Androgen deprivation therapy in men with node-positive prostate cancer treated with postoperative radiotherapy

Bravi, C.A.; Tin, A.; Vertosick, E.; Mazzone, E.; Bandini, M.; Dell'Oglio, P.; ... ; Vickers, A.

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 38 (2020) 204–209

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Androgen deprivation therapy in men with node-positive prostate cancer treated with postoperative radiotherapy

Carlo Andrea Bravi[a,b,*], Amy Tin[b], Emily Vertosick[b], Elio Mazzone[a], Marco Bandini[a], Paolo Dell'Oglio[a], Armando Stabile[a], Giorgio Gandaglia[a], Nicola Fossati[a], Daniel Sjoberg[b], Karim Touijer[c], Cesare Cozzarini[d], Alberto Briganti[a], Francesco Montorsi[a], James Eastham[c], Andrew Vickers[b]

[a] *Division of Oncology, Unit of Urology, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy*
[b] *Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY*
[c] *Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*
[d] *Department of Radiotherapy, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy*

Received 24 July 2019; received in revised form 19 September 2019; accepted 22 September 2019

Abstract

Background: In men with node-positive prostate cancer after radical prostatectomy there are limited data on the value of adding androgen deprivation therapy (ADT) to postoperative radiotherapy.

Objective: To determine whether there is a clear oncologic benefit to ADT in the setting of node-positive prostate cancer treated with postoperative radiotherapy.

Methods: We analyzed data for 372 prostate cancer patients treated at San Raffaele Hospital with postoperative radiotherapy for node-positive disease after radical prostatectomy, 272 received both ADT and radiotherapy. Eighty-six men were followed without an event for more than 10 years.

Results: Patients who received postoperative radiotherapy + ADT had more aggressive disease, with higher preoperative PSA level, higher rate of ISUP grade 5, pT3b-T4 tumors and ≥3 positive nodes. At multivariable Cox regression, the comparison between men treated by postoperative radiotherapy + ADT vs. radiotherapy alone did not show a significant difference for overall (hazards ratio: 0.91; 95% confidence interval: 0.45, 1.84; $P = 0.8$) and cancer-specific survival (hazards ratio: 5.39; 95% confidence intervalI: 0.70, 41.39; $P = 0.11$). These results remained consistent in a number of sensitivity analyses, including propensity score matching. Consideration of 95% CIs suggests that a clinically significant benefit of ADT in node-positive patients receiving radiotherapy after surgery is unlikely.

Conclusions: We can exclude the sort of large survival benefit that would be required to justify the risks and toxicities of ADT in men with node-positive disease receiving postoperative radiotherapy. Awaiting larger and more powered studies on this topic, men with pN+ prostate cancer treated with postoperative radiotherapy should not receive ADT outside well-controlled clinical trials.

Keywords: Node-positive prostate cancer; Radical prostatectomy; Androgen deprivation therapy; Postoperative radiotherapy

1. Introduction

Lymph node metastases are found in approximately 15% of patients treated by radical prostatectomy. Although nodal involvement is clearly a poor prognostic sign, it is not an inevitable harbinger of recurrence: about 1 in 3 patients with positive lymph nodes remain recurrence free at long-term follow-up even in the absence of postoperative treatment [1]. This suggest prognostic heterogeneity in men with positive lymph nodes that should be taken into consideration in order to avoid overtreatment.

Androgen deprivation therapy (ADT) is the gold standard treatment for metastatic prostate cancer. Historically,

*Corresponding author. Tel.: +39-022-643-7286.
E-mail address: bravi.carloandrea@hsr.it (C.A. Bravi).

https://doi.org/10.1016/j.urolonc.2019.09.018
1078-1439/

patients with nodal metastases after radical prostatectomy were managed with ADT on the grounds of improved survival over postoperative observation [2]. Subsequent evidence that a combination of ADT and adjuvant radiotherapy is beneficial over ADT alone [3] has contributed to a shift in the treatment paradigm, with positive lymph nodes no longer considered a sign of disseminated disease but potentially cured by treatments aimed at local control. The rationale behind the use of radiotherapy in this setting is that nodal metastases are deemed an adverse pathologic feature after radical prostatectomy, expression of advanced, high-risk (but localized) disease. Given this premise, it seems reasonable that cancer control might result from local rather than systemic therapy, in keeping with overwhelming evidence that adjuvant radiotherapy is beneficial in node-negative patients with other adverse pathologic features [4,5]. This raises the obvious question of the relative contribution of ADT to treatment effect. Research data are sparse on this point [6], having focusing predominantly on whether radiotherapy adds to ADT rather than the other way around [7,8].

