End-of-radiation PSA as a novel prognostic factor in patients undergoing definitive radiation and androgen deprivation therapy for prostate cancer

AK Narang1,4, J Trieu1,4, N Radwan1,4, A Ram1, SP Robertson1, P He2, C Gergis1, E Griffith1, H Singh1, TA DeWeese1, S Honig1, A Annadadam1, S Greco1, C DeVille1, T McNutt1, TL DeWeese1,3, DY Song1,3 and PT Tran1,3

ORIGINAL ARTICLE

INTRODUCTION

Accurate risk stratification of men with localized prostate cancer is paramount in selecting optimal treatment intensity. As such, multiple risk stratification systems have been developed using combinations of pre-treatment prognostic factors, most commonly initial PSA level, biopsy Gleason score and clinical stage.1–5 Despite these tools, reliable identification of patients at risk for failure has remained elusive, as evidenced by heterogeneous outcomes seen within risk groupings, highlighting the limitations of available pre-treatment prognostic factors.6 In patients treated with neoadjuvant androgen deprivation therapy (ADT), emerging literature suggests that the biochemical response to neoadjuvant ADT may provide dynamic prognostic value beyond initial risk grouping and help identify men with disease that is more biologically aggressive than suggested by standard pre-treatment variables.7–18 In these men, PSA response to neoadjuvant ADT may offer an earlier time point at which to consider modification of the treatment regimen.

Similarly, in men undergoing definitive radiation for localized prostate cancer, assessment of the biochemical response at the completion of radiation may serve as a helpful biomarker but has not been previously analyzed. Indeed, an end-of-radiation (EOR) PSA level may be a more useful biomarker for guiding adjuvant treatment strategies than assessment of biochemical response before radiation and may also be applicable to men undergoing definitive radiation alone. At our institution, it has been the standard practice of one provider to obtain an EOR PSA during the last week of treatment in men with localized prostate cancer undergoing definitive radiation. Herein, we examine the prognostic value of the EOR PSA in a cohort of prostate cancer patients with long-term follow-up after being treated at our institution with definitive radiation.

MATERIALS AND METHODS

Study population

The study was approved by the institutional review board of Johns Hopkins Hospital (Baltimore, MD, USA). We reviewed a prospectively acquired database of 936 patients with clinically localized prostate cancer who were consecutively treated with definitive radiation between 1993 to 2006 and who had an end-of-radiation (EOR) PSA (n = 688, median follow-up 11.2 years). We analyzed the association of an EOR PSA level, obtained during the last week of radiation, with survival outcomes. Multivariable-adjusted cox proportional hazards models were constructed to assess associations between a detectable EOR PSA (defined as ≥ 0.1 ng ml−1) and biochemical failure-free survival (BFFS), metastasis-free survival (MFS), prostate cancer-specific survival (PCSS) and overall survival (OS). Kaplan–Meier survival curves were constructed, with stratification by EOR PSA.

RESULTS

At the end of radiation, the PSA level was undetectable in 30% of patients. Men with a detectable EOR PSA experienced inferior 10-year BFFS (49.7% versus 64.4%, P < 0.001), 10-year MFS (84.8% versus 92.0%, P = 0.003), 10-year PCSS (94.3% versus 98.2%, P = 0.007) and 10-year OS (75.8% versus 82.5%, P = 0.01), as compared to men with an undetectable EOR PSA.

Among National Comprehensive Care Network (NCCN) intermediate- and high-risk men who were treated with definitive radiation and androgen deprivation therapy (ADT), a detectable EOR PSA was more strongly associated with PCSS than initial NCCN risk level (EOR PSA: HR 5.89, 95% CI 2.37–14.65, P < 0.001; NCCN risk level: HR 2.01, 95% CI 0.74–5.42, P = 0.168). Main study limitations are retrospective study design and associated biases.

CONCLUSIONS: EOR PSA was significantly associated with survival endpoints in men who received treatment with definitive radiation and ADT. Whether the EOR PSA can be used to modulate treatment intensity merits further investigation.

