>0·5 ng/mL [p=0·89] and ≤0·5 ng/mL [p=0·40]). Therefore the randomised treatment group was no longer associated with PCSM when the candidate surrogates were included in the model and both PSA metrics satisfied Prentice criteria for surrogacy.

PSA nadir and a PSA end concentrations of more than 0·5 ng/mL are surrogates for PCSM in men with localised or locally advanced prostate cancer and are able to explain at least 75% of the treatment effect of addition of 6 months of androgen suppression to radiotherapy (table 4). No more than 1·70% (ie, the upper 95% CI bound for pPVE; table 4) of this treatment effect is explained by the superior treatment once the surrogate information is known (ie, after discounting the effect on outcomes predicted by the surrogate [PSA concentration]). When the PTE value was more than 1·0 (as it was for the TROG study and a PSA nadir >0·5 ng/mL) then the treatment effect explained by the surrogate is equal to PTE divided by (PTE–1) or 9·33 times as high as the treatment effect not explained by the surrogate.

The point estimates of the PTE and pPVE for a PSA nadir (>0·5 ng/mL) were greater than were estimates of PSA end (>0·5 ng/mL; table 4, figure). This difference can be understood on the basis that the median times to PSA nadir in both trials were greater than were the median times to PSA end, so some men with a PSA end concentration of more than 0·5 ng/mL might subsequently reach a nadir of less than 0·5 ng/mL. We noted this outcome in 27 (27%) of 100 men in DCFI and 74 (28%) of 263 men in the TROG trial who underwent radiotherapy and 6 months of androgen suppression.

For men with a PSA end value of more than 0·5 ng/mL, 20% (95% CI 15–24) of those treated with radiotherapy alone had PCSM by 8 years compared with 16% (8–25) of those who were treated with radiotherapy and androgen suppression. For men with a PSA end value of 0·5 ng/mL or less, 4% (<1–19) of those treated with radiotherapy alone had PCSM by 8 years compared with 7% (3–10) of those who were treated with radiotherapy and androgen suppression (figure).

For men with a PSA nadir value of more than 0·5 ng/mL, 27% (95% CI 21–33) of those treated with radiotherapy alone had PCSM by 8 years compared with 28% (15–42) of those who were treated with radiotherapy and androgen suppression. For men with a PSA nadir value of 0·5 ng/mL or less, 4% (<1–11) of those treated with radiotherapy alone had PCSM by 8 years compared with 6% (4–10) of those who were treated with radiotherapy and androgen suppression (figure).

Discussion

Measurement of the concentration of PSA at two time-points before PSA failure can act as a surrogate for future PCSM in men with localised or locally advanced prostate cancer. Furthermore, such measurements can account for at least three-quarters of the treatment effect of addition of 6 months of androgen suppression to radiotherapy with no more than 1·70% of the treatment effect explained by an effective treatment (in this case 6 months of androgen suppression and radiotherapy) once the surrogate information is known (panel).

Clinically, our findings suggest that the early assessment of treatment efficacy of radiotherapy and 6 months of androgen suppression is possible, allowing identification of men with localised (DFCI and TROG trials) or locally advanced (TROG trial) and high-risk prostate cancer who might benefit from long-term androgen suppression. Moreover, this identification could be achieved without interruption to treatment by use of the PSA end value. Although investigations of docetaxel are in progress for men with newly diagnosed high-risk prostate cancer[20] (NCT00116142), men whose PSA does not subsequently nadir lower than 0·5 ng/mL despite radiotherapy and at least 6 months of androgen suppression could be identified early and considered for clinical trials investigating drugs such as abiraterone[21] and docetaxel.[22,23] Such drugs can extend survival in men with castration-resistant metastatic prostate cancer.

Several points need further discussion. First, the surrogates defined with Prentice criteria in our study only apply to the drugs being tested. Other drugs could affect the PSA concentration differently from androgen suppression causing the surrogates to fail.[24] Our criteria also assume that salvage therapies are ineffective in achieving cure once the surrogate is achieved, which might change as salvage therapy is improved over time.

Second, we chose PCSM and not all-cause mortality for our study because of competing risks (eg, cardiovascular disease) in our elderly male population (median age of approximately 70 years). Such risks can make definition of a surrogate for all-cause mortality difficult, especially if death from prostate cancer is not the predominant cause (table 1).