ADT causes a large number of side effects, including hot flashes, fatigue and impaired libido, as well as risks such as metabolic and cardiovascular complications [9]. For these reasons, the use of ADT in combination with postoperative radiotherapy for node-positive prostate cancer would only be justified if it resulted in a substantial decrease in cancer-specific death.

To test whether the addition of ADT to postoperative radiotherapy improves survival compared to radiotherapy alone, we examine a cohort of node-positive prostate cancer patients treated at high-volume institution.

2. Methods

We analyzed data of 643 prostate cancer patients who received postoperative radiotherapy with or without ADT for node-positive disease after radical prostatectomy. All patients received surgery as primary treatment at San Raffaele Hospital between 1991 and 2017. An extended pelvic lymph node dissection was performed in all the cases, which included the removal of obturator, external iliac, and hypogastric nodes. Postoperative treatments were administered within 6 months from surgery and all patients were followed for more than 6 months. The decision to administer additional ADT was based on the clinical judgement of each treating physician according to individual patient and cancer characteristics. Prostate specific antigen (PSA) level within eight weeks of surgery was available for 187 (50%) patients. We excluded patients who received neoadjuvant treatment ($n = 229$) and those who had missing pathologic data ($n = 42$), resulting in 372 men eligible for the analyses.

Postoperative radiotherapy consisted of local radiation to the prostatic bed with or without the seminal vesicle bed and pelvic lymph nodes area (whole-pelvis radiotherapy). All patients were treated with high-energy photon beams (6–18 mV) at conventional fractionation (1.8–2 Gy/ fraction), at a median dose of 68 Gy (interquartile range [IQR]: 66, 70) using previously described techniques [3,10]. A full description of the methods of radiotherapy is available in Supplementary appendix A.

ADT consisted of either bilateral orchiectomy or luteinizing hormone releasing hormone agonist. ADT was generally intended to be lifelong. However, given the retrospective nature of our study, it is uncertain whether patients discontinued treatment after a period of ADT.

The primary outcome of the study was cancer-specific survival. Secondary outcomes were overall survival and clinical recurrence, defined as positive imaging plus PSA $\geq$ 0.2 ng/ml in two consecutive measurements. The cause of death was defined by the attending urologist or oncologist who followed the patients or by death certificate.

Statistical analyses

Our statistical analyses consisted of several steps. First, we compared disease characteristics between the groups using the Wilcoxon rank-sum and Chi-squared tests. Second, Kaplan-Meier methods were used to estimate cancer-specific and overall survival in the two groups. Cox proportional hazards regression was used to compare survival between the groups. The Cox model was adjusted for age, number of positive nodes (categorized as 1–2 vs. 3+) and the risk of biochemical recurrence derived from the MSKCC nomogram [11], which includes preoperative (PSA level) and pathologic variables (grade, stage, nodal involvement, and margins status). Third, we built a competing risk regression model with cancer-specific mortality as the outcome and death from other causes as the competing event. Finally, we conducted a number of sensitivity analysis to assess the robustness of our findings. To explore whether differences in outcome were related to baseline differences between groups, we restricted our analysis to men with pathologic International Society of Urological Pathology (ISUP) grade 3 to 5. In a separate analysis, we also excluded patients treated before 2005, when a different ISUP grading system was used. Moreover, we repeated the analyses after excluding patients with PSA persistence, defined as PSA $\geq$ 0.1 ng/ml within 8 weeks of surgery. To test whether the effect of ADT might differ according to nodal burden, we repeated the analyses in patients with 1 to 2 vs. 3+ positive nodes [12]. Moreover, since the probability of being treated by radiotherapy alone or in combination with ADT may be affected by disease characteristics, we used a propensity score approach. The individual probability of receiving postoperative radiotherapy + ADT was calculated using a logistic regression model according to age, MSKCC nomogram-derived risk of biochemical recurrence (BCR) and number of positive nodes. This likelihood was then used to match in a 1:2 ratio patients in the radiotherapy group to men treated by radiotherapy + ADT with similar ($\pm$ 5%) probability in order to create a more homogeneous subcohort.

