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Original Article

Definitive radiotherapy for prostate cancer in Norway 2006–2015: Temporal trends, performance and survival

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ABSTRACT

Background: More studies are needed to document nation-wide use and effectiveness of curative definitive radiotherapy (Def-RT) in the treatment of prostate cancer (PCa).

Patients and methods: For 38,960 men diagnosed with PCa without distant metastases from 2006 to 2015 data from the Norwegian Prostate Cancer Registry and a national radiotherapy database (NoRadBase) was analyzed. Overall survival and PCa-specific mortality were described comparing EQD-2 < 74 Gy ("low-dose") with EQD-2 ≥ 74 Gy ("escalated dose").

Results: Use of Def-RT decreased (27–24%) whereas the proportion of radical prostatectomies (RPs) increased (31–38%). In high-risk patients the use of RP doubled (18–36%), while the proportion of Def-RT remained stable (about 35%). Before 2010, almost a quarter of patients received low-dose Def-RT with gradual increase of escalated Def-RT thereafter. Escalated Def-RT was associated with significantly more favorable 10-year PCa-specific mortality (4.4% [95% CI: 2.7–10.7%]) than observed after low-dose Def- RT (8.8% [95% CI: 6.2–9.8%), with the most beneficial effects in high-risk patients. Our analyses indicated the need to expand the NoRadBase by consensus-based quality measures.

Conclusion: In this nationwide cohort, the overall use of Def-RT decreased slightly. In high-risk patients the provision of Def-RT remained stable and was accompanied by doubling of patients with RP and reduction of a "no curative treatment" strategy. Escalated dose Def-RT significantly reduced 10-year PCa-specific mortality compared to low-dose Def-RT. Aiming for cancer care equity national radiotherapy registries for PCa should regularly monitor data based on consensus-based quality measures enabling feedback to the responsible hospitals.

Standard local curative treatment options in patients with prostate cancer (PCa) without distant metastases comprise Radical Prostatectomy (RP) and Definitive Radiotherapy (Def-RT) with or without androgen deprivation therapy (ADT) [1,2].

Multiple registry-based studies have been published comparing survival after RP and Def-RT, most often showing better survival after RP than after Def-RT [3–7]. In contrast, recent randomized trials described similar 10-year survival following Def-RT and RP, mostly in patients with low or intermediate risk PCa [8].

During the last three decades, Def-RT for PCa, mostly given as external beam radiotherapy (EBRT) has undergone important technical improvements [9–11]: dose escalation of conventionally fractionated EBRT (CONV-RT (2 Gy/day [12–14]), hypofractionation (HYPO-RT [15]), combination of EBRT with low or high dose- rate brachytherapy (EBRT-BT [16,17]) and the use of neo-adjuvant ADT [18]. In a registry-based analysis comprising patients with intermediate- and high-risk PCa Kalbasi et al. [19] documented a survival-prolonging effect of a target dose of >75.6 Gy as compared to lower doses. When compared to CONV-RT with a target dose of 78 Gy the number of deaths due to PCa was in Pettersson et al's study significantly reduced by EBRT-BT [20]. These findings of dose–response relationship need confirmation in additional population-based cohorts.

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Def-RT for PCa has been used in Norway since 1974 [21] and is today available as CONV-RT (2–2.4 Gy/day), HYPO-RT [22], EBRT-BT [23] or BT monotherapy. Low dose-rate brachytherapy is not offered in Norway. Since 1997, each patient's coded radiotherapy information is automatically transferred to a database (NoRadBase) at the Cancer Registry of Norway (CRN) [24]. The quality of data collection related to Def-RT has so far not been evaluated, but can be assessed by combining data from the NoRadBase and the Norwegian Prostate Cancer Registry (NoPCR) [25] Combination of these two databases also enables the assessment of time trends in the treatment of non-metastatic PCa patients in Norway and the analyses of post-radiotherapy survival/mortality. Secondarily the findings can assist validation of PCa-related data registered in the NoRadBase. (For general management strategies of PCa in Norway confer Supplement 1.)

The present historical prospective cohort study has thus three aims:

1. In patients with PCa diagnosed in Norway from 2006 to 2015 to assess temporal trends of the use of Def-RT as compared to RP and a policy implying no curative local treatment (NoCurTrT) [26]).
2. To document the quality of performance of Def-RT as reflected by data from the NoRadBase.
3. To study the relation between the target dose to the prostate and post-radiotherapy overall survival and PCa- specific mortality.

