

A comparison of survival and mortality outcomes for older men with localized prostate cancer treated with either primary androgen deprivation therapy or primary observation

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Abstract

Background

Androgen deprivation therapy (ADT) remains the primary treatment for localized prostate cancer (PCa) even though there is no evidence that its use is beneficial in the absence of curative treatment.

Material and methods

Finnish Cancer Registry data were utilized in this population-based study. Men aged > 70 years (n = 16534) diagnosed with localized PCa from 1985–2014, and treated either by primary observation or ADT in the absence of curative treatment, were included. The relative risk (RR) of PCa-specific mortality (PCSM) and other cause-specific mortality was determined. A life table for cause-specific survival (CSS) (i.e., PCa) and other-cause survival was created. Two age groups (70–79 years and > 80 years) and three time-based cohorts (1985–1994, 1995–2004, and 2005–2014) were compared following propensity score matching with four covariates (age, year of diagnosis, socioeconomic status, and hospital district). Follow-ups continued until death or 31 December 2015.

Results

PCSM risk was higher in men aged 70–79 years undergoing primary ADT compared to those managed with observation only (RR of 1.70, 95% confidence interval [CI]: 1.29–2.23 [1985–1994]; RR of 1.55, 95% CI: 1.35–1.84 [1995–2004]; and RR of 2.71, 95% CI: 2.08–3.53 [2005–2014]). Similar risk was observed in men aged > 80 years in two latest groups. Men in their 70s undergoing observation also had better propensity score-matched 10-year CSS than those undergoing ADT.

Conclusion

Conservative management is a valid option for patients with localized PCa in whom curative treatment is not possible.

Background

Androgen deprivation therapy (ADT) has been the cornerstone of treatment for locally advanced and metastatic (M+) prostate cancer (PCa) since the 1940s (1). Immediate ADT or ADT combined with docetaxel or with abiraterone acetate is the current treatment of choice for M+ PCa (2). However, the use of ADT increased sharply between 1989 and 2001 in the USA despite the fact that $\leq 5\%$ of patients with newly diagnosed PCa have distant metastases at first presentation compared with 20–25% ≥ 20 years ago (3, 4). While the increased use of ADT is partly accounted for by the uptake of neoadjuvant and adjuvant treatment along with radiation therapy, it is primarily elucidated by ADT for localized disease, especially for elderly patients (5). Thus, ADT is commonly used to treat localized PCa although it has not been shown to improve survival (6).

The risk of metastases or death from conservatively managed clinical stage T1/T2 cancers was estimated in a meta-analysis of six studies from the pre-prostate-specific antigen (PSA) era (7). The risk of metastasis at 10 years was found to be 19%, 42%, and 74% for well-differentiated, moderately differentiated, and poorly differentiated tumors, respectively (7). Similarly, the long-term clinical outcomes of localized PCa without initial treatment with curative intent during the PSA era were assessed [8]. Thirty per cent of the patients died of PCa and 30% of other causes within a 12-year period (8). A landmark Swedish study demonstrated a benign course of well- or intermediately differentiated PCa in the absence of initial treatment with curative intent (9). Thus, the clinical course of localized high-risk PCa can be progressive, but the majority of cancers are indolent and slow to progress (2). According to current guidelines, observation with the option of later treatment in the case of disease progression (i.e., watchful waiting) is recommended for localized and locally advanced PCa in elderly patients with competing co-morbidities.

Thus, the current study objective was to investigate mortality in elderly PCa patients primarily treated with ADT or observation only during a long follow-up in Finland.

