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Original Article

High efficacy of hypofractionated proton therapy with 4 fractions of 5 Gy as a boost to 50 Gy photon therapy for localized prostate cancer

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ABSTRACT

Purpose: We report the outcome of hypofractionated proton boost as an alternative to high dose-rate brachytherapy boost, aimed at an equivalent dose exceeding 86 Gy in 2 Gy fractions, for patients with localized prostate cancer and all risk groups.

Methods: Proton boost of 20 Gy given in 4 daily fractions to the prostate was followed after a one-week rest by photon therapy to 50 Gy in 2 Gy fractions. Outcomes are presented per risk group according to both NCCN and ISUP classifications. Advanced imaging was performed for adequate staging, and at an early stage of rising PSA, to identify the relapse site. Endpoints were PSA relapse-free-, locoregional relapse-free-, and distant metastasis-free- survival. Prostate cancer-specific-, metastasis-free-, and overall survival were also estimated. Genitourinary (GU) and gastrointestinal (GI) toxicity were based on patients' questionnaires and physicians' records.

Results: We treated 531 patients between 2002 and 2015; 504 had localized disease. The cohort included 180 patients with T3/T4 disease (36%). The majority of the 50% with high-/very high-risk disease received ADT, 9–24 months; 92 had adjuvant pelvic node treatment. Median follow-up was 113 months (43–193). For low-, intermediate-, high-, and very high-risk patients, the 5-year PSA relapse-free survival was 100%, 94%, 82%, and 72%, respectively. Prolonged ADT improved biochemical control and nodal treatment regional control. The NCCN classification had higher predictive discrimination than the ISUP classification. The 5-year prevalence grade 3+ was 2% for GU and 0% for GI toxicity in pre-treatment symptom-free patients, and not worsened by nodal treatment.

Conclusion: Dose escalation with hypofractionated proton boost was as effective as reported with high dose-rate brachytherapy boost, and the GU and GI toxicity profile was very similar. The proton boost was also appropriate for patients with larger prostate volume, higher T-stage, and high-risk disease encompassing elective regional node photon therapy.

Technical advances have made it possible to create highly conformal dose distributions using photon-based radiotherapy, prompting interest in hypofractionated radiotherapy. Prostate cancer shows higher fractionation sensitivity and a lower α/β ratio than healthy tissue; thus, the rationale is to use higher doses per fraction compared with conventional fractionation [1–3]. Randomized studies have shown that moderate hypofractionation was not inferior to conventional fractions [4–6], but they have not demonstrated the concept of biological dose escalation i.e. either improved efficacy with equal toxicity [7,8] or reduced toxicity with maintained efficacy [9].

Proton beam radiotherapy allows highly conformal dose coverage of the prostate with superior normal tissue sparing compared to photon therapy. However, the clinical benefits of proton therapy have yet to be proven. In a randomized dose escalation trial, proton therapy was used to boost 50 Gy photon treatment up to either 70 Gy (Relative Biological Effectiveness, RBE) or 79 Gy (RBE) using conventional fractions. The higher dose improved biochemical control without any increase in severe urinary or rectal side effects [10].

We used hypofractionated proton therapy with fractions of 5 Gy to –20 Gy, to boost 50 Gy photon treatment. This represents a more efficient dose escalation of the tumor target than a boost with conventional fractions. In total, 70 Gy was applied, which corresponds to 87 Gy (RBE) or more in 2 Gy fractions for an α/β ratio of 3 Gy or lower. The 5-year results for the first 278 patients showed promising efficacy and safety [11].

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We decided to use a proton boost due to the need for an alternative to high dose-rate brachytherapy boost with 2 fractions of 10 Gy added to 50 Gy, which was the standard protocol for prostate cancer at our clinic in 2002. Here we report the outcome for a cohort of 531 patients treated from 2002 to 2015 at the proton facility at The Svedberg Laboratory in Uppsala, which was closed down for clinical use in 2015. Tumor outcome measures are shown per risk group both according to the National Comprehensive Cancer Network (NCCN) classification [12] and the International Society of Urological Pathology (ISUP) classification [13]. Toxicity analyses are based on a combination of SOMA-LENT [14] and RTOG scales [15].

Materials and methods

Patients and treatment

Between November 2002 and June 2015, 531 patients with prostate cancer were treated with a proton boost of 20 Gy in 4 daily fractions. After a one-week rest, this was followed by photon therapy (50 Gy in 2 Gy fractions). Assuming a relative biological effectiveness (RBE) of 1.1, and an α/β ratio of 3 Gy or 1.5 Gy, the equivalent dose in 2 Gy fractions (EDQ2) is 87 and 94 Gy (RBE), respectively, at the prescribed dose to the isocenter. Including the RBE correction, the proton fraction was 5.5 Gy (RBE). Before the treatment decision was finalized, the pathologic diagnosis of prostate cancer was reviewed at the Department of Pathology at Uppsala University Hospital.

The proton boost was given with the patient immobilized in the lithotomy position using a table that was constructed in-house for perineal treatment. A 180 MeV beam was delivered at The Svedberg Laboratory in Uppsala. An individually shaped aperture was applied to the perineal beam entrance. A rectal retraction rod was fixed at a length of 7–8 cm and was in place during the computer tomography (CT) for treatment planning and for each proton fraction. Three or four radiopaque gold markers allowed us to verify the position of both the prostate and the rectal rod at the CT imaging facility. The markers were also used for patient positioning at the daily proton fraction by orthogonal X-ray imaging. The details regarding the positioning, fixation, and dose distribution using the rectal retraction rod were described previously [16].

Photon therapy was given with the patient in a supine position, and 3D-conformal radiotherapy was used for local prostate treatment. The details regarding clinical target volume (CTV) and the margins for the various risk categories and radiation technique were described previously [11]. Patients allocated to elective irradiation of the pelvic lymph nodes received intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) in 2 Gy fractions to 50 Gy.

Follow-up

Tumor response was assessed clinically and by PSA analysis every 3 months for 2 years, then every 6 months up to 5 years, and thereafter yearly until death. Biochemical failure was defined according to the RTOG-ASTRO Phoenix criteria [17]. At an early stage of PSA relapse, or if tumor recurrence or metastases were suspected based on clinical symptoms, extended radiological imaging was performed to localize any disease relapse. We aimed to distinguish between locoregional failure and distant metastases. Imaging included bone scan, CT of the abdomen and thorax, and magnetic resonance imaging (MRI) of the pelvis. If these were negative, ^{11}C-acetate positron emission tomography (PET)/CT and (18) F-NaF PET/CT were also performed. Biopsies of the relapse site were generally not performed.

