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Undertreatment of Men in Their Seventies with High-risk Nonmetastatic Prostate Cancer

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Abstract

Background: Many elderly men with high-risk nonmetastatic prostate cancer (HRnMPCa) do not receive radical treatment, despite the high mortality associated with conservative management.
Objective: To investigate how age and comorbidity affect treatment of men with HRnMPCa.
Design, setting, and participants: This was an observational nationwide register study during 2001–2012. We identified 19 190 men of <80 yr of age diagnosed with HRnMPCa in the National Prostate Cancer Register of Sweden and 95 948 age-matched men without prostate cancer in the register of the total population.
Outcome measurements and statistical analysis: The outcome was the proportion of men with HRnMPCa receiving radical treatment (radical prostatectomy or radiotherapy). Vital status and the Charlson comorbidity index (CCI) were obtained from nationwide registers. The 10-yr survival of men without prostate cancer, stratified by age and CCI, was used as a measure of the life expectancy of the men with prostate cancer.
Results and limitations: The proportions receiving radical treatment varied with life expectancy among men younger than 70 yr, whereas use of these treatments did not match the long life expectancy of men in their seventies with CCI 0–1. Only 10% of men aged 75–80 yr with CCI 0 received radical treatment despite 52% probability of 10-yr life expectancy, compared with approximately half of the men younger than 70 yr with a similar life expectancy. The use of radical treatment for HRnMPCa increased with time in all Swedish counties, but a threefold difference between counties remained in 2009–2012 for patients aged 70–80 yr with CCI 0-1. Uncertain external validity is a study limitation, and the impact of physician versus patient preferences on treatment selection could not be assessed.
Conclusions: Otherwise healthy men in their seventies with HRnMPCa were less likely to receive radical treatment than younger men with a similar life expectancy, although increasing use of radical treatment was observed during the study period. Our findings highlight the need for improved methods for clinical decision-making, including improved assessment of life expectancy.

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Patient summary: We performed a nationwide register study that showed that many healthy men in their seventies live for at least another 10 yr. Despite this long life expectancy, men in their seventies with high-risk nonmetastatic prostate cancer were often not treated with radical prostatectomy or radiotherapy, possibly because their life expectancy was underestimated. Our study highlights the need for improved clinical decision-making, which should incorporate an assessment of the patient's life expectancy.

1. Introduction

Radical prostatectomy and radiotherapy are commonly used in elderly men with low- or intermediate-risk prostate cancer [1–6] despite high-level evidence of the absence of a survival benefit within 10 yr [7–10]. Therefore, it is difficult to understand why so many men in their seventies with high-risk nonmetastatic prostate cancer do not receive treatment with curative intent [2,5,6,11]. Two randomised studies showed a survival benefit from radiotherapy in combination with androgen deprivation therapy for men with high-risk prostate cancer [12,13], with a similar effect for men younger and older than 67 yr [12]. The survival benefit is apparent within 6–8 yr after treatment [12,13]. Without curative treatment, the 10-yr cancer-specific mortality from high-risk prostate cancer is approximately 30%, including in men older than 75 yr at the time of their diagnosis [14].

It is possible that the results from the SPCG-4 study have contributed to the low use of treatment with curative intent among older men with high-risk prostate cancer [8,9]. Subgroup analysis in the first reports from the SPCG-4 study indicated that the positive treatment effect of radical prostatectomy was confined to men younger than 65 yr [8,9]. However, most men in the SPCG-4 study had intermediate-risk disease. Men with poorly differentiated or locally advanced prostate cancer were excluded, and the results from SPCG-4 can therefore not be used to guide treatment of men with high-risk disease [8]. Furthermore, in the final analysis of the SPCG-4 study, radical prostatectomy was associated with significantly lower risks of metastasis and androgen deprivation therapy for men older than 65 yr [10].

The number of elderly men affected by prostate cancer is rapidly increasing around the world [15,16], so optimisation of their treatment is essential. The International Society of Geriatric Oncology recently expressed concerns about undertreatment of healthy elderly men with high-risk prostate cancer [17]. They pointed out that individual health status rather than chronological age should guide treatment decisions [17].

One possible reason for the undertreatment of elderly cancer patients is that their life expectancy is underestimated [6,18]. The aim of the present study was to investigate how treatment decisions for men with high-risk nonmetastatic prostate cancer are influenced by age and comorbidity, and to determine whether the use of radical prostatectomy and radiotherapy is in accordance with patients' life expectancy.