Methods

Study population

The nationwide population-based Finnish Cancer Registry collects information on the annual incidence of cancer from hospitals, outpatient clinics, and healthcare facilities and separately from histopathological laboratories in Finland. The registry has estimated coverage of 99% for male genital cancers [(10)]. The complete tumor, nodes, and metastasis (TNM) classification data for all PCa cases covered by the Finnish cancer registry were retrieved in the current study. A search was conducted to identify PCa patients aged > 70 years diagnosed with localized disease (clinical stage T1/T2) from 1985–2015 and undergoing primary ADT or observation in the absence of radical treatment with curative intent. Of those identified ($n = 16534$), 11572 and 4962 patients were diagnosed with PCa aged 70–79 years and > 80 years, respectively. Treatment was ADT (ADT group) and no treatment (observation group), both within four months of diagnosis. The four-month period was chosen because mandatory reports to the Finnish Cancer Registry include information about primary treatment within four months of the diagnosis. However, it is possible that patients in the observation group received later treatment with ADT and/or other palliative treatment for disease progression. There were 9704 patients in the ADT group and 6830 in the observation group (Table 1). The survival outcomes of the patients (70–79 years and > 80 years) were compared over three periods (1985–1994, 1995–2004, and 2005–2015). The Finnish Cancer Registry data were linked to the Finnish population register center database to determine the date of death. The cause of death for cancer patients was obtained from Statistics Finland.

[Insert Table 1 near here.]

Detailed information on the Gleason scores and PSA values were not available. Age-specific, all-cause, and cancer-specific mortality for the entire Finnish male population was obtained from Statistics Finland as it details the specific cause of death for each Finnish individual. Thus, solid information was obtained for every patient. The study protocol was approved by the institutional review board of the Hospital District of Southwest Finland. The National Institute for Health and Welfare (Finland) approved access to the registry data (study number 182/5.05.00/2015). Statistics Finland approved access to the data on the cause of death (study number TK-53-86-17).

Statistical analysis

CSS (PCa) and other-cause survival was evaluated using the life table method (11). The Poisson regression model was used to quantify differences in patient mortality between the defined groups. The results were reported as the relative risk (RR) of PCa-specific mortality (PCSM) and mortality from causes other than PCa. Propensity score matching was performed using four covariates (age at diagnosis, year of diagnosis, socioeconomic status/education level, and hospital district).

Statistical analysis was performed using R[®] 3.2.3 (popEpi[®])(12).

Results

The study population is described in Table 1. An increase in PCSM for patients undergoing primary ADT, compared to that for those undergoing observation only, was evident in both age cohorts (subjects aged 70–79 years: RR of 1.70 for PCSM, 95% CI: 1.29–2.23 [1985–1994]; RR of 2.71 for PCSM, 95% CI: 2.08–3.53 [2005–2014]; subjects aged > 80 years: RR of 1.30 for PCSM, 95% CI: 0.89–1.88[1985–1995]; RR of 1.65 for PCSM, 95% CI: 1.19–2.29 [2005–2014]).

However, the risk of death from causes other than PCa was shown to decrease over time for patients aged 70–79 years undergoing primary ADT compared to that for those undergoing observation only (RR of 1.22, 95% CI: 1.00–1.49 [1985–1994]; RR of 1.07, 95% CI: 0.97–1.18 [1995–2004]; and RR of 1.03, 95% CI: 0.92–1.16 [2005–2014]). Nonetheless, this difference was without statistical significance from 1995–2004 and 2005–2014. A clear difference in mortality due to causes other than PCa between the groups was not evident for patients aged > 80 years. The periodic treatment effect of ADT was nonsignificant in both age groups ($p = 0.083$) (Table 2).

[Insert Table 2 near here.]

The PCa-specific survival of patients aged 70–79 years in the observation-only group was higher than that of subjects in the ADT group throughout the entire period. Similar results were observed following propensity score matching. This finding was particularly evident from 1985–1994. The CSS of the patients improved throughout the study. Propensity score-matched five-year CSS in patients in their 70s undergoing primary observation was 83% for 1985–1994 [95% CI: 78–87%], 94% for 1995–2004 [95% CI:

93–95%], and 97% for 2005–2014 [95% CI: 96–98%] (Table 3, Figure 1). However, a minimal difference in CSS was observed between patients aged > 80 years undergoing either primary ADT or observation although a small difference in favor of observation was evident from 1995–2004 and 2005–2014. The results remained similar following propensity score matching (Table 3, Figure 2).

[Insert Table 3 near here.]

[Insert Figure 1 near here.]

[Insert Figure 2 near here.]

