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A multicentre phase II study of hypofractionated stereostatic boost in intermediate risk prostate carcinoma: a 5-year analysis of the CKNO-PRO trial

Short running title: Stereotactic boost in prostate carcinoma

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Conflict of interest statement:

The Oscar Lambret Center had a collaboration agreement with Accuray Incorporated between 2009 and 2017. Pr. Lartigau reports grants from Accuray, during the conduct of the study. The other authors have no conflict of interest to declare.

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A multicenter phase II study of hypofractionated stereotactic boost in intermediate risk prostate carcinoma: a 5-year analysis of the XXXX trial

Abstract

Background

The aim of this analysis was to assess the 5-year tolerance and survival in patients undergoing hypofractionated stereotactic boost after external beam radiotherapy (EBRT) for intermediate-risk prostate cancer.

Methods and material

Between August 2010 and April 2013, 76 patients with intermediated-risk prostate carcinoma were included in the study. A first course delivered 46 Gy using conventional fractionation. The second course delivered a boost of 18 Gy (3x6Gy) within 10 days using stereotactic body radiation therapy (SBRT). Gastrointestinal (GI) and genitourinary (GU) toxicities were assessed according to NCI-CTCAE (v4.0). Secondary outcome measures were overall, biochemical relapse-free, relapse-free survival, PSA kinetics, and patient functional status (urinary and sexual) according to the IIEF5 and IPSS questionnaires.

Results

Sixty (79%) patients were treated by Cyberknife and 16 (21%) by linear accelerator. Median follow-up was 62 months (range, 29-69 months). The cumulative incidence of GU and GI grade ≥ 2 toxicities at Month 60 after the end of RT was 1.4% (95% CI: 0.1%-6.6%) and 9.3% (95% CI: 4.1%-17.1%), respectively. Biochemical relapse-free and relapse-free survival rates at 5 years were 87.4% (95% CI: 77.1%-93.2%) and 86.2% (95% CI: 75.8-92.3), respectively. The mean (SD) PSA variation within 3 months and 5 years post-RT was -1.20 ng/mL/month (0.79) and -1.30 ng/mL/year (1.05), respectively. There was no significant difference between the IPSS QoL score between inclusion and month 60. For IIEF-5 there was a significant difference between inclusion and month 60 ($p=0.005$) with a higher proportion of severe/non-interpretable disorders at 60 months.

Conclusions

The results of the trial demonstrate that the EBRT and SBRT combination is well tolerated and yields good efficacy results. These data provide a good basis for comparing EBRT and brachytherapy boost to EBRT and SBRT boost in future prospective studies .

Trial registration: ClinicalTrials.gov NCTXXXX.

Introduction

Public awareness with earlier detection and improved treatments have led to lower death rates among patients with prostate cancer. With longer life expectancies, the challenge lies now in maintaining urinary and sexual functioning as well as diminishing side effects that impair quality of life (QoL).

According to the 2019 NCCN guidelines, radiation therapy (RT) is recommended for men with intermediate-risk prostate cancer (1). External beam radiotherapy (EBRT) or brachytherapy (BT) alone may be used for favourable intermediate risk cancer; in cases of unfavourable risk, low dose rate (LDR) or high dose rate (HDR) BT boost can be used together with EBRT. However, and despite improved biochemical relapse-free survival rates, the addition of BT is associated with an increase in toxicity, especially urinary (2, 3).

Stereotactic body radiation therapy (SBRT) may provide an alternative to BT. It delivers a high dose in a limited number of fractions with high accuracy. Despite higher doses per fraction, in patients treated exclusively by SBRT, the toxicity profile has been shown to be comparable to that with conventionally fractionated RT (4, 5).

We launched a study in which patients were treated with hypofractionated stereotactic boost after conventional RT for intermediate-risk prostate cancer. In our interim analysis, we reported promising gastrointestinal (GI) and genitourinary (GU) toxicity profiles and relapse-free survival results (6).

The aim of the current analysis was to assess the updated (5-year) tolerance and survival data in patients undergoing hypofractionated stereotactic boost after conventional RT for intermediate-risk prostate cancer.

Materials and methods

Patients

The design and methodology of this national phase II multicenter study, conducted in 4 centers in France has been described already (6). Patients were included if they had histologically proven prostate adenocarcinoma and intermediate-risk prostate cancer according to the D'Amico classification (T2b and/or prostate specific antigen [PSA] between 10 and 20 ng/mL and/or a Gleason score of 7), ECOG performance status ≤ 1 , prostatic volume ≤ 80 cc, no adenopathy (lymph node < 1.5 cm on scanner or MRI and/ or in lymph node dissection), no metastasis (bone scan), no prior prostate cancer treatment (prostatectomy, chemotherapy, hormonotherapy > 3 months) or pelvic irradiation, IPSS score ≤ 10 , and a life expectancy ≥ 10 years.

The protocol was approved by the local ethics board (XXXX) and the study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent to participate. The study was registered on clinicaltrial.gov (XXXX) after initiation due to an administrative delay.

