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ORIGINAL ARTICLE

Fifteen-year mortality after radical prostatectomy: Which factors are available for patient counselling?

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Abstract

Objective. The aims of this study were to establish 15-year postprostatectomy prostate cancer-specific mortality (PCSM), explore the time to prostate-specific antigen (PSA) relapse and identify clinically available prognostic factors. *Material and methods.* From 1987 to 2004, 309 men (median age 62 years, range 40–74 years) were prostatectomized for localized prostate cancer at a tertiary referral cancer centre. Slightly modified D'Amico risk groups were identified. PSA relapse was defined as PSA ≥ 4 μg/l before 2000, and thereafter as PSA > 0.2 μg/l. Radical prostatectomy (RP) 3–12 months after diagnosis represented "deferred" RP. PCSM was assessed with competing risk modelling. The level of significance was set at $p < 0.05$. *Results.* After a median of 12 years, 41 men were dead from prostate cancer and 68 due to other causes [15-year PCSM 15%, 95% confidence interval (CI) 10–19%], with no significant difference in PCSM between the low- and intermediate-risk groups, and the "conventional" high-risk group having 24% PCSM (95% CI 16–32%). PCSM was 33% (95% CI 20–46%) for men with two high-risk factors. The median time to PSA relapse ($n = 152$) was 5 (range 0–17) years, with a median of 7 (range 0–17) years' survival thereafter. Deferral of RP for up to 1 year had no impact on PCSM for all patients combined. *Conclusions.* Approximately one in seven men with localized prostate cancer, prostatectomized before the PSA era, will die from the disease within the 15 years post-RP. Men with two high-risk criteria have a particularly poor prognosis. After PSA relapse the median survival is 7 years. The data on deferral of RP need confirmation, taking into account risk group allocation.

Key Words: *Biochemical relapse, prostate cancer, 15-year prostate-specific survival.*

Introduction

To an increasing degree, patients with prostate cancer considering radical prostatectomy (RP) ask for detailed information about their risk of relapse and their post-RP survival chances. During patient counselling the responsible doctor considers pre-RP available factors with impact on prostate cancer-specific mortality (PCSM), overall mortality and the risk of prostate-specific antigen (PSA) relapse. After receiving such information patients may need weeks or even months to reach their final decision about their treatment. Considering referral routines and hospital resources more time may elapse before they can be operated. Thus, the question arises as to whether such deferral of RP negatively impacts on the final outcome. Finally, some prostatectomized patients with biochemical relapse will ask for information about their chances of subsequent survival.

Several groups have published 10- or 15-year post-RP PCSM rates [1–9] showing that post-RP deaths from prostate cancer only exceptionally occur during the first 5 years and that PCSM continues to rise even after 10 years. Therefore, meaningful interpretation of PCSM requires follow-up of at least 10 years. Furthermore, 10-year PCSM rates vary from below 3% (1- to 6–8% (4,6), with 15-year rates approaching 15% [7,8]; these percentages depend, among other things,

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Table I. Risk group allocation used in the current study.

Conventional risk group	DRE		PSA (μg/l)		Gleason score
Low	No or unilateral tumour ("T1" or "T2 one-sided")	*and*	< 10	*and*	≤ 6
Intermediate	T1 or T2 one-sided or bilaterally palpable tumour ("T2 two-sided")	*and*	10–20	*and/or*	7a or 7b
High	T1 or T2	*and*	> 20	*and/or*	8–10

DRE = Digital rectal examination.
[a]7a = Gleason grade 3 + 4; 7b = Gleason grade 4 + 3.

on the calendar year of RP, use of opportunistic PSA testing and risk group distribution [5].

In Norway, opportunistic PSA testing has become increasingly popular since 1996 [10]. In 2000 only approximately 10% of Norwegian men underwent a PSA test. This figure increased to about 15% in 2005. Before the late 1990s the performance of RP represented an exception rather than the routine curative treatment of prostate cancer patients. At the Norwegian Radium Hospital (NRH) RPs have been performed since 1987, enabling mature assessment of 15-year survival. Although the results of such analyses may not be completely comparable to RP series in the PSA era, emerging observations may provide information useful for counselling today's patients, not least those men with newly diagnosed prostate cancer from countries in which widespread PSA screening is still rare.