Enhanced 10-year survival from causes other than PCa was observed in patients in their 70s undergoing observation compared to those undergoing ADT from 1985–2004. This difference was reduced following propensity score matching and was without statistical significance. Furthermore, when five-year survival from causes other than PCa was evaluated, the difference between patients undergoing observation or primary ADT was small for patients aged 70–79 years, and was further diminished after propensity score matching

(Table 3, Figure 1). A significant difference in survival due to causes other than PCa over the study period was not observed in subjects aged > 80 years, and the findings remained similar following propensity score matching (Table 3, Figure 2).

Discussion

A comparison of PCa and other-cause survival and mortality in elderly male patients (aged > 70 years) with PCa was performed in this population-based study in Finland. PCSM and mortality from causes other than PCa was reduced for patients monitored with primary observation versus those managed with primary ADT. In particular, this difference was evident in patients aged 70–79 years at the time of the PCa diagnosis. CSS and survival from any cause other than PCa was also enhanced in subjects in this age group undergoing primary observation. By contrast, a smaller difference was observed between patients undergoing either ADT or primary observation with respect to PCSM, while a clear difference was not seen for other-cause mortality in elderly patients (> 80 years). Subjects in this age group undergoing primary observation had better CSS (but not other-cause survival) than those managed with primary ADT.

An increased risk of PCSM was observed in patients undergoing primary ADT, compared to those managed with primary observation, while a decrease in the risk of other-cause mortality was seen in the younger patient group with primary observation. This suggests that in recent times, primary ADT without curative treatment was generally selected for patients with aggressive disease. A 10-year three-fold risk of PCSM was associated with poorly differentiated PCa among patients with conservatively managed localized PCa in the Surveillance, Epidemiology, and End Results (SEER) Program (13). Most male patients with conservatively managed localized PCa, aged > 66 years with competing co-morbidities died

from causes other than PCa at 10 years, irrespective of age and tumor aggressiveness [14]. The use of primary ADT was also beneficial for patients with aggressive disease and few co-morbidities (14).

Unfortunately, information was missing on patients' co-morbidities in the current study. However, other-cause mortality was reduced in subjects treated with observation rather than ADT. It was assumed that a treatment shift, from ADT to a more radical treatment, may have occurred for patients with good general health status. Since an increasing number of PCa cases have been diagnosed in recent years, and observation is widely utilized in Finland, it is likely that observation was selected for patients with less aggressive histology and without advanced disease. Consequently, fewer male patients died of cancer owing to the slow, natural disease course.

Survival from other-cause mortality (apart from PCa) was diminished in patients aged 70–79 years initially treated with ADT in the current study. It is still difficult to draw a conclusion from this finding owing to the absence of data on patient co-morbidities. However, increased morbidity and mortality from ADT-related side-effects was possible. Thus, the survival benefits of ADT are partly offset by its wide toxicity.

Many population-based analyses suggest that gonadotropin-releasing hormone (GnRH) agonist use is associated with a greater risk of coronary artery disease, myocardial infarction, and diabetes mellitus (DM) (15–17). Subsequent reports have suggested that male patients with co-morbidities or prior cardiovascular disease treated with GnRH agonists might be at increased risk of cardiovascular mortality (18, 19). Based on these observations, a science advisory consensus statement on GnRH agonist therapy and cardiovascular risk was issued, together with a U.S. Food and Drug Administration safety warning to address concerns of increased risk of myocardial infarction, stroke, sudden cardiac death, and DM [(20). However, conflicting results have been reported. In a recent meta-analysis, ADT use was not associated with an increased risk of cardiovascular death, but with a lower risk of PCSM and all-cause mortality (21). Studer et al. also reported that ADT for localized PCa may even reduce cardiovascular mortality if started immediately after diagnosis (22).

The current study findings did not support the life-prolonging effects of primary ADT for localized PCa. Several reports have shown similar results: In a prior population-based cohort study on 66717 Medicare patients diagnosed between 1992 and 2009, and who received no definitive local therapy within 180 days of prostate cancer diagnosis, primary ADT was not associated with improved overall long-term CSS or the CSS of patients with localized PCa (23). Instead, there is evidence that primary ADT led to inferior outcomes [24]. Low overall survival rates were reported for male patients with localized disease treated with primary ADT rather than observation in a previous population-based study (24). In addition, Potosky et al. reported that primary ADT was neither associated with an enhanced risk of all-cause mortality (hazard ratio [HR] of 1.04, 95% CI: 0.97–1.11) nor PCa-specific mortality (HR of 1.03; 95% CI: 0.89–1.19) after adjusting for the sociodemographic and clinical characteristics of patients with localized PCa. However, primary ADT was associated with a decreased risk of all-cause mortality, but not PCSM, among patients at high risk of PCa progression (25).

