Orginal Article – Urological Oncology

Grand J Urol 2022;2(2):47-52
DOI: 10.5505/GJU.2022.02986

Our Experience with Radical Prostatectomy and Extended Pelvic Lymph Node Dissection in the Treatment of Clinical Stage T3 Prostate Cancer and Its Possible Advantages

Klinik Evre T3 Prostat Kanserinin Tedavisinde Radikal Prostatektomi ve Genişletilmiş Pelvik Lenf Nodu Diseksiyonu Deneyimimiz ve Uygulamanın Olası Avantajları

Ibrahim Guven Kartal[1], Okan Alkis[1], Mehmet Sevim[1], Oguzhan Yusuf Sonmez[1], Serkan Telli[2], Bekir Aras[1]

[1]Department of Urology, Kutahya Health Sciences University, Kutahya, Turkey
[2]Department of Anaesthesia, Kutahya Health Sciences