RESEARCH ARTICLE

Editorial Process: Submission:09/14/2021 Acceptance:07/13/2022

Adjuvant Treatment Approaches after Radical Prostatectomy with Lymph Node Involvement

Hasan Hüseyin Tavukçu[1], Oğuzcan Erbatu[2], Bülent Akdoğan[3], Volkan İzol[4], Uğur Yücetaş[5], Sinan Sözen[6], Güven Aslan[7], Bahadır Şahin[8], İlker Tinay[9], Talha Müezzinoğlu[2], Sümer Baltacı[10]

Abstract

Objective: The aim of this study was to evaluate the adjuvant treatment preferences and effects on disease progression in patients with pathologically positive lymph node prostate cancer. **Methods:** Patients who underwent radical prostatectomy from the prostate cancer database of the Turkish Urooncology Association with lymph node involvement were included in the study. Database includes prostate cancer patients from many experience Urooncology centers of Turkey. Adjuvant treatment approaches and the factors that effect the PSA recurrrence was analysed. **Results:** Postoperative median 2 (1-3) lymph nodes were found to be positive, and the median lymph node density was reported as 0.13 (0.07-0.25). Seventy-four percent of patients received adjuvant treatment postoperatively. Seventy four of the patients (46.54%) received hormonal therapy in combination with radiotherapy; 47 of them (29.55%) received only hormonal treatment and 20(12.57%) only received radiotherapy. The number of lymph nodes removed was less in the group requiring adjuvant treatment, and this group had a higher rate of surgical margin positivity and seminal vesicle invasion. In addition, adjuvant treatment group had a statistically significant higher lymph node density. There was no significant difference in Kaplan-Meier method comparing 5-year PSA recurrence-free survival in patients with and without adjuvant therapy. When the patient clustered as non-adjuvant, only hormonal therapy and hormonal therapy with radiotherapy, a significant survival advantage was found in the hormonal therapy with radiotherapy group compared to the other two groups (p=0.043). **Conclusion:** No significant difference was found between two groups in terms of time until PSA recurrence during our follow-up. In subgroup analysis survival advantage was found in the hormonal therapy with radiotherapy group compared to non-adjuvant and only hormonal therapy groups.

Keywords: Adjuvant- lymph node metastases- pelvic lymph node dissection- prostate cancer- radical prostatectomy

Asian Pac J Cancer Prev, **23 (7)**, 2279-2284

Introduction

In recent years, as radical prostatectomy is performed in locally advanced patients and in high risk patients, the number of patients with pathological lymph node involvement has also increased. For many years, this patient group was considered to be inoperable and has systemic disease, so early hormonal therapy was recommended for these patients (Denlinger et al., 2020; Motet et al., 2020). Messing et al., (2006) which is still the only randomized study on pathological lymph node involvement after radical prostatectomy and lymph node dissection, reported that early adjuvant hormonal therapy significantly increased overall survival, disease-specific survival and progression-free survival in this patient group. However, since this study was in a period when PSA was not widely used, it is thought to be insufficient for patients nowadays (Abdollah et al., 2018).

It has been reported that if a more extended lymph node dissection is performed, it increases cancer-specific survival in patients with LNI, therefore, extended lymph node dissection should be planned in patients with high preoperative lymph node involvement risk (Abdollah et al., 2015; Mottet et al., 2020). Several studies have