PSA screening practices have increased exponentially over a 30-year period, and regular PSA testing is used frequently among all socioeconomic groups in Scandinavia and Finland (26, 27). In the early years of the present study, a diagnosis of localized PCa was generally performed via a digital rectal examination or using pathological specimens obtained following a transurethral resection of the prostate. In recent years, most localized PCa cases have been diagnosed by prostate biopsies prompted by elevated PSA values. Moreover, although a proven benefit of the PSA screening of older males has not been shown, PSA testing is frequently performed for elderly patients (28). The wide-stage migration of PCa from advanced to indolent disease has been reported over ≥ 20 years (29). Thus, a commonly employed but poorly organized screening policy explains the increased rate of PCa in past decades in Finland. Consequently, the number of elderly male patients with PCa has also increased. This implies that the more favorable outcomes associated with the use of primary observation compared to ADT in patients with PCa, especially those in their 70s, can be attributed to PSA-related “lead time” rather than life extension. However, this was difficult to determine in the absence of information on PSA testing or screening of the present study cohort.

The current study had several limitations. Information was not captured on patient co-morbidities and detailed PCa characteristics (i.e., Gleason scores and PSA values), so it was not possible to adjust for differences in morbidity and mortality with a potential link to ADT. Thus, study outcomes in terms of PCSM and CSS could not be compared between the different groups. Also, the absence of data on patient co-morbidities and PCa characteristics was a major study limitation. It was not possible to determine who would benefit from primary ADT in localized PCa. However, propensity score matching, particularly when applied to socioeconomic status, might have mitigated some of the co-morbidity-based limitations. Detailed information on cancer treatment was also incomplete for both study treatment groups. Although men in the observation treatment group did not receive ADT or radical treatment in the four months following diagnosis, it was thought that some of them might have received treatment later. This limitation could have had a substantial effect on the study outcomes. Furthermore, although the current study population included patients with localized PCa, the reliability of staging procedures over time is debatable. TNM staging of the study population was based on mandatory reports obtained from hospitals and pathological laboratories. In other words, clinical practices in Finland were governed by national and/or European prostate cancer guidelines at the time. Consequently, the risk of metastases was evaluated according to these guidelines. It was assumed that this information was as valid as that of any registry information containing data for up to > 30 years from now.

Notwithstanding these limitations, the study had several strengths. Few data compare primary ADT with conservative treatment or any other established treatment option in patients with localized PCa. Furthermore, population-based cohorts yield important information about PCa treatment in real-life situations as the populations in randomized controlled trials are selected using stringent criteria. However, also in population-based studies patients are allocated to different treatments, and the results interpreted from those can be subject to errors when co-morbidities are involved. From an epidemiological perspective, these data define the Finnish results obtained for patients treated with primary ADT or observation. This study was based on nationwide data for PCa and incorporates close to 100% of

patients in Finland over a nearly 30-year period. Previous population-based results from Finland on this subject have not been published. Similar complete population-based coverage is not available in many European countries.

Conclusion

The risk of PCSM was shown to increase in patients aged > 70 years with localized PCa and with primary ADT in the current study. Primary ADT outcomes were compared with observation-only outcomes from 1985–2014. Other-cause mortality (other than PCa) declined during this time, especially in subjects in their 70s treated with primary ADT. Thus, conservative management is considered to be a valid option for localized PCa if treatment with curative intent is not possible. However, the current study results may have been affected by patient selection or intention to treat as a consequence of general health and healthcare service-related factors.