Prostate Cancer and Prostatic Diseases (2017) 20, 203–209; doi:10.1038/pcan.2016.67; published online 17 January 2017

1365-7852/17 © 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved

www.nature.com/pcan
1 January 1993 and 31 December 2006 by a single provider (TL DeWeese). Biopsies that were performed at an outside hospital were reviewed by the genitourinary pathologists at our institution before treatment. Patients without complete clinical or pathologic information were excluded (n = 19), as were patients with less than 24 months of follow-up (n = 30). Patients who did not have an EOR PSA drawn were also excluded (n = 200). Notably men lacking an EOR PSA did not differ from men with an EOR PSA with respect to age, race, initial PSA level, clinical stage, Gleason score or National Comprehensive Care Network (NCCN) risk level (data not shown, all P > 0.05). The final study population comprised 688 men with clinically localized disease.

Treatment
Patients were treated with definitive radiation using either three-dimensional conformal radiation therapy (79%) or intensity-modulated radiation therapy (21%), with the latter technique increasingly utilized at the end of the study period. For NCCN low- and intermediate-risk patients, treatment fields generally included the prostate and seminal vesicles, with a boost to the prostate. For NCCN high-risk men, treatment generally consisted of an initial whole pelvis field, which included the prostate, seminal vesicle and pelvic lymph nodes, followed by a boost field to the prostate. Seminal vesicles were also included in the boost field if there was high suspicion of involvement based on clinical exam. The prescription dose for the initial field was 45–46 Gy, delivered in 1.8–2 Gy fractions. The prescription dose for the boost field varied over the study period, with higher doses administered in more recent years. Median total dose for the cohort was 70.2 Gy (range: 64.8–75.6 Gy). When administered, neoadjuvant ADT was initiated 2 months before the radiation start date and consisted of a luteinizing hormone-releasing hormone agonist and an oral antiandrogen. Duration of luteinizing hormone-releasing hormone agonist administration was dictated by disease characteristics. Complete information regarding the duration of oral antiandrogen use was unavailable.

Following treatment, patients underwent routine follow-up with serial PSA measurements and digital rectal exam, generally at 6-month intervals. Frequency of PSA measurements and digital rectal exams was altered based on the PSA trend and clinical symptoms. Similarly, clinical imaging was obtained in the setting of concerning PSA trends or clinical symptoms. Salvage ADT was administered based on the discretion of the treating provider, but was generally influenced by PSA doubling time, co-morbidity and life expectancy. No patients received salvage local therapy, except for one patient who underwent salvage prostatectomy at an outside institution.

Statistical analysis
The primary endpoint of our study was prostate cancer-specific survival (PCSS). Prostate cancer-specific death was recorded if patient had a documented history of hormone-refractory metastatic prostate cancer, evidence of a rising PSA at last follow-up visit, and no other obvious cause of death. In addition, the National Death Index was cross-referenced to confirm cause of death. Secondary endpoints included biochemical failure-free survival (BFSS), metastasis-free survival (MFS) and overall survival (OS). Biochemical failure, defined as nadir PSA plus 2.0 ng ml$^{-1}$, was based on the Radiation Therapy Oncology Group—American Society for Therapeutic Radiation Oncology Phoenix Consensus Conference definition. For the purpose of calculating BFSS, patients without biochemical failure were censored at time of last PSA measurement. Metastasis was defined by a radiographic abnormality on bone scan and/or computed tomography, with biopsy performed as needed for confirmation. Failure points were measured from the last day of radiation.

Differences in patient and treatment characteristics were compared between men with a detectable EOR PSA (defined as $>0.1$ ng ml$^{-1}$ and measured during the last week of the radiation schedule) and men with an undetectable EOR PSA using the $\chi^2$ test. A PSA threshold of 0.1 ng ml$^{-1}$ was selected based on the minimum PSA that was detectable by the assay in use at our institution during the study period. Thresholds for dichotomous variables were defined in accordance with the literature. Univariate and multivariable-adjusted hazard ratios were calculated using a Cox proportional hazards model to associations between the EOR PSA and BFSS, MFS, PCSS and OS. Covariates in the multivariable model were based on significance in univariate analysis and included age, race, initial PSA level, clinical stage, Gleason score, perineural invasion, radiation dose, use of intensity-modulated radiation therapy and administration of ADT (data not shown). Kaplan–Meier survival curves were also constructed for all survival endpoints, with stratification by EOR PSA and comparison using the log-rank test.

All analyses were performed with Stata software (Stata/IC10.0). Two-sided significance testing was used, and a P-value of 0.05 was considered statistically significant.