*[1]Department of Urology, University of Health Sciences, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey. [2]Department of Urology, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Turkey. [3]Department of Urology, Hacettepe University School of Medicine, Ankara, Turkey. [4]Department of Urology, Cukurova University School of Medicine, Adana, Turkey. [5]Department of Urology, Istanbul Education and Research Hospital, Ministry of Health, Istanbul, Turkey. [6]Department of Urology, Faculty of Medicine, Gazi University, Ankara, Turkey. [7]Department of Urology, Dokuz Eylul University School of Medicine, Izmir, Turkey. [8]Department of Urology, Marmara University School of Medicine, Istanbul, Turkey. [9]Department of Urology, Anadolu Medical Center, Istanbul, Turkey. [10]Department of Urology, Ankara University School of Medicine, Ankara, Turkey. *For Correspondence: hhtavukcu@yahoo.com*

reported that LNI requires a systemic treatment as well as a multimodal treatment with local disease control (Briganti et al., 2011; Abdollah et al., 2014). In a study of the same group, it was reported that adjuvant radiotherapy was more effective in moderately high risk group with 2 or fewer lymph node involvement, and in patients with 3-4 lymph involvement that were not limited to the prostate (Abdollah et al., 2014). In another study, while 3 or more lymph node involvement was associated with a poor prognosis in patients with extended lymph node dissection, better long-term results were reported in patients with 2 or less lymph involvement (Schumacher et al., 2008). As a result of these studies, European Association of Urology(EAU) and National Cancer Comprehnsive Network (NCCN) guidelines recommend radical prostatectomy in selected patients as a part of multimodal treatment for patients with pathological LNI. EAU guidelines recommend radical prostatectomy as a part of multimodal treatment to locally advanced patients with a weak recommendation. Recommendations on what to do in patients with pathological LNI are still with weak level of evidence, and include hormonal therapy, hormonal therapy with radiotherapy or follow-up for those with less lymph node involvement (Mottet et al., 2020).

In addition to the benefits of hormonal therapy and radiotherapy, there is still no standard approach for patients with pathological lymph node involvement due to possible side effects and lack of sufficient evidence. We aimed to investigate the approach to patients with pathological LNI in our country and the effectiveness of adjuvant therapies used.

Materials and Methods

Patients who had undergone radical prostatectomy and pelvic lymph node dissection and reported pathological LNI from the database of the Turkish Urooncology Association were included in the study. The database was Redcap based patient information system from twenty centers and 5,242 patients who had radical prostatectomy for localised /locally advanced prostate cancer were involved since 2010. The database of the Turkish Urooncology Association includes demograhic, radiologic, laboratory, pathologic details as well as survival status of the patients. In this study we used patient data from ten different centers that were from İstanbul, Ankara, İzmir, Adana and Manisa provinces. These provinces are from middle and west Geographic part of Anatolia in Turkey. Study data were collected and managed using REDCap electronic data capture tools hosted at Marmara University (Harris et al., 2009; Harris et al., 2019). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Local ethics committee approval was obtained for the study. Those who were followed up for less than 3 months were excluded from the study for further examination. The patients were classified as adjuvant hormonal therapy, radiotherapy, chemotherapy and high intensity focused ultrasound(HIFU) as first adjuvant approach. Any late PSA, radiological and clinical progression after adjuvant therapy or non, was defined as requiring salvage therapy from database.

Statistical analysis

Data such as age, preoperative PSA value, total lymph node number, positive lymph node number, lymph node density, Gleason grade group, presence of tumor at the surgical margin, extracapsular invasion and seminal vesicle involvement were compared in two groups with and without adjuvant therapy using Mann Whitney and X^2 Tests. In addition, both groups were compared with the Kaplan Meier plot in terms of time to PSA progression. In the subgroup analysis, patient groups who did not receive adjuvant therapy, only hormonal therapy, and received hormonal therapy and radiotherapy were compared in terms of 5-year PSA recurrence with the Kaplan Meier plot.