Table 1
Descriptive characteristics of 372 patients treated by radical prostatectomy who had N+ disease at surgical pathology, stratified by postoperative treatments

	Postoperative radiotherapy ($N = 100$; 27%)	Postoperative radiotherapy + ADT ($N = 272$; 73%)	*P* value
Year of surgery			
<2005	17 (17%)	98 (36%)	0.002
2006-2010	39 (39%)	90 (33%)	
>2010	44 (44%)	84 (31%)	
Age, y	67 (60, 71)	64 (60, 69)	0.077
Preoperative PSA level, ng/ml	9.4 (6.6, 19.0)	11.1 (7.3, 19.5)	0.2
Pathologic ISUP grade			
1-2	22 (22%)	44 (16%)	0.5
3	26 (26%)	69 (25%)	
4	14 (14%)	34 (13%)	
5	38 (38%)	125 (46%)	
Pathologic stage			
T2-T3a	39 (39%)	83 (31%)	0.12
T3b-T4	61 (61%)	189 (69%)	
Positive surgical margins	46 (46%)	157 (58%)	0.044
Number of positive nodes			
1-2	82 (82%)	172 (63%)	0.001
3+	18 (18%)	100 (37%)	
PSA persistence (≥0.1 ng/ml)	14 (14%)	40 (15%)	0.2
Unknown	37 (37%)	148 (54%)	

ADT = androgen deprivation therapy.

3. Results

Table 1 describes the characteristics of our study cohort. Although differences between the groups were statistically significant only in few cases, men receiving radiotherapy + ADT generally had more aggressive disease, including higher preoperative PSA level, higher rate of ISUP grade 5, pT3b-T4 tumors and greater metastatic burden (≥3 positive nodes).

There were 48 all-cause and 18 cancer-specific deaths. Median follow-up for survivors was 77 months (interquartile range: 44, 113) with 86 patients followed for more than 10 years without an event. The predicted 10-year overall survival was 81% (95% confidence interval [CI]: 63%,

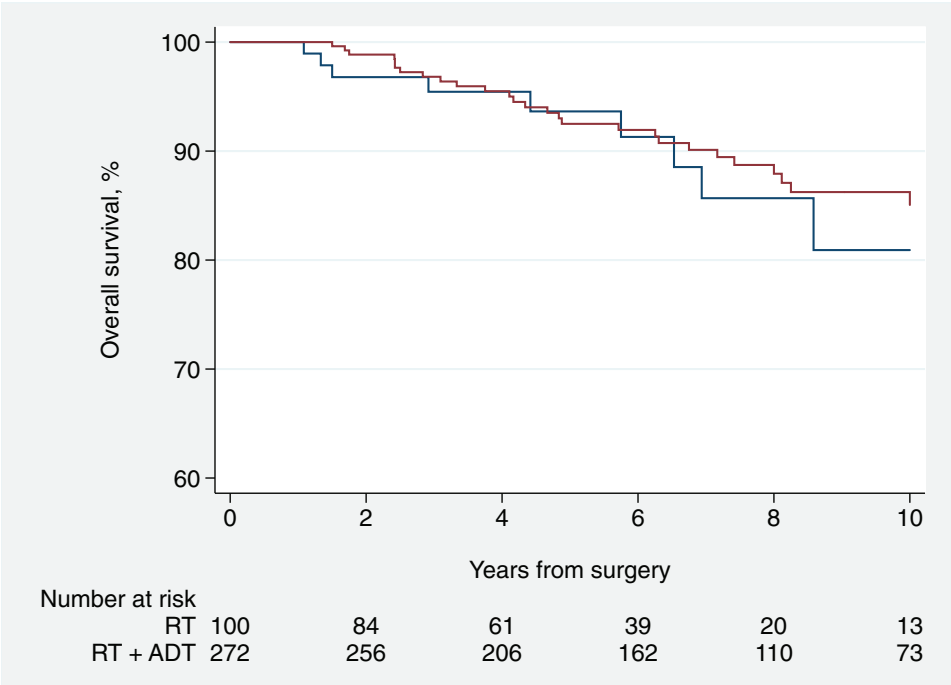

Fig. 1. Kaplan Meier curves for overall survival stratified by treatment group. Blue line: radiotherapy (RT). Red line: radiotherapy + androgen deprivation therapy (ADT). (Color version of figure is available online).