Patients and methods

Data sources

Each patient's data were extracted from the **NoPCR**: date of diagnosis and RP, Gleason scores, clinical T and N-category, PSA at diagnosis, risk group [27], hormone treatment (recorded by the CRN if started within four months since diagnosis), WHO performance status (representing a proxy for co-morbidity), date and underlying cause of death.

Based on national codes the **NoRadBase,** identifies the responsible radiotherapy center and provides start and end dates of Def-RT, the total prostatic target dose, daily doses and the number of fractions. To allow comparison between the different treatment strategies, EQD -2 was calculated for each patient's Def-RT, applying an alpha/beta coefficient of 1.8. The data set included intention of treatment (curative versus palliative/other), but failed to separate patients with irradiation to the prostate only from those with additional pelvic lymph node radiotherapy as these data were not consistently registered. In 2006, 3D-conformal Def-RT had been established at all radiotherapy units with subsequent implementation of IMRT, IGFR and CT/MR-based dose planning. The NoRadBase does, however, not provide individualized information about these techniques and does neither contain information about dose constraints to the rectum or bladder. Data on acute or long-term toxicity are not routinely collected.

Use of guidelines

Def-RT: Before 2009 Def-RT was based on the guidelines of the European Association of Urology (EAU) which before 2015 do not specify a minimum curative target dose above 70 Gy. However, since 2007 the beneficial effect of escalated Def-RT and of (neo-) adjuvant ADT is in depth discussed for high-risk PCa [28].

The first Norwegian guidelines from 2009 recommended a target dose of at least 74 Gy and (neo-) adjuvant ADT (2–3 years) for patients with intermediate and high-risk PCa [29].These recommendations are still valid today. Pelvic radiotherapy was optional in patients with documented or suspected N+ disease.

RP: In Norway RP has been a therapeutic option in patients with non-metastatic PCa since 1990 [29].

NoCurTrT: Based on the responsible physician's assessment and the patient's preference, patients were observed with or without ADT. During the study period the NoPCR did not reliably separate active surveillance from a "watchful waiting" policy [26].

Patients

Evaluable patients were diagnosed between 2006 and 2015 with adenocarcinoma of the prostate without distant metastases (M0/MX) *and* PSA $\leq$100 ng/ml) excluding a first-time PCa diagnosis at autopsy or after cysto-prostatectomy. For the temporal trend analyses we identified three groups based on their local treatment: RP, Def-RT and NoCurTrt.

Patients included in the analyses regarding Def-RT fulfilled additional *criteria:* no prostatectomy preceding Def-RT recorded in the CRN *and* curatively intended radiotherapy provided before December 31.2016, OR any radiotherapy with a target dose of EQD-2 $\geq$ 74 Gy. (A target dose comparable to EDQ-2 $\geq$ 74 Gy would before 2016 not routinely be used in patients with palliative radiotherapy or in those receiving post-RP radiotherapy.)

Measures

The numbers of patients undergoing RP, Def-Rad, and NoCurTrT were identified for three diagnostic periods; 2006–2009, 2010–2012 and 2012–2015. Patients receiving Def-RT were stratified according to age at diagnosis and at start of radiotherapy ($\leq$70 vs >70 years) and according to health regions in Norway indicating the responsible institution's geographical location (I: South-East; II: West; III: Central IV: Northern). The time between diagnosis and start of radiotherapy ($\leq$12; >12–60; >60 months) was calculated. Separate analyses were performed for high-risk patients, also identifying patients with very high risk: Gleason score >8 and/or recorded pelvic lymph node metastases. For survival/mortality analyses patients with EQD-2 < 74 Gy ("low-dose") were separated from those with EQD-2 $\geq$ 74 Gy ("escalated-dose"). Within the highest EQD-2 sublevel ($\geq$78 Gy) patients receiving CONV-RT, HYPO-RT (most often 2.7 Gy $\times$ 25) or EBRT-BT were identified.

Theory/calculation

Related to increasing use of RP [30] a time-dependent decrease of Def-RT was anticipated together with increasing application of escalated Def-RT, the latter being associated with increased overall survival and reduced PCa-specific mortality. We expected that our analyses would indicate tasks which could improve registration of Def-RT at the NoRadBase.