RESULTS
Of the 688 men in our cohort treated with definitive radiation, 368 patients (41%) died during the study period, including 74 patients (8%) who died of prostate cancer. Median follow-up was 11.2 years (range: 2.0–20.6 years) for all patients, and 12.1 years (range: 2.0–20.6 years) for surviving patients.

Demographic, tumor and treatment characteristics are outlined in Table 1. By the end of radiation, an undetectable PSA was achieved by 30% of patients, including 12% of NCCN low-risk patients, 39% of NCCN intermediate-risk patients and 41% of NCCN high-risk patients. Men with a detectable EOR PSA were

| Characteristic | Undetectable EOR PSA (n = 206) | Detectable EOR PSA (n = 482) | P-value |
|---------------|-------------------------------|-------------------------------|--------|
| Median age (range), years | 68 (50–80) | 69 (49–82) | 0.07 |
| Africa-American race, n (%) | 40 (19) | 126 (26) | 0.06 |
| Initial PSA, ng ml$^{-1}$ | | | |
| < 10, n (%) | 128 (62) | 318 (66) | 0.25 |
| 10–20, n (%) | 54 (26) | 99 (21) |
| > 20, n (%) | 24 (12) | 65 (13) |
| Gleason score | | | |
| 3+3 | 84 (41) | 289 (60) | < 0.001 |
| 3+4 | 64 (31) | 80 (17) |
| 4+3 | 17 (8) | 38 (8) |
| 4+4 | 22 (11) | 30 (6) |
| 4+5 | 14 (7) | 18 (4) |
| 5+4 | 5 (2) | 8 (2) |
| 5+5 | 0 (0) | 3 (1) |
| T-stage, % | | | 0.001 |
| T1 | 81 (39) | 229 (48) |
| T2 | 83 (40) | 205 (43) |
| T3/T4 | 42 (20) | 48 (10) |
| NCCN risk level | | | < 0.001 |
| Low | 28 (14) | 214 (44) |
| Intermediate | 91 (44) | 144 (30) |
| High | 87 (42) | 124 (26) |
| Perineural invasion on biopsy | | | < 0.001 |
| None | 64 (31) | 71 (15) |
| Neadjuvant and concurrent only | 7380 (6840–7560) | 7200 (6480–7560) | < 0.001 |
| Intensity-modulated radiation therapy | 74 (36) | 107 (22) | < 0.001 |
| Androgen deprivation therapy | | | < 0.001 |
| None | 7 (3) | 287 (60) |
| Neoadjuvant and concurrent only | 117 (57) | 101 (21) |
| Neoadjuvant, concurrent, and adjuvant | 82 (40) | 94 (19) |

Abbreviations: EOR, end-of-radiation; NCCN, National Comprehensive Care Network.
Table 2. Univariate associations between EOR PSA and survival endpoints for entire cohort and within NCCN risk groupings

| Survival Endpoint | Hazard ratio (95% CI) | P-value |
|-------------------|-----------------------|---------|
| **Entire cohort** |                        |         |
| Biochemical failure-free survival | 2.69 (1.77–4.08) | < 0.001 |
| Metastasis failure-free survival | 2.62 (1.36–5.04) | 0.004 |
| Prostate cancer-specific survival | 3.08 (1.33–7.10) | 0.008 |
| Overall survival | 1.52 (1.14–2.03) | 0.004 |
| **Low risk** |                        |         |
| Biochemical failure-free survival | 6.86 (0.93–50.83) | 0.06 |
| Metastasis failure-free survival | 2.04 (0.26–16.20) | 0.50 |
| Prostate cancer-specific survival | Not enough failure events | — |
| Overall survival | 1.17 (0.53–2.58) | 0.69 |
| **Intermediate risk** |                        |         |
| Biochemical failure-free survival | 1.98 (0.95–4.12) | 0.07 |
| Metastasis failure-free survival | 3.65 (0.76–17.59) | 0.11 |
| Prostate cancer-specific survival | 4.98 (0.59–41.78) | 0.14 |
| Overall survival | 0.74 (0.44–1.25) | 0.26 |
| **High risk** |                        |         |
| Biochemical failure-free survival | 4.21 (2.20–8.09) | < 0.001 |
| Metastasis failure-free survival | 4.04 (1.82–8.94) | 0.001 |
| Prostate cancer-specific survival | 4.15 (1.56–11.08) | 0.004 |
| Overall survival | 2.69 (1.58–4.60) | < 0.001 |