Abbreviations

ADT = androgen deprivation therapy

PCa = prostate cancer

RR = relative risk

PCSM = prostate cancer-specific mortality

CSS = prostate cancer-specific survival

Declarations

Ethics approval and consent to participate: The study protocol was approved by the institutional review board of the Hospital District of Southwest Finland (Study number: ETMK:116/1802/2014).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: AK, PB, NM and JP designed the study. HS and KS made the data acquisition. KS, HS and JP analyzed and interpreted the data regarding the prostate cancer and androgen deprivation therapy. HS, AK and NM wrote the manuscript draft. AK, NM, JP, PB revised the text for important

intellectual content. AK, PB and NM supervised the work. All authors read and approved the final manuscript.

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Tables

Table 1. Study population of prostate cancer patients

Sample	All patients				Matched pairs			
	ADT		Observation		ADT		Observation	
	N	%	N	%	N	%	N	%
Age at diagnosis								
18-24	3096	(31.9)	2850	(41.7)	2135	(37.4)	2190	(38.3)
25-34	3411	(35.2)	2215	(32.4)	2006	(35.1)	1951	(34.1)
35-44	2170	(22.4)	1227	(18.0)	981	(17.2)	1078	(18.9)
45-54	832	(8.6)	438	(6.4)	487	(8.5)	399	(7.0)
55-64	195	(2.0)	100	(1.5)	106	(1.9)	97	(1.7)
Total	9704	(100)	6830	(100)	5715	(100)	5715	(100)
Year of diagnosis								
1989	785	(8.1)	208	(3.0)	237	(4.1)	200	(3.5)
1994	1197	(12.3)	337	(4.9)	295	(5.2)	332	(5.8)
1999	1724	(17.8)	797	(11.7)	866	(15.2)	788	(13.8)
2004	2159	(22.2)	1313	(19.2)	1190	(20.8)	1268	(22.2)
2009	2280	(23.5)	2194	(32.1)	1765	(30.9)	1801	(31.5)
2014	1559	(16.1)	1981	(29.0)	1362	(23.8)	1326	(23.2)
Total	9704	(100)	6830	(100)	5715	(100)	5715	(100)
Education level								
Below primary	6920	(71.3)	4421	(64.7)	3752	(65.7)	3854	(67.4)
Primary	1325	(13.7)	1074	(15.7)	982	(17.2)	895	(15.7)
Lower secondary	1459	(15.0)	1335	(19.5)	981	(17.2)	966	(16.9)
Total	9704	(100)	6830	(100)	5715	(100)	5715	(100)
Regional district								
Uusmaa	932	(9.6)	786	(11.5)	595	(10.4)	628	(11.0)
Uusiki	812	(8.4)	698	(10.2)	476	(8.3)	521	(9.1)
Uus-Suomi	835	(8.6)	628	(9.2)	499	(8.7)	591	(10.3)

unta	500	(5.2)	281	(4.1)	309	(5.4)	273	(4.8)
-Hame	471	(4.9)	322	(4.7)	304	(5.3)	299	(5.2)
maa	1187	(12.2)	614	(9.0)	587	(10.3)	595	(10.4)
-Hame	668	(6.9)	304	(4.5)	316	(5.5)	291	(5.1)
laakso	433	(4.5)	182	(2.7)	269	(4.7)	164	(2.9)
Karjala	321	(3.3)	179	(2.6)	231	(4.0)	164	(2.9)
Savo	158	(1.6)	102	(1.5)	86	(1.5)	77	(1.3)
vo	76	(0.8)	64	(0.9)	42	(0.7)	47	(0.8)
is-Karjala	149	(1.5)	178	(2.6)	134	(2.3)	119	(2.1)
is-Savo	466	(4.8)	403	(5.9)	334	(5.8)	319	(5.6)
Suomi	374	(3.9)	557	(8.2)	249	(4.4)	276	(4.8)
Pohjanmaa	522	(5.4)	386	(5.7)	316	(5.5)	348	(6.1)
	285	(2.9)	182	(2.7)	162	(2.8)	160	(2.8)
Pohjanmaa	136	(1.4)	128	(1.9)	87	(1.5)	90	(1.6)
is-Pohjanmaa	610	(6.3)	372	(5.4)	311	(5.4)	354	(6.2)
u	265	(2.7)	99	(1.4)	87	(1.5)	92	(1.6)
Pohja	280	(2.9)	132	(1.9)	140	(2.4)	115	(2.0)
	190	(2.0)	177	(2.6)	148	(2.6)	160	(2.8)
	34	(0.4)	56	(0.8)	33	(0.6)	32	(0.6)
	9704	(100)	6830	(100)	5715	(100)	5715	(100)