Outcome analyses and statistics

We analyzed several outcome measures, including the probability of being free of PSA relapse, locoregional relapse, and distant metastasis. Prostate cancer-specific survival, metastasis-free survival, and overall survival were also estimated. All endpoints were measured from the radiotherapy start date. Metastasis-free survival (MFS) was recently shown to be a strong surrogate for overall survival [18]. When estimating MFS, the events of interest were distant metastasis (not including locoregional relapse) or death from any cause.

Outcome analyses were performed for risk group classification according to both the NCCN [12] and the ISUP guidelines [19]. The NCCN classification is based on a four-tiered Gleason grouping as well as on T-stage and pre-treatment PSA. ISUP classification is based on a five-tiered Gleason grade grouping (GGG) that is defined as follows: Group 1, Gleason's score ≤6; Group 2, Gleason's

Table 1
Patient characteristics.

	N = 504
Year of treatment (%)	
≤2005	136 (27.0)
>2005	368 (73.0)
Age at diagnosis	
Median (Min, Q1, Q3, Max)	66 (45, 62, 70, 79)
T stage (%)	
T1/T2a	225 (44.6)
T2b/T2c	99 (19.6)
T3a	126 (25.0)
T3b	42 (8.3)
T4	12 (2.4)
N stage (%)	
N0	389 (77.2)
N1	0 (0.0)
NX/Missing	115 (22.8)
M stage (%)	
M0	294 (58.3)
M1	0 (0.0)
MX/Missing	210 (41.7)
Gleason's score (%)	
≤6	201 (39.9)
7	176 (34.9)
8–10	127 (25.2)
Gleason's Grade Group (%)	
1 (6)	201 (39.9)
2 (3 + 4)	123 (24.4)
3 (4 + 3)	53 (10.5)
4 (8)	56 (11.1)
5 (9–10)	71 (14.1)
PSA ng/mL	
Median (Min, Q1, Q3, Max)	11 (1, 6.7, 19, 158)
PSA ng/mL (%)	
<10	227 (45.0)
10–20	167 (33.1)
>20	110 (21.8)
Prostate volume mL	
Median (Min, Q1, Q3, Max)	37 (14, 27.5, 50, 120)
Missing (%)	17 (3.4)
NCCN risk group (%)	
Low risk	94 (18.7)
Intermediate risk	158 (31.3)
High risk	135 (26.8)
Very high risk	117 (23.2)
Planned ADT (%)	
Yes, <6 months	119 (23.6)
Yes, ≥6 months	158 (31.3)
No	227 (45.0)

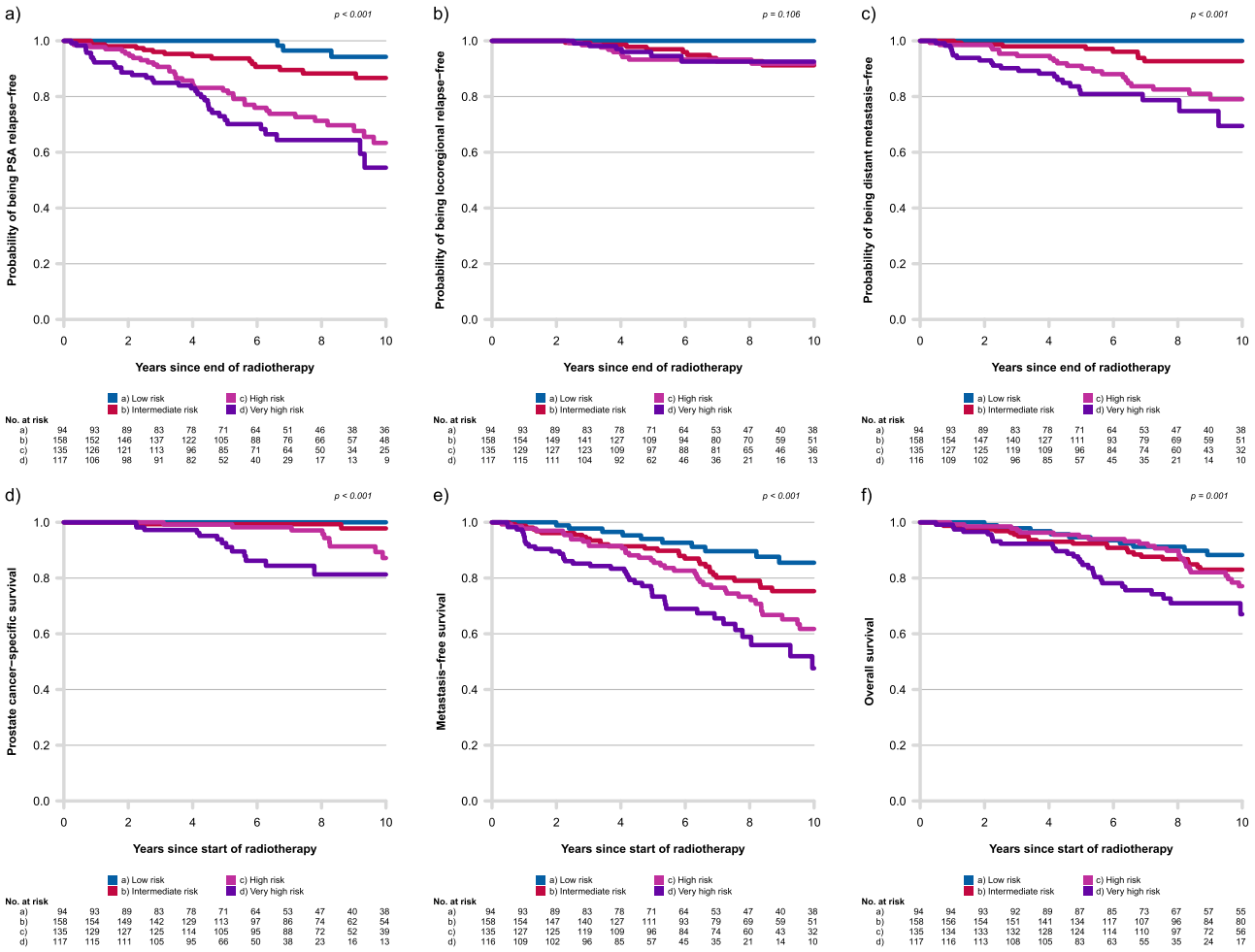

Fig. 1. Outcomes according to NCCN risk groups (a) PSA relapse-free (b) locoregional relapse-free (c) distant metastasis-free (d) prostate cancer-specific survival (e) metastasis-free survival (f) overall survival.

score 3 + 4; Group 3, Gleason's score 4 + 3; Group 4, Gleason's score 8; and Group 5, Gleason's score 9–10.