2. Patients and methods

The Prostate Cancer Data Base Sweden (PCBaSe) 3.0 was created through record linkages between the National Prostate Cancer Register (NPCR) of Sweden and several other population-based, nationwide health care registers and demographic databases. The database has previously been described in detail [19]. The capture rate of the NPCR is 98% compared to the Swedish Cancer Register, to which registration is mandated by law [20]. Demographic data for men in PCBaSe Sweden were obtained from the register of the total population. Information on underlying and contributing causes and on the date of death was obtained from the cause of death register, which captures all deaths in Sweden. The quality and completeness of the Swedish national registers and databases are high, and notifications are regularly reviewed by Statistics Sweden. The overall agreement between the cause of death register and reviewed medical records is approximately 86% (95% confidence interval [CI] 85–87%) [21].

High-risk nonmetastatic prostate cancer was defined as prostate cancer with no evidence of metastasis (N0 or Nx, M0 or Mx) and at least one of the following three criteria: Gleason score 8–10, local clinical stage T3, or prostate-specific antigen (PSA) 20–49 ng/ml. The upper PSA limit was chosen because the Swedish guidelines did not recommend radical treatment in men with PSA $\geq$50 ng/ml during the time period studied. PCBaSe does not include information on subcategories T2a, T2b, and T2c for local clinical stage. Only 12 men registered in the NPCR aged $>$80 yr at the time of diagnosis were treated with radical prostatectomy or radiotherapy. We therefore restricted the analysis to men aged $<$80 yr. The study included men diagnosed between January 1, 2001 and December 31, 2012.

For each prostate cancer case in PCBaSe, we identified five men in the Swedish register of the total population who matched the cases for date of birth ($\pm$1 yr) and county of residence, but who were not diagnosed with prostate cancer. A total of 95 948 men without prostate cancer were identified and included in PCBaSe. Of these, 3608 were subsequently diagnosed with prostate cancer during follow-up. These latter men were censored at the time of diagnosis and were included in the life expectancy estimates only before the date of their prostate cancer diagnosis. All men were followed until death, emigration, or to December 31, 2012, whichever occurred first.

For each man in PCBaSe, a Charlson comorbidity index (CCI) on the date of diagnosis was constructed by grouping International Classification of Diseases (ICD) codes in the discharge diagnoses in the inpatient register, as previously described [22,23]. The prostate cancer diagnosis was not included in the CCI. The term *healthy men* is used for men with no registered comorbidity (CCI 0).

Differences among the 21 counties of Sweden and temporal trends in the use of radical prostatectomy and radiotherapy were also analysed. Radiotherapy was recommended in the Swedish guidelines as the

Table 1 – Characteristics of men younger than 80 yr diagnosed with high-risk nonmetastatic prostate cancer and of men without prostate cancer matched to the prostate cancer cases for date of birth (±1 yr) in the Prostate Cancer Database Sweden

	Men with prostate cancer, *n* (%)	Men without prostate cancer, *n* (%)
Total number of men	19 190 (100)	95 948 (100)
Year of diagnosis		
2001–2003	4627 (24.1)	23 134 (24.1)
2004–2006	5167 (26.9)	25 835 (26.9)
2007–2009	4778 (24.9)	23 890 (24.9)
2010–2012	4618 (24.1)	23 089 (24.1)
Age		
<65 yr	4483 (23.4)	22 383 (23.3)
65–69 yr	4262 (22.2)	21 349 (22.3)
70–74 yr	4957 (25.8)	24 915 (26.0)
75–79 yr	5488 (28.6)	27 301 (28.5)
Charlson comorbidity index (CCI)		
CCI 0	14 261 (74.3)	70 387 (73.4)
CCI 1	2677 (13.9)	13 174 (13.7)
CCI 2	1404 (7.3)	7231 (7.5)
CCI ≥ 3	848 (4.4)	5156 (5.4)
Prostate cancer category		
Localised, high risk [a]	10 992 (57)	–
Locally advanced [b]	8198 (43)	–
Primary treatment		
Noncurative treatment [c]	9614 (50.1)	–
Radical prostatectomy	3236 (16.9)	–
Radiotherapy	5522 (28.8)	–
Other treatment with curative intent	166 (0.9)	–
No primary treatment registered	652 (3.4)	–

[a] T1–2 and Gleason score 8–10 and/or prostate-specific antigen (PSA) 20–49 ng/ml.
[b] T3, any Gleason score, PSA ≤49 ng/ml.
[c] Watchful waiting, gonadotropin-releasing hormone analogue, orchidectomy, antiandrogen therapy, or other treatment.

treatment of choice for locally advanced prostate cancer (local stage T3), whereas radical prostatectomy and radiotherapy were both recommended options for localised disease. Radical prostatectomy was performed in all counties and radiotherapy was available in most counties.