ADT= androgen deprivation therapy, N=number

Table 2. Risk for prostate cancer and other-cause mortality among men with primary androgen deprivation therapy compared to observation only based on propensity matched pairs

Time period (age)	Relative risk for PCa mortality (95% CI)		Relative risk for mortality from other-causes than PCa (95% CI)	
	ADT	Observation	ADT	Observation
1985-1994 (70-79y)	1.70 (1.29- 2.23)	1.00 (ref)	1.22 (1.00-1.49)	1.00 (ref)
1995-2004	1.55 (1.31- 1.84)	“	1.07 (0.97-1.18)	“
2005-2014	2.71(2.08- 3.53)	“	1.03 (0.92-1.16)	“
1985-1994 (>80y)	1.30 (0.89- 1.88)	“	1.09 (0.85-1.39)	“
1995-2004	1.49 (1.13- 1.97)	“	1.05 (0.92-1.20)	“
2005-2014	1.65 (1.19- 2.29)	“	1.06 (0.91-1.23)	“

Test for treatment effect on prostate cancer specific mortality between age groups;
p=0.083

PCa= prostate cancer, CI=confidence interval, ADT=androgen deprivation therapy.
ref=reference

Table 3. Prostate cancer-specific and other-cause 5-year and 10-year survival percentages

Variable			All patients				Matched pairs			
			ADT		Observation		ADT		Observation	
			CSS	Other-cause	CSS	Other-cause	CSS	Other-cause	CSS	Other-cause
Year of diagnosis	Age at diagnosis									
1985-1994	70-79y	5-year survival-% (95%CI)	77 (74-79)	67 (65-70)	83 (78-87)	75 (70-79)	77 (72-82)	70 (65-75)	83 (78-87)	75 (70-79)
		10-year survival-% (95%CI)	52 (48-56)	36 (33-39)	69 (63-74)	46 (40-51)	53 (46-59)	39 (32-45)	69 (63-75)	46 (40-52)
1995-2004		5-year survival-% (95%CI)	89 (87-90)	76 (74-78)	94 (93-95)	81 (78-82)	89 (87-90)	77 (75-79)	94 (93-95)	80 (78-82)
		10-year survival-% (95%CI)	75 (73-77)	50 (48-52)	86 (84-88)	55 (52-57)	76 (74-79)	51 (48-54)	86 (83-88)	54 (51-57)
2005-2014		5-year survival-%(95%CI)	93 (91-94)	80 (79-82)	97 (96-98)	82 (80-83)	93 (91-94)	81 (79-83)	97 (96-98)	81 (79-83)
		10-year survival-%(95%CI)	82 (79-85)	53 (49-56)	93 (91-94)	56 (52-59)	82 (79-85)	55 (51-59)	93 (90-94)	54 (50-58)
1985-1994	>80y	5-year survival-%(95%CI)	66 (61-70)	47 (43-51)	69 (60-76)	49 (41-57)	64 (55-72)	43 (35-51)	69 (60-76)	48 (40-56)
		10-year survival-%(95%CI)	40 (33-47)	13 (10-17)	45 (33-57)	13 (7-20)	36 (22-50)	10 (5-17)	48 (35-59)	12 (7-19)
1995-2004		5-year survival-%(95%CI)	83 (80-85)	49 (46-52)	86 (82-89)	53 (48-57)	81 (77-85)	48 (44-53)	87 (83-90)	53 (48-57)
		10-year survival-%(95%CI)	64 (59-68)	18 (16-21)	74 (68-79)	19 (15-22)	60 (53-66)	18 (15-22)	75 (69-80)	19 (15-22)
2005-2014		5-year survival-%(95%CI)	86 (84-89)	57 (54-60)	93 (90-95)	60 (57-64)	86 (83-89)	58 (53-61)	93 (90-95)	60 (56-63)
		10-year survival-%(95%CI)	69 (60-76)	17 (13-22)	73 (59-83)	21 (15-28)	69 (60-77)	17 (11-24)	70 (50-83)	18 (11-27)