Against this background, this observational long-term study presents overall mortality, PCSM and data related to PSA relapse in patients who had undergone RP at the NRH up to 25 years previously. The aim was to confirm well-known prognostic factors, but also to identify new parameters to be used during pre-RP counselling and in patients who experience a PSA relapse.

Material and methods

The cohort comprised men with prostate cancer who underwent open retropubic prostatectomy at the NRH, a tertiary referral comprehensive cancer centre, between 1987 and 2004. The first author (HW) was responsible for treatment and follow-up. Based on a retrospective review of the medical records, the indications for RP were the diagnosis of an intraprostatic tumour without known metastases, life expectancy of at least 10 years and age less than 75 years. The individual preoperative PSA value and histological grade (World Health Organization grading at that time) did not contribute to the selection criteria. All available histological material was revised in 2007 by a uropathologist reporting the biopsy Gleason score. Based on preoperative examinations (digital rectal examination under general anaesthesia, PSA and Gleason score), the patients were allocated to one of three "conventional" risk groups [5], with slight modifications to the current European Association of Urology guidelines (www.uroweb.org) as to palpability of the primary tumour. These modifications are shown in Table I.

RP was performed through a suprapubic incision preceded by obturator lymph-node dissection in patients with PSA greater than 10 μg/l if perioperatively taken lymph-node biopsies were tumour free.

The patients had a follow-up visit 1–3 months after RP and were thereafter followed up by the first author or, for geographic reasons, by a local urological unit in the country with regular reports to the first author. Adjuvant radiotherapy and/or hormone treatment was not routinely applied. but was started in cases of postoperative PSA elevation and/or demonstration of metastases.

PSA was determined by the Hybritech Tandem–PSA method until 1993, followed by a Wallac Prostatus PSA free/total kit (1993–1995), and an in-house immunofluorometric assay from 1995 [11], both calibrated against Stanford PSA calibrators and performed on the AutoDELFIA automated system. Before 2000, PSA relapse was defined by a PSA value above 4 μg/l and rising levels thereafter. Along with the introduction of more sensitive PSA analyses this cut-off value was gradually reduced, and has been 0.2 μg/l since 2002.

In patients operated within 12 months since diagnosis, deferred RP was defined as RP performed more than 3 months since diagnosis, but before 12 months had elapsed.

Statistics

Continuous data are described with medians and ranges, and categorical variables with proportions and percentages.

SPSS (PC version 18) with Mann–Whitney test was used to assess differences. Differences between categorical data were calculated by the chi-squared test. The National Cause of Death Registry provided the date and underlying cause of death. When modelling time to event data, Kaplan–Meier methodology was used for overall mortality, adjusted for competing risk modelling for PCSM and PSA

Table II. Patient characteristics (n = 309).

(a) Before prostatectomy	
Age at RP (years)	62 (40–74)
≤ 65	211 (68)
> 65	98 (32)
Extent of primary tumour	
No palpable tumour	29 (9)
Tumour palpable in one lobe (T1/T2a)	96 (30)
Tumour palpable in both lobes (T1/T2a)	184 (58)
Preoperative PSA (μg/l)	11 (0.5–96)
< 10	146 (47)
10–20	91 (29)
> 20	71 (23)
Missing	1
Gleason	
≤ 6	70 (23)
7a	98 (32)
7b	55 (18)
8–10	85 (28)
Missing	1
Risk group	
Low	12 (4)
Intermediate	174 (56)
High	121 (39)
1 Risk factor	89
2 Risk factors	32
Missing	2 (1)
Time from initial diagnosis to RP (months)	3 (1–65)
≤ 3	127 (41)
> 3 to < 12	164 (53)
≥ 12	18 (6)
(b) Postprostatectomy follow-up	
Observation time since RP (years)	
All	12 (0–22)
Vital status at 31 December 2010	
Alive	200
Dead	109
Prostate cancer	41
Other causes	68
PSA relapse	
No	157 (51)
Yes	152 (49)
Years to PSA relapse (n = 152)	4.8. (0.2–16.7)
Years from PSA relapse to date of last observation	7.3 (0.2–17.3)