Treatment and follow-up

The first clinical target volume (CTV1) was the prostate and proximal half of the seminal vesicles; CTV2 boost was prostate only. Magnetic resonance imaging (MRI) and computerized tomography (CT) image fusion based on intra-prostatic fiducials was mandatory to define CTVs. Planning target volume for the first part of the treatment (PTV1) was defined as the addition of a 1 cm margin around the corresponding CTV1 and lowered to 0.5 cm posteriorly to spare the rectum. PTV2 was obtained by expanding 5 mm around CTV2. During the first part of the treatment, 23 fractions (2 Gy/session) were delivered for a total dose of 46 Gy using 3D conformal radiotherapy or intensity modulated radiation therapy (IMRT).

During the second treatment part, hypofractionated stereotactic boost (3 fractions of 6 Gy) was delivered over 5 to 9 days every other day for a total dose of 18 Gy. The choice of radiation technique varied according to the centre. Planning requirements were the same for CyberKnife- and linear accelerator- based treatments. 95% of PTV received 18 Gy with a maximum of 115% of the prescribed dose. When feasible, the dose to the urethra volume + 3 mm had to be as close as possible to 6 Gy, and lower than 6.5Gy per fraction.

Fiducials were implanted before the first radiation to allow daily image-guided radiation therapy (IGRT) in patients treated with Cyberknife and linear accelerator (with tracking for

patients treated with Cyberknife). Daily IGRT was mandatory during the two parts of the treatment. Before dosimetry scanning and at each treatment session, patients were administered an enema in order to empty the bowels if necessary. Patients were instructed to drink 250-300 mL of water 45-60 minutes prior to RT. Rectal spacers were not used.

During the first part of the treatment, the mean (SD) rectum V46 and V40 were 3.0% (5.9%) and 28.4% (10.7%), respectively, and mean (SD) bladder V46 and V40 were 3.7% (4.9%) and 23.3% (10.8%), respectively.

For the stereotactic boost, the mean (SD) rectum V10, V13.5 and V18 were 28.6% (8.4%), 17.1% (5.7%) and 2.5% (3.8%), respectively, and mean (SD) bladder V10, V13.5 and V18 were 22.1% (10.6%), 12.9% (6.6%) and 2.4% (2.8%), respectively.

Patients did not take any androgen deprivation therapy (ADT) throughout the study. Digital rectal examinations and PSA assessments were performed every 3 months up to 1 year, then every 6 months up to 3 years and then every year up to 5 years.

IPSS and IIEF5 assessment

The prevalence of erectile and urinary dysfunctions at inclusion, and at 3, 6, 9, 12, 18, 24, 30, 36, 48 and 60 months was determined in all patients by using the 5-item version of the International Index of Erectile Function (IIEF-5) (7) and the International Prostate Symptom Score (IPSS), respectively (8). The possible scores for the IIEF-5 range from 1 to 25 and a score ≥ 22 is considered as normal erectile function and < 22 , erectile dysfunction. According to this scale, erectile dysfunction was classified into five categories: non-interpretable (1–4), severe (5–7), moderate (8-11), mild to moderate (12-16), mild (17-21), and normal erectile function (22–25). The non-interpretable category corresponds to patients that have fully completed the assessment, but whose score is equal to or lower than 4. It corresponds to patients having no or very little sexual activity and for whom erectile dysfunction is difficult to evaluate. The patients also responded to the IPSS Quality of Life Scale at the end of the questionnaire, with possible responses on feeling about the urinary conditions being « delighted », « pleased », « mostly satisfied », « mixed », « mostly dissatisfied », « unhappy » and « terrible ». Questionnaires were self-administered.

Statistical analyses:

The sample size was estimated using a single-step Fleming design (9). The incidence of grade 3–4 toxicity free below which the treatment does not warrant further investigations (p_0) was set at 85%. The minimal incidence of grade 3–4 toxicity required for the treatment to be deemed efficient and interesting (p_1) was set at 95%. With a type I error set at 5%, 76 evaluable patients were required to be recruited to achieve 90% power.

Categorical variables were described in terms of numbers and proportions (with 95% confidence interval [CI]). Continuous variables were summarized using medians and ranges. Primary outcomes were GI and GU toxicity according to the NCI-CTCAE v4.0 scale. Change from baseline in gastrointestinal function was assessed every 3 months following boost irradiation for 1 year and then every 6 months for 2 years and then every year. Toxicity occurring beyond 6 months after the end of RT are reported. Cumulative toxicity incidence was calculated using a competing risk approach considering the time interval from the end of RT to the occurrence of toxicity, with death without toxicity considered as a competing event; patients alive without toxicity were censored at the date of last follow-up.

Secondary outcome measures were PSA kinetics, overall, biochemical relapse-free and relapse-free survival, sexual toxicity according to the IIEF-5 questionnaire, and urinary discomfort according to the IPSS questionnaire.

Survival function was estimated from inclusion using the Kaplan-Meier method. Overall survival was calculated considering time to death from any cause. Biochemical relapse-free survival was estimated considering time to biochemical progression as defined by the Phoenix criteria for PSA increase (an increase of at least 2 ng/ml over PSA nadir) or to death from any cause. Relapse-free survival was estimated considering time to biochemical progression, local or distant relapse or to death from any cause. For all these survival functions, patients alive and without events were censored at the time of last news.