The Kaplan–Meier method was used to estimate the probability of being event-free. Differences between risk groups were determined with the log-rank test. Multivariable Cox proportional hazards models were used to assess the independent impact of GGG after adjustment for T-stage, pre-treatment PSA, and endocrine therapy. The year of treatment was classified as being before 2005 or later due to a change in Gleason's grading by ISUP that was implemented that year [13]. Adjusted Kaplan–Meier's curves were produced from the Cox proportional hazards models for each of the five ISUP risk groups. The underlying distribution of the other covariates in the models was used in the calculations of the adjusted curves.

The discrimination of the formerly three-tiered [12] and the current four-tiered NCCN [20] classifications and the newly proposed five-tiered GGG by ISUP [19] were compared using receiver operating characteristic curves and the corresponding areas under the curves [21]. Statistical analyses were performed using the R statistical software package [22].

Toxicity analyses for bladder and bowel function were based on both the physician's evaluations and patient self-administered questionnaires before the start of any therapy and at every follow-up visit. The questionnaire translated from SOMA-LENT [14] covered scoring (score 0–10) of functions and symptoms from the genitourinary and gastrointestinal tract. The information in these questionnaires was for the present analyses converted to the RTOG grading system for GU and GI pre-treatment symptoms and treatment induced side effects [15]. The adverse events' details were reported previously for the first 278 patients [11].

Estimates of the probability of late toxicities were calculated using the Kaplan–Meier method. The analysis of toxicity included only events occurring or persisting at least three months after the end of radiotherapy; patients were censored at the date of PSA relapse. Multivariate analysis was performed using Cox proportional hazards models, and results are presented as hazard ratios with 95 percent confidence intervals. The variables used in this analysis included age, NCCN risk group, nodal RT, smoking, diabetes, PTV proton volume, TUR-P, and baseline RTOG score. The prevalence of late toxicities was estimated using the Aalen–Johansen estimator [23] for multi-state models. This gives an estimate of the probability of a patient suffering from toxicity at a certain time point, given that the patient is still alive.

The Regional Ethical Review Board in Uppsala approved the study. All patients gave their informed consent. The data base was closed for analysis first of January 2019.

Results

Out of the 531 treated patients, 14 were lost to follow-up. Eleven patients with N1 disease, and 2 patients with M1 disease were excluded. A total of 504 patients with stages T1-T4NX-N0MX-M0 disease were included in the efficacy analyses. The characteristics of the patients are listed in Table 1. The median age at diagnosis was 66 years (45–79), and the median follow-up of the surviving patients was 113 months (43–193).

The T-classification was based on digital rectal examination. MRI was used in 356 (71%) of the patients for target definition and lymph node assessment. Surgery for pelvic lymph node analysis was performed in 78 (15%) patients. Bone scintigraphy was performed in high-risk patients. The high-risk and very high-risk patients were usually staged by extensive imaging, including whole body MRI, (11)C-acetate PET/CT, and (18)F-NaF PET/CT, due to their enrollment in imaging studies [24].

Out of the 504 patients, 94 were low risk and 158 intermediate risk; 118 patients (75%) in the intermediate risk group had more than one risk factor, or Gleason's score 4 + 3, or 50% or more positive core biopsies, and were classified as unfavourable risk according to the NCCN classification [12]. High-risk disease was diagnosed in 135 patients and very high risk in 117, together constituting 50% of the patients in the cohort; the very high-risk group included patients with Gleason's score 8 in more than 4 core biopsies, or 4 + 5 in more than 4 biopsies, or 5 + 4, or 10, or stage T3b/T4 according to the NCCN classification [12].

Table 2a
Kaplan–Meier's estimates at 5 and 10 years after start of radiotherapy with 95% confidence limits in parentheses, per NCCN risk group.

	5 years	10 years
Net probability of being PSA relapse-free		
NCCN risk group		
Low risk	1.000 –	0.942 (0.881–1.000)
Intermediate risk	0.937 (0.897–0.978)	0.867 (0.803–0.936)
High risk	0.821 (0.756–0.892)	0.633 (0.535–0.750)
Very high risk	0.715 (0.631–0.811)	0.545 (0.410–0.723)
Net probability of being locoregional relapse-free		
NCCN risk group		
Low risk	1.000 –	1.000 –
Intermediate risk	0.970 (0.941–1.000)	0.912 (0.857–0.971)
High risk	0.933 (0.888–0.979)	0.918 (0.867–0.972)
Very high risk	0.946 (0.899–0.994)	0.925 (0.867–0.988)
Net probability of being distant metastasis-free		
NCCN risk group		
Low risk	1.000 –	1.000 –
Intermediate risk	0.980 (0.958–1.000)	0.927 (0.878–0.978)
High risk	0.910 (0.861–0.962)	0.790 (0.710–0.879)
Very high risk	0.809 (0.734–0.892)	0.694 (0.563–0.856)
Prostate cancer-specific survival		
NCCN risk group		
Low risk	1.000 –	1.000 –
Intermediate risk	0.993 (0.980–1.000)	0.978 (0.947–1.000)
High risk	0.992 (0.976–1.000)	0.872 (0.793–0.958)
Very high risk	0.925 (0.873–0.981)	0.813 (0.718–0.920)
Metastasis-free survival		
NCCN risk group		
Low risk	0.940 (0.891–0.993)	0.855 (0.773–0.946)
Intermediate risk	0.906 (0.860–0.954)	0.753 (0.676–0.839)
High risk	0.864 (0.805–0.926)	0.617 (0.523–0.729)
Very high risk	0.733 (0.652–0.825)	0.476 (0.348–0.652)
Overall survival		
NCCN risk group		
Low risk	0.946 (0.902–0.993)	0.883 (0.816–0.955)
Intermediate risk	0.924 (0.883–0.966)	0.830 (0.768–0.897)
High risk	0.948 (0.911–0.986)	0.771 (0.694–0.857)
Very high risk	0.857 (0.795–0.925)	0.670 (0.563–0.798)

Stage T3/T4N0M0 disease was diagnosed in 180 (36%) patients, and a pre-treatment PSA >40 ng/ml in 31 (6%). Of note, 146 (29%) patients had a prostate volume larger than 55 cc, and 56 (11%) patients larger than 75 cc.