Data are shown as n (%) or median (range).
RP = radical prostatectomy; PSA = prostate-specific antigen.

relapse. The results are presented as cumulative incidences with 95% confidence intervals (CIs). The differences between groups regarding crude overall survival were assessed using the log-rank test. The effect of selected covariates was assessed using competing risk modelling [12]. The follow-up time was calculated from the date of RP or PSA relapse until death or 31 December 2010, whichever came first. Time to PCSM after PSA relapse was defined from the date of PSA relapse. A p value less than 0.05 was considered statistically significant. These analyses were performed using Stata, version 11.

Ethics

The study was approved by the ethics committee of the South-East Health Region in Norway.

Results

From 1987 to 2004, 349 patients underwent retropubic RP at the NRH and 309 of these (89%) were found to be eligible for the present study. Their median age at RP was 62 years (range 40–74 years) and 211 men (68%) were aged 65 years or younger (Table II). Only 32 patients (10%) were diagnosed after 2000. The "conventional" high-risk group consisted of 121 men. The median preoperative PSA was 11 μg/l (range 0.5–96 μg/l). None of the patients was lost to follow-up for the endpoints in question.

After a median observation time of 12 years (range 0–22 years), 200 patients were alive, 41 had died of prostate cancer and 68 were dead due to other causes, resulting in a 15-year PCSM rate of 13.8% (95% CI 9.7–18.6%) and a overall mortality rate of 48.8% (95% CI 41.2–55.9%), the latter displaying significant differences between the two age categories, 65 or younger versus older than 65 years. Compared to older men, significantly fewer patients aged 65 or younger died from causes other than prostate cancer, with no difference related to PCSM (Figure 1a–c).

Statistically significant differences emerged for patients with Gleason scores of 7a or lower compared to Gleason scores of 7b or above (Figure 2a). Men with PSA greater than 20 μg/l and those with bilaterally palpable tumours had the poorest outcome ($p < 0.05$) (Figure 2b,c). Significantly different PCSM outcomes were observed for the "conventional" high-risk group compared to the intermediate- or low-risk group (Figure 2d), with only eight prostate cancer deaths among 196 men at 15 years in the combined low/intermediate group. This finding and suspected heterogeneity in the high-risk group led to the definition of three new risk groups: "new low-risk": combined low/intermediate group; "new high-risk": PSA ≥20 μg/l *or* Gleason score 8–10; and "very-high-risk": PSA greater than 20 μg/l and Gleason 8–10, leading to significantly different PCSM outcomes, the figures being 3.8%, 15.7%, and 32.7%,