Time to biochemical relapse was estimated considering time to biochemical progression as defined by the Phoenix criteria; time to relapse was estimated considering time to biochemical progression, local or distant relapse; patients alive or dead without events were censored at the time of last news. Baseline PSA variation from baseline to follow-up at 3 months and 5 years post-RT was estimated for each patient by the coefficient of the linear regression model (variation in ng/mL/month or year).

IPSS and IIEF-5 at baseline and at 60 months were compared with each other using the McNemar test for paired data, in the population of patients evaluable at baseline and at 60 months.

All analyses were performed on intent-to-treat basis (ITT). An *ad-hoc* sensitivity analysis of efficacy was conducted excluding patients who did not meet D'Amico intermediate risk criteria. An *ad-hoc* sensitivity analysis of safety was performed excluding patients whose baseline IPSS score was >10.

Stata v15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP) was used for the statistical analyses.

Results

Patients

Between August 2010 and April 2013, 76 patients were prospectively included in this study. The median duration of first RT treatment was 34 days (range, 31–40). For the second part of the treatment, 60 (79%) patients were treated by Cyberknife and 16 (21%) by linear accelerator. The median gap between the two courses was 5 days (range, 1-17). Demographic, clinical and pathological characteristics of patients are presented in Table 1.

Median follow-up was 62 months (range, 29-69 months). All patients were included in the main ITT toxicity and efficacy analyses. Seventy-two patients were included in the sensitivity analysis of efficacy, excluding 3 patients with T2c staging and one patient with a baseline PSA level >20 ng/mL. Seventy-one patients were included in the sensitivity analysis of safety, excluding 5 patients with at baseline an IPSS level >10.

Toxicity

Grade ≥ 2 acute GI and GU toxicities were 13.2% and 23.7%, respectively. Further details are presented in a previous report (6).

Late GU toxicity:

One patient (1%) presented a late toxicity event of grade 2 related to treatment: urgency incontinence. No late grade >2 toxicity event was reported. The cumulative incidences of grade ≥ 1 GU toxicity at 36 and 60 months after the end of RT were 34.3% (95% CI: 23.9%-44.9%) and 38.5% (95% CI: 27.6%-49.3%), respectively. The cumulative incidence of grade ≥ 2 GU toxicity at 60 months after the end of RT was 1.4% (95% CI: 0.1%-6.6%) (Figure 1).

Late GI toxicity:

Eight patients (10.5%) presented grade ≥ 2 GI toxicity: 4 patients had radiation proctopathy (n=2 grade 2 and n=2 grade 3); 3 patients presented grade 2 proctitis; and one patient had grade 3 proctitis, grade 3 rectal haemorrhage, grade 2 gastrointestinal motility disorder and mucous stools. All toxicities were related to treatment.

The cumulative incidence of GI grade ≥ 2 toxicity at 60 months after the end of RT was 9.3% (95% CI 4.1%-17.1%) (Figure 2).

The results of the sensitivity analysis of safety are close to those from the ITT population and are presented in Appendix 1.

Survival

Six (7.9%) patients of the ITT population died during the study. The 5-year overall survival rate was 91.5% (95% CI: 81.9%-96.1%).

Biochemical relapse-free survival rate at 5 years was 87.4% (95% CI: 77.1%-93.2%) (Figure 3). Five-year time to biochemical relapse rate was 94.3% (95% CI: 85.6%-97.8%).

Five-year relapse free survival rate was 86.2% (95% CI: 75.8-92.3). Five-year time to relapse rate was 93.0% (95% CI: 84.1%-97.1%). The results of the sensitivity analysis of efficacy are close to those from the ITT population and are presented in Appendix 2

PSA kinetics

Median (range) PSA at inclusion was 7.48 ng/mL (2.91-22.40 ng/mL). Median (range) PSA between the two RT courses was 6.21 ng/mL (2.26-21.08 ng/mL) and at 3 months post-treatment it was 2.11 ng/mL (0.47-10.72 ng/mL). At 5 years, median PSA was 0.38 ng/mL (0.01-14.38 ng/mL) (Figure 4).

The mean (SD) PSA variation within 3 months post-RT was -1.20 ng/mL/month (0.79). The mean (SD) PSA decrease within 5 years (end of follow-up) was -1.30 ng/mL/year (1.05) and the median decrease was -1.02 ng/mL/year (range: -7.2 ; -0.35 ng/mL/year). The spaghetti plot of PSA over time is presented in Appendix 3.

IPSS

The median IPSS score related to urinary symptoms at inclusion was 5 (range 0-22) and 6 (range 0-22) at 60 months.

Regarding the IPSS quality of life score, at inclusion (N=74), 80% (N=59) of patients felt "mostly satisfied", "pleased" or "delighted", 12% (N=9) had a "mixed" feeling, and 8% (N=6) felt "unhappy" or "terrible" about their urinary condition.

At 60 months post-RT (N=41), over 81% (N=33) of patients felt "mostly satisfied", "pleased" or "delighted", 17% (N=7) had "mixed" feelings, and 2% (N=1) felt either "unhappy" or "terrible".