Third, a randomised controlled trial by the European Organization for Research in the Treatment of Cancer (EORTC)[10] assessing radiotherapy plus 3 years of androgen suppression versus radiotherapy plus 6 months

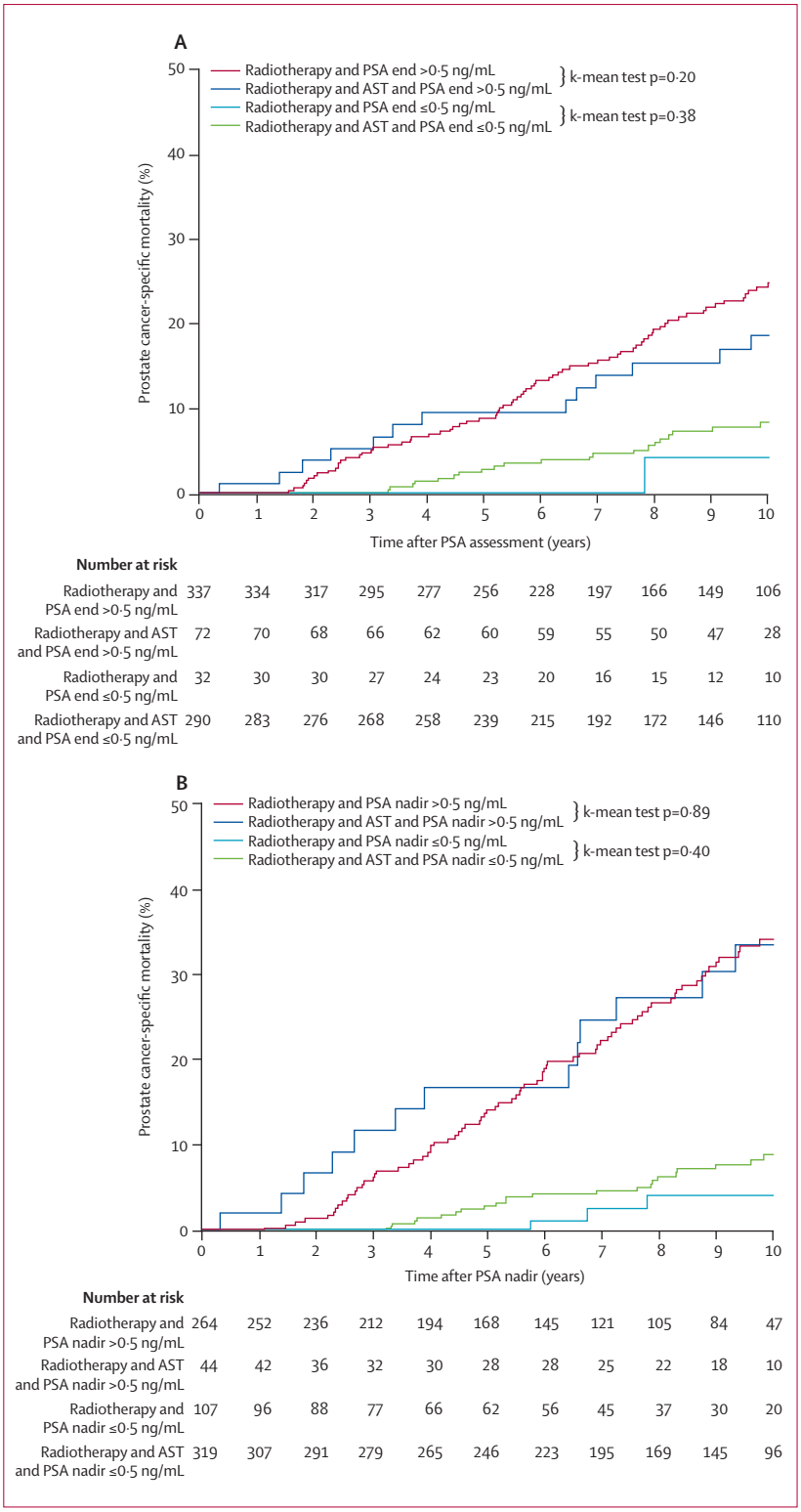

Figure: **Cumulative incidence[18] of prostate cancer-specific mortality at PSA end (A) and PSA nadir (B) assessments**

Stratified by treatment group (radiotherapy alone *vs* radiotherapy plus AST) and PSA concentration (>0·5 ng/mL *vs* ≤0·5 ng/mL). Time 0 was defined on the date of PSA end or the date of PSA nadir. PSA=prostate-specific antigen. AST=androgen suppression therapy.