Statistics

Multivariable logistic regression models estimated the odds ratios (ORs) and confidence intervals (CIs) for the use of escalated Def-RT being the dependent variable. The independent factors were age at treatment, WHO performance status, prior cancer, period of diagnosis, risk group and health regions. For survival analyses comparing the effect of low with escalated Def-RT patients were followed from date of start of Def-RT to December 31. 2017 (end of the study period), date of the event of interest, or emigration whatever occurred first. The Kaplan-Meier method was used for overall survival. PCa-specific mortality was estimated using the Aalen-Johansen estimator, treating death from other causes than PCa as a competing risk. Multivariable Cox-regressions were

used to estimate hazard ratios (HRs) and CIs for selected covariates. The level of significance was $p < 0.05$, using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 25 and Stata version 16.0.

Ethics

The Regional Committee for Medical Research Ethics approved this study (2011/1746).

Results

Among the 38,960 evaluable patients (supplementary Fig. 1) the proportion of curative local treatment remained relatively stable during the study period (from 58% to 61%).The percentage of patients undergoing RP rose from 31% to 38% and the percentage of Def-RT decrease from 27% to 24% (Table 1). For high-risk patients the percentage of RP doubled (18% to 36%), whereas the proportion of irradiated high-risk patients remained unchanged with one of three undergoing Def-RT.

High-risk patients without curative treatment were 79 years old (median) at diagnosis, and a WHO performance status of 3 or 4 were recorded in 27% of them. In contrast, high-risk patients with RP or Def-RT were aged 67 years, with only 3% of them registered with a performance status of 3 or 4.

By the end of 2016, 9943 patients (26%) had Def-RT (supplementary Fig. 1, Table 2). During the study period the median age at diagnosis increased from 67 to 71 years, combined with a slight decrease in the proportion of patients with performance status 0. About sixty percent of the patients had high-risk PCa, with extra- prostatic extension in half of them. Of the high-risk tumors 27% were categorized as very high risk cases.

Curative intention was coded in 97% of the evaluable patients (Supplementary Table 1). According to the registration in the NoRadBase only 8% of the patients received irradiation of the pelvic lymph nodes in addition to prostatic radiotherapy, this percentage being 11% in high-risk patients and 21% in men with recorded regional lymph node metastases.

Overall, about 4 of 5 (83%) patients started Def-RT within one year of diagnosis (Table 3A), the comparable percentage being 89% in high-risk patients (Table 3B). Half of the 437 patients starting radiotherapy more than 5 years after diagnosis were diagnosed with low-risk tumors (data not shown). CONV-RT was used in 7716 (78%) patients, of whom about 1% received daily doses of 2.4 Gy. A total of 704 men (7%) had EBRT-BT and 1523 (15%) underwent HYPO-RT. During the first time interval low-dose radiotherapy (EQD-2 < 74 Gy) was applied in about one of four patients, also in high-risk patients, and 81% of all low-dose radiotherapy series were applied in Health region I. The application of low-dose Def-RT decreased gradually during the study period.

According to the multivariable logistic regression analysis (Table 4), the probability to receive escalated radiotherapy rose significantly during the study period and with increasing risk group. Overall, patients treated in health region II, III or IV were significantly more likely to receive escalated-dose Def-RT than those irradiated in heath region I. In general, increasing age or poor performance status did not significantly impact on the use of escalated Def-RT.

After a median observation time of six years, 1377 patients (14%) had died, 0fof which 296 (3%) due to PCa (Supplementary Table 2). The 10-year PCa-specific mortality for all patients was 5.5%, being 8.8% after low-dose radiotherapy compared to 4.4% after escalated doses.

Both in the entire cohort and in the subgroup of high-risk patients, overall survival was significantly higher and PCa-specific mortality significantly lower following escalated compared to low-dose radiotherapy (Fig. 1). Escalated Def-RT decreased PCa specific mortality in men with low and intermediate risk PCa (p: 0.003), though without impact on overall survival.

The risk of death from any cause was positively associated with increasing age at treatment, decreasing performance status, a prior cancer diagnosis and increasing risk-group (Table5). Importantly, the overall mortality hazard was significantly reduced by 20% for patients receiving escalated-dose Def-RT compared to low-dose Def-RT (HR = 0.8[CI = 0.70–0.95]), after controlling for other available risk factors. The risk of PCa-mortality increased with risk group categorization, and decreased with period of diagnosis. The risk of PC-death was more than halved in patients with escalated Def-RT. After escalated radiotherapy the risk of death due to PCa was half of that emerging after low-dose Def-RT (HR = 0.45[CI = 0.33–0.60]). The results did not change principally when only analyzing high-risk patients (data not shown).