Androgen deprivation therapy (ADT) was given to 277 patients (55%). ADT comprised 4 weeks of bicalutamide therapy; 2 weeks after starting bicalutamide therapy, the patients also began receiving gonadotropin-releasing hormone (GNRH) therapy. A total of 16 (17%) low-risk and 51 (32%) intermediate-risk patients received ADT for a median time of 5 months. Of the high-risk and very high-risk patients, 103 (76%) and 107 (91%) received ADT for a median of 9 and 24 months, respectively. Adjuvant treatment with 50 Gy in 25 fractions to the pelvic lymph nodes was prescribed to 16% of the high-risk and to 60% of the very high-risk patients, in total 92 patients.

A total of 93 (18%) patients developed PSA relapse. The probability of being PSA relapse-free stratified by NCCN risk category is shown in Fig. 1a and Table 2a; notably, the probability was significantly dependent on risk group ($p < 0.001$). The adjusted probability of being PSA relapse-free is shown for GGG 1–5 in Fig. 2a and Table 2b. GGG 2–5 were independently predictive compared with GGG 1. In addition, higher T-stage and PSA above 20 ng/ml were independent predictors of higher risk of PSA relapse, while ADT $\geq$6 months reduced the risk (Table 3 suppl.).

Locoregional failure occurred in 29 (5.8%) patients. Local failure was diagnosed in 17 (3.4%) patients by functional MRI and/or (11) C-acetate PET/CT. Regional lymph node relapse was identified in 17 (3.4%) patients, 16 of whom had not received pelvic nodal treatment. Notably, 5 patients had both local and lymph node relapse in the pelvis; these 5 had also distant metastases and belonged to the very high risk-group. There was no regional relapse in the low- risk group, but 3 in the unfavourable intermediate-risk group. Notably, among the 252 patients with high or very high-risk disease, regional relapse occurred in 1 out of 92 patients (1.1%) and in 13 out of 160 patients (8%), receiving prophylactic nodal irradiation compared to those who did not, respectively ($p < 0.05$, Fisher's exact test).

The probability of being locoregional relapse-free stratified by NCCN risk category is shown in Fig. 1b and Table 2a, and was independent of risk group ($p = 0.106$). The adjusted probability of being locoregional relapse-free is shown for GGG 1–5 in Fig. 2b and Table 2b. Only T3/T4 stage was associated with significantly higher risk of locoregional failure ($p = 0.013$) (Table 3 suppl.).

A total of 56 (11%) patients had distant metastases: 13 patients only had peripheral lymph node metastases, 25 patients only had bone metastases, and 18 patients had both. The probability of being distant metastasis-free stratified by NCCN risk category is shown in Fig. 1c and Table 2a, and was dependent on the risk group ($p < 0.001$). The adjusted probability of being distant metastasis-free is shown for GGG 1–5 in Fig. 2c and Table 2b. GGG 2, 3 and 5 compared with GGG 1, higher T-stage, and PSA >20 ng/ml were independent risk factors for distant metastasis (Table 3 suppl.).

In this cohort, 27 (5%) patients died from prostate cancer. The probability of prostate cancer-specific survival stratified by NCCN risk category is shown in Fig. 1d and Table 2a, and was dependent on the risk group ($p < 0.001$). Adjusted prostate cancer-specific survival is shown for GGG 1–5 in Fig. 2d and Table 2b. GGG 5 and T3/T4-stage were the only risk factors observed for prostate cancer-specific survival (Table 3 suppl.).

The probability of metastasis-free survival stratified by NCCN risk group is shown in Fig. 1e and Table 2a, and was dependent on the risk group ($p < 0.001$). Adjusted metastasis-free survival for GGG 1 to 5 is shown in Fig. 2e and Table 2b. GGG 2 and GGG 5 were independently predictive compared to GGG 1. PSA >20 ng/ml was also an independent risk factor (Table 3 suppl.).