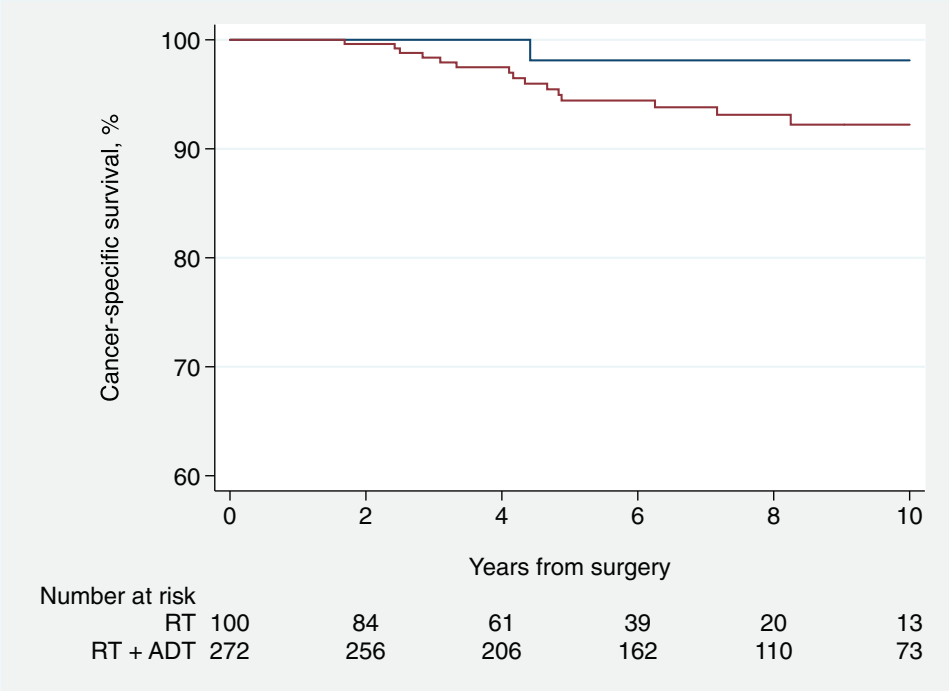

Fig. 2. Kaplan Meier curves for cancer-specific survival stratified by treatment group. Blue line: radiotherapy (RT). Red line: radiotherapy + androgen deprivation therapy (ADT). (Color version of figure is available online).

91%) for patients treated by radiotherapy alone and 85% (95%CI: 78%, 90%) for those who received radiotherapy and ADT (Fig. 1). The predicted 10-year cancer-specific survival was 98% (95%CI: 87%, 100%) for the radiotherapy group and 92% (95%CI: 87%, 95%) for men who received radiotherapy + ADT (Fig. 2).

The results of our Cox regression analyses are shown in Table 2. There was no significant difference in overall survival between men treated by radiotherapy + ADT vs. radiotherapy alone (hazards ratio [HR]: 0.91; 95%CI: 0.45, 1.84; $P = 0.8$). Similarly, the risk of cancer-specific death was not significantly different between men treated with radiotherapy + ADT vs. those who received radiotherapy alone (HR: 5.39; 95%CI 0.70, 41.39; $P = 0.11$). This finding was confirmed in the competing risk analysis used to predict cancer-specific death with death from other causes as the competing event (HR: 5.60; 95%CI 0.68, 45.86; $P = 0.11$). Although consideration of the 95% C.I. indicates that a clinically relevant effect of ADT cannot be excluded, these results are compatible with a limited oncologic benefit of ADT when administered in combination with radiotherapy for node-positive prostate cancer.