There was no significant difference between the IPSS QoL score between inclusion and month 60 ($p= 0.56$ with the McNemar test for paired data). Among the 40 patients with a calculable score at inclusion and at 60 months, 92.5% of patients ($N=37$) felt pleased both at inclusion and at 60 months. Two patients felt unhappy at inclusion and pleased at 60 months. Only one patient felt worse at 60 months (unhappy) compared to inclusion (pleased).

IIEF

The median IIEF-5 score at inclusion ($N=68$ patients) was 15.5 (range, 1-25). Respectively, 9% ($N=6$), 6% ($N=4$), 16% ($N=11$) and 24% ($N=16$) of patients had severe, moderate, mild to moderate or mild disorders and 21% ($N=14$) had a normal erectile function at inclusion; for 25% ($N=17$) of patients the score was not interpretable.

The median IIEF-5 score at 36 months ($N=55$) was 6 (range, 1-24). Respectively 7% ($N=4$), 7% ($N=4$), 16% ($N=9$) and 18% ($N=10$) of patients experienced severe, moderate, mild to moderate or mild disorders and 6% ($N=3$) had a normal erectile function at 36 months; for 46% ($N=25$) of patients the score was non interpretable.

Fifty-four patients had a score at inclusion and at 36 months. Among the 54 patients, 48% ($N=26$) of patients had a normal function/mild/moderate dysfunction both at inclusion and at 36 months; 32% ($N=17$) had severe or non-interpretable dysfunction both at baseline and at 36 months; 20% ($N=11$) of patients had a normal function/mild/moderate dysfunction at inclusion and had a severe or non-interpretable dysfunction at 36 months. The score difference between inclusion and Month 36 was statistically significant ($P=0.0009$ Mc Nemar test for paired data) with a greater proportion of severe/non interpretable disorders at Month 36.

The median IIEF-5 score at 60 months ($N=36$) was 2 (range, 1-23).

Respectively, 6% ($N=2$), 11% ($N=4$), 3% ($N=1$) and 14% ($N=5$) of patients reported severe, moderate, mild to moderate or mild disorders and 3% ($N=1$) reported a normal erectile function at 60 months; for 64% ($N=23$) of patients the score was uninterpretable.

Thirty-four patients had a calculable score at both inclusion and 60 months.

There was a significant difference between inclusion and Month 60 ($P=0.005$ in the Mc Nemar test for matched data) with a higher proportion of severe / non-interpretable disorders at 60 months. Eight patients (24%) had normal function with moderate onset disorders and had severe or uninterpretable disorders at 60 months.

Results of IPSS and IIEF on the population of safety sensitivity analysis are presented in appendix 1.

Discussion

To our knowledge this is the first report on a prospective trial of dose escalation using SBRT as a boost for intermediate-risk prostate cancer patients. The primary aim of this study was to assess the dose-escalated radiation treatment-related late GU and GI toxicity levels at 5 years. While the evidence on the benefit of adding a boost to EBRT in terms of efficacy outcomes is large, toxicity remains an issue. In this study, acute and late toxicity levels were low and most of them resolved within the five-year follow-up period.

BT as a boost has been the most extensively studied technique, and its superiority over EBRT reported by many. Three randomized trials including 720 men tested the benefit of adding BT to EBRT (with or without ADT) and in all of them the boost provided improved biochemical control (3, 10, 11).

The clinical benefit of adding BT boost, on the other hand, is not clear, and biochemical control should not be considered a surrogate for survival (12)(13). Dayes et al reported recently the long-term (14 years) outcomes of a trial that recruited patients with intermediate- and high-risk prostate cancer. The results suggested that the biochemical control does not translate into an improvement in distant control, prostate cancer-specific or overall survival (14). The trial however was not powered to detect the differences in survival. Metastatic-free survival (MFS) is now validated as a surrogate of overall survival. In the Dayes et al trial (14), metastasis-free survival rates were similar between EBRT and EBRT + BT. In the 14-year follow-up update, they reported that ten patients (20%) developed a metastasis in the BT arm to 15 (28%) in the EBRT arm, but the difference was not statistically significant (HR= 0.70, 95% CI: 0.32-1.57). In the ASCENDE RT trial, MFS was similar between the EBRT alone and the EBRT + BT boost arms (3). A longer follow-up and a meta-analysis of these trials could clarify potential clinical benefits.

Rodda et al analysed the GU and GI morbidity profiles of patients treated in the ASCENDE-RT trial (2). The use of BT led to an increased use of catheters and/or incontinence pads. At 5 years the cumulative incidence of grade 3 GU was significantly higher in the LDR-BT arm compared to the EBRT arm (18.4% vs 5.2%; $p < 0.001$). The 5-year rate of cumulative incidence of grade 3 GI events was also higher in the BT arm, although the difference was not significant (8.1% vs 3.2%, $p = 0.124$).

In our study, the cumulative incidence of GU grade ≥ 2 toxicity at 5 years after the end of RT was 1.4% and of GI 9.3%. While direct comparison is prevented due to heterogeneity among populations, these rates contrast favourably to those arising with BT.