2.1. *Statistical analysis*

Cumulative survival probabilities for the men without prostate cancer, stratified by age and comorbidity, were analysed using the Kaplan-Meier method, and 95% CIs were calculated. We assumed that the 10-yr survival probability would be equivalent to the 10-yr survival for men with prostate cancer at the same age and with the same CCI, if cured of their prostate cancer. The 10-yr survival probability for men without prostate cancer was then used as a measure of the life expectancy for the men with prostate cancer. Two-sided 95% CIs for proportions of men receiving radical prostatectomy or radiotherapy were calculated using the Wilson score method [24]. The statistical analysis was performed with R, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We identified 19 190 men aged <80 yr with high-risk nonmetastatic prostate cancer diagnosed between 2001 and 2012, and 95 948 age-matched men from the general population without prostate cancer (Table 1). The proportions of men with prostate cancer younger than 70 yr who received radical prostatectomy or radiotherapy varied together with the 10-yr survival probability for men without prostate cancer, but did not for men with prostate cancer aged 70–80 yr (Fig. 1 and Table 2). For example, despite a 52% probability of 10-yr survival (95% CI 51–52%) for men aged 75–80 yr with CCI 0, only 10% (95% CI 9–11%) of these men with high-risk prostate cancer had a radical prostatectomy or radiotherapy, compared with 52% (95% CI 41–63%) of men aged <65 yr with CCI 3, who had a similar 10-yr survival

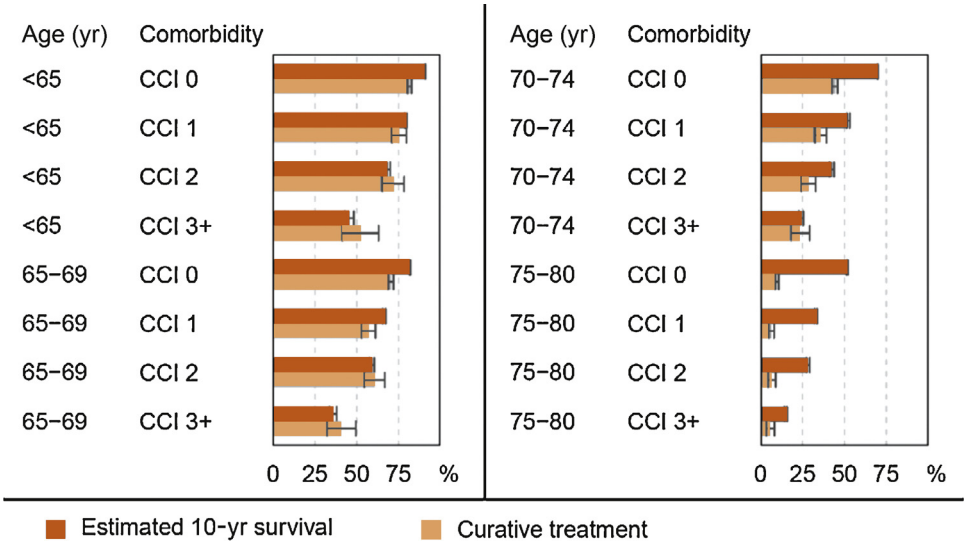

Fig. 1 – The 10-yr survival probability for men in the general population without prostate cancer and the proportion of men with high-risk nonmetastatic prostate cancer treated with radical prostatectomy or radiotherapy, stratified by age and Charlson comorbidity index (CCI). Men without prostate cancer were matched to the men with prostate cancer for date of birth (±1 yr) and county of residence. The survival of men without prostate cancer was counted from the date of diagnosis for the corresponding cases. The data are listed in Table 2.

Table 2 – Proportion of 19 190 men with high-risk nonmetastatic prostate cancer treated with radical prostatectomy or radiotherapy, and 10-yr survival probability for 95 948 men in the general population without prostate cancer, stratified by age and comorbidity [a]

	Men with prostate cancer (*n*)	Men with prostate cancer receiving RP or RT, % (95% CI)	10-yr survival of men without prostate cancer, % (95% CI)
Age <65 yr			
CCI 0	3817	82 (80–83)	91 (91–91)
CCI 1	389	76 (71–80)	79 (79–80)
CCI 2	191	72 (65–78)	68 (67–70)
CCI ≥3	86	52 (41–63)	46 (43–48)
Age 65–69 yr			
CCI 0	3322	70 (69–72)	82 (82–82)
CCI 1	552	57 (53–61)	66 (66–67)
CCI 2	255	61 (54–67)	59 (56–60)
CCI ≥3	133	41 (32–49)	36 (33–38)
Age 70–74 yr			
CCI 0	3547	44 (43–46)	70 (70–70)
CCI 1	736	36 (32–39)	52 (51–53)
CCI 2	437	28 (24–33)	42 (41–44)
CCI ≥3	237	23 (18–29)	24 (23–25)
Age 75–79 yr			
CCI 0	3575	10 (9–11)	52 (51–52)
CCI 1	1000	6 (5–8)	33 (32–34)
CCI 2	521	3 (4–9)	28 (27–29)
CCI ≥3	392	5 (3–8)	15 (14–16)

CCI = Charlson comorbidity index; CI = confidence interval; RP = radical prostatectomy; RT = radiotherapy.