Discussion

In this population-based study, a slight decrease of the use of Def-RT was observed in patients with PCa diagnosed from 2006 to 2015, accompanied by an increase of RPs. In high-risk patients the number of RPs doubled whereas the use of Def-RT remained unchanged. About one of three patients underwent Def-RT. Early in the study inter-institutional variations of the total target dose were found, but since 2010 the use of escalated Def-RT was more

Table 1
Temporal trends in use of Definitive Radiotherapy (Def-RT) compared to Radical prostatectomy and NoCurative Treatment (NoCurTrT). A: All patients B: High-Risk patients.

A. All patients				
	Years of diagnosis			
	2006–2009 n:14 127	2010–2012 n:11 997	2013–2015 n:12 836	Total n:38 960
Definitive radiotherapy	**3832 (27%)**	**3090 (26%)**	**3021 (24%)**	**9943 (26%)**
Radical prostatectomy	4373 (31%)	4576 (38%)	4820 (38%)	13 769 (35%)
NoCurTrT*	5922 (42%)	4331 (36%)	4995 (39%)	15 248 (39%)
B. High risk patients				
	Years of diagnosis			
	2006–2009 n:6321	2010–2012 n:4983	2013–2015 n:5127	Total n:16 431
Definitive radiotherapy	**2190 (35%)**	**1751 (35%)**	**1777 (35%)**	**5718 (35%)**
Radical prostatectomy	1121 (18%)	1451 (29%)	1822 (36%)	4394 (27%)
NoCurTrT*	3010 (48%)	1781 (36%)	1528 (30%)	6319 (39%)

*No curative local treatment

Table 2
Medical variables in patients with Definitive Radiotherapy.

	2006–2009 (n:3832)	2010–2012 (n:3090)	2013–2015 (n:3021)	Total (n:9943)
Age (diag.) Median, (range)	67 (45–84)	69 (45–87)	71 (40–85)	69 (40–87)
≤70	2707 (71%)	1794 (58%)	1386 (46%)	5887 (59%)
>70	1125 (29%)	1296 (42%)	1635 (54%)	4056 (41%)
WHO perf.status				
0	2626 (69%)	1923 (62%)	1711 (57%)	6260 (63%)
1	530 (14%)	507 (16%)	452 (15%)	1489 (15%)
≥2	161 (4%)	145 (5%)	133 (4%)	439 (4%)
Missing	515 (13%)	145 (5%)	725 (24%)	1755 (18%)
Prior cancer				
No	3562	2829	2710	9101
Yes	270 (7%)	261 (9%)	311 (10%)	842 (9%)
Risk groups				
Low	293 (8%)	196 (6%)	99 (3%)	588 (6%)
Intermediate	1115 (29%)	1122 (36%)	1129 (37%)	3366 (34%)
High	2190 (57%)	1751 (57%)	1777 (59%)	5718 (58%)
Missing	234 (6%)	21 (1%)	16 (1%)	271 (3%)
Tumor extension				
Intra-prostatic	2235(58%)	1884 (61%)	1638 (54%)	5757 (58)
Extra-prostatic	1267 (33%)	854 (28%)	867 (29%)	2988 (30%)
Missing	330 (9%)	252 (11%)	516 (17%)	1198 (12%)
PSA category(ng/ml)				
<10	1280 (33%)	1114 (36%)	1105 (37%)	3499 (35%)
10–20	1277 (33%)	988 (32%)	898 (30%)	3163 (32%)
>20–50	766 (20%)	531 (17%)	423 (14%)	1720 (17%)
>50–<100	145 (4%)	111 (4%)	97 (3%)	353 (4%)
Missing	364 (10%)	246 (11%)	498 (17%)	1208 (12%)
N-category				
N0	1985 (52%)	1500 (49%)	1334 (44%)	4819 (49%)
N1	138 (4%)	260 (8%)	258 (9%)	656 (7%)
NX	1709 (45%)	1330 (43%)	1429 (47%)	4468 (45%)
Gleason Score				
6	1024 (27%)	633 (21%)	342 (11%)	1999 (20%)
7a	1047 (27%)	868 (28%)	867 (29%)	2782 (29%)
7b	610 (16%)	603 (20%)	653 (22%)	1866 (19%)
8	583 (15%)	574 (19%)	640 (21%)	1797 (18%)
9–10	266 (7%)	377 (12%)	493 (16%)	1136 (11%)
Missing	302 (8%)	35(1%)	16 (1%)	363 (4%)