Results

Two hundred and thirty patients with lymph node involvement after radical prostatectomy and pelvic lymph node dissection from the database of the Turkish Urooncology Association were included in our study. After further evaluation, 213 patients were included in the study and the median age at the time of operation was 64 (59-68 and the median preoperative PSA values were calculated as 14.0 (8.1-24.6 ng / ml). The mean follow-up time in our study was 33.9 months, and there was no difference between the two groups in terms of follow-up time. (Table 1) According to pathologic investigations median 2 lymph nodes (1-3) were found to be positive and the median lymph node density was reported as 0.13 (0.07-0.25). Postoperatively 74.6% of the patients received adjuvant treatment; hormonal therapy (42.7%), radiotherapy (26.3%), chemotherapy (4.7%) and HIFU (0.9%), respectively. Since the second adjuvant therapy, the patients received radiotherapy, hormonal therapy, chemotherapy, chemotherapy with hormonotherapy and chemotherapy with radiotherapy; it was determined as in order 19.7%, 18.3%, 2.3%, 0.5% and 0.5%. Seventy four of those(46.54%) receiving adjuvant therapy received hormonal therapy in combination with radiotherapy; 47 of them(29.55%) received only hormonal treatment and 20(12.57%) only received radiotherapy.

In our study, only 15 patients were found to require salvage therapy; 12 patients received radiotherapy, and one patient received hormonal therapy, chemotherapy and chemotherapy combined with radiotherapy in each group. Thirteen of the patients who received salvage therapy had received any previous adjuvant therapy. Eight of our patients died in the follow-up time, only one of them died because of prostate cancer related problems.

When the patients who received and did not receive adjuvant treatment were compared, no significant difference was found in parameters such as age,

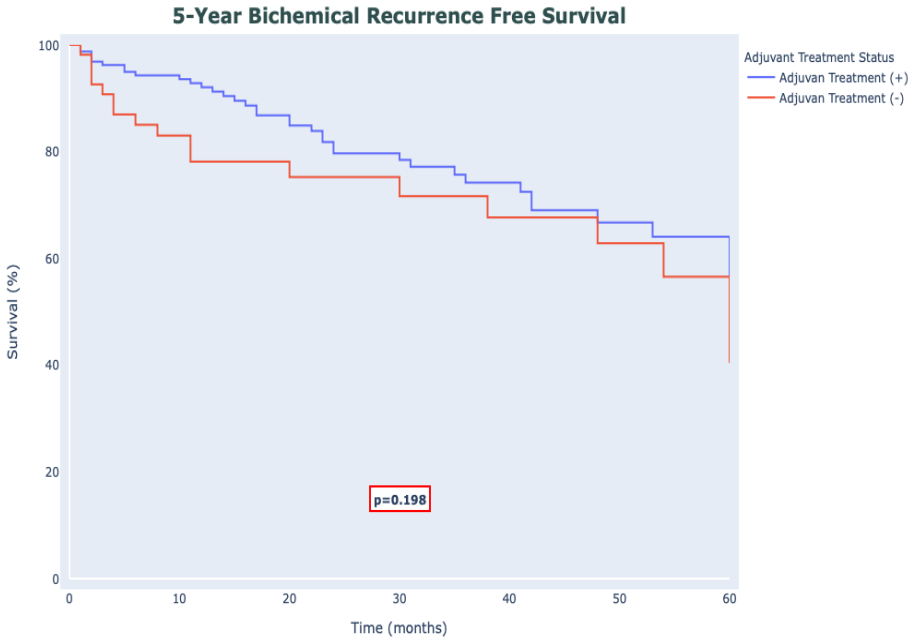

Figure 1. Kaplan-Meier Method Comparing 5-year PSA recurrence-free Survival in Patients with and without Adjuvant Therapy