**Abbreviations**: EOR, end-of-radiation; NCCN, National Comprehensive Care Network.

Table 3. Multivariable-adjusted associations between EOR PSA and survival endpoints for entire cohort and within NCCN risk groupings

| Survival Endpoint | Hazard ratio (95% CI) | P-value |
|-------------------|-----------------------|---------|
| **Entire cohort** |                        |         |
| Biochemical failure-free survival | 3.56 (2.24–5.65) | < 0.001 |
| Metastasis failure-free survival | 5.32 (2.58–10.97) | < 0.001 |
| Prostate cancer-specific survival | 6.02 (2.44–14.84) | < 0.001 |
| Overall survival | 1.67 (1.18–2.35) | 0.004 |
| **Low risk** |                        |         |
| Biochemical failure-free survival | 8.02 (1.06–60.73) | 0.04 |
| Metastasis failure-free survival | 3.19 (0.37–27.28) | 0.29 |
| Prostate cancer-specific survival | Not enough failure events | — |
| Overall survival | 1.10 (0.05–2.43) | 0.81 |
| **Intermediate risk** |                        |         |
| Biochemical failure-free survival | 1.77 (0.82–3.80) | 0.15 |
| Metastasis failure-free survival | 6.36 (0.98–39.59) | 0.06 |
| Prostate cancer-specific survival | 6.49 (0.74–56.73) | 0.09 |
| Overall survival | 0.87 (0.51–1.46) | 0.59 |
| **High risk** |                        |         |
| Biochemical failure-free survival | 3.69 (1.79–7.60) | < 0.001 |
| Metastasis failure-free survival | 5.76 (2.31–14.39) | < 0.001 |
| Prostate cancer-specific survival | 8.99 (2.74–29.50) | < 0.001 |
| Overall survival | 2.60 (1.46–4.64) | 0.001 |

**Abbreviations**: ADT, androgen deprivation therapy; EOR, end-of-radiation; NCCN, National Comprehensive Care Network. Multivariable model adjusted for age, race, initial PSA, Gleason score, T-stage, perineural invasion on biopsy, radiation dose, use of intensity-modulated radiation and duration of ADT.
more likely to have had NCCN low-risk disease, including a lower Gleason score and less advanced T-stage, and less likely to have had perineural invasion on biopsy (all \( P \leq 0.001 \)). Men with a detectable EOR PSA also received a lower median radiation dose, were less likely to have received intensity-modulated radiation therapy and were less likely to have received neoadjuvant-concurrent ADT (all \( P < 0.001 \)).

Univariate and multivariable-adjusted associations between EOR PSA and survival endpoints are summarized in Tables 2 and 3, respectively. Hazard ratios for the associations between all covariates included in the multivariable model and survival endpoints are also summarized (Supplementary eTable 1). A detectable EOR PSA was independently associated with significantly inferior BFFS (all \( P < 0.001 \)), MFS (all \( P < 0.001 \)), PCSS (all \( P < 0.001 \)) and OS (all \( P = 0.004 \)). Figure 1 displays Kaplan–Meier survival estimates, stratified by EOR PSA level. Men with a detectable EOR PSA experienced inferior 10-year BFFS (49.7% versus 64.4%, \( P < 0.001 \)), 10-year MFS (84.8% versus 92.0%, \( P = 0.003 \)), 10-year PCSS (94.3% versus 98.2%, \( P = 0.007 \)) and 10-year OS (75.8% versus 82.5%, \( P = 0.01 \)), as compared to men with an undetectable EOR PSA.