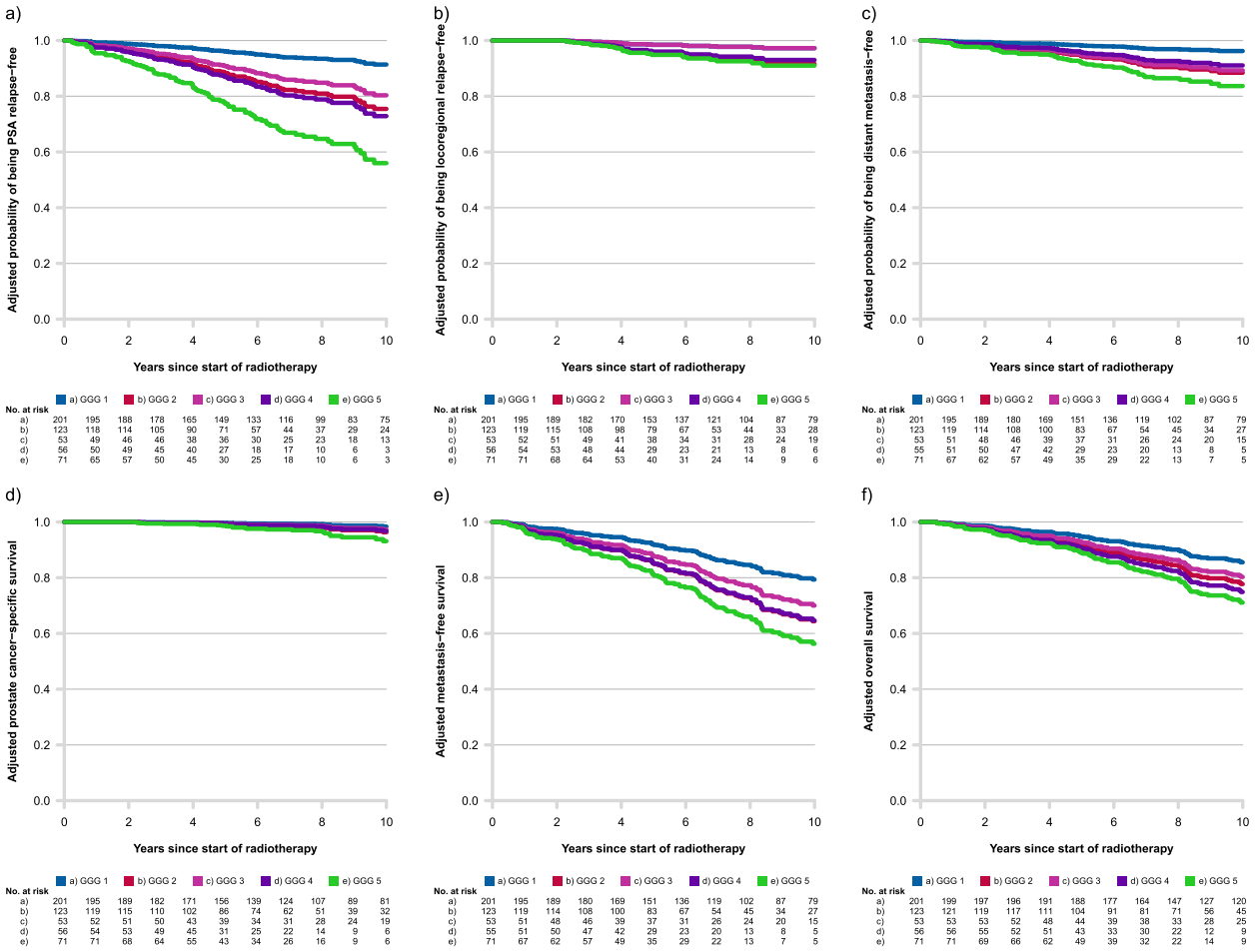

Fig. 2. Outcomes according to ISUP risk group (a) adjusted PSA relapse-free (b) adjusted locoregional relapse-free (c) adjusted distant metastasis-free (d) adjusted prostate cancer-specific survival (e) adjusted metastasis-free survival (f) adjusted overall survival.

There were 115 deaths. The probability of overall survival stratified by NCCN risk group is shown in Fig. 1f and Table 2a, and was dependent on the risk group ($p = 0.001$). The adjusted overall survival for GGG 1–5 is shown in Fig. 2f and Table 2b. Only GGG 5, as compared to GGG 1, had a significant impact on overall survival ($p = 0.026$) (Table 3 suppl.).

The concordance index (C-index) as determined for the three- and four-tiered Gleason grouping (former NCCN and current NCCN classifications) and the five-tiered GGG (ISUP classification) and for each outcome measure is shown in Table 4 suppl. The newly proposed GGG did not improve discrimination for any of the endpoints. Rather, the three-tiered NCCN classification performed at least as well as the four- and five-tiered groupings.

In the whole cohort of 504 patients, 444 were evaluated for GU- and 436 for GI-toxicity. The distribution of RTOG baseline score for GU pre-existing symptoms was: 174 score 0, 164 score 1, 106 score 2, 22 score 3 and missing data for 38 patients. The baseline score for GI was: 389 score 0, 67 score 1, 19 score 2, 1 score 3 and missing data for 29 patients. The risk estimates of adverse events were restricted to patients with baseline score 0–2.

The multivariate analysis, presented in Table 5 suppl., showed that baseline score 2 was the strongest independent risk factor for the incidence of GU grade 3+ adverse events (HR 4.31, $p < 0.001$). Having diabetes (62 patients, HR 2.18, $p = 0.010$) and passed pre-treatment TUR-P (18 patients, HR 2.32, $p = 0.047$) were also independent risk factors. For the incidence of GI grade 2+ adverse events, baseline score 1 was the most important predictor (HR 4.71, $p < 0.001$), followed by nodal RT (HR 2.2, $p = 0.012$).

The incidence and prevalence of GU and GI adverse events grade 3+ over a 10 year period are presented in Fig. 3 and Table 6 suppl. At 5 years the incidence of GU adverse events for patients with baseline score 0, 1 and 2 was 8%, 11% and 35%, respectively; the corresponding figures for the prevalence was 2%, 7% and 11%. At 10 years the incidence figures were 13%, 11% and 35%, and the prevalence 6%, 7% and 11%, respectively.

At 5 years the incidence of GI adverse events grade 3+ for patients with baseline score 0 and 1 was 1% and 5%, respectively, and the prevalence 0% in both cases. At 10 years the outcome was the same, i.e. no progress of GI morbidity was observed between 5 and 10 years.

Discussion

The 5- and 10-year biochemical control rates were 100% and 94% in low-risk patients; 94% and 87% in intermediate-risk patients; 82% and 63% in high-risk patients; and 72% and 55% in very high-risk patients. This was achieved using a proton boost with 4 daily fractions of 5 Gy followed by 50 Gy photon therapy, i.e. a total of 70 Gy, equivalent to 87 Gy (RBE) ($\alpha/\beta = 3$ Gy) and 94 Gy (RBE) ($\alpha/\beta = 1.5$ Gy) in 2 Gy fractions. The key question is whether this treatment protocol is as good as treatments described by other studies in terms of tumor control and safety.

Table 2b
Adjusted outcome estimates at 5 and 10 years after start of radiotherapy with 95% confidence limits in parentheses, per Gleason's Grade Group. Estimates from the multivariate Cox proportional hazards models shown in Table 3.