preoperative PSA value, extracapsular extension, total number of positive lymph nodes and length of follow up. In contrast, it was observed that the number of lymph nodes removed was less in the adjuvant treatment group and also surgical margin positivity and seminal vesicle invasion were higher in this group significantly. In addition, when these two groups were compared, it was observed that the adjuvant treatment group had a statistically significant higher lymph node density (Table 1). A higher rate of high-risk and pathological advanced disease was detected in the adjuvant group while these were not statistically signficant between groups (Table 2). There was no significant difference in Kaplan-Meier method comparing 5-year PSA recurrence-free survival in patients with and without adjuvant therapy (Figure 1). When the patient clustered as non-adjuvant, only hormonal therapy and hormonal therapy with radiotherapy in terms of 5-year PSA recurrence-free survival, a significant survival advantage was found in the hormonal therapy with radiotherapy group compared to the other two groups (p=0.043) (Figure 2). This difference was particularly significant between the non-adjuvant group and hormonal therapy with radiotherapy group (p=0.013). However, there was no statistical difference between the hormonal treatment group with radiotherapy and only the hormonal treatment group (p=0.069), and also between the hormonal treatment group and the non-adjuant group (p=0.659).

Discussion

Since the follow-up time in our study, no significant difference was found between patients with lymph node involvement after radical prostatectomy between two groups in terms of 5-year PSA recurrence free survival. Nearly seventy five percent of our patients received any

Table 1. Comparison of two groups results with demograhic and pathological findings.

		Adjuvant treatment (n: 159)	No adjuvant treatment (n: 54)	p-value
Age at operation time	Median (IQR)	63.0 (58.0 - 68.0)	64.0 (60 - 70)	0.209
Preoperative PSA(ng/ml)	Median (IQR)	14.72 (8.22 - 25.3)	11.73 (7.22 - 23.98)	0.248
Total nodes removed	Median (IQR)	14.0 (9 - 21)	18.0 (12 - 27)	0.008
Positive Nodes	Median (IQR)	2.0 (1 - 3)	1.0 (1 - 3)	0.492
Lymph node density	Median (IQR)	0.14 (0.08 - 0.26)	0.11 (0.06 - 0.18)	0.029
Pathologic Gleason Grade Group	Median (IQR)	4.0 (3.0 - 5.0)	4.0 (2.25 - 5.0)	0.092
Positive surgical margin	No	35 (22.01%)	25 (46.3%)	0.001
	Yes	124 (77.99%)	29 (53.7%)	
Extracapsular extension	No	18 (11.32%)	9 (16.67%)	0.308
	Yes	141 (88.68%)	45 (83.33%)	
Seminal vesicle invasion	No	44 (27.67%)	23 (42.59%)	0.041
	Yes	115 (72.33%)	31 (57.41%)	
Follow up time (month)	Median (IQR)	28.0 (13.0 - 46.0)	26.0 (10.25 - 48.0)	0.418

Table 2. EAU Risk Groups and Pathologic Stages of Each Group

	Overall n (%) 213 (100)	Adjuvant treatment n (%) 159 (74.6)	No adjuvant treatment n (%) 54 (25.4)	P value
EAU risk groups				
Low+Intermediate-risk	33 (15.49)	21 (9.85)	12 (5.64)	
High-risk	180 (84.51)	138 (64.79)	42 (19.72)	0.114
Pathologic stage				
T2	14 (6.57)	8 (3.75)	6 (2.82)	
T3a	54 (25.35)	37 (17.37)	17 (7.98)	
T3b	145 (68.07)	114 (53.52)	31 (14.55)	0.103