Similarly, in Sathya et al's study, while not significant, late (>18 months after treatment) grade ≥ 3 GI and GU toxicity rates were higher in the EBRT + BT combination compared to the EBRT alone arm (GI: 3.9% vs 1.9% and GU: 13.7% vs 3.8%) (10). In Hoskin et al's RCT, over the first 8 years after treatment, the highest and lowest prevalence of severe urinary events was 14% and 4% for EBRT + HDRBT, and 10% and 0% for EBRT alone, respectively (11). The prevalence of urinary toxicity was significantly greater in the EBRT + HDR-BT arm only at 5.5 years (14% vs 0%, $p=0.02$).

In our study, urinary QoL was maintained throughout the follow-up period of 5 years compared to baseline. In the ASCENDE trial HR-QoL was analysed using a scale that had several items including 4 for urinary function and 6 items for sexual function (15). Results revealed a larger decline for both physical function and urinary function mean scores in the LDR-BT arm compared to the EBRT alone arm. At 12 months there was a significantly larger drop in mean scores for LDR-BT patients vs EBRT patients for most functions, including sexual ($p=0.02$). The drop in urinary function remained similar in both arms. Likewise, at 6 years, there was a significantly larger drop in mean scores in LDR-BT arm compared to EBRT arm for physical function (-15.3 vs -6.9; $p=0.03$) and urinary function (-3.6 vs -0.5; $p=0.04$). There was also a clinically significant drop in mean scores for both arms in sexual function but the difference was not statistically significant. Among men reporting adequate baseline erections, 45% of LDR-BT patients reported similar erectile function at 5 years, versus 37% after EBRT ($p=0.30$).

Results of recent large RCTs provide compelling evidence for the use of hypofractionated treatment. The NRG, The CHHiP and PROFIT RCTs demonstrated that a hypofractionated schedule was non inferior to conventional fractionation in terms of biochemical failure-free survival (16–18). Except for the NRG trial, there was no difference regarding long-term side effects or GI and GU toxicity, and authors concluded that dose-escalated hypofractionated treatment should be considered as a new standard of care option for treating localised and intermediate-risk prostate cancer. While 97% of patients in the CHHiP trial received ADT versus 5% of patients in the PROFIT trial, the impact of hypofractionation was similar.

Other strengths of the study reported here are its prospective design and the long follow-up. The main limitation is that the Zumsteg classification (19) was not used during the implementation of this trial, and the number of positive biopsies was not collected. According

to the Zumsteg classification, based on the Gleason score, PSA and clinical stage at least 40 patients (52.6%) had an unfavourable intermediate risk cancer. In addition, the study did not collect patient reported outcome data, which were rarely measured at the time the study was launched.

In conclusion, the 5-year follow-up results of the XXXX trial demonstrate that EBRT and SBRT combination is well tolerated and yield good efficacy results. To our knowledge no prospective study has been done that compares EBRT and BT boost to EBRT and SBRT boost. While more evidence is needed for the use of EBRT and SBRT boost, these data provide a good basis for comparing, in the context of a clinical trial, these schedules (with or without the use of hormone therapy) in future prospective studies in patients with intermediate- or even high-risk prostate cancer.