[a] Men without prostate cancer were matched to the men with prostate cancer for date of birth (±1 yr) and county of residence. Survival of the men without prostate cancer was counted from the date of diagnosis for the corresponding cases diagnosis. The number of men without prostate cancer was five times the number of men with prostate cancer in each group. The data are also illustrated in Figure 1.

probability (46%, 95% CI 43–48%). For men without prostate cancer aged 70–74 yr with CCI 0, the 10-yr survival probability (70%, 95% CI 70–70%) was similar to that for men younger than 65 yr with CCI 2 (68%, 95% CI 67–70%). However, otherwise healthy men aged 70–74 yr with high-risk prostate cancer were much less likely to receive radical prostatectomy or radiotherapy (44%, 95% CI 43–46%) than men younger than 65 years with CCI 2 (72%, 95% CI 65–78%).

The proportion of men with high-risk prostate cancer receiving radical prostatectomy or radiotherapy increased during the study period from 38% in 2001–2004 to 44% in 2005–2008 and 58% in 2009–2012 (Fig. 2). The increase was greater among men aged 70–79 yr (from 15% in 2001–2004 to 38% in 2009–2012) than for those younger than 70 yr (from 69% in 2001–2004 to 80% in 2009–2012). Although increasing use of radical prostatectomy and radiotherapy was observed in all 21 counties and the differences among counties decreased, use still varied in the last time period (2009–2012) from 47% in the county with the lowest use to 83% in the county with the highest use. For men aged 70–80 yr with CCI 0–1, variation from 25% to 77% between counties remained during 2009–2012. The proportion receiving radiotherapy was not associated with the distance to a radiation oncology department.

4. Discussion

Otherwise healthy Swedish men in their seventies with high-risk nonmetastatic prostate cancer were significantly less likely to receive radical prostatectomy or radiotherapy than younger men with similar life expectancy. This disparity suggests that the life expectancy of healthy elderly men was commonly underestimated.

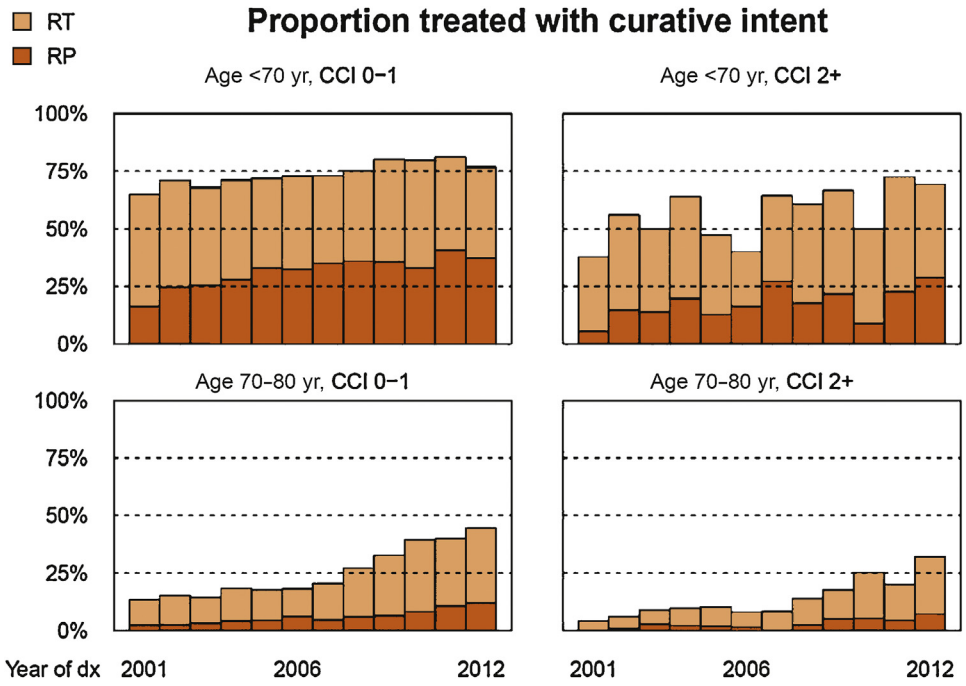

Fig. 2 – Time trends for the use of radical prostatectomy (RP) and radiotherapy (RT) in men with high-risk nonmetastatic prostate cancer in Sweden during 2001–2012. CCI = Charlson comorbidity index; dx = diagnosis.