Given that EOR PSA was significantly influenced by the use of neoadjuvant-concurrent ADT, which was primarily dictated by NCCN risk level, we performed a subset analysis to explore associations between EOR PSA and survival endpoints within NCCN risk groups, restricting the analysis to men who received ADT in accordance with modern standards. Notably, among NCCN low-risk men who received radiation alone (\( n = 204 \)), only 2% achieved an undetectable EOR PSA, precluding analysis in this subset. We did analyze whether higher EOR PSA thresholds offered prognostic utility in this subset, but results were not significant (data not shown). Similarly, among NCCN intermediate-risk patients who received neoadjuvant-concurrent ADT (\( n = 168 \)), a detectable EOR PSA was not associated with BFFS, MFS, PCSS or OS, which may again reflect too few events in this subset. However, in NCCN high-risk men who received neoadjuvant-

Table 4. Multivariable-adjusted associations between EOR PSA, initial NCCN risk grouping and survival endpoints in NCCN intermediate-risk and high-risk patients undergoing neoadjuvant-concurrent ADT.

| Survival Endpoint | EOR PSA \( \geq 0.1 \text{ ng ml}^{-1} \) versus \( < 0.1 \text{ ng ml}^{-1} \) | Hazard Ratio (95% CI) | \( P \)-value |
|------------------|-------------------------------------------------|---------------------|------------|
| **Biochemical failure-free survival** | NCCN risk group | 3.25 (2.00–5.28) | < 0.001 |
| Metastasis failure-free survival | NCCN risk group | 4.56 (2.20–9.45) | < 0.001 |
| Prostate cancer-specific survival | NCCN risk group | 5.89 (2.37–14.65) | < 0.001 |
| Overall survival | NCCN risk group | 1.60 (1.10–2.31) | 0.01 |

Abbreviations: ADT, androgen deprivation therapy; EOR, end-of-radiation; NCCN, National Comprehensive Care Network. Multivariable model adjusted for age, race, perineural invasion on biopsy, radiation dose, use of intensity-modulated radiation and duration of ADT.

Figure 1. Survival outcomes for cohort stratified by end-of-radiation (EOR) PSA level, including (a) biochemical failure-free survival, (b) metastasis-free survival, (c) prostate cancer-specific survival and (d) overall survival. Red curves represent men with a detectable EOR PSA. Blue curves represent men with an undetectable EOR PSA.
concurrent and long-term adjuvant ADT \((n = 188)\), a detectable EOR PSA was significantly associated with inferior BFFS (HR 3.82, 95% CI: 1.80–8.09, \(P < 0.001\)), MFS (HR 5.20, 95% CI: 2.06–13.10, \(P < 0.001\)), PCSS (HR 9.88, 95% CI: 2.84–34.44, \(P < 0.001\)) and OS (HR 2.69, 95% CI: 1.51–4.83, \(P = 0.001\)). Furthermore, when NCCN intermediate- and high-risk men who received neoadjuvant-concurrent ADT were analyzed together, a detectable EOR PSA was more strongly associated with survival outcomes than initial NCCN risk level, as illustrated in Table 4.

Figure 2 displays Kaplan–Meier survival endpoints stratified by EOR PSA in NCCN intermediate- or high-risk men who received neoadjuvant-concurrent ADT; men with a detectable EOR PSA was more strongly associated with survival outcomes than initial NCCN risk level, as illustrated in Table 4. Figure 2 displays Kaplan–Meier survival endpoints stratified by EOR PSA in NCCN intermediate- or high-risk men who received neoadjuvant-concurrent ADT; men with a detectable EOR PSA experienced inferior 10-year BFFS (43.5% versus 59.1%, \(P < 0.001\)), 10-year MFS (74.3% versus 88.4%, \(P < 0.001\)), 10-year PCSS (87.2% versus 96.8%, \(P = 0.002\)) and 10-year OS (66.2% versus 78.4%, \(P < 0.001\)), as compared to men with an undetectable EOR PSA.

Covariates included in the multivariable model were based on significance in univariate analysis, but the inclusion of too many covariates risks overfitting.\(^{20}\) As such, we repeated the analysis, reducing the number of covariates to one per ten prostate cancer deaths by eliminating from the model the least significant covariates of age, race and radiation technique, with similar results (Supplementary eTables 2 and 3).