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Figure captions

Figure 1. Cumulative incidence of grade ≥ 2 late GU toxicities

Footnotes: Abbreviations: GU=genitourinary

Figure 2. Cumulative incidence of grade ≥ 2 late GI toxicities

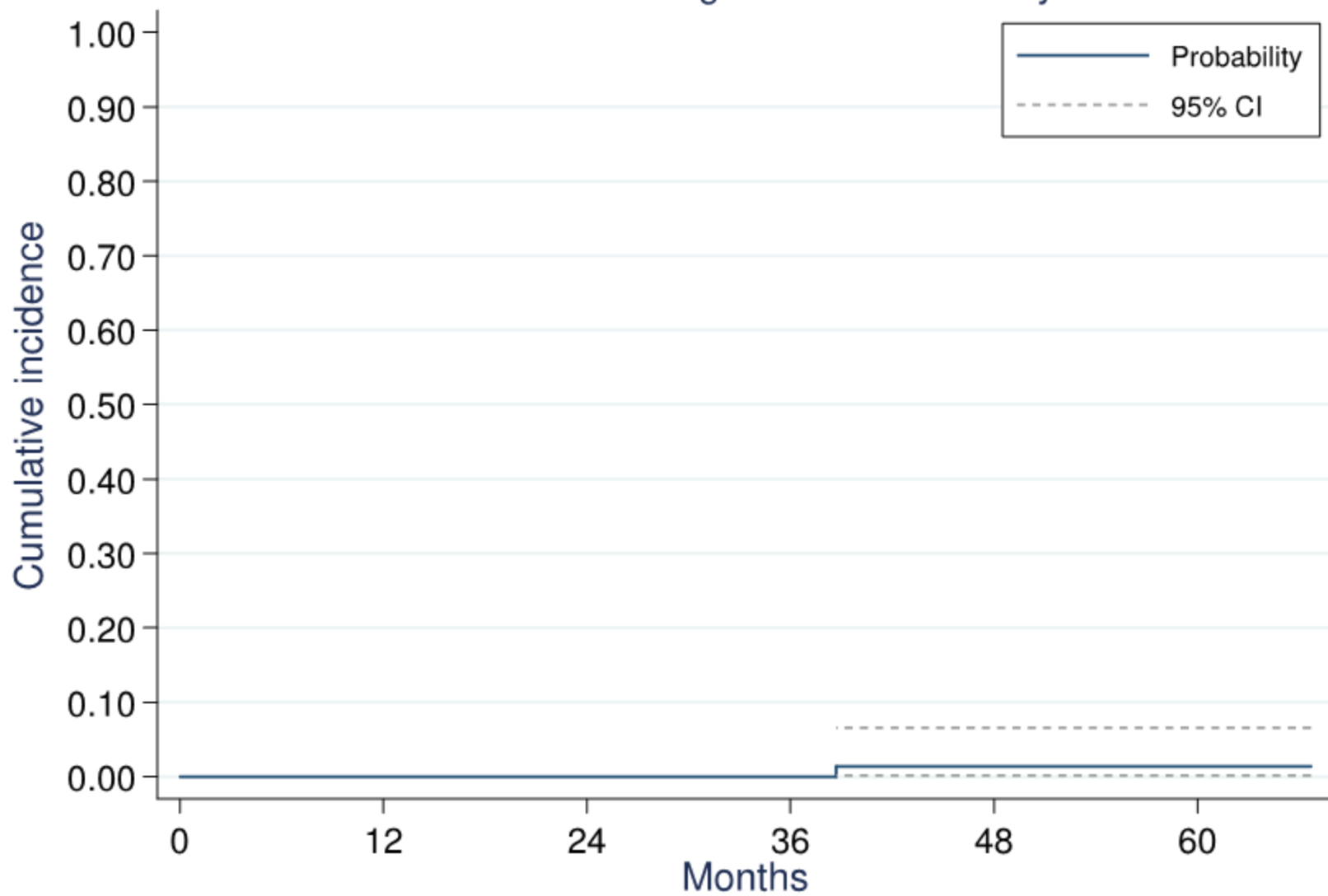
Footnotes: Abbreviations: GI=gastrointestinal

Figure 3. Kaplan Meier curve for biochemical relapse-free survival and time to biochemical relapse

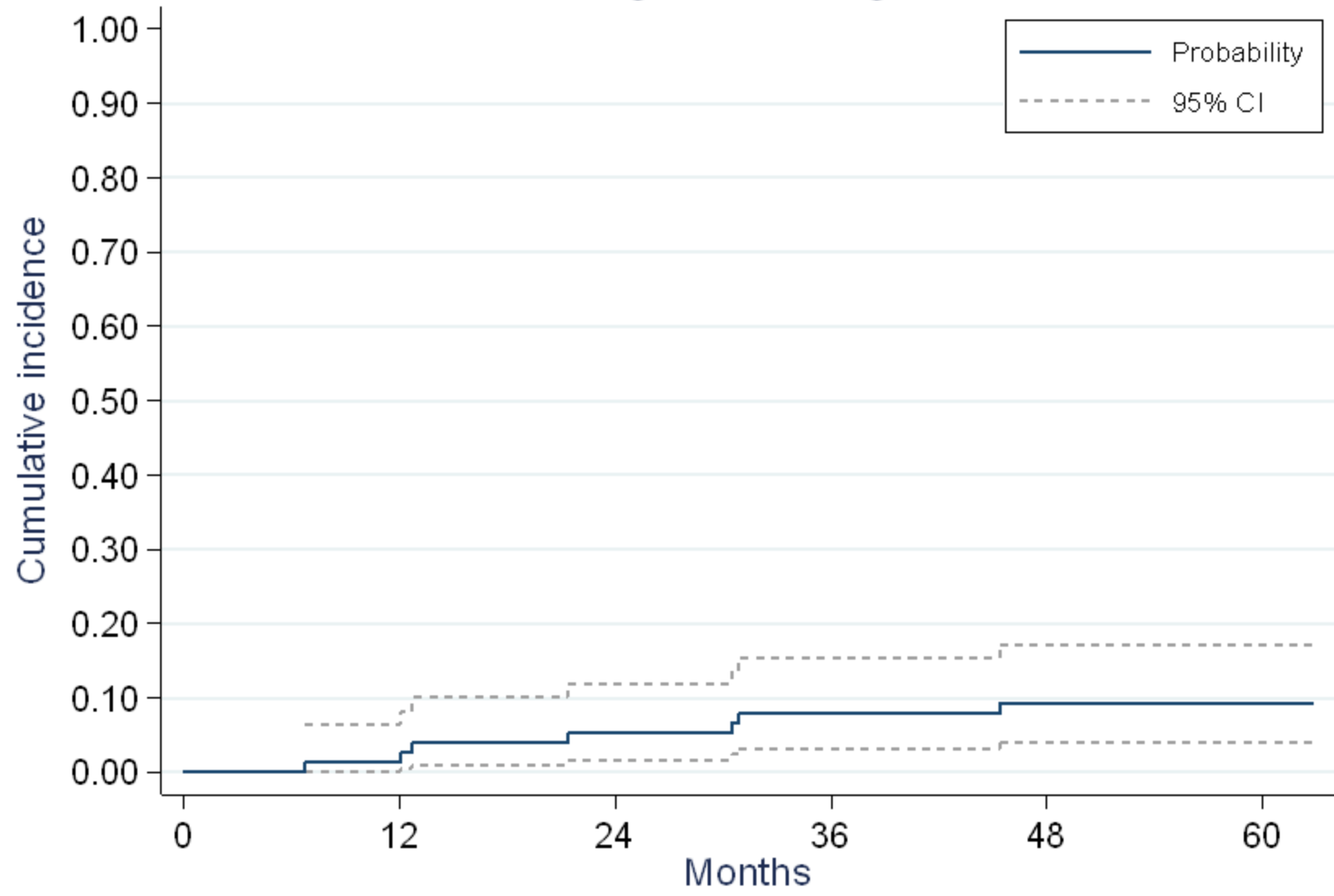
Figure 4. PSA distribution at inclusion, during radiotherapy and during follow-up