	5 years	10 years
Net probability of being PSA relapse-free		
Gleason's Grade Group		
1 (6)	0.961 (0.938–0.984)	0.914 (0.868–0.962)
2 (3 + 4)	0.882 (0.833–0.935)	0.755 (0.662–0.860)
3 (4 + 3)	0.907 (0.853–0.965)	0.803 (0.703–0.918)
4 (8)	0.869 (0.791–0.955)	0.729 (0.591–0.898)
5 (9–10)	0.773 (0.672–0.889)	0.560 (0.409–0.766)
Net probability of being locoregional relapse-free		
Gleason's Grade Group		
1 (6)	0.984 (0.970–1.000)	0.972 (0.947–0.998)
2 (3 + 4)	0.952 (0.918–0.988)	0.916 (0.859–0.976)
3 (4 + 3)	0.985 (0.962–1.000)	0.973 (0.934–1.000)
4 (8)	0.960 (0.912–1.000)	0.930 (0.848–1.000)
5 (9–10)	0.949 (0.895–1.000)	0.910 (0.822–1.000)
Net probability of being distant metastasis-free		
Gleason's Grade Group		
1 (6)	0.982 (0.968–0.997)	0.962 (0.932–0.993)
2 (3 + 4)	0.945 (0.911–0.980)	0.884 (0.819–0.955)
3 (4 + 3)	0.949 (0.910–0.990)	0.893 (0.818–0.975)
4 (8)	0.958 (0.919–0.998)	0.910 (0.834–0.994)
5 (9–10)	0.921 (0.866–0.979)	0.837 (0.733–0.955)
Prostate cancer-specific survival		
Gleason's Grade Group		
1 (6)	0.997 (0.992–1.000)	0.984 (0.962–1.000)
2 (3 + 4)	0.993 (0.983–1.000)	0.963 (0.921–1.000)
3 (4 + 3)	0.995 (0.986–1.000)	0.973 (0.935–1.000)
4 (8)	0.994 (0.983–1.000)	0.967 (0.919–1.000)
5 (9–10)	0.986 (0.968–1.000)	0.931 (0.851–1.000)
Metastasis-free survival		
Gleason's Grade Group		
1 (6)	0.919 (0.889–0.951)	0.794 (0.729–0.863)
2 (3 + 4)	0.852 (0.802–0.905)	0.644 (0.553–0.749)
3 (4 + 3)	0.878 (0.818–0.942)	0.700 (0.583–0.841)
4 (8)	0.853 (0.781–0.932)	0.646 (0.511–0.818)
5 (9–10)	0.811 (0.733–0.898)	0.563 (0.428–0.741)
Overall survival		
Gleason's Grade Group		
1 (6)	0.948 (0.925–0.971)	0.855 (0.806–0.908)
2 (3 + 4)	0.917 (0.882–0.954)	0.777 (0.704–0.858)
3 (4 + 3)	0.927 (0.885–0.972)	0.803 (0.706–0.912)
4 (8)	0.906 (0.851–0.964)	0.749 (0.631–0.888)
5 (9–10)	0.889 (0.832–0.951)	0.711 (0.590–0.856)

Zietman et al. [10] used a proton boost with 16 conventional fractions followed by 50 Gy photon therapy to 79 Gy (RBE). In their study, the 5- and 10-year biochemical control rates were 95% and 93% in low-risk patients and 79% and 70% in intermediate-risk patients (D'Amico risk groups, ASTRO definition of PSA failure, and no ADT). A comparison of their study with ours suggests that proton therapy boost with high doses per fraction results in biological dose escalation that is at least as efficient as dose escalation with conventional fractions. Regarding adverse events, the prevalence of grade $\geq$3 GU and GI toxicity at 5 years was 2 % and 0%, respectively, for baseline symptom-free patients, the same as reported by Zietman et al. [10,25].

The results of three recent large non-inferiority trials [4–6] suggest that moderate hypofractionation with 2.5–3.0 Gy fractions can replace conventional fractionation of 74–78 Gy, at least for low- and intermediate-risk patients. The outcomes of three recent superiority trials [7–9] suggest that moderate hypofractionation with 2.7–3.4 Gy fractions is not superior to conventional fractionation of 76–80 Gy for intermediate- and high-risk patients.

Randomized trials have not yet shown improvement in tumor control using biological dose escalation above 80 Gy with external beam radiotherapy only. To understand the potential benefit of dose escalation, Zaorsky et al. developed guidelines to address the question, "What is the ideal radiotherapy dose to treat prostate cancer?" The guidelines were based on a meta-analysis of the efficacy of biologically equivalent dose (BED) escalation [26]. Using an α/β ratio of 1.5 Gy, the 5-year biochemical control rate was determined as a function of BED over the 144–307 Gy range. External photon beam therapy with both hypofractionation and conventional fractionation was included in the analysis. Notably, BED above 200 Gy was reached using various high dose-rate brachytherapy techniques. There was a strong relationship between biochemical control and a BED up to 200 Gy that reflects the efficacy of biological dose escalation up to that level, corresponding to 86 Gy in 2 Gy fractions. In contrast, at a BED of 200 Gy, the biochemical control rate plateaued at 96% (95 CI: 94–97), 89% (82–98), and 81% (67–96) for the low-, intermediate-, and high-risk groups, respectively. Therefore, increasing efficacy should not be expected above a BED of 200 Gy.

Importantly, the first and only randomized study so far, the ASCENDE-RT trial [27], confirmed the conclusion from the meta-analysis that improvement in biochemical control can be reached by exceeding the current standard dosage, 78 Gy in 2 Gy given with external photon therapy, for intermediate- and high-risk patients albeit this was achieved at the expense of higher late GU morbidity [28].

The BED for the present study was 220 Gy. The 5-year probabilities for PSA control were 100%, 94%, and 82% for the low-, intermediate-, and high-risk groups, respectively, reaching the highest possible level as predicted by the meta-analysis. Also, the probability of 72% PSA control reached for the very high-risk patients can be considered satisfactory.

In the present study, the outcome of each event, except for local–regional relapse, was significantly dependent on the NCCN risk group (Fig. 1). Fig. 2 shows the independent predictive impact of the ISUP GGG on all outcome measures. Multivariate analyses showed that the GGG predicted the risk of PSA relapse. In particular, GGG 5 was associated with increased risk of distant metastasis as well as with prostate cancer-specific, metastasis-free, and overall survival (Table 3 suppl.). Notably, neither the NCCN nor the ISUP classification predicted the risk of locoregional relapse, supporting the notion from the meta-analysis that the proton boost schedule we used results in the maximum level of tumor control, that might be possible to achieve.