**DISCUSSION**

In a large cohort of men who underwent definitive radiation at our institution for localized prostate cancer, an EOR PSA level, measured during the last week of radiation therapy, was significantly associated with BFFS, MFS, PCSS and OS; moreover, these associations persisted after controlling for standard pre-treatment prognostic factors. Notably, in the subset of men with NCCN intermediate- or high-risk disease who underwent neoadjuvant-concurrent ADT, achievement of an undetectable PSA level was more strongly associated with survival outcomes than initial NCCN risk grouping. Whether the EOR PSA can be used to dictate treatment intensification in NCCN intermediate- and high-risk men undergoing neoadjuvant-concurrent ADT merits further investigation. In contrast, the utility of the EOR PSA was less pronounced in men with NCCN low-risk disease who were treated with definitive radiation alone. As only 2% of NCCN low-risk patients treated with definitive radiation alone achieved an undetectable PSA, the last week of radiation likely represents too early of a time point to yield useful information in the NCCN low-risk population.

Currently, the duration of androgen suppression for men with localized prostate cancer undergoing definitive radiation is dictated by pre-treatment tumor characteristics, with salvage therapy generally based on the follow-up PSA trend. While PSA failure serves as an excellent surrogate for risk of eventual metastasis and death from prostate cancer, current definitions of PSA failure often require considerable time to elapse before the criteria for failure have been satisfied, during which the window of opportunity for effective escalation of therapy may have passed.\(^{19}\) In other disease sites, treatment modulation based on mid-treatment response assessment has allowed for individualization of therapy earlier in the treatment course.\(^{21}\) Whether such a paradigm can be applied to prostate cancer through earlier PSA response assessment is unclear. To date, several studies have...
ACKNOWLEDGEMENTS

PT Tran was supported by the Keeling Family; The Motta Family; The Irene and Bernard L. Schwartz Scholar Award from the Patrick C. Walsh Prostate Cancer Research Foundation; A Movember-Prostate Cancer Foundation award; Grant numbers: DoD W81XWH-11-1-0272; Sidney Kimmel Foundation SKF-13-021; ACS 122688-RSG-12-196-01-TBG; NIH/NCI R01CA166348.

REFERENCES

1 D’Amico AV, Whittington R, Malkowicz SB, Schulz D, Blank K, Broderick GA et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. J Am Med Assoc 1998; 280: 969–974.
2 Mohler JL, Armstrong AJ, Bahnsen RR, D’Amico AV, Davis BJ, Eastham JA et al. Prostate cancer, version 1.2016. J Natl Compr Canc Netw 2016; 14: 19–30.
3 Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Coksson MS et al. Guidance for the management of clinically localized prostate cancer: 2007 update. J Urol 2007; 177: 2106–2113.
4 Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011; 59: 61–71.
5 Cooperberg MR, Porter DJ, Ekin EP, Litwin MS, Latini DM, Du Chane J et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005; 173: 1938–1942.
6 Loeb S, Schaeffer EM, Tock BJ, Epstein JJ, Humphreys EB, Walsh PC. What are the outcomes of radical prostatectomy for high-risk prostate cancer? Urology 2010; 76: 710–714.
7 Zelofska MJ, Lyass O, Fuku S, Wolfe T, Burman C, Ling CC et al. Predictors of improved outcome for patients with localized prostate cancer treated with neoadjuvant androgen deprivation therapy and three-dimensional conformal radiotherapy. J Clin Oncol 1996; 16: 3380–3385.
8 Sumi M, Ikeda H, Tokuyoe K, Kagami Y, Murayama S, Tobisu K et al. The external radiotherapy with three-dimensional conformal boost after the neoadjuvant androgen suppression for patients with locally advanced prostate carcinoma. Int J Radiat Oncol Biol Phys 2000; 48: 519–528.
9 Ludgate CM, Bishop DC, Pai H, Eldridge B, Lim J, Berthelet E et al. Neoadjuvant hormone therapy and external-beam radiation for localized high-risk prostate cancer: the importance of PSA nadir before radiation. Int J Radiat Oncol Biol Phys 2005; 62: 1309–1315.
10 Alexander AS, Mydin A, Jones SO, Christie J, Lim JT, Truong PT et al. Extreme-risk prostate adenocarcinoma presenting with prostate-specific antigen (PSA) > 40 ng/ml: prognostic significance of the preradation PSA nadir. Int J Radiat Oncol Biol Phys 2011; 81: e713–e719.
11 Mitchell DM, McAleese J, Park RM, Stewart DP, Stranex S, Eakin RL et al. Failure to achieve a PSA level ≤ 1 ng/ml after neoadjuvant LHRHa therapy predicts for lower biochemical control rate and overall survival in localized prostate cancer treated with radiotherapy. Int J Radiat Oncol Biol Phys 2007; 69: 1467–1471.
12 Foo M, Laviere M, Pickles T. Impact of neoadjuvant prostate-specific antigen kinetics on biochemical failure and prostate cancer mortality: results from a prospective patient database. Int J Radiat Oncol Biol Phys 2013; 85: 385–392.
13 McGuire SE, Lee AK, Cerne JZ, Munsell MF, Levy LB, Kudchadker RJ et al. PSA response to neoadjuvant androgen deprivation therapy is a strong independent predictor of survival in high-risk prostate cancer in the dose-escalated radiation therapy era. Int J Radiat Oncol Biol Phys 2013; 85: e39–e46.
14 Zelofska MJ, Gomez DJ, Polkinghorn WR, Pai X, Kollmeier M. Biochemical response to androgen deprivation therapy before external beam radiation therapy predicts long-term prostate cancer survival outcomes. Int J Radiat Oncol Biol Phys 2013; 86: 529–533.
15 Zilli T, Jorcano S, Escude L, Linero D, Rouzaud M, Dubochoz A et al. Hypofractionated external beam radiotherapy to boost the prostate with ≥ 85 Gy/equivalent dose for patients with localized disease at high risk of lymph node involvement: feasibility, tolerance and outcome. Clin Oncol 2014; 26: 316–322.
16 Crook J, Ludgate C, Malone S, Perry G, Eapen L, Bowen J et al. Final report of multicenter Canadian phase III randomized trial of 3 versus 8 months of neoadjuvant androgen deprivation therapy before conventional-dose radiotherapy for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2009; 73: 327–333.
17 Alexander A, Crook J, Jones S, Malone S, Bowen J, Truong P et al. Is biochemical response more important than duration of neoadjuvant hormone therapy before radiotherapy for clinically localized prostate cancer? An analysis of the 3-versus 8-month randomized trial. Int J Radiat Oncol Biol Phys 2010; 76: 23–30.
18 Heymann JJ, Benson MC, D’Toole KM, Malyszko B, Brody R, Vecchio D et al. Phase II study of neoadjuvant androgen deprivation followed by external-beam radiotherapy with 9 months of androgen deprivation for intermediate- to high-risk localized prostate cancer. J Clin Oncol 2007; 25: 77–84.