Footnotes: Abbreviations: PSA=prostate specific antigen

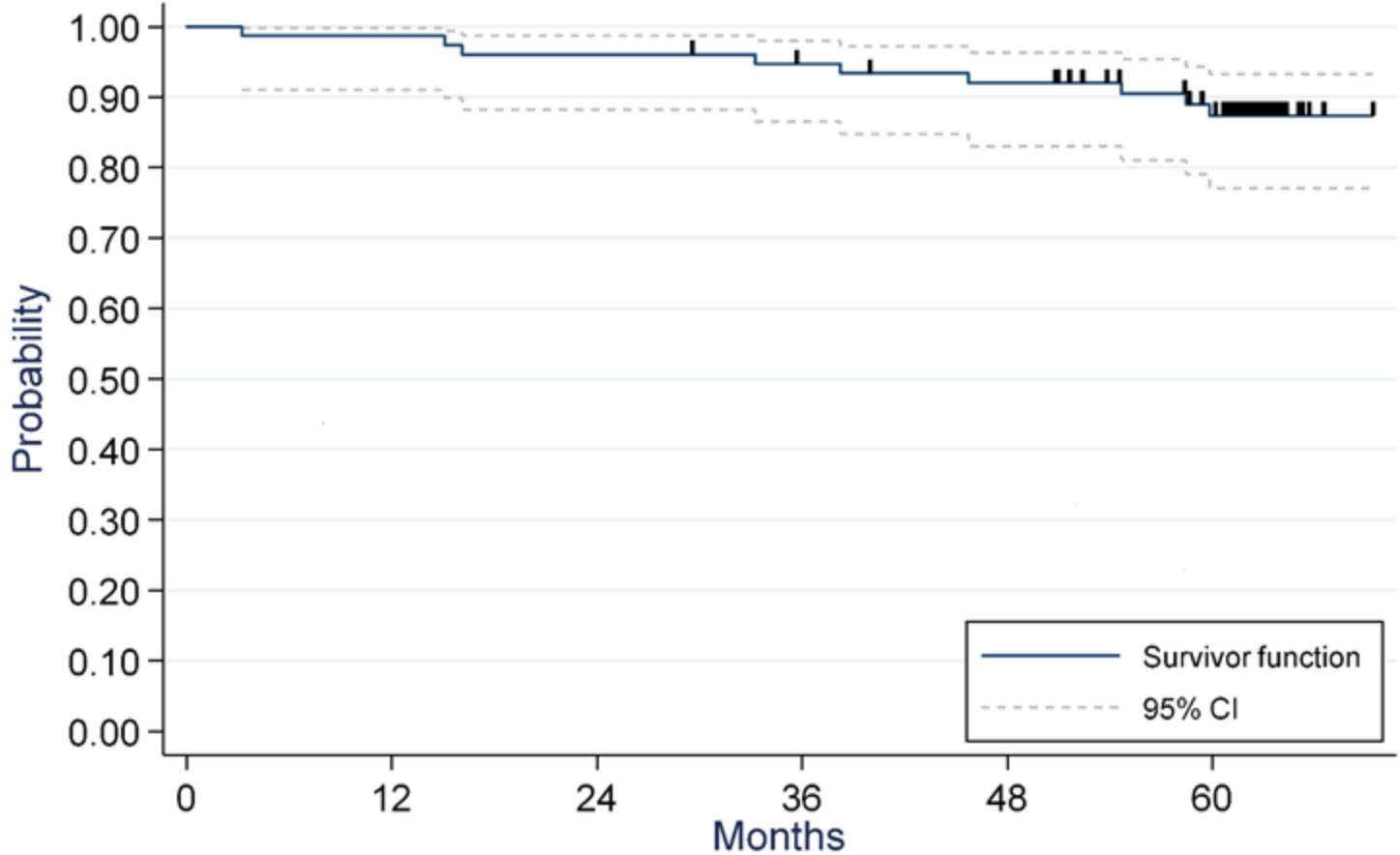
Cumulative incidence of grade ≥ 2 late urinary toxicities