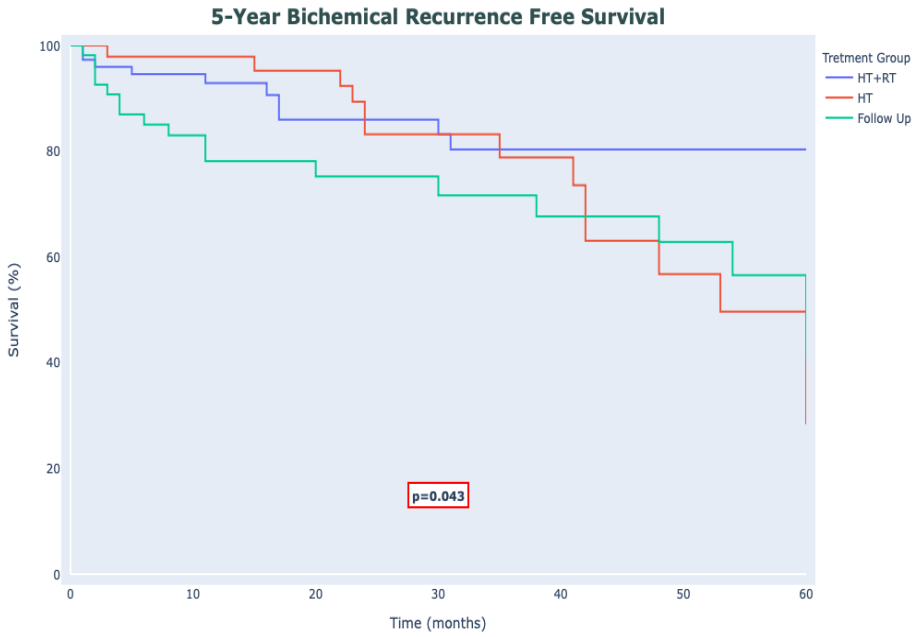

Figure 2. Kaplan-Meier Method Comparing 5-Year PSA Recurrence-Free Survival in Patients Non-Adjuvant, only Hormonal Therapy and Hormonal Therapy with Radiotherapy

adjuvant treatment, while 25% of them did not require any additional treatment during follow-up. It should be kept in mind that a real staging can be done in this patient group with radical prostatectomy and lymphadenectomy, and one fourth of the patients can be followed up without additional treatment.

In our study, it was found that statistically less lymph nodes were removed in the adjuvant group in terms of the total number of lymph nodes removed (p=0.018). While the median number of lymph nodes removed was 17.5 in the non-adjuvant therapy group, it was 14 in the group receiving adjuvant treatment. In Abdollah et al.,'s (2015) previous study, a positive relationship was found between the number of lymph nodes removed and cancer-specific survival; in other words, if more extended lymphadenectomy is performed, survival is affected more positively. In the same study, a cut-off value was 14 that was determined for the number of lymph nodes removed, and also survival rates of patients with 14 or more lymph nodes removed were found to be statistically significantly higher. In contrast, other studies have reported that there is no relationship between the number of lymph nodes removed and overall or cancer-specific survival even in high-risk patients (Murphy et al., 2010; Pierorazio et al., 2013; Touijer et al., 2014). But still, EAU guidelines recommend extended lymphadenectomy as if lymphadenectomy will be performed during radical prostatectomy for many years.

Lymph node density is considered to be the ratio of the number of tumor-positive lymph nodes to all removed lymph nodes. In our study, no significance were detected in terms of positive lymph node numbers, but we found that the lymph node density was higher in the adjuvant group with statistical significance. (p=0.029) Although some prostate cancer studies in previous years have proven that lymph node density can be a better stratification tool for survival, Passoni et al., (2014) reported lymph node density as a stronger predictor of cancer-specific survival than positive lymph nodes in their multivariate analysis (Daneshmand et al., 2004; Palapattu et al., 2004; Cai et al., 2011).

Another significant finding between the two groups in our study was the positive surgical margin, and it was higher in the adjuvant group. (p=0.001) Similar to our study, Tilki et al., (2017) found statistically significant higher surgical margin positivity rates in those receiving

adjuvant therapy, but they reported that it was not significant in terms of survival or recurrence in univariate and multivariate analyzes. Touijer et al., (2014) reported that surgical margin positivity was not associated with mortality from prostate cancer in univariate analysis, while its effect on PSA recurrence was not shown in multivariate analysis, it was reported to be significant in terms of distant metastasis. In some other studies, surgical margin positivity was not found to be an effective factor in the need for adjuvant treatment or prognosis (Schumacher et al., 2008; Briganti et al., 2009; Briganti et al., 2011).