Table 2
Multivariable Cox proportional hazard model to assess the association between postoperative treatments and survival outcomes

Variable	Hazards ratio	95% confidence interval	*P*-value
All-cause mortality			
Postoperative treatment			
Radiotherapy	Ref		
Radiotherapy + ADT	0.91	0.45, 1.84	0.8
Cancer-specific mortality			
Postoperative treatment			
Radiotherapy	Ref		
Radiotherapy + ADT	5.39	0.70, 41.39	0.11
Clinical recurrence			
Postoperative treatment			
Radiotherapy	Ref		
Radiotherapy + ADT	2.41	1.09, 5.31	0.029

ADT = androgen deprivation therapy.
Models adjusted for age, risk of BCR according to the MSKCC nomogram and number of positive nodes (1-2 vs. 3+).

A total of 77 patients developed clinical recurrence. The predicted 10-year clinical recurrence-free survival was 92% (95%CI: 82%, 96%) for patients treated by radiotherapy alone and 70% (95%CI: 63%, 76%) for those who received radiotherapy and ADT. At multivariable analyses, the risk of clinical recurrence was higher in the radiotherapy and ADT group compared to radiotherapy alone (HR: 2.41; 95%CI: 1.09, 5.31; $P = 0.029$; Table 2).

Results of our sensitivity analyses are described in supplementary appendix B. In brief, our findings were unaltered when the analyses were restricted to patients with ISUP grade 3 to 5 tumors, to the subgroup treated after 2005 and after excluding patients with PSA persistence. We did not find evidence of a different effect of ADT according to the number of positive nodes: the risk of clinical recurrence in the ADT group did not differ in case of positivity in 1 to 2 (HR: 2.05, 95% CI: 0.79, 5.33; $P = 0.14$) vs. 3+ (HR: 3.93, 95% CI: 0.93, 16.65; $p = 0.063$) nodes. In our propensity score analysis, there were no statistically significant differences in baseline characteristics between

radiotherapy vs. radiotherapy + ADT after adjusting for propensity score (supplementary appendix C). Results were similar to our main analysis, with no significant difference between radiotherapy + ADT vs. radiotherapy alone for cancer-specific survival (HR: 3.27; 95% CI: 0.37; 28.46; $P = 0.3$). Results were also similar to our primary analysis for clinical recurrence (HR: 2.18; 95% CI: 0.88, 5.41; $P = 0.094$).

4. Discussion

We were not able to demonstrate a survival benefit from ADT administered with postoperative radiotherapy in men with node-positive prostate cancer. Moreover, the lower bound of the 95% C.I. for the effect of ADT on cancer-specific survival excluded a benefit sufficient enough to warrant treatment-related risks and toxicities [9].

Previous evidence showed improved survival for ADT over postoperative observation [13], but a prognostic advantage over other treatment strategies such as radiotherapy has never been observed in this patient group. In an observational study of 773 patients with node-positive disease, Tilki et al. compared oncologic outcomes of men treated with adjuvant radiotherapy, adjuvant ADT or observation followed by salvage radiotherapy in case of relapse. After a median follow-up of 33 months, patients receiving adjuvant radiation therapy had better metastasis-free survival than those treated with adjuvant ADT; there was no difference in survival between patients receiving adjuvant ADT without radiotherapy compared to those who were initially observed [14]. Similarly, a population-based study on postoperative treatments for pN+ patients showed better 5-year overall survival for men undergoing radiotherapy than for those receiving hormonal therapy [15]. Although limited by short follow-up and the lack of strong oncologic endpoints such as cancer-specific death, these data suggest that if an intervention is needed in case of nodal involvement at surgical pathology, that should be radiotherapy rather than ADT. This is consistent with literature showing a benefit from the addition of radiotherapy to postoperative ADT. In a series of 1,107 patients treated with hormonal therapy for pN+ prostate cancer, radiation therapy significantly improved cancer-specific survival after a median follow-up of seven years [16], a finding confirmed by several other papers [3,17,18]. Taken together, these findings support the administration of radiotherapy for node-positive disease. However, we do not see evidence that ADT is of additional value to radiotherapy in this population. The literature on this issue is limited, and the hypothesis that ADT improves survival of men receiving radiation therapy has never been directly addressed in a prospective study. The relative contribution of hormonal therapy in this setting may be extrapolated from a subgroup analysis of the RTOG 85-31 trial. Therein, investigators assessed the impact of ADT in N+ patients undergoing radiotherapy: in a subcohort of 42 patients treated after radical prostatectomy, the study did not show oncologic benefit associated with hormonal therapy [19]. Given the lack of studies on this topic, the added value of a combination strategy over radiotherapy alone is far from established. In this regard, our results are compatible with the hypothesis that the benefit from ADT observed by Messing et al. [13] might not hold true in patients receiving postoperative radiotherapy for node-positive disease.

