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ORIGINAL ARTICLE

# The survival impact of neoadjuvant hormonal therapy before radical prostatectomy for treatment of high-risk prostate cancer

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**BACKGROUND:** Several randomized controlled trials assessed the outcomes of patients treated with neoadjuvant hormonal therapy (NHT) before radical prostatectomy (RP). The majority of them included mainly low and intermediate risk prostate cancer (PCa) without specifically assessing PCa-related death (PCRD). Thus, there is a lack of knowledge regarding a possible effect of NHT on PCRD in the high-risk PCa population. We aimed to analyze the effect of NHT on PCRD in a multicenter high-risk PCa population treated with RP, using a propensity-score adjustment.

**METHODS:** This is a retrospective multi-institutional study including patients with high-risk PCa defined as: clinical stage T3–4, PSA $>20$ ng ml$^{-1}$ or biopsy Gleason score 8–10. We compared PCRD between RP and NHT+RP using competing risks analysis. Correction for group differences was performed by propensity-score adjustment.

**RESULTS:** After application of the inclusion/exclusion criteria, 1573 patients remained for analysis; 1170 patients received RP and 403 NHT+RP. Median follow-up was 56 months (interquartile range 29–88). Eighty-six patients died of PCa and 106 of other causes. NHT decreased the risk of PCRD (hazard ratio (HR) 0.5; 95% confidence interval (CI) 0.32–0.80; $P=0.0014$). An interaction effect between NHT and radiotherapy (RT) was observed (HR 0.3; 95% CI 0.21–0.43; $P<0.0008$). More specifically, of patients who received adjuvant RT, those who underwent NHT+RP had decreased PCRD rates (2.3% at 5 year) compared to RP (7.5% at 5 year). The retrospective design and lack of specific information about NHT are possible limitations.

**CONCLUSIONS:** In this propensity-score adjusted analysis from a large high-risk PCa population, NHT before surgery significantly decreased PCRD. This effect appeared to be mainly driven by the early addition of RT post-surgery. The specific sequence of NHT +RP and adjuvant RT merits further study in the high-risk PCa population.

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## INTRODUCTION

Both radical prostatectomy (RP)+extended pelvic lymph node dissection (ePLND) and external beam radiotherapy (RT)+long-term androgen-deprivation therapy represent gold standard treatments for high-risk prostate cancer (PCa).[1,2] Neoadjuvant hormonal therapy (NHT) before RP was assessed in different randomized controlled trials[3] showing higher rates of down-staging and lower rates of positive surgical margins (PSM) compared to RP alone, but failing to demonstrate a survival benefit. This might be explained by the fact that most of the cancers considered in these trials were low or intermediate risk PCa, follow-ups were short and statistical power was too low to demonstrate effects on PCa-related death (PCRD) and overall mortality. Therefore, data about a possible survival impact of NHT in the high-risk PCa setting are lacking.

We hypothesized that if NHT would result in a survival benefit, it would be in patients with high-risk features. As a primary endpoint, we aimed to assess the impact of NHT before RP on PCRD in a high-risk PCa population. As a secondary endpoint, seen the radiosensitizing effect of androgen-deprivation therapy (ADT),[4,5] we aimed to assess the possible survival impact of adjuvant RT following NHT+RP.

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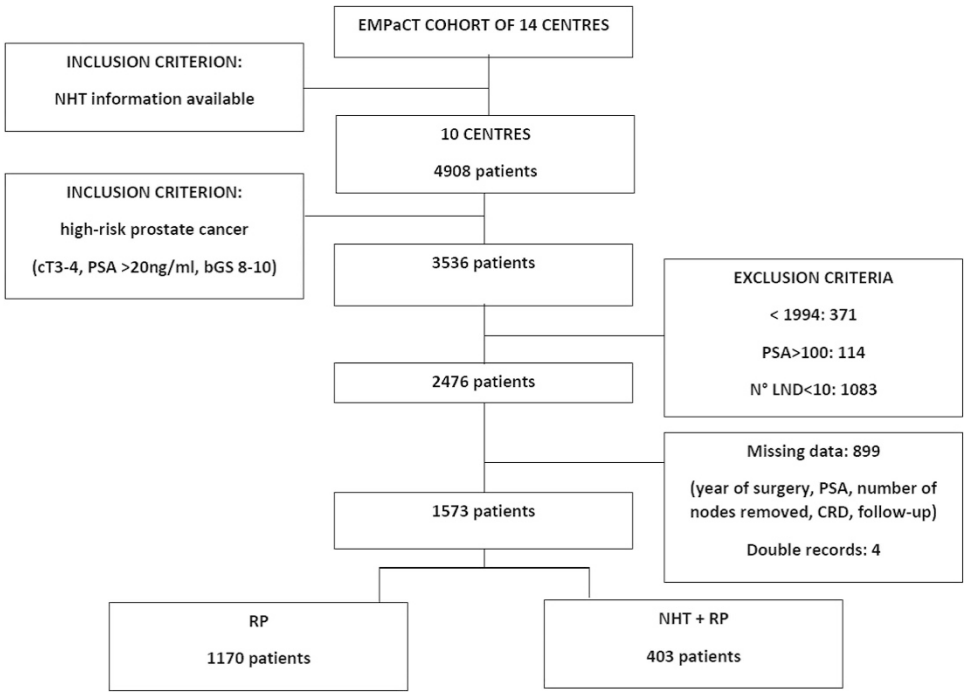