A significant difference was found between the two groups in terms of seminal vesicle invasion in our study. In their study,Tilki et al., (2017) reported that being ≥T3b or ≤T2 in multivariate analysis was not an effective factor in terms of biochemical recurrence and survival, and there was no difference in this regard between the groups who received and did not receive adjuvant therapy. Touijeret al., (2014) found that seminal vesicle invasion was significant in terms of death caused by prostate cancer in univariate analysis, but did not find it as a significant factor in terms of biochemical recurrence and distant metastasis in multivariate analysis.

In our study, when the EAU risk groups of the patients were examined, it was observed that those adjuvant treatment included a higher rate of high risk group, but this was not statistically significant. Similarly, a higher rate of advanced stage was observed in the adjuvant group but this was not significant. In the study of Briganti et al.,'s (2011) which comparing adjuvant hormonal therapy and hormonal therapy with radiotherapy, no difference was reported in terms of patients with lymph node involvement according to the pathological stage. In another similar study, no difference was reported between the groups who received hormonal treatment and those who received hormonal therapy together with radiotherapy in terms of pathological stage (Abdollah et al., 2015). Briganti et al.,'s (2009) previous study, the pathological stage was reported to be significantly higher in patients had hormonal therapy with radiotherapy patients compared to patients with hormonal therapy alone.

Hormonal therapy with radiotherapy group had significant 5 year biochemical recurrence free survival than others while our follow up time is limited. In a population-based study, no significant difference in survival was reported between radiotherapy groups with follow-up, adjuvant hormonal therapy and hormonal therapy in patients with pathological lymph involvement (Rusthoven et al., 2014). In a study by Guptaet al., (2019) patients with adverse pathological features reported that radiotherapy combined with adjuvant hormonal therapy provided an overall survival advantage. They defined as adverse pathological factors; ≥pT3b, Gleason score ≥9, three or more lymph node involvement or surgical margin positivity that ≥pT3b and surgical margin positivity were statiscially different between adjuvant and non-adjuvant groups in our study.

Many studies have tried to provide informations on whether to add adjuvant radiotherapy to adjuvant hormonal therapy in prostatic cancer patients with pathological lymph node involvement (Briganti et al., 2009; Abdollah et al., 2018). Although we have a retrospective or limited follow-up period, it should be considered valuable in terms of comparing patients who were not given adjuvant therapy with those who received adjuvant therapy. Essentially we aimed to examine the approach to prostate cancer patients with pathological lymph involvement in our country; that seventy four of those (46.54%) receiving adjuvant therapy received hormonal therapy in combination with radiotherapy; 47 of them (29.55%) received only hormonal treatment and 20(12.57%) only received radiotherapy. While 54(25.4%) of the patients had no treatment and were in observation. The main approach in adjuvant therapy in this patient group, which is controversial in many years, is observed as hormonal therapy with current literature from worldwide. According to the results we obtained from our database, we can say that hormonal treatment is not used as much as in Europe or United States and that a significant number of patients are followed up without adjuvant treatment.

In this study, its retrospective design, limited number of patients and limited follow-up period can be considered as limitations.

In conclusion according to our study results, statistically significant fewer lymph nodes were removed and higher surgical margin positivity in those receiving adjuvant therapy. While during the relatively limited follow-up time of our study, there was no significant difference between the groups that adjuvant and non-adjuvant therapy in terms of 5-year PSA recurrence time.

Author Contribution Statement

Concept: H.H.T., O.E., T.M., S.B., Design: H.H.T., O.E., T.M., S.B. Data Collection and Processing: H.H.T., O.E., B.A., V.İ., U.Y., S.S. G.A., B.Ş., İ.T., T.M., S.B., Analysis or Interpretation: H.H.T., O.E. B.Ş., Literature Search: H.H.T., S.B., Writing: H.H.T., İ.T., S.B.

Acknowledgment. We thank Levent Türkeri and Saadettin Eskiçorapçı for valuable support for data.