Note that we do not claim that ADT increases the risk of cancer death but, rather, that the CI for cancer-specific survival does not seem to include a clinically relevant effect. Since a clear survival benefit is necessary to justify the increased risk of death from other causes associated with ADT [3], caution should be paid in administering ADT to men with pN+ prostate cancer treated with postoperative radiotherapy. Awaiting confirmatory studies, our results suggest that a combination strategy should not be given outside well-controlled clinical trials. Note also that we are not making a general claim about the value of ADT in prostate cancer patients undergoing radiotherapy. ADT is of proven benefit for patients undergoing initial treatment by radiotherapy [20] or in the case of salvage radiotherapy for patients with node-negative disease [21].

Our study is not devoid of limitations. For example, we cannot rule out residual confounding from known or unknown variables. Since the study included patients treated over more than 25 years, it is possible that aspects of clinical care that have changed over time might influence our results. That said, our results remained consistent in a number of sensitivity analyses. Still, we cannot exclude that future advances in imaging modalities or better understanding of disease biology might allow for the identification of certain subgroups of patients who may benefit from ADT. In addition, consideration of baseline characteristics might raise concerns for selection bias, that is, patients treated by radiotherapy and ADT had more aggressive disease. To address this issue, we performed propensity score matching with no meaningful differences in survival results. Moreover, it is noteworthy that a similar concern has been raised in a prior paper [3]. However, patients treated with radiotherapy + ADT had better overall and cancer-specific survival than those who received ADT alone despite worse prognostic profile and as such, the added value of radiotherapy was claimed. In our study, although men treated by radiotherapy and ADT had similarly more aggressive disease, we did not observe a survival difference. This seems more compatible with a limited contribution of ADT than with a selection bias.

Our results argue against current guidelines that recommend a combination of ADT and radiotherapy as treatment option for node-positive disease [7,8]. Rather, our findings support the inclusion of radiotherapy alone among postoperative strategies. Historically, identification of nodal metastases during radical prostatectomy was an indication for discontinuing surgery. The belief that nodal metastases were a sign of systemic cancer was the rationale for the use of ADT, the standard of care for metastatic prostate cancer. Consideration of nodal involvement has changed, and nowadays it is unlikely that a patient would be told he has

systemic disease in case of N+ pathology. By contrast, the administration of ADT seems guided by cultural inheritance, that is, evidence of metastases mandates systemic therapy. However, it has been demonstrated that patients with nodal metastases have remarkably better prognosis that those who have bone or visceral metastases [22,23], suggesting that these are biologically different phases of tumor spread. For this reason, it is plausible that ADT might not be as effective in nodal metastases as it is for systemic disease. Having said that, while radiotherapy is a well-established treatment for node-positive disease after radical prostatectomy, there is currently no evidence supporting the addition of ADT to radiation therapy. Our findings have thus also implications for empirical research. The benefits and harms of ADT in combination with postoperative radiotherapy should be properly assessed (i.e. using the adequate reference group). In this regard, we call for randomized controlled trials testing radiotherapy vs. radiotherapy + ADT in patients with node-positive prostate cancer after radical prostatectomy.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.09.018.

References

[1] Touijer K, Mazzola CR, Sjoberg DD, Scardino PT, Eastham JA. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. Eur Urol 2014;65(1):20–5. https://doi.org/10.1016/j.eururo.2013.03.053.

[2] Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341(24):1781–8. https://doi.org/10.1056/NEJM199912093412401.

[3] Touijer KA, Karnes RJ, Passoni N, et al. Survival outcomes of men with lymph node-positive prostate cancer after radical prostatectomy: a comparative analysis of different postoperative management strategies. Eur Urol 2018;73(6):890–6. https://doi.org/10.1016/j.eururo.2017.09.027.