of androgen suppression for men with locally advanced prostate cancer reported a 3·80% overall survival benefit and 1·50% prostate cancer-specific survival benefit at 5 years after a median follow-up of 6·80 years in the treatment group. Because of the increased toxicity of long-term androgen suppression[25] and the small survival benefit, the clinical significance of this benefit is uncertain. Thus, identification of men in whom radiotherapy and 6 months of androgen suppression is insufficient for cure is important. Although the results of our study provide evidence to support the use of the PSA end concentration to identify men who would benefit from extended therapy, that all men with a PSA end value of more than 0·5 ng/mL will benefit from an additional 2·5 years of androgen suppression is not certain. However, some men will probably benefit, especially since 5-year estimates of PCSM in the radiotherapy and 6 months of androgen suppression groups in the two trials in this study[1,2] and in EORTC[10] were much the same (3·32% [95% CI 1·81–5·56] in this study and 4·7% [2·7–6·7] in EORTC). Notably, the 5-year rates were identical for the EORTC[10] and TROG[2] studies. Thus, the lower overall rate of PCSM noted in the DFCI and TROG studies is attributable to the DFCI study, which included men with localised instead of locally advanced high-risk prostate cancer. This factor was consistent with reports that 6% of men in the DFCI achieved a PSA end value of more than 0·5 ng/mL compared with 25% of men in the TROG studies (table 1).

Fourth, higher radiotherapy doses than were assessed here can now be delivered safely with advanced radiotherapy techniques. Such techniques are sometimes practised in the USA. Although reporting only weak evidence at an interim report (p=0·11), a randomised trial[26] has suggested efficacy of addition of 4 months of androgen suppression in the setting of 80 Gy radiotherapy on disease-free survival; however, whether this technique will affect PCSM needs to be assessed. Future studies could use a high radiotherapy dose with androgen suppression as a standard arm in men with high-risk localised and locally advanced prostate cancer. Nevertheless, with a high radiotherapy dose the PSA end and PSA nadir value that would need to be exceeded to act as a surrogate for PCSM will need further study.

Finally, a contrary interpretation of the results of our study should not necessarily be made. Men whose PSA nadir or PSA end level is 0·5 ng/mL or less are not without risk of PCSM. Although estimates of PCSM are low in these men, they are not zero (figure). Therefore, although the results of this study can be used to recommend an increase of androgen suppression use beyond 6 months in some men, they do not ensure that radiotherapy and 6 months of androgen suppression is adequate to avoid PCSM in others.

Overall, both PSA nadir and PSA end concentrations of more than 0·5 ng/mL are surrogates for PCSM, permitting early identification of men in whom radiotherapy and 6 months of androgen suppression is insufficient for cure. Men whose PSA value exceeds 0·5 ng/mL following radiotherapy and 6 months of androgen suppression should be considered for long-term androgen suppression. Men whose PSA does not subsequently nadir lower than 0·5 ng/mL, despite the administration of at least 6 months of androgen suppression, should be considered for studies investigating drugs that have extended survival in men with castration-resistant metastatic prostate cancer.

Panel: Research in context

Systematic review

We searched PubMed for clinical trials published between Jan 1, 1966, and April 1, 2011, in English that investigated whether addition of 6 months of androgen suppression to radiotherapy improved survival. We only accepted level 1 evidence of a benefit and thus we restricted our search to randomised controlled trials. We identified two such trials[1,2] and applied Prentice criteria[9] for candidate surrogate endpoints to each study individually to establish whether prostate-specific antigen (PSA) concentrations were predictive of prostate cancer-specific mortality.

Interpretation

Because 3 years of androgen suppression was associated with toxic effects and very modest survival benefit (3·80% at 5 years) compared with 6 months of androgen suppression plus radiotherapy in the randomised European Organisation for Research in the Treatment of Cancer study,[10] we believed that identification of men in whom 6 months of androgen suppression was insufficient for cure was important. The clinical significance of the identification of two early PSA metrics as surrogate endpoints is twofold. First, practising doctors can inform men who have been identified as having high-risk prostate cancer and who need combined radiotherapy and androgen suppression that, if the patients' PSA concentrations remain higher than 0·5 ng/mL after radiotherapy and 6 months of androgen suppression, they will be recommended to continue androgen suppression for 3 years. Second, clinical researchers can use the PSA nadir of more than 0·5 ng/mL as an eligibility criteria for an early (at time of PSA nadir) versus delayed (at time of PSA failure) intervention with salvage androgen suppression in a randomised controlled trial or as an eligibility criteria for entrance in trials assessing the effect on survival of drugs that prolong survival in men with castration-refractory metastatic prostate cancer. However, the surrogates defined with Prentice criteria in this study only apply to the drug class being tested, because drugs other than those used for androgen suppression in this study could have a different effect on the PSA concentration. Therefore, future randomised trials of addition of drugs to radiotherapy other than androgen suppression should not necessarily use the surrogates identified in this study to predict prostate cancer-specific mortality.

Contributors

AVD'A designed the study and had administrative oversight. AVD'A, DSL, PWK, and JWD provided patients for the study. M-HC did the statistical analyses and interpretation and had administrative oversight of the statistics. MdC helped with the statistical analysis and interpretation. AVD'A, ML, DSL, AS, PWK, and JWD analysed and interpreted the data. All authors wrote and reviewed the final report.

Conflicts of interest

We declare that we have no conflicts of interest.

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