19 Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006; 65: 965–974.

20 Hawkins DM. The problem of overfitting. J Chem Inf Comput Sci 2004; 44: 1–12.

21 Schwartz CL, Constine LS, Villaluna D, London WB, Hutchison RE, Sposto R et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. Blood 2009; 114: 2051–2059.

22 Ryan CJ, Smith A, Lal P, Satagopan J, Reuter V, Scardino P et al. Persistent prostate-specific antigen expression after neoadjuvant androgen depletion: an early predictor of relapse or incomplete androgen suppression. Urology 2006; 68: 834–839.

23 Spratt DE, Evans MJ, Davis BJ, Doran MG, Lee MX, Shah N et al. Androgen receptor upregulation mediates radioresistance after ionizing radiation. Cancer Res 2015; 75: 4688–4696.

24 D’Amico AV, Chen M, de Castro M, Loffredo M, Lamb DS, Steigler A et al. Surrogate endpoints for prostate cancer-specific mortality after radiotherapy and androgen suppression therapy in men with localised or locally advanced prostate cancer: an analysis of two randomised trials. Lancet Oncol 2012; 13: 189–195.

25 Cury FL, Hunt D, Roach M, Shipley W, Gore E, Hsu I et al. Prostate-specific antigen response after short-term hormone therapy plus external-beam radiotherapy and outcome in patients treated on Radiation Therapy Oncology Group study 9413. Cancer 2013; 119: 1999–2004.

26 De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995–2005.

27 Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–433.

28 Narang AK, Gergis C, Robertson SP, He P, Ram AN, McNutt TR et al. Very high-risk localized prostate cancer: outcomes following definitive radiation. Int J Radiat Oncol Biol Phys 2016; 94: 254–262.

29 Morris WJ, Tyldelesy S, Pai HH, Halperin R, McKenzie MR, Duncan G et al. ASCENDE-RT*: a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. In: ASCO Annual Meeting Proceedings, 2015.

30 Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR et al. Long-term results of the MD Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008; 70: 67–74.