B: High-risk only

	2006–2009 (n:2190)	2010–2012 (n:1751)	2013–2015 (n:1777)	Total (n:5718)
Age (diag.) Median, (range)	67 (45–84)	70 (45–87)	71 (46–85)	69 (45–87)
≤70	1522 (70%)	980 (56%)	770 (43%)	3272 (57%)
>70	668 (31%)	771 (44%)	1007 (57%)	2446 (43%)
WHO perf. status				
0	1593 (72%)	1114 (64%)	1053 (59%)	3760 (66%)
1	316 (14%)	333 (19%)	310 (17%)	959 (17%)
≥2	98 (5%)	85 (5%)	87 (5%)	270 (5%)
Missing	183 (8%)	219 (13%)	327 (18%)	729 (13%)
Prior cancer				
No	2040	1592	1590	5222
Yes	150 (7%)	159 (9%)	187 (11%)	496 (9%)
Tumor extension				
Intra-prostatic	858 (39%)	788 (45%)	727 (41%)	2373 (42%)
Extra-prostatic	1267 (58%)	854 (49%)	867 (49%)	2988 (52%)
Missing	65 (3%)	109 (6%)	183 (10%)	357 (6%)
N-Category				
N0	968 (44%)	578 (33%)	534 (30%)	2080 (36%)
N1	133 (6%)	248 (14%)	244 (14%)	625 (11%)
NX	1089 (50%)	925 (535)	999 (56%)	3013 (53%)
PSA category(ng/ml)				
<10	504 (23%)	478 (27%)	550 (31%)	1532 (27%)
10–20	688 (31%)	516 (30%)	532 (30%)	1736 (30%)
>20–50	766 (35 %)	531 (30%	423 (24%)	1720 (30%)
>50–100	145 (7%)	111 (6%)	97 (6%)	353 (6%)
Missing	87 (4%)	115 (7%)	175 (10%)	5718 (7)

Table 2 (*continued*)

B: High-risk only				
	2006–2009 (n:2190)	2010–2012 (n:1751)	2013–2015 (n:1777)	Total (n:5718)
Gleason score				
6	332 (15%)	135 (8%)	80 (5%)	547 (10%)
7a	555 (25%)	339 (19%)	259 (15%)	1148 (20%)
7b	389 (18%)	312 (18%)	296 (17%)	997 (17%)
8	583 (27%)	574 (33%)	640 (36%)	1797 (31%)
9–10	266 (12%)	377 (22%)	493 (28%)	1136 (20%)
Missing	79 (3%)	14 (1%)	9 (1%)	93(2%)
Very High Risk	377/2190 (18%)	538/1715 (31%)	652/1777 (37%)	1567/5718 (27%)

Table 3
Radiotherapy-related variables: A:All patients B: High risk.

A: All patients				
	Years of diagnosis			
	2006–2009 (n:3832)	2010–2012 (n:3090)	2013–2015 (n:3021)	Total (n:9943)
Months Diag-RT				
Median (range)	7 (1–122)	7 (1–79)	6 (1–42)	8 (1–122)
≤12	2976 (78%)	2536 (82%)	2736 (91%)	8248 (83%)
>12–60	577 (15%)	445 (14%)	236 (8%)	1258 (13%)
>60	279 (7%)	109 (4%)	49 (2%)	437 (4%)
Age at Def_RT				
Median (range)	68 (46–89)	70 (46–87)	72 (41–86)	69 (41–89)
≤70	2318 (61%)	1538 (50%)	1175 (39%)	5031 (51%)
>70	1514 (39%)	1552 (50%)	1846 (61%)	4912 (49%)
EQD-2[Gy]				
<70	58 (2%)	72 (2%)	135 (5%)	265 (3%)
70–<74	929 (24%)	218 (7%)	104 (3%)	1251 (13%)
74–<78	928 (24%)	1054 (34%)	1142 (38%)	3124 (31%)
≥78	1917 (50%)	1746 (47%)	1640 (54%)	5303 (53%)
2–2.4 Gy/day	*1279*	*878*	*919*	*3076*
Hypofractionation > 2.4 Gy/day	*280*	*669*	*574*	*1523*
HDR-BT	*358*	*199*	*147*	*704*
B: High-risk patients				
	Years of diagnosis			
	2006–2009 (n:2190)	2010–2012 (n:1751)	2013–2015 (n:1777)	Total (n:5718)
Months Diag-Rad				
Median (range)	8 (2–122)	7 (1–77)	6 (1–39)	8 (1–122)
≤12	1081 (82%)	1555 (89%)	1705 (96%)	5061 (89%)
>12–60	248 (11%)	137 (8%)	51 (3%)	436 (8%)
>60	141 (6%)	59 (4%)	21 (1%)	221 (4%)
Age at Def-RT				
Median (range)	68 (46–89)	70 (46–87)	72 (48–86)	70 (46–89)
≤70	1331 (61%)	859 (49%)	668 (38%)	2849 (50%)
>70	859 (39%)	901 (51%)	1109 (62%)	2869 (50%)
EQD-2[Gy]				
<70	30 (1%)	43 (3%)	66 (4%)	139 (2%)
70–<74	449 (21%)	108 (6%)	61 (3%)	618 (11%)
74–<78	532 (24%)	620 (35%)	681 (38%)	1833 (32%)
≥78	1179 (54%)	980 (56%)	969 (55%)	3128 (55%)
2–2.4 Gy/day	*770*	*556*	*588*	*1914*
Hypofractionation > 2.4 Gy/day	*153*	*303*	*293*	*749*
HDR-BT	*256*	*121*	*88*	*465*
Hormone therapy				
Yes	1016(46%)	392(22%)	647(36%)	2055(36%)
No	417(19%)	61(4%)	167(9%)	640(11%)
Missing	757(35%)	1298(75%)	968(55%)	3023(53%)