[4] Bolla M, van Poppel, MD PH, MD PBT, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). The Lancet 2012;380(9858):2018–27. https://doi.org/10.1016/S0140-6736(12)61253-7.

[5] Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181(3):956–62. https://doi.org/10.1016/j.juro.2008.11.032.

[6] Stabile A, Muttin F, Zamboni S, et al. Therapeutic approaches for lymph node involvement in prostate, bladder and kidney cancer. Expert Rev Anticancer Ther 2019;3:1–17. https://doi.org/10.1080/14737140.2019.1659135.

[7] Mottet N., Bellmunt J., Briers E., Bolla M., Bourke L., Cornford P., et al. Members of the EAU – ESTRO – ESUR –SIOG Prostate Cancer Guidelines Panel. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. Retrieved From: https://Uroweb.org/Guideline/Prostate-Cancer/. Access Date [Insert Date the Information Was Accessed].

[8] NCCN Clinical Practice Guidelines in Oncology. Version 2018 - Prostate Cancer. August 20181–151.

[9] Allan CA, Collins VR, Frydenberg M, McLachlan RI, Matthiesson KL. Androgen deprivation therapy complications. EndocrRelat Cancer 2014;21(4):T119–29. https://doi.org/10.1530/ERC-13-0467.

[10] Cozzarini C, Fiorino C, Deantoni C, et al. Higher-than-expected Severe (grade 3-4) late urinary toxicity after postprostatectomy hypofractionated radiotherapy: a single-institution analysis of 1176 patients. Eur Urol 2014;66(6):1024–30. https://doi.org/10.1016/j.eururo.2014.06.012.

[11] MSKCC Nomograms. https://www.Mskcc.org/Nomograms/Prostate. Access Date: 06/2019.

[12] Briganti A, Karnes JR, Da Pozzo LF, et al. Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. a new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol 2009;55(2):261–70. https://doi.org/10.1016/j.eururo.2008.09.043.

[13] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7(6):472–9. https://doi.org/10.1016/S1470-2045(06)70700-8.

[14] Tilki D, Preisser F, Tennstedt P, et al. Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. BJU Int 2016;119(5):717–23. https://doi.org/10.1111/bju.13679.

[15] Wong AT, Schwartz D, Osborn V, Safdieh J, Weiner J, Schreiber D. Adjuvant radiation with hormonal therapy is associated with improved survival in men with pathologically involved lymph nodes after radical surgery for prostate cancer. Urol Oncol 2016;34(12):529.e15–20. https://doi.org/10.1016/j.urolonc.2016.06.017.

[16] Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. JCO 2014;32(35):3939–47. https://doi.org/10.1200/JCO.2013.54.7893.

[17] Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. Eur Urol 2011;59(5):832–40. https://doi.org/10.1016/j.eururo.2011.02.024.

[18] Gupta M, Patel HD, Schwen ZR, Tran PT, Partin AW. Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. BJU Int 2018;123(2):252–60. https://doi.org/10.1111/bju.14241.

[19] Lawton CA, Winter K, Grignon D, Pilepich MV. Androgen suppression plus radiation versus radiation alone for patients with stage D 1/pathologic node-positive adenocarcinoma of the prostate: updated results based on National Prospective Randomized Trial Radiation Therapy Oncology Group 85-31. JCO 2005;23(4):800–7. https://doi.org/10.1200/JCO.2005.08.141.

[20] Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11(11):1066–73. https://doi.org/10.1016/S1470-2045(10)70223-0.

[21] Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376(5):417–28. https://doi.org/10.1056/NEJMoa1607529.

[22] Moschini M, Sharma V, Zattoni F, et al. Natural history of clinical recurrence patterns of lymph node—positive prostate cancer after radical prostatectomy. Eur Urol 2016;69(1):135–42. https://doi.org/10.1016/j.eururo.2015.03.036.

[23] Gandaglia G, Karakiewicz PI, Briganti A, et al. Impact of the site of metastases on survival in patients with metastatic prostate cancer. Eur Urol 2015;68(2):325–34. https://doi.org/10.1016/j.eururo.2014.07.020.