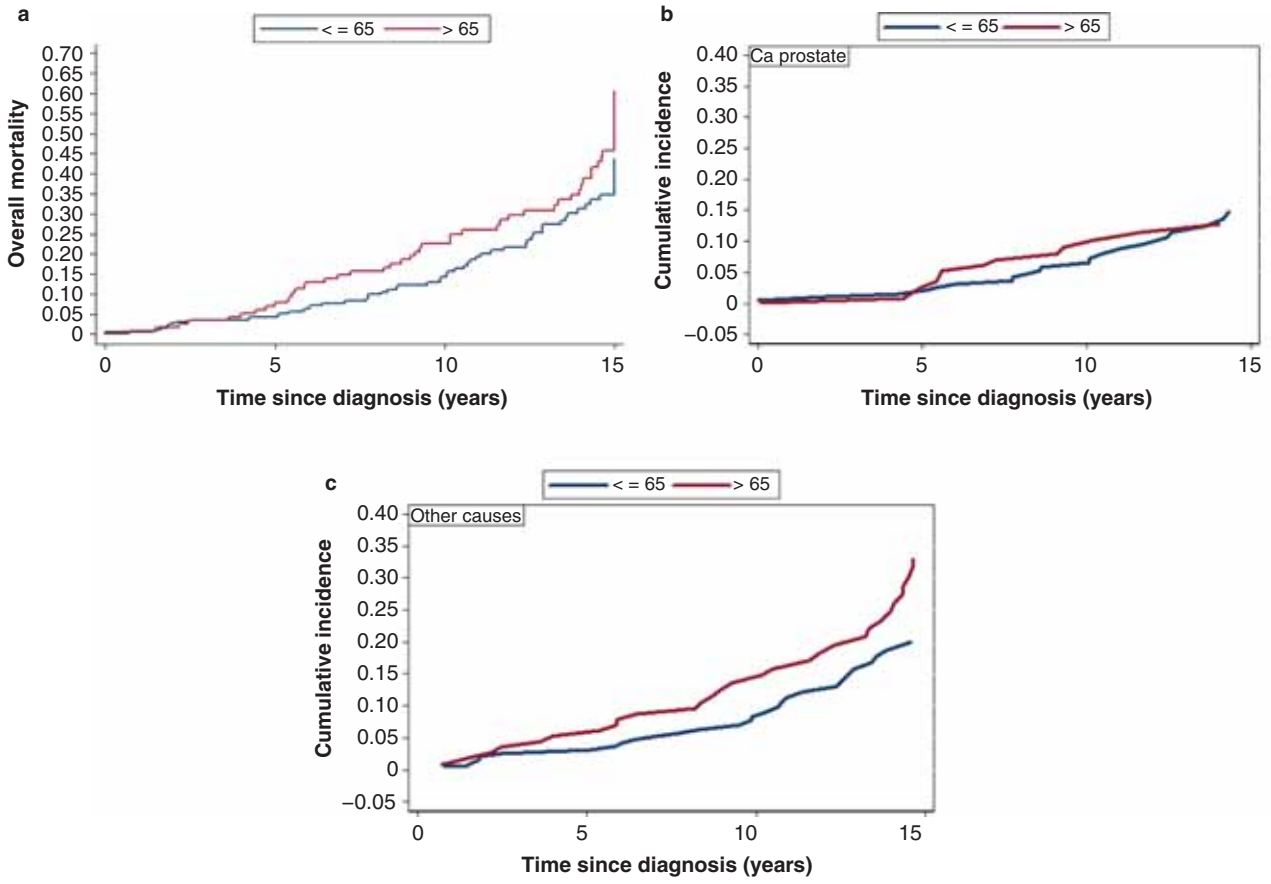

Figure 1. Fifteen-year postprostatectomy mortality and age ($n = 309$): ≤ 65 years ($n = 211$) and > 65 years ($n = 98$). (a) Overall mortality: 48.8% (95% confidence interval 34.9–53.8%) vs 60.8% (50.0–71.7%), $p = 0.028$; (b) prostate cancer-specific mortality: 12.7% (97.1–20.1%) vs 14.7% (9.2–21.4%); (c) mortality due to other causes: 20.2% (13.6–27.3%) vs 33.0% (23.2–43.0%), $p = 0.04$.

respectively, for the new low-, new high- and very-high-risk groups (Figure 2e). Separation of all 15-year PCSM curves started around 5 years after RP.

PSA relapse was recorded in 152 patients after a median of 4.8 years (range 0.2–16.7 years), the 15-year rate for PSA relapse for patients in the new low-risk group being significantly lower than the relapse risk of the two new risk groups (Figure 3a). Of 12 patients in the conventional low-risk group three men developed a PSA relapse after 3, 6 and 7 years. No biochemical relapse was observed in six low-risk patients who survived for at least 10 years. After PSA relapse the median time to prostate cancer-specific death was 7.3 years (range 0.2–17.3 years). Patients from the very-high-risk group tended to have the poorest PCSM (Figure 3b).