Cumulative incidence of grade ≥ 2 late gastrointestinal toxicities



Biochemical relapse-free survival



Number at risk (number of events)
76 (1) 75 (2) 73 (1) 70 (2) 67 (3) 55

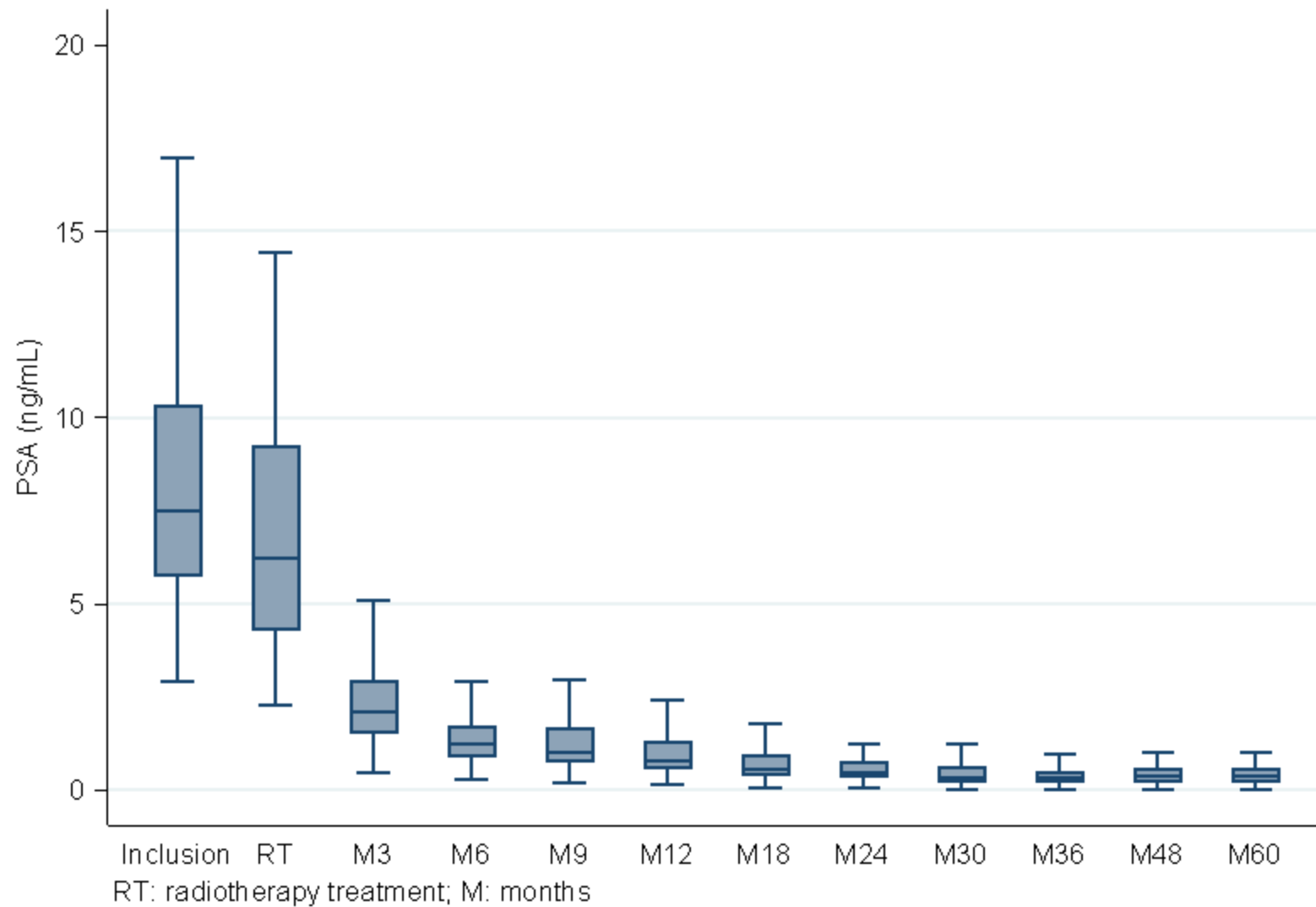


Table 1. Patient and disease characteristics at baseline

Characteristics	n	%
Age (median, range)	71 years (45-84)	
BMI (kg/m²)		
Underweight (<18.5)	1	1.4
Normal (18.5-25)	27	37.0
Overweight (25-30)	32	43.8
Obese (≥30)	13	17.8
Unknown	3	
T TxNOMO		
T1c	33	43.4
T2a	16	21.1
T2b	24	31.6
T2c	3	3.9
Gleason score		
6	18	23.7
7	58	76.3
3 + 4	40	52.6
4 + 3	18	23.7
WHO performance status		
0	67	88.2
1	9	11.8
Prostate volume(cc), mean(sd)	60.9 cc (16.7)	
PSA (ng/mL), median (range)	7.48 ng/mL (2.91-22.40)	

Abbreviations: BMI= body mass index; WHO= World Health Organization; PSA= prostate specific antigen; SD= standard deviation