homogeneous, with increasing use of escalated Def-RT since 2010. Compared to low-dose Def-RT, escalated Def-RT was associated with significantly more favorable 10-year overall survival and reduced PCa-specific mortality, most evident in high-risk patients.

Table 4
Multivariate logistic regression analyses with escalated Def-RT as independent variable (Reference: low dose Def-RT).

	All patients			High-risk patients		
	OR	*p*-value	95% CI	OR	*p*-value	95% CI
Age at Def-RT	1	0.177	1.00–1.02	1	0.91	0.99–1.01
ECOG						
0	Ref.			Ref.		
1	0.97	0.746	0.82–1.16	1.14	0.269	0.90–1.44
2	0.89	0.417	0.67–1.18	0.68	0.026	0.48–0.95
Prior cancer						
0	Ref.			Ref.		
1	0.97	0.767	0.76–1.23	0.97	0.871	0.71–1.34
Time period						
≤2009	Ref.			Ref.		
2010–2012	3.26	0	2.77–3.84	2.89	0	2.33–3.58
2013–2015	4.33	0	3.60–5.21	4.07	0	3.21–5.16
Risk group						
1	Ref.					
2	1.48	0.002	1.16–1.90			
3	1.93	0	1.52–2.45			
Health region						
1	Ref.			Ref.		
2	4.22	0	3.49–5.10	3.83	0	2.92–5.02
3	9.89	0	7.28–13.43	7.04	0	4.98–9.95
4	5.38	0	3.97–7.30	4.74	0	3.19–7.07