Excluding 18 patients who underwent RP 12 months or longer since diagnosis (probably surveillance cases), deferral of RP for 3 and up to 12 months had no impact on the survival of 291 patients (Figure 4). In a Cox regression analysis including deferral of RP and the three new risk groups as covariates, deferral of RP for more or less than 3 months was not statistically significant. However, being a patient in the new high-risk and very-high-risk group remained significantly associated with worse PCSM compared to being allocated to the new low-risk group (data not shown).

Discussion

In this "personal" series of 309 patients diagnosed with localized prostate cancer before the PSA era and all operated on by the first author at a tertiary referral centre, approximately one out of seven men died from prostate cancer after a median postprostatectomy observation time of 12 years. After PSA relapse, observed in 152 men a median of 4.8 years after RP, the median overall survival was 7.3 years. The "conventional" high-risk group as defined by D'Amico et al. [5] is heterogeneous, as patients with both PSA greater than 20 μg/l and Gleason score 8–10 had a particularly poor prognosis compared with those presenting with only one risk factor. Postdiagnosis delay of RP for up to 1 year did not negatively impact on PCSM.

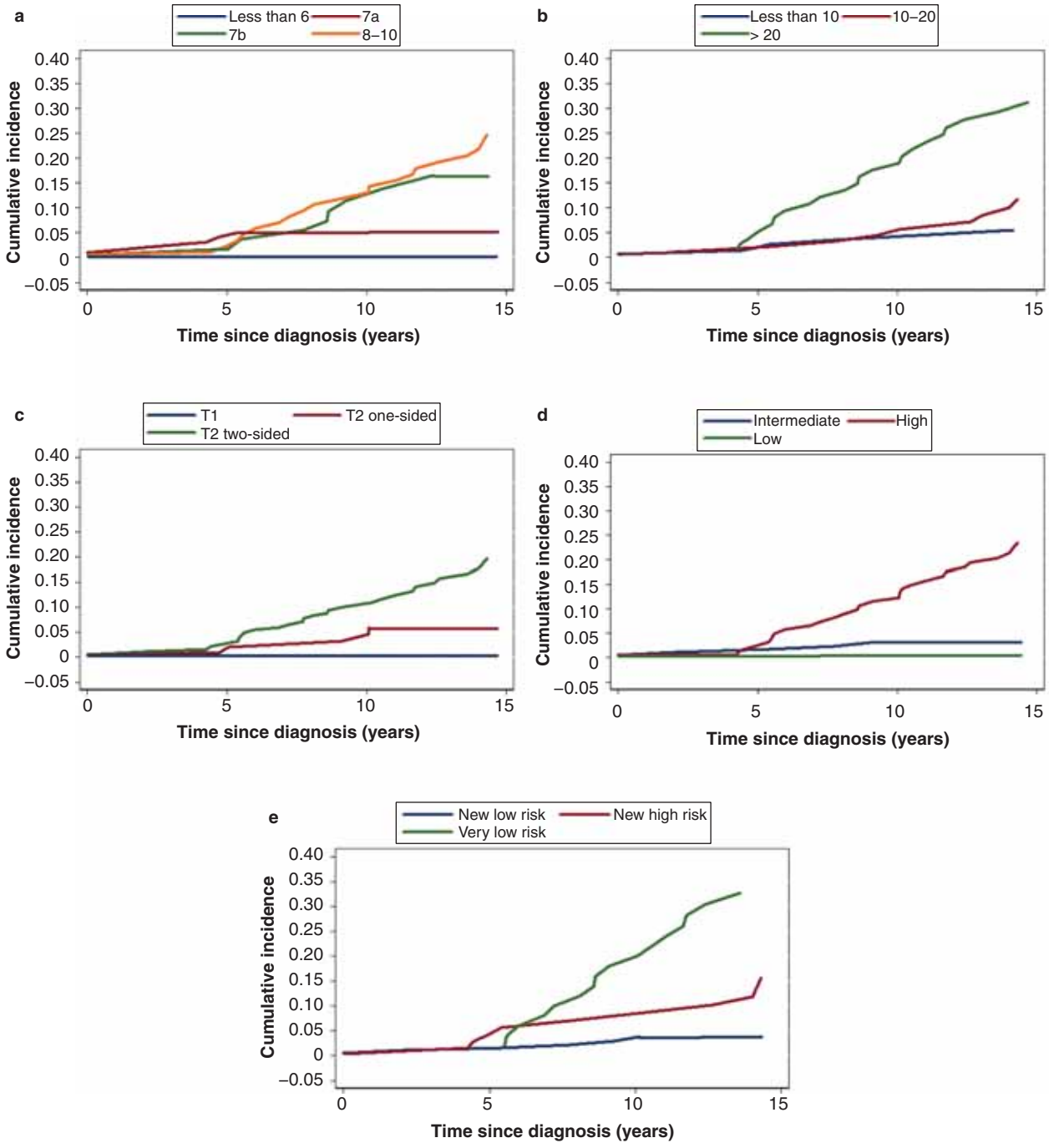

Figure 2. Fifteen-year prostate cancer-specific mortality rates according to: (a) biopsy Gleason score: ≤ 6, 2.4% (95% confidence interval 0.2–10.9%); 7a, 5.1% (1.9–10.7%); 7b, 16.5% (7.5–28.3%); 8–10, 24.7% (15.0–34.5%); (b) preoperative PSA (μg/l): < 10, 5.6% (1.9–11.8%); 10–20, 10.4% (4.8–18.7%); > 20, 28.7% (18.6–40.0%); (c) tumour category: T1, 0%; unilateral T2, 5.9% (2.2–12.3%); bilateral T2, 19.7% (13.5–26.8%); (d) D'Amico risk group: low, 0%; intermediate, 3.1% (1.1–6.8%); high, 23.5% (16.1–31.6%); and (e) new risk group: new low-risk (low plus intermediate risk), 3.8% (1.5–7.8%); new high-risk (Gleason score 8–10 *or* PSA > 20 μg/l), 15.7% (8.0–25.7%); very-high-risk (Gleason score 8–10 *and* PSA > 20 μg/l), 32.7% (20.1–45.9%).

The 15-year PCSM rate found here for all patients and after stratification according to conventional risk groups is comparable to the published post-RP series with 10-year or longer median observation times [7,8]. For the new low-risk group the 15-year PCSM rates are comparable to the 15-year prostate cancer-specific survival rates after radiotherapy without hormone manipulation published from the NRH by Berg et al. [13]. For the conventional high-risk group the presented 10-year PCSM rates are within