Ethical approve

The study protocol was approved by Institutional Review Board of Marmara University Faculty of Medicine (approval number: 09.2020.639).

Conflict of interest

Authors declared no conflict of interest.

References

Abdollah, F, Karnes RJ, Suardi N, et al (2014). Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol*, **32**, 3939-47.

Abdollah F, Karnes RJ, Suardi N, et al (2014). Predicting survival of patients with node-positive prostate cancer following multimodal treatment. *Eur Urol*, **65**, 554-62.

Abdollah F, Gandaglia G, Suardi N, et al (2015). More extensive pelvic lymph node dissection improves survival in patients with node-positive prostate cancer. *Eur Urol*, **67**, 212-9.

Abdollah F, Dalela D, Sood A, et al (2018). Impact of Adjuvant Radiotherapy in Node-positive Prostate Cancer Patients: The Importance of Patient Selection. *Eur Urol*, **74**, 253-6.

Briganti A, Karnes JR, Da Pozzo LF, et al (2009). 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*, **55**, 261-70.

Briganti A, Karnes RJ, Da Pozzo LF, et al (2011). 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*, **59**, 832-40.

Cai, T, Nesi G, Tinacci G, et al (2011). Clinical importance of lymph node density in predicting outcome of prostate cancer patients. *J Surg Res*, **167**, 267-72.

Daneshmand S, Quek ML, Stein JP, et al (2004). Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. *J Urol*, **172**, 2252-5.

Denlinger CS, Sanft T, Moslehi JJ, et al (2020). NCCN Guidelines Insights: Survivorship, Version 2.2020: featured updates to the NCCN Guidelines. *J Nat Comprehensive Cancer Network*, **18**, 1016-23.

Gupta M, Patel HD, Schwen ZR, Tran PT, Partin AW (2019). Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. *BJU Int*, **123**, 252-60.

Harris PA, Taylor R, Thielke R, et al (2009). Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*, **42**, 377-81.

Harris PA, Taylor R, Minor BL, et al (2019). REDCap Consortium, The REDCap consortium: Building an international community of software partners. *J Biomed Inform*, **95**, 103208.

Messing EM, Manola J, Yao J, et al (2006). Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*, **7**, 472-9.

Mottet N, Conford P, van den Bergh RCN, et al (2020). ed. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020, EAU Guidelines Office, Arnhem, The Netherlands.

Murphy AM, Berkman DS, Desai M, et al (2010). The number of negative pelvic lymph nodes removed does not affect the risk of biochemical failure after radical prostatectomy. *BJU Int*, **105**, 176-9.

Palapattu GS, Allaf ME, Trock BJ, Epstein JI, Walsh P (2004). Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: results of long-term followup. *J Urol*, **172**, 1860-4.

Passoni NM, Abdollah F, Suardi N, et al (2014). Head-to-head comparison of lymph node density and number of positive lymph nodes in stratifying the outcome of patients with lymph node-positive prostate cancer submitted to radical prostatectomy and extended lymph node dissection. *Urol Oncol*, **32**, 29 e21-8.

Pierorazio PM, Gorin MA, Ross AE, et al (2013). Pathological and oncologic outcomes for men with positive lymph nodes at radical prostatectomy: The Johns Hopkins Hospital 30-year experience. *Prostate*, **73**, 1673-80.

Rusthoven CG, Carlson JA, Waxweiler TV, et al (2014). The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. *Int J Radiat Oncol Biol Phys*, **88**, 1064-73.

Schumacher MC, Buckhard FC, Thalman GN, Fleischmann A, Studer UE (2008). Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. *Eur Urol*, **54**, 344-52.

Tilki D, Preisser F, Tennstendt P, et al (2017). 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*, **119**, 717-23.

Touijer KA, Mazzola CR, Sjoberg DD, Scardino PT, Easthem JA (2014). Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. *Eur Urol*, **65**, 20-5.