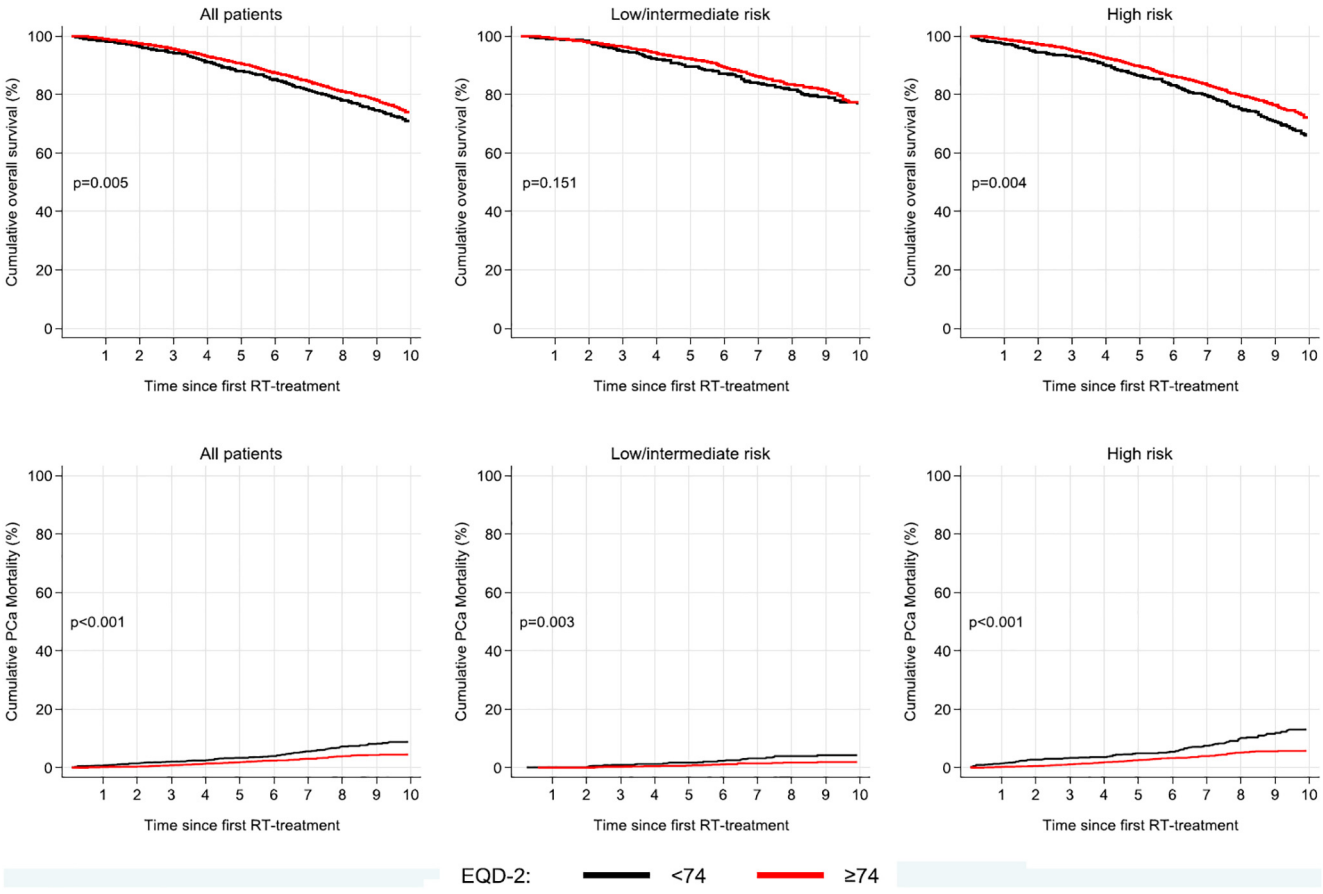

Fig. 1. Prostate cancer specific 10- year mortality and overall survival, stratified for risk groups.

Temporal trends

The percentage of patients without curative treatment decreased since 2010. However, at the end of the study period still 30% of high risk patients, mainly the eldest and those with a reduced performance status did not undergo curative treatment. This percentage complies with a current pragmatically defined quality indicator valid in Norway: a minimum of 70 % percent of *all* high-risk patients should be curatively treated [29]. As in the

Table 5
Cox regression analysis with mortality as outcome: ALL patients with Def-RT.

	Overall mortality			PCa specific mortality		
	HR	*p*-value	95% CI	HR	*p*-value	95% CI
EQD-2						
<74	Ref.			Ref.		
≥74	0.82	0.008	0.70–0.98	0.45	0	0.33–0.60
Age at Def-RT	1.04	0	1.02–1.04	1.02	0.088	1.00–1.04
ECOG						
0	Ref.			Ref.		
1	1.42	0	1.23–1.64	1	0.979	0.71–1.40
≥2	1.83	0	1.47–2.28	0.86	0.633	0.45–1.62
Prior cancer						
0	Ref.			Ref.		
1	1.51	0	1.26–1.82	1.16	0.531	0.73–1.84
Time period						
≤2009	Ref.			Ref.		
2010–2012	0.93	0.36	0.80–1.08	0.66	0.014	0.47–0.92
2013–2015	1.01	0.918	0.81–1.26	0.2	0	0.08–0.45
Risk group						
1	Ref.			Ref.		
2	1.42	0.025	1.05–1.94	3.51	0.036	1.09–11.32
3	1.74	0	1.29–2.35	8.34	0	2.66–26.17
Health region						
1	Ref.			Ref.		
2	1	0.951	0.85–1.16	1.02	0.917	0.72–1.44
3	1.05	0.58	0.89–1.23	1.11	0.573	0.76–1.63
4	1.04	0.692	0.85–1.28	1.34	0.204	0.86–2.00

USA the use of Def-RT declined slightly during the study period together with increasing numbers of RPs [30,31]. Before 2010 Def-RT was considered to be "the curative treatment of choice" in high-risk patients aged ≤70 years in Norway .With the urologists' increasing surgical competence and based on expanding literature [3–7,32] RP became a preferred choice for patients with high-risk PCa. However, so far no randomized trials have shown better survival rates after RP than after Def- RT. The final role of Def-RT versus RP in high-risk patients has to be clarified e.g. by the ongoing SPCG 15 trial [33].