CI=Confidence interval, ADT= androgen deprivation therapy, CSS=cause specific survival (i.e., prostate cancer)

Figures

Age at diagnosis 70-79

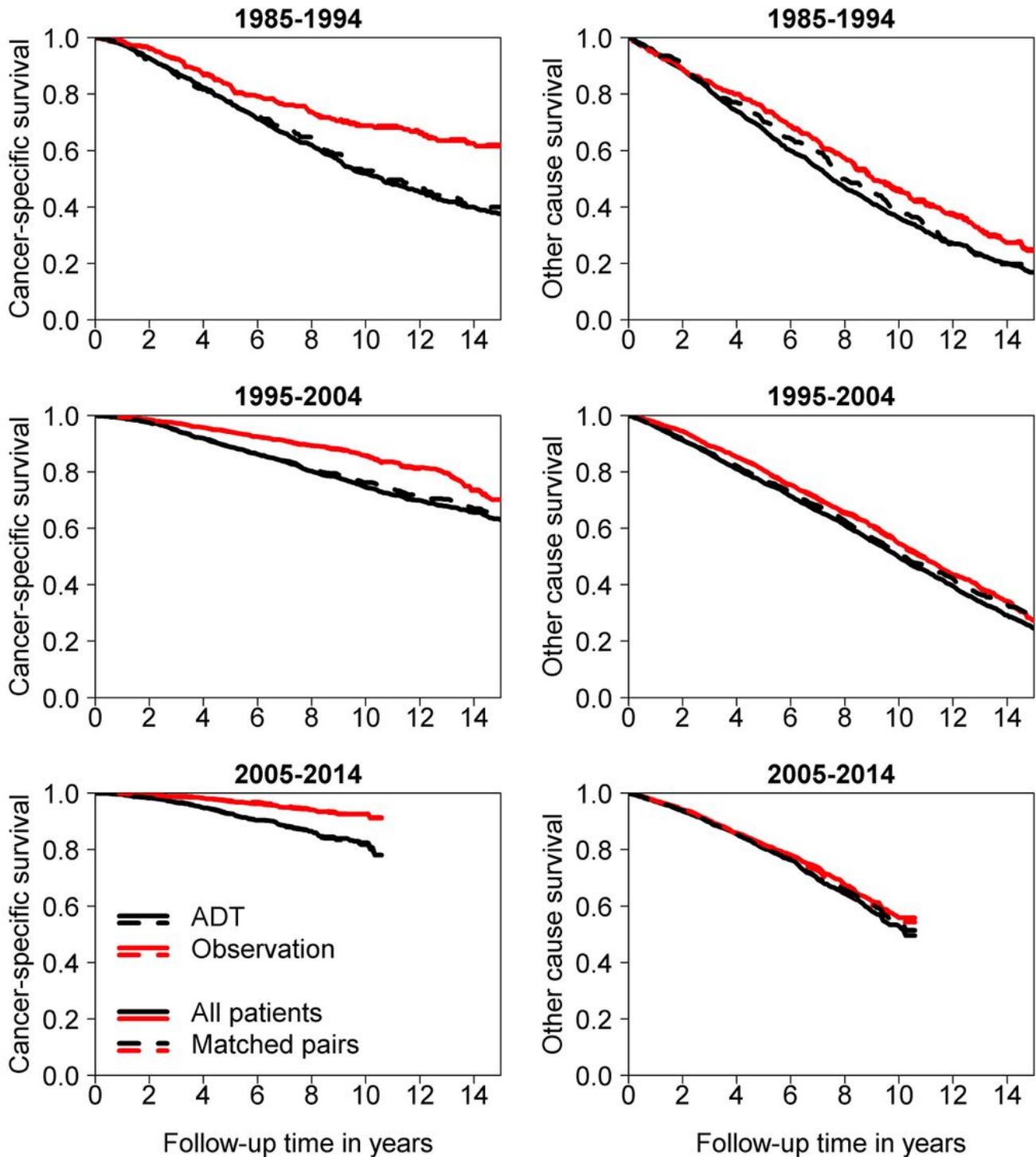


Figure 1

Cancer-specific and other-cause specific survival among men between 70-79 years of age