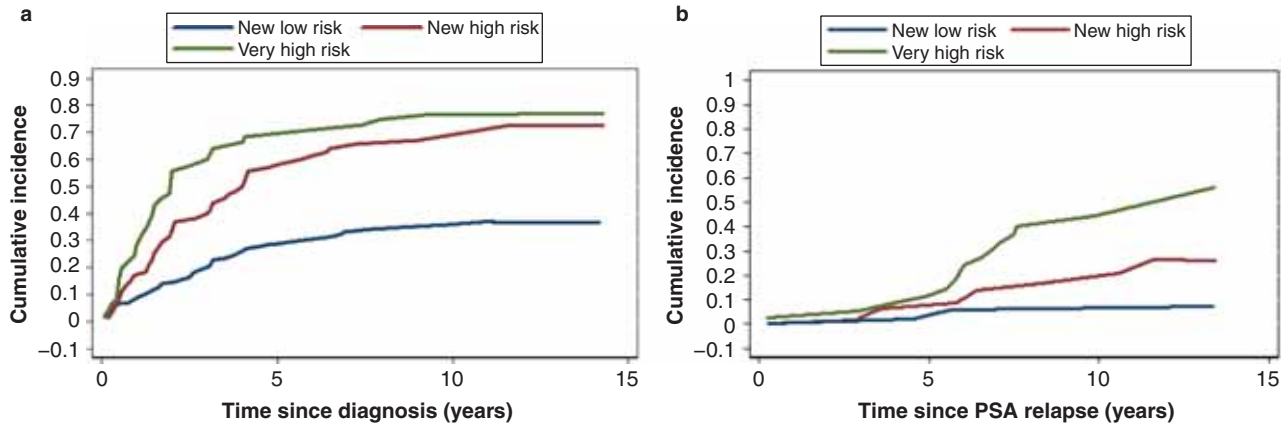

Figure 3. Rates of prostate-specific antigen (PSA) relapse and prostate cancer-specific mortality after PSA relapse according to new risk group: (a) PSA relapse: new low-risk, 37.1% (95% confidence interval 30.0–44.4%); new high-risk, 72.8% (59.5–82.4%); very-high-risk, 76.8% (62.1–86.4%); (b) prostate cancer-specific mortality: new low-risk, 5.7% (1.5–14.3%); new high-risk, 26.2% (12.0–43.7%); very-high-risk, 55.9% (29.3–75.9%). See legend to Figure 3 for definitions of new risk groups.

the ranges presented by several groups after radiotherapy combined with (neo)adjuvant androgen deprivation [1,14–16]. In the present series the number of patients in the conventional low-risk group is low (4%) as both cryotherapy and active surveillance were contemporary therapeutic options at the NRH and were selected by 124 and 167 men, respectively. The limited number of conventional low-risk patients may be one reason why no prostate cancer deaths were observed in this group and no significant difference in PCSM was found between the low- and intermediate-risk groups. This justified the combination of these two risk groups in the sample. In more modern RP series of asymptomatic men diagnosed through PSA testing, patients in the low-risk group represent 40–60% of the operated patients [1,17,18]. The high proportion of low-risk patients also explains the low long-term mortality rates in the more recent series. Even after PSA relapse the PCSM rates remain low for many years, as shown in the present series and also emphasized by Boorijan et al. [19]. However, PSA relapses have been recorded in 10% of the patients [1,14], meaning that one has to expect prostate cancer deaths during the second post-RP decade. These findings have impact for young patients presenting with a life expectancy of 20 years or more who present with low risk prostate cancer, though many of them might benefit from a surveillance strategy in the first place [20,21].

The modified tumour (T) classification used in this study is based on a preoperative digital rectal examination performed under general anaesthesia, as most patients were diagnosed before the PSA era in Norway. It is likely, therefore, that these patients presented with more advanced disease than today's patients, most of whom are diagnosed by PSA and present without a palpable prostatic tumour. Not least in series based on public registries, it remains sometimes doubtful whether all Gleason scores and all tumour categories truly represent preoperative variables, as also discussed by Abdollah et al. [22]. As the aim in the present study was to contribute to improve pre-RP information of patients, evaluable variables were only analysed preoperatively when assessing post-RP outcomes. In particular, for this reason no analysis of the emerging pT categories was carried out.

The present authors recognized the heterogeneity of the conventional high-risk group as did Pierorazio et al. [23]. In contrast to those authors and in an attempt to use strictly preoperatively available parameters, the present very-high-risk group was defined based only on preoperative PSA and biopsy Gleason, whereas Pierorazio et al. included the pT

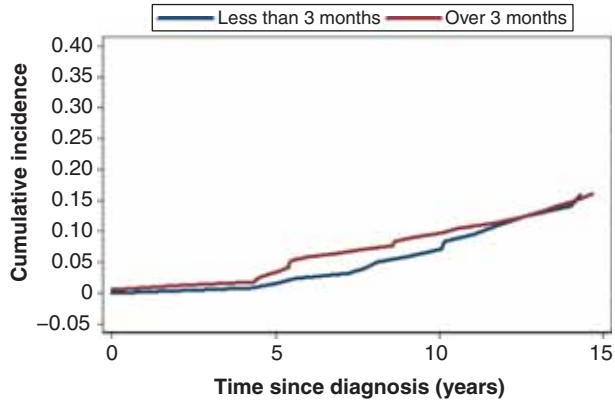

Figure 4. Deferred radical prostatectomy and 15-year prostate cancer-specific mortality rates: ≤ 3 months, 15.9% (95% confidence interval 8.8–24.7%); > 3 to < 12 months, 14.0% (8.8–20.4%).

and pN category in the very-high-risk group. Future analyses of larger series which also include cT3 tumours will have to prove or disprove the clinical value of the identification of a very-high-risk group among patients considered for RP.