Our findings add to the concerns about undertreatment of healthy elderly men with high-risk prostate cancer expressed by The International Society of Geriatric Oncology [17]. As the society pointed out, men with prostate cancer should be managed according to their individual health status rather than their age. Our study revealed that the opposite appears to occur frequently. The low use of radical prostatectomy and radiotherapy observed for men in their seventies is in accordance with a US study showing that men older than 75 yr with high-risk nonmetastatic prostate cancer are those most often undertreated in comparison to the National Comprehensive Cancer Network treatment guidelines [6], and with a report from Ireland on the relation between age and treatment for localised prostate cancer [5].

During the first years of the time period studied, evidence was still scarce on benefits of radical treatment in elderly men with high-risk nonmetastatic prostate cancer. The first randomised clinical trial showing that a combination of radiotherapy and hormonal therapy improves survival for this group of patients was published in 2009 [12]. The combined treatment resulted in a 10% absolute reduction and a 32% relative reduction in overall 10-yr mortality, with a similar effect in men younger and men older than 67 yr [12]. Another randomised study published in 2011 confirmed these results [13]. A recent register study indicated that radical treatment of high-risk prostate cancer is associated with reduced mortality, even in men older than 65 yr with comorbidities [1]. The results from the two randomised studies probably contributed to the increased use of radical prostatectomy and radiotherapy in the last time period in our study.

Although the use of radical prostatectomy and radiotherapy increased in all 21 Swedish counties, considerable variations among counties remained throughout the study period. The variation was up to threefold for the group of men aged 70–80 years with CCI 0 or 1 during the last study period (2009–2012). We believe that these large geographic differences reflect variations in physician practice patterns. A systematic review of treatment decisions for men with localised prostate cancer suggests that variations in treatment decisions are more indicative of differences in the information provided to patients than of differences in patient preferences [25]. Multidisciplinary conferences reduce the impact of the views of individual physicians [26], and are therefore recommended by Europa Uomo, the European organisation for prostate cancer patients [27]. However, whether the potential benefits of radical prostatectomy or radiotherapy outweigh the risks of side effects is a decision that only the patient himself can make. Consensus is building on the importance of shared clinical decision-making, with an emphasis on assessment of the patient's personal preferences and values [28]. Our study suggests that too much weight is put on chronological age in clinical decisions and that better assessment of life expectancy is needed to improve the outcome for men with high-risk prostate cancer.

Strengths of our study include the nationwide and population-based design with a large sample size. One limitation is that we did not know the proportion of men who were recommended radical prostatectomy or radiotherapy, but chose not to be treated. Another limitation is that we assessed comorbidity by CCI based on discharge diagnoses in the inpatient register, which may have led to underestimation of comorbidity. Furthermore, our study included men classified as having Mx disease, some of whom would likely have had distant metastases detected if a staging investigation had been performed. However, we felt it appropriate to include these men since withholding of staging procedures (thereby categorising the disease stage as Mx) may represent the first step towards inappropriate withholding of a potentially curative treatment. In addition, the 10-yr survival probabilities for Swedish men without prostate cancer are not directly applicable to populations with a short median lifespan, as the 80-yr median lifespan of Swedish men is among the longest in the world. Finally, the treatment patterns for high-risk prostate cancer may be different in other countries, but similar concerns regarding undertreatment of elderly men have been raised on both sides of the Atlantic [5,6].

5. Conclusions

Our nationwide population-based study of men with high-risk nonmetastatic prostate cancer revealed lower use of radical prostatectomy and radiotherapy among otherwise healthy men in their seventies than among younger men with a similar life expectancy, suggesting that treatment decisions relied more on chronological age than on life expectancy. Although increasing use of radical treatments was observed during the study period, many elderly men with high-risk prostate cancer are probably still undertreated. The large geographic differences in the use of radical prostatectomy and radiotherapy, with persistent low use in many counties, highlight the need for improved methods for clinical decision-making, including improved assessment of patients' life expectancy.

Author contributions: Ola Bratt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Akre, Bratt, Carlsson, Drevin, Eriksson, Folkvaljon, Lissbrant, Stattin.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Bratt.
Critical revision of the manuscript for important intellectual content: All authors.
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