Overall, both the three- and four-tiered Gleason groupings in the NCCN classifications showed higher predictive discrimination than the ISUP 5-tired GGG for all outcome measures (Table 4 suppl.). In contrast, Spratt et al. [21] found that the ISUP risk grouping showed higher discrimination than the three-tiered NCCN classification, when validated for PSA-relapse, distant metastasis, and prostate cancer-specific survival after radiotherapy. The distribution of the GGGs was similar in both studies. Notably, the proportion of patients with T3/T4 tumors was only 10% in the cohort analyzed by Spratt et al., whereas the proportion was 36% in our study. The inclusion of the T-stage as a risk factor supported the use of NCCN classification in our analysis.

Prolonged ADT for 6 months or more, reduced the risk of PSA relapse (HR 0.45, $p = 0.018$), and resulted in a trend for lower risk of locoregional failure (HR 0.30, $p = 0.06$) and distant metastasis (HR 0.57, $p = 0.20$); no benefit was observed for prostate cancer-specific, metastasis-free and overall survival (Table 3 suppl.).

Importantly, adjuvant regional lymph node treatment to high- and very high-risk patients significantly reduced the risk of relapse in pelvic nodes, without increasing GU or GI grade 3+ events.

Regarding treatment failure, 93 patients (18%) in our study developed PSA relapse, and the relapse sites were identified in 78 patients before ADT was prescribed. For those with first and only

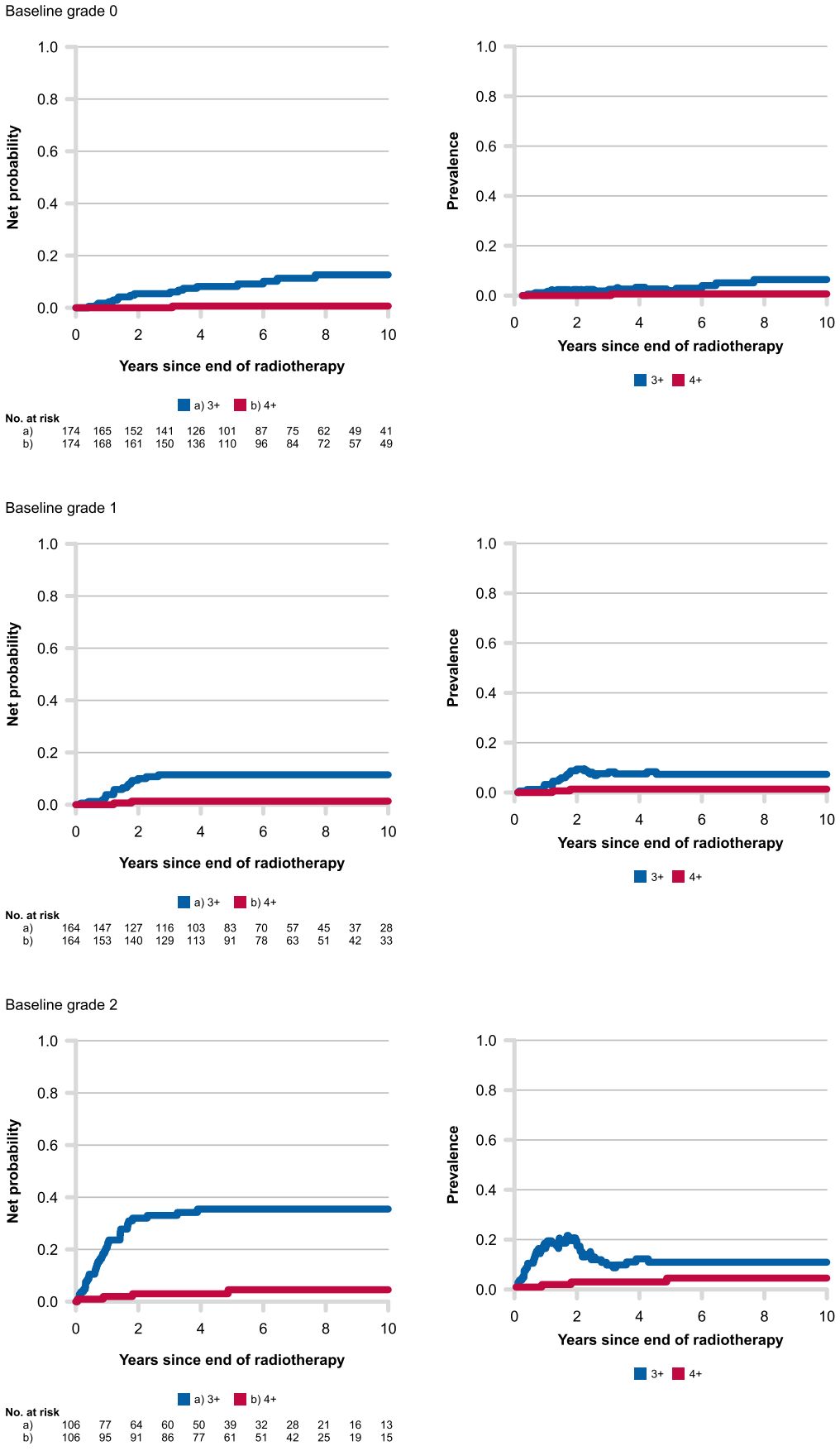

Fig. 3. Incidence and prevalence for GU and GI adverse events separated by baseline RTOG score.