**Figure 1.** Flow chart with inclusion/exclusion criteria. CRD, cancer related death; LND, lymph node dissection; NHT, neoadjuvant hormonal therapy; RP, radical prostatectomy.

## MATERIALS AND METHODS

This is a retrospective multi-institutional study on high-risk PCa patients. All were treated in one of 14 tertiary referral centres between 1985 and 2015. Patients meeting one or more of the following criteria were included: clinical stage T3–4, PSA $>20$ ng ml$^{-1}$ or biopsy Gleason score 8–10. The indication, duration and type of NHT depended on institutional protocols. The sample was defined after exclusion of the following patients: surgery before the PSA era ($<1994$), PSA $>100$ ng ml$^{-1}$ as proxy of metastatic disease or missing data on initial PSA, number of removed lymph nodes $<10$ or unknown, missing survival data and/or follow-up duration. We set the minimal number of removed lymph nodes at 10 as a proxy for ePLND considering the evidence from a prospective mapping study that the number of nodes removed in ePLND should reach a median number of 16 (range 10–21) with 10 being the lower end of the range.[6] Cancer-related death was defined as death due to PCa. Cause of death was based on individual patients file reviews and/or death certificates. The Institutional Review Boards or independent Ethical Committees of each participating institution approved the study.

For the comparison of patient and treatment characteristics between groups, we used the $\chi^2$ test for categorical variables or Mann–Whitney *U* test for continuous variables. We graphically explored the cumulative risk of PCRD stratifying patients per treatment group. A treatment group effect with respect to PCRD was analyzed using a Cox proportional hazards model with a competing risk approach,[7] and correcting for group inequalities by the means of propensity scores.[8] Inference was based on a robust sandwich estimate for the covariance matrix to account for clustering by institution.[9] Propensity-score correction for group inequalities is indicated in case of non-random assignment of patients to treatment groups while the number of variables on which groups differ is too large to be included as separate variables in a multivariable model. Propensity scores were estimated by logistic regression with treatment group as binary response variable and with the following preoperative features as explanatory variables: clinical T-stage, initial PSA, biopsy Gleason score, age, year of surgery and institution. These scores were then added as a single variable to the analysis model.

An interaction effect was modeled between NHT (NHT+RP versus RP alone) and adjuvant RT (no/yes) to assess possible synergistic interactions of RT and NHT. We considered RT as adjuvant when it was delivered at PSA $<0.2$ and within 6 months post RP. All tests were two-sided and a 5% significance level was assumed for all tests. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute, Cary, NC, USA). The analytical codes are available through the corresponding author.

## RESULTS

### Primary endpoint: cancer-related death

A total of 1573 high-risk patients remained for analysis after application of the exclusion criteria (flow chart in Figure 1). Clinico-pathologic characteristics are shown in Table 1. The median number of lymph nodes removed was 18 (interquartile range (IQR): 13–24) that can be considered as a good proxy for an ePLND.[10] Of the overall sample, 1170 (74%) patients underwent surgery alone and 403 (26%) received NHT+surgery. Median follow-up was 56 months (IQR: 29–88) in the overall group, 57 and 54 months, respectively, in the RP and NHT+RP groups. In total, 192 (12%) patients died: 86 from PCa in (45%) and 106 from other causes (55%). Cumulative incidence curves for PCRD are plotted in Figure 2. There was a beneficial effect of NHT added to RP on PCRD (hazard ratio (HR) 0.5; 95% CI 0.32–0.80; $P=0.0014$).