Age at diagnosis 80+

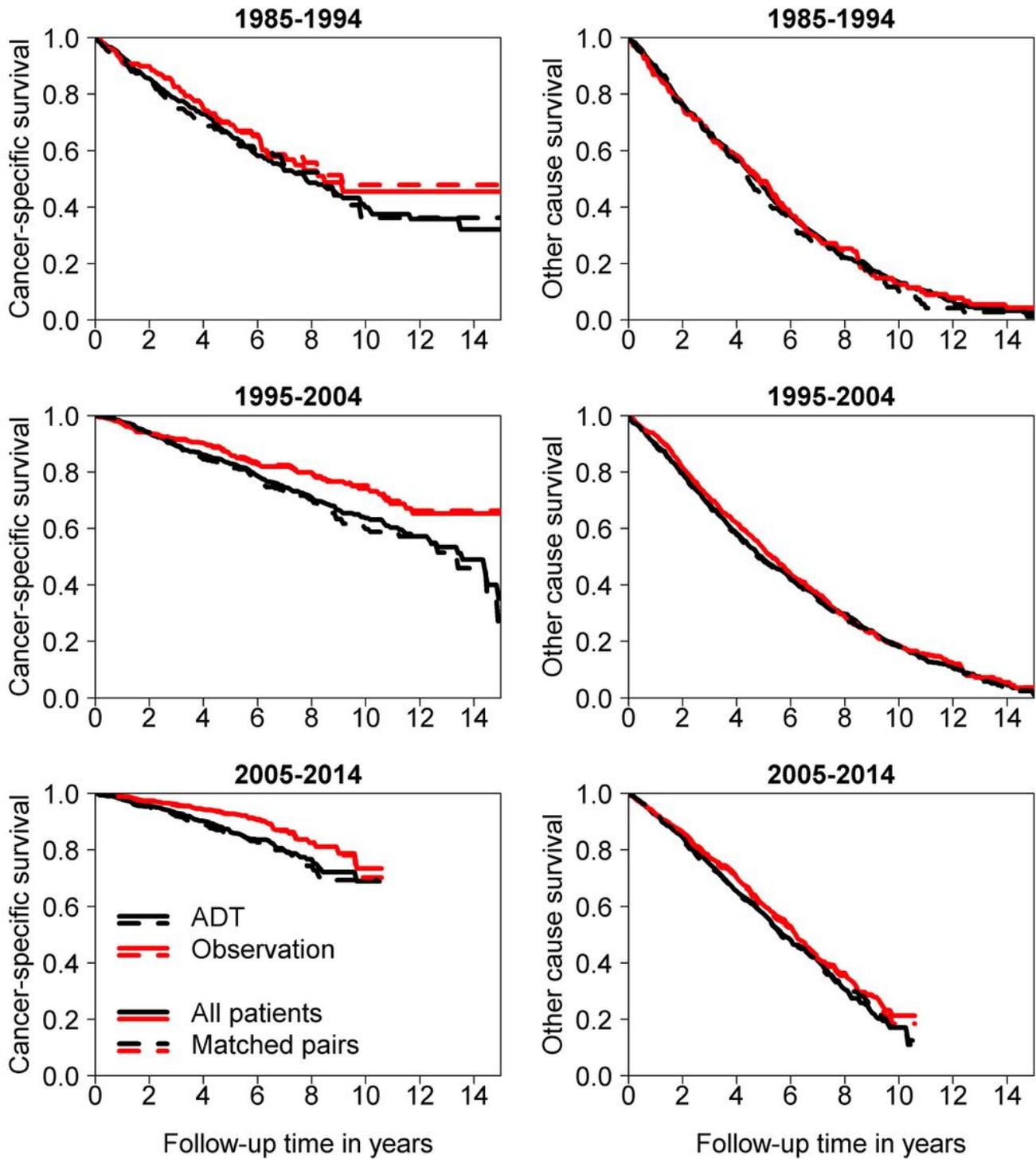


Figure 2

Cancer-specific and other-cause specific survival among men of 80 years and older