During pretreatment counselling of prostate cancer patients PCSM is usually considered. However, many publications have documented that men in the age group of prostate cancer diagnoses have a non-neglectable and considerable risk of dying from competing causes. It is generally accepted that RP should be restricted to patients with a life expectancy of at least 10 years (www.uroweb.org), based on the view that any prostate cancer-specific survival benefit from RP emerges first after 8–10 years. The clinical benefit of RP in men with the risk of dying within the first post-RP decade from comorbid conditions is thus questionable, not least as most of them experience post-RP adverse effects with impact on quality of life [24]. Therefore, one should aim for an optimal balance between PCSM and overall, admitting that clinicians have difficulties predicting an individual's life expectancy based on available comorbidity scales [25].

In the authors' clinical experience, patients with newly diagnosed prostate cancer need some time to decide on their treatment. Other patients may be placed on the hospital's waiting list for RP. The finding of unaltered PCSM after up to 1 year post-diagnosis deferral of RP may therefore be clinically important, although the relatively low number of patients does not permit risk group stratification of this analysis. Korets et al. [26] published similar observations for patients in whom RP was deferred for up to 90 days. Neither could Holmstrøm et al. [27] detect significant differences in the presence of adverse pathological features or in PCSM comparing primary versus deferred RP in men with low/intermediate-risk prostate cancer. In contrast, Sun et al. recently showed that delay beyond 3 months may reduce the post-RP functional outcomes [28]. These findings and the present preliminary data showing impaired PCSM after deferral of RP in the conventional high-risk group warrant further evaluation of the impact of delayed RP on survival. Furthermore, clinicians should be aware of the psychological burden that delaying RP can place on the patient and his family.

This study primarily reflects the personal experience of the first author from a period when RP was not a widespread therapeutic option in the Nordic countries. The study has several limitations. First, Most of the patients were diagnosed before the era of opportunistic PSA screening in Norway. On the background of the prolonged life expectancy during the past decade in the general population and the increasing number of patients with T1c tumours, the question remains open whether these results are comparable to long-term survival rates in today's prostate cancer patients, who most often are diagnosed following PSA testing. The majority of them have non-palpable tumours (T1c), as opposed to only 9% in this cohort. Secondly, no information was available on pretreatment comorbidity impacting on overall mortality. Thirdly, a modified tumour categorization had to be applied. Finally, the endpoint "cause of death" is based on data from death certificates, with the well-known uncertainty about the validity of this information, particularly in older patients [29].

It may be regarded as a strength that the survival analyses were based on strictly preoperatively available variables, obtained in routine clinical practice, and on clinical data achievable at the time of PSA relapse. Together with the long follow-up, even after PSA relapse, these analyses provide clinical information which, in the authors' view, is valuable today for pretreatment counselling of new patients and those experiencing post-RP PSA increases. The data on the heterogeneity of the high-risk group are relatively new from a scientific point of view, but need confirmation in larger series.

Bearing in mind that the results are based on patients from the pre-PSA era, the authors nevertheless conclude that prostate cancer patients can be counselled about the excellent post-RP long-term overall mortality and PCSM dependent on risk group stratification. Furthermore, today's pretreatment counselling could probably be improved by taking into account results from magnetic resonance imaging [30]. Even after PSA relapse most patients survive for at least 7 years. The expected benefit of the operation must be balanced against the individual's risk of death from competing causes. A very-high-risk group needs to be separated from the conventional high-risk group. Deferral of RP for up to 12 months does not seem to increase PCSM. These two latter findings need confirmation in larger samples.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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