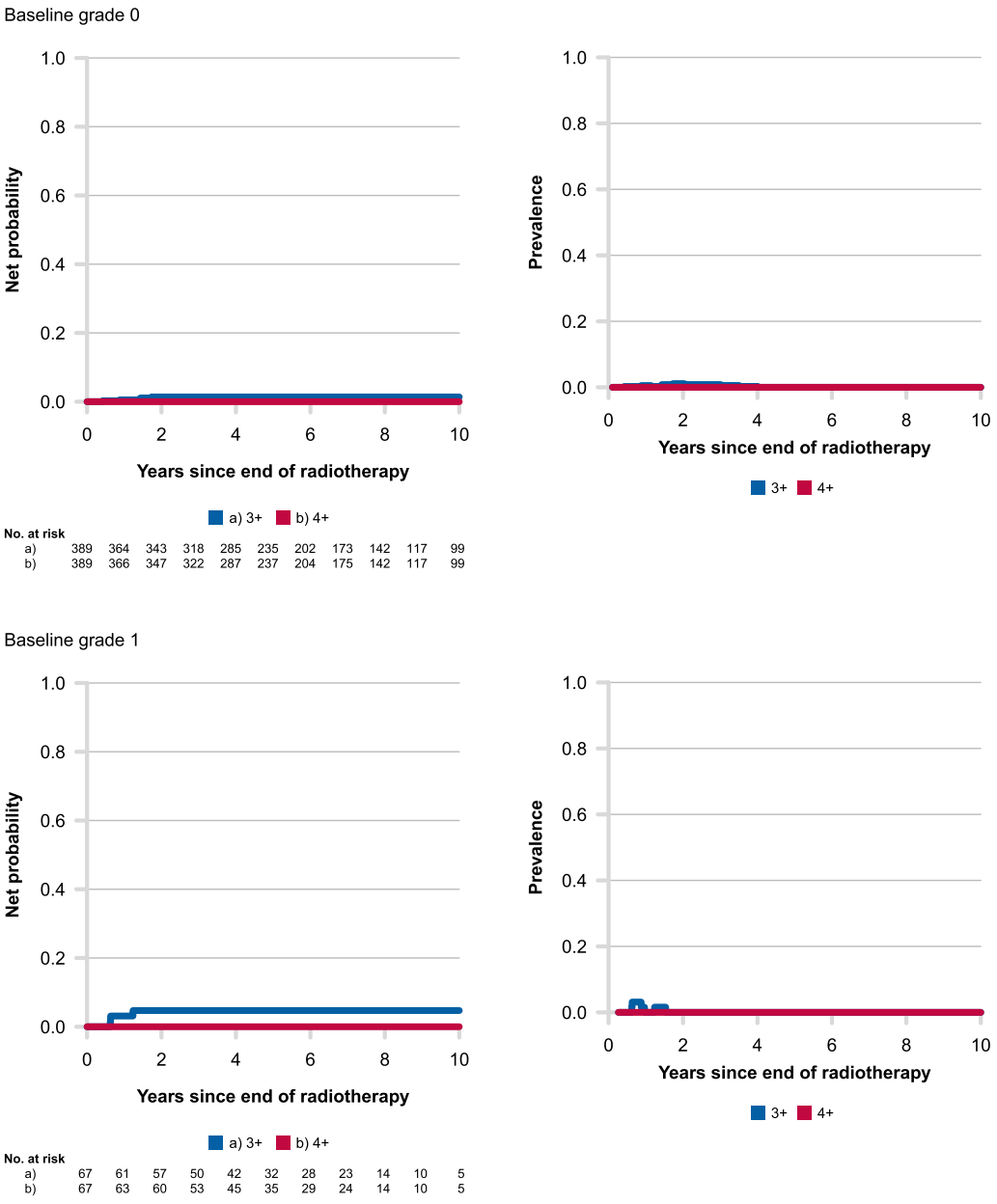

Fig. 3 (*continued*)

relapse, the relapse sites were as follows: 12 local, 12 pelvic lymph nodes, 25 bone, and 13 peripheral lymph nodes. The outcomes might be improved by the use of intra-prostatic boost based on imaging and by the use of systematic pelvic nodal irradiation plus long-term ADT in patients with high-risk and very high-risk disease. The advantages of such measures include the use of advanced imaging in the staging procedure and accurate contouring of the prostate and the organ at risk for dose planning.

The hypofractionated proton therapy that was delivered in a single perineal beam and the high dose-rate brachytherapy schedule used at our clinic to boost 50 Gy corresponded to BED 220 Gy and BED 270 Gy, respectively. The long-term outcomes for biochemical relapse, distant metastasis, and prostate cancer-specific survival per risk group were very similar for both treatments [29].

Concerning grade 3+ toxicity over a 10 year period the prevalence of GI adverse events was 0–1% and for GU adverse events 6–11% for both techniques [11,29,30]. Of note, in the use of proton boost pretreatment symptoms predicted a higher risk of adverse events, Table 5 suppl. and Table 6 suppl. The advantage with the proton boost compared to the brachytherapy boost is that it is applicable to patients with a large prostate volume. In the present study 29% of the patients had a prostate volume larger than 55 cc and 11% larger than 75 cc. Importantly, neither the proton boost volume nor the pelvic node treatment had impact on the long-term risk of GU and GI grade 3+ toxicity.

Both pre-treatment TUR-P and diabetes doubled the risk of GU grade 3+ adverse advents (Table 5 suppl.), and therefore determined substantially the late prevalence. Furthermore, patients with other comorbidity like rheumatoid arthritis on methotrexate treatment, and Parkinson's disease were also included and contributed to grade 3+ events.

The perineal proton boost using a rectum retracting device was introduced by Shipley at al at the Massachusetts General Hospital already in the seventies [31]. This treatment set up has been eval-

uated in two phase 3 trials supporting the efficacy of dose escalation up to 76–79 Gy for low-, intermediate- and high-risk prostate cancer [10,32]. We have done dosimetry comparisons between the perineal boost technique and non-perineal dose delivery with IMPT. In general, perineal boost gave a superior dose distribution (data not shown).

Our cohort includes 180 patients (36%) with T3/T4 tumors. Of note, very few data on 5-year tumor outcome have been reported for this locally advanced group: Harvard [32] 103 patients, Loma Linda [33] 50 patients, Uppsala [11] 81 patients, Florida [34] 14 patients, and Japan [35] 219 patients. Therefore, there is a need of a lot more experience of the use of proton radiotherapy for locally advanced disease to settle the question about the proper indications for protons.

The main strength of our study was its use of extensive imaging both for staging and for identification of the relapse site upon PSA failure. One weakness of the study was the retrospective nature of the data, and another weakness was the lack of biopsies to confirm tumor relapse. There was no new central pathology review to ensure consistency in Gleason's scoring to validate the ISUP classification.

Here we report tumor curability and toxicity for patients with localized prostate cancer who were uniformly treated during a 13-year period using the proton facility at The Svedberg Laboratory in Uppsala. Proton boost with 5 Gy fractions to 20 Gy followed by 50 Gy photon therapy showed excellent long-term efficacy with acceptable late GU and very low GI side effects. The biochemical disease control of the physical dose of 70 Gy corresponded to a biological dose escalation that is at least equal to 86 Gy in 2 Gy fractions. This study provides evidence that supports the need for a prospective trial of hypofractionated proton boost using the new clinical proton facility at the Skandion Clinic in Uppsala, Sweden.

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Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.036.

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