Performance of radiotherapy

Based on randomized trials [13,14,34,35] and supported by a registry-based analysis [19] current EAU guidelines recommend escalated Def-RT for patients with intermediate and high-risk PCa [28]. Regular monitoring of compliance to consensus-based recommendations will effectively reduce the risk of insufficient and/or varying target doses, evident in randomized trials [36] and in our study as inter-regional variations of the target doses. The frequent use of low-dose Def-RT early in the study is in part explained by the expectation that low-dose Def-RT compared to escalated radiotherapy would be effective and reduce toxicity. After 2010 and following reports of improved outcomes high-dose Def-RT became the nation-wide standard. Similar gradual dose escalation was also observed in USA [37].We can only speculate about the reasons why a rising percentage of patients (from 2 to5%) had low-dose Def-RT comparable to EQD-2 < 70 Gy: In particular during the last time period at least 100 patients per year undergo RP outside Norway [38]. For these patients the CRN may not have registered the date of RP. In these patients subsequent pelvic radiotherapy may in our study falsely be categorized as Def-RT. An intolerable acute toxicity mandating early discontinuation of radiotherapy may have represented an alternative reason for low target doses.

This study is based on real-world data as documented in a national radiotherapy database [25]. Similar data bases exist in the US, in Sweden [19,20] and other co-operative groups. Such registries enable scientific discussions between involved clinicians, adjustment of treatment strategies and thereby increasing equity and quality of a country's Def-RT strategies. However, our study uncovered necessary improvements of the structure and the registration routines of the NoRadBase. We believe that similar challenges exist also for other population-based radiotherapy registries. Firstly, regular monitoring of the collected data and feed-back to the responsible radiotherapy units is needed. Further, the compliance with consensus-based quality measures for PCa radiotherapy registries should be documented [39–41]. However, Gandaglia et al. [42] point to the risk of "overloading" data collection, leading to increased erroneous coding and missing of essential data, evident also in our study. Clinicians who co-operate in the TrueNTH Global Registry have therefore restricted data collection to start and end of radiotherapy, prostatic target dose, ADT use and patient-reported toxicity [43]. Except for the latter two variables these measures are dealt with in the present study.

Survival/mortality

Most randomized trials have shown beneficial oncological outcomes after escalated Def-RT, most often as reduced risk of biochemical recurrence [13,14,33,34]. Pasalic et al. and Michalski et al have in randomized trials shown a positive association between dose-escalated Def-RT and PCa specific survival [44,45]. Increased overall survival is supported by the current and two population-based analyses [19,20]. Importantly the difference of survival/mortality between low- and escalated-dose Def-RT was in our study greatest in high-risk patients. This is in agreement with published data that high-risk patients benefit most from the highest possible target dose to the primary tumor, provided by high dose-rate brachytherapy [20,46]. Overall, our population-based experience is thus in line with today's recommendations from the EAU that Def-RT should involve escalated doses [28]. A secondary consequence of our observations is that future registry-based survival comparisons between Def-RT and other

curatively intended therapies of PCa should consider the prostatic target dose.

Our study has several limitations as the high percentages of missing data related to the use of ADT and inconsistent documentation of the irradiated region. Our analyses are based on the traditional three-tiered risk grouping [27] mainly based on digital rectal examination of the prostate. Increasing use of new diagnostic examinations during more recent years (CT, MR) may have led to migration bias related to cT and cN categorization and hence risk classification. A risk of "over-registration" of PCa-specific death in men dying at age >80 years should not be overlooked [47]. The lack of patient-reported toxicity data is a further limitation. Finally, our alpha/beta coefficient can be debated, but reflects what was viewed as valid during our study period [48].Our analyses of a large population-based cohort with real-world data from national registries represent the study's major strength.

In summary, in spite of increasing use of RP Def-RT has remained the curative treatment in Norway in about 25% of *all* patients and in one of three men with high-risk PCa. With a median observation time of six years and compared to low-dose Def-RT dose-escalated Def-RT significantly reduced PCa-specific mortality for all patients (8.8% versus 4.4%), the difference being greatest in men with high-risk PCa (5.7% versus 13.0%). Finally, correct and clinically relevant data collection in national or co-operative radiotherapy registries requires regular and careful monitoring of the structure of the data base and of the collected data using consensus-based radiotherapy quality indicators.

Conflict of interest

None.

Data sharing statement

This study was based on data from the Cancer Registry of Norway. The authors do not own this data and are not permitted to share them in the original form (only in aggregate form eg. publications).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.10.022.

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