### Secondary endpoint: interaction between NHT and adjuvant RT

Thirty-three percent of patients received adjuvant RT after RP. The interaction between NHT and adjuvant RT was significant ($P=0.0008$). RT decreases the risk of PCRD if associated to NHT +RP versus RP alone (HR 0.30; 95% CI 0.21; 0.43; $P<0.0001$). The descriptive statistics related to this analysis are shown in Table 2. Both patient and tumor characteristics in the NHT+RP+RT versus RP+RT groups were not different: pT3b–4 60 versus 67% ($P=0.3$), positive surgical margins (PSM) 59 versus 54% ($P=0.5$) and pN1 48 versus 56% ($P=0.08$)). Patients who received RP+RT had 5- and 10-year PCRD of 7.5% (95% CI 5.71–9.89) and 19% (95% CI 14.82–24.33), respectively; patients who received NHT+RP+RT showed 5- and 10-year PCRD of 2.3% (95% CI 1.39–3.89) and 6.1% (95% CI 3.79–9.92), respectively. In the subgroup of patients who did not receive adjuvant RT, no such effect was seen for NHT (HR 0.74; 95% CI 0.42–1.32; $P=0.3103$). The cumulative mortality curves for the different treatment sequences are shown in Figure 3.

**Table 1.** Preoperative and postoperative clinico-pathological features

| *Variable* | *Overall* | | *NHT+RP* | | *RP* | | P-*value* |
|---|---|---|---|---|---|---|---|
| | N | *%/(IQR)* | N | *%/(IQR)* | N | *%/(IQR)* | |
| *Preoperative characteristics* | | | | | | | |
| Median age years (IQR) | 66 | (61–71) | 67 | (62–71) | 66 | (61–70) | 0.02 |
| Preoperative PSA (ng ml$^{-1}$) | | | | | | | |
| Median PSA | 13 | (7–27) | 11 | (7–25) | 14 | (7–28) | 0.02 |
| PSA $\leqslant 20$ | 971 | 61.7 | 259 | 64.3 | 712 | 60.9 | 0.2 |
| PSA $>20$ | 602 | 38.3 | 144 | 35.7 | 458 | 39.2 | |
| Clinical T-stage | | | | | | | $<0.001$ |
| cT $<3$ | 530 | 33.7 | 169 | 41.9 | 361 | 30.9 | |
| cT3 | 914 | 58.1 | 202 | 50.1 | 712 | 60.9 | |
| cT4 | 33 | 2.1 | 6 | 1.5 | 27 | 2.3 | |
| Missing | 96 | 6.1 | 26 | 6.5 | 70 | 6 | |
| Biopsy Gleason score | | | | | | | 0.1 |
| $<7$ | 396 | 25.2 | 113 | 28 | 283 | 24.2 | |
| 7 | 508 | 32.3 | 111 | 27.5 | 397 | 33.9 | |
| 8–10 | 637 | 40.5 | 170 | 42.2 | 467 | 40 | |
| Missing | 32 | 2 | 9 | 2.2 | 23 | 2 | |
| *Postoperative characteristics* | | | | | | | |
| Pathological T-stage | | | | | | | $<0.001$ |
| pT $<3$ | 467 | 29.7 | 151 | 37.5 | 316 | 27 | |
| pT3a | 457 | 29 | 98 | 24.3 | 359 | 30.7 | |
| pT3b–4 | 643 | 40.9 | 154 | 38.2 | 489 | 41.8 | |
| Missing | 6 | 0.4 | 0 | 0 | 6 | 1 | |
| Pathological Gleason score | | | | | | | 0.6 |
| $<8$ | 904 | 57.5 | 235 | 58.3 | 669 | 57.2 | |
| $\geqslant 8$ | 576 | 36.6 | 141 | 35 | 435 | 37.2 | |
| Missing | 93 | 5.9 | 27 | 6.7 | 66 | 5.6 | |
| Surgical margins status | | | | | | | 0.04 |
| Negative | 993 | 63.1 | 234 | 58.1 | 759 | 64.9 | |
| Positive | 578 | 36.8 | 168 | 41.7 | 410 | 35 | |
| Missing | 2 | 0.1 | 1 | 0.3 | 1 | 0.1 | |
| LND removed | | | | | | | |
| Median (IQR) | 18 | (13–24) | 19 | (14–25) | 17 | (13–24) | 0.02 |
| LND $<20$ | 919 | 58.4 | 221 | 54.8 | 698 | 59.7 | 0.09 |
| LND $\geqslant 20$ | 654 | 41.6 | 182 | 45.2 | 472 | 40.3 | |
| Pathological N stage | | | | | | | 0.05 |
| Negative | 1026 | 65.2 | 283 | 70.2 | 743 | 63.5 | |
| Positive | 542 | 34.5 | 119 | 29.5 | 423 | 36.2 | |
| Missing | 5 | 0.3 | 1 | 0.3 | 4 | 0.3 | |
| Adjuvant RT | | | | | | | 0.001 |
| No | 1052 | 66.9 | 241 | 59.8 | 811 | 69.3 | |
| Yes | 519 | 33 | 162 | 40.2 | 357 | 30.5 | |
| Missing | 2 | 0.1 | 0 | 0 | 2 | 0.2 | |
| Adjuvant ADT | | | | | | | $<0.001$ |
| No | 539 | 34.3 | 32 | 7.9 | 507 | 43.3 | |
| Yes | 402 | 25.6 | 79 | 19.6 | 323 | 27.6 | |
| Missing | 632 | 40.2 | 292 | 72.5 | 340 | 29.1 | |
| Salvage RT | | | | | | | $<0.001$ |
| No | 1363 | 88 | 369 | 93 | 994 | 86.3 | |
| Yes | 186 | 12 | 28 | 7.1 | 158 | 13.7 | |
| Death | | | | | | | |
| Cancer-specific | 86 | 6 | 13 | 3 | 73 | 6 | |
| Other cause | 106 | 7 | 27 | 7 | 79 | 7 | |

Abbreviations: ADT, androgen-deprivation therapy; IQR, interquartile range; LND, lymph node dissection; *N*, number; NHT, neoadjuvant hormonal treatment; RP, radical prostatectomy+pelvic lymph node dissection; RT, external beam radiotherapy.

## DISCUSSION

The primary endpoint of our study was the assessment of PCRD for patients treated with NHT+RP versus RP alone in a series of high-risk PCa patients. We performed formal competing risk analyses correcting for group inequalities. There was a significant PCRD advantage for NHT. Previous randomized trials[3] mainly assessed survival in low- and intermediate risk PCa, thus it is possible that no PCRD or overall survival (OS) benefit was detected because of low disease aggressiveness in combination to a relatively short follow-up. Only few trials have assessed the outcomes of NHT before RP in the high-risk PCa setting. Recently, the long-term results of SWOG 9109 were published. In this small, phase II, single arm study, 55 patients with cT3–4 N0 M0 PCa received NHT with goserelin acetate and flutamide followed by radical prostatectomy.[11] The 10-year OS estimate was 68%, which is comparable to large retrospective series of patients treated with

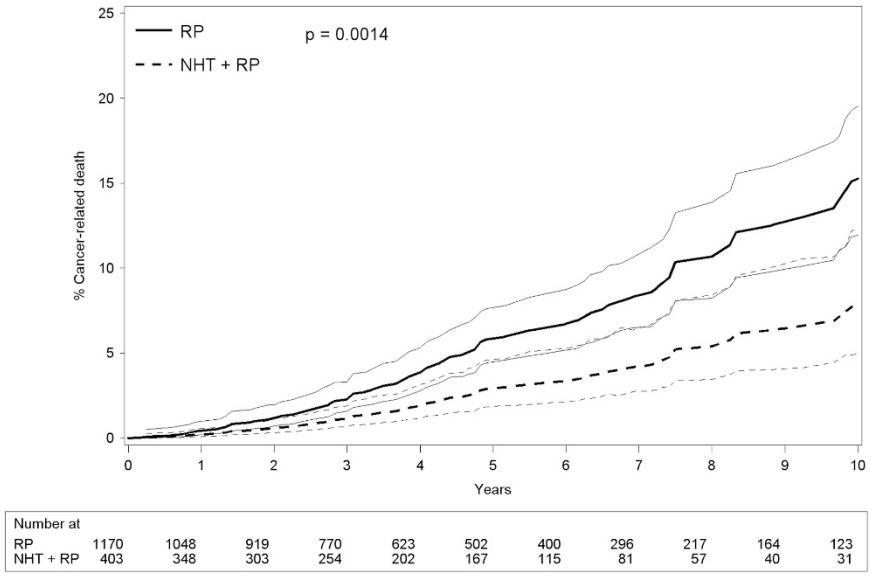



**Figure 2.** Cumulative mortality curves of radical prostatectomy (RP) with or without neoadjuvant therapy (NHT). Bold lines represent the median incidence and thin lines represent the respective confidence intervals.

**Table 2.** Descriptive statistics according to different multimodality schemes

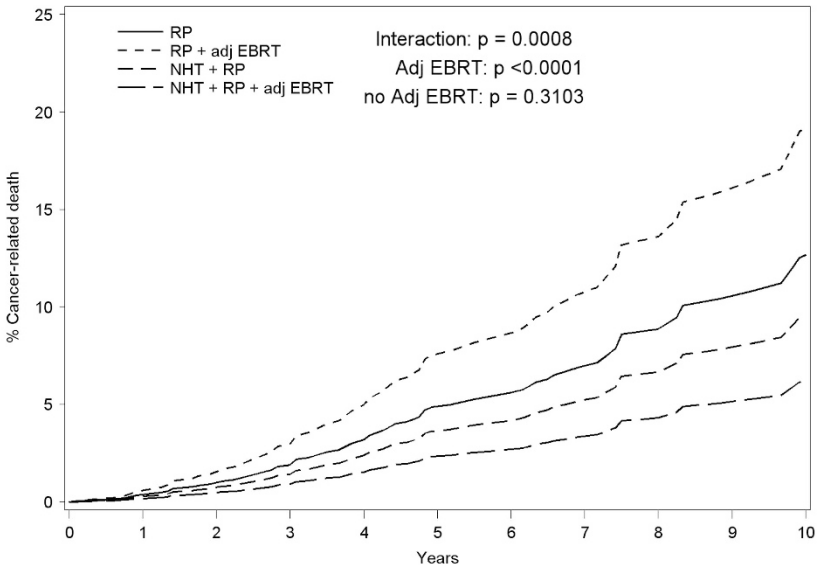
| *Variable* | *RP* | *NHT+RP* | *RP+adj RT* | *NHT+RP+adj RT* |
|---|---|---|---|---|
| *Total* | N *(%)* | N *(%)* | N *(%)* | N *(%)* |
| *Pathologic T-stage (pT)* | | | | |
| pT < 3 | 290 (35.8) | 136 (56.4) | 26 (7.3) | 15 (9.3) |
| pT3a | 266 (32.8) | 48 (20) | 92 (25.8) | 50 (30.9) |
| pT3b–4 | 249 (30.7) | 57 (23.7) | 239 (67) | 97 (59.9) |
| Missing | 6 (0.7) | 0 (0) | 0 (0) | 0 (0) |
| *Pathologic Gleason score (pGS)* | | | | |
| < 8 | 517 (63.8) | 171 (71) | 151 (42.3) | 64 (39.5) |
| ⩾ 8 | 249 (30.7) | 64 (26.6) | 185 (51.8) | 77 (47.5) |
| Missing | 45 (5.6) | 6 (2.5) | 21(5.9) | 21 (13) |
| *Surgical margins status* | | | | |
| Negative | 596 (73.5) | 169 (70.1) | 162 (45.4) | 65 (40.1) |
| Positive | 215 (26.5) | 72 (29.9) | 194 (54.3) | 96 (59.3) |
| Missing | 0 (0) | 0 (0) | 1 (0.3) | 1 (0.6) |
| *Number of lymph nodes removed* | | | | |
| Median | 17 | 19 | 19 | 19 |
| Range | (13–23) | (13–23) | (14–25) | (14–27) |
| *Lymph node invasion (pN)* | | | | |
| pN1 | 224 (27.6) | 42 (17.4) | 199 (55.7) | 77 (47.5) |
| pN0 | 583 (71.9) | 198 (82.2) | 158 (44.3) | 85 (52.5) |
| Missing | 4 (0.5) | 1 (0.4) | 0 (0) | 0 (0) |
| *pT downstaging* | | | | |
| No | 439 (67.8) | 78 (49.1) | 206 (90.8) | 79 (94) |
| Yes | 209 (32.3) | 81 (50.9) | 21 (9.3) | 5 (6) |

Abbreviations: IQR, interquartile range; *N*, number; NHT, neoadjuvant hormonal treatment; RP, radical prostatectomy+pelvic lymph node dissection; RT, external beam radiotherapy.

surgery without NHT, showing 10 year OS between 65% and 71%.[12–14]

The role of surgery is shifting towards more aggressive PCa and recent data even suggest a possible survival benefit in selected patients with metastatic PCa.[15] From this perspective, the application of multimodality treatments including NHT will likely increase with the goal to downstage the primary tumor and facilitate the resectability of locally advanced disease and possibly to extend life. It has been hypothesized that the application of more active compounds such as chemotherapy and novel androgen receptor signaling inhibitors might be more effective than NHT in patients with bulky disease. Early phase II studies have addressed this issue. A neoadjuvant randomized phase II trial of luteinizing hormone releasing hormone (LHRH) agonist with abiraterone acetate (AA) was conducted in patients with localized high-risk PCa ($n = 58$). For the first 12 weeks, patients were randomly assigned to LHRH versus LHRH+AA. After a prostate biopsy, all patients received 12 additional weeks of LHRH+AA followed by radical prostatectomy. Tumor burden and intra-prostatic levels of dihydrotestosterone and testosterone were significantly lower in the study arm compared to the control arm.[16] Recently, the results of another randomized, open label, parallel group study on neoadjuvant enzalutamide (ENZA) were published; patients affected by intermediate or high-risk PCa received ENZA or ENZA+dutasteride+leuprolide before surgery.[17] Authors reported no statistically significant difference in terms of complete pathologic response compared to historical controls but minimal residual disease was seen significantly less frequent in the ENZA alone group. Neoadjuvant ENZA+AA+LHRH analog versus AA+LHRH analog in localized high-risk PCa was tested in a Phase 2 randomized controlled trial (NCT01946165). Pathologic down-staging (⩽pT2N0) occurred in 13/44 (30%) ENZA+AA+LHRH patients versus 11/21 (52%) AA+LHRH ($P = 0.07$).[18] Next to second generation antiandrogens and androgen receptor pathway inhibitors, there is current research that associates chemotherapy to ADT: the CALGB 9203 (NCT00430183) is an ongoing trial that is assessing biochemical progression-free survival for patients randomized to docetaxel+LHRH agonist+surgery versus surgery alone. The ACDC trial (NCT02543255) is assessing pathologic complete response in patients randomized to AA+prednisone +leuprolide ± cabazitaxel, and results are expected in the future.

As a secondary endpoint, we aimed to assess the interaction of NHT with adjuvant RT on PCRD. We observed a beneficial interaction of adjuvant RT in association to NHT. In the group of patients who received adjuvant RT, NHT+RP+RT had decreased PCRD rates compared to RP+RT. It is likely that the significant




| Number at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| RP | 811 | 720 | 623 | 518 | 419 | 335 | 266 | 196 | 139 | 101 | 72 |
| RP + adj EBRT | 357 | 326 | 294 | 251 | 204 | 167 | 134 | 100 | 78 | 63 | 51 |
| NHT + RP | 241 | 201 | 174 | 146 | 120 | 99 | 66 | 50 | 35 | 24 | 18 |
| NHT + RP + adj EBRT | 162 | 147 | 129 | 108 | 82 | 68 | 49 | 31 | 22 | 16 | 13 |

**Figure 3.** Cumulative mortality curves of radical prostatectomy (RP) with or without neoadjuvant therapy (NHT) and adjuvant radiotherapy (RT). EBRT, external beam RT.

effect of NHT in the overall analysis was largely driven by the specific combination of NHT and RT rather than NHT per se considering the absence of a similar effect in patients who did not receive adjuvant RT (HR 0.7; 95% CI 0.42–1.32; $P = 0.3$). Another possible explanation might be differences in disease aggressiveness between groups. However, when groups were compared, no important differences in adverse disease features were seen between the NHT+RP+RT and RP+RT groups. Moreover, the 95% CI's of the cumulative mortality curves do not overlap, supporting the robustness of our observation. The probable rationale behind these results might be the fact that the adjuvant RT was delivered at a time when the effect of the NHT was still present. Furthermore, NHT could also have decreased the residual tumor burden which might have improved the RT efficacy. Indeed, there is a known radiosensitizing effect of ADT with radiotherapy.[19] It has been shown that the DNA repair mechanism is strongly related to androgen receptor activation;[20] DNAPKcs (DNA-dependent protein kinase, catalytic subunit) is an androgen-regulated component of the non-homologous end-joining mechanism of DNA repair,[21] and for this reason it represents a marker of DNA repair inhibition. Neoadjuvant leuprorelin before RT has been shown to significantly decrease the expression of phosphorylated DNAPKcs and to increase the expression of γ-H2AX, marker of DNA unrepaired breaks, compared to RT alone. These findings confirmed an increased DNA damage in neoadjuavant ADT groups due to an inhibiting effect on the DNA repair mechanism.[22] Our results support the addition of ADT to adjuvant RT in patients with adverse pathologic features. Indeed, a recent publication showed improved PCRD when adding long-term androgen-deprivation therapy to adjuvant RT in patients with high-risk disease features.[23] These results suggest that the sequence of different therapies could have a survival effect in this group of patients. Further studies should therefore specifically assess the role of treatment sequencing.

Our study is not devoid of limitations. First, this was a retrospective analysis, potentially affected by selection bias. Second, our data had significant numbers of missing values in certain covariates. Particularly important was the lack of details regarding adjuvant ADT. Duration and type of ADT were not standardized across the participating institutions and there were no data available on testosterone levels at the time of adjuvant RT. Although we compensated for these issues by applying propensity-score correction and including a large sample size from a multi-institutional database, the results can never be as robust as having no missing data or as a prospective trial. Third, the PLND was not standardized but was quite extensive considering the high median number of lymph nodes removed. Fourth, this cohort had a relatively short median follow-up, which may have impacted long-term PCRD predictions. Finally, there was no central pathology review, but all the tertiary centres had dedicated uro-pathologists.

Notwithstanding these limitations, this study of $>1500$ men is the largest study of NHT before RP in high-risk PCa, and suggests a difference in PCRD between the study groups. This difference appears to be mainly driven by the association of adjuvant RT to NHT. The specific combination of NHT+RP+adjuvant RT should be further studied in the high-risk PCa population.

## CONFLICT OF INTEREST

LT: research grants from Bayer, Ipsen, Ferring, Janssen; consulting or advisory role for Ipsen; travel, accommodation, expenses from Astellas, Bayer and Pierre-Fabre. SJ: company consultant for Astellas, Ipsen, Bayer, Sanofi and Janssen; has received company speaker honoraria from Astellas, Amgen, Bayer, Sanofi, Janssen and Ipsen; has participated in trials for Astellas, Janssen and Bayer; has received fellowship and travel grants from Astellas, Amgen, Bayer, Sanofi, Janssen, Ipsen and Pfizer; and has received grant and research support from Astellas, Bayer and Janssen. MA: travel, accommodation, expenses from Astellas, Amgen and Bayer. WE: travel, accommodation, expenses from Astellas. RJK: research funding from GenomeDX; patents, royalties, other intellectual property from GenomeDX. PG: honoraria from Janssen, Ipsen; Speaker's Bureau from Medacs; research funding from Astellas; travel, accommodation, expenses from Janssen. TVdB: travel, accommodation, expenses from Ipsen. FKC: consulting or advisory role from Astellas, UroTech. HVDP: honoraria from Intuitive Surgical; consulting or advisory role from Astellas; research funding from Astellas, Storz; travel, accommodation, expenses from Intuitive Surgical, Storz. BT: honoraria from Amgen, Astellas, Bayer, Ferring, Sanofi and Janssen; consulting or advisory role—Astellas, Bayer, Ferring, Janssen, Takeda, Steba Biotech, Sanofi; Speaker's Bureau—Amgen, Janssen; research funding—Ferring; travel,

accommodation, expenses—Amgen, Astellas, Bayer, Ferring Janssen, Sanofi. GM: Speaker's Bureau from Ipsen, Takeda; travel, accommodation, expenses from Ipsen, Takeda and Ferring. GDM: honoraria from Astellas, Ipsen, AstraZeneca, Bayer, Ferring, Sanofi, Janssen; consulting or advisory role—Astellas, Bayer, Ferring, Janssen, Ipsen, Sanofi; research funding—Ipsen; travel, accommodation, expenses—all of the above. AB: honoraria from Astellas, Ipsen, Ferring; consulting or advisor role from Janssen; Speaker's Bureau from Ipsen, Ferring and Janssen; travel, accommodation, expenses from Ipsen. Remaining authors declare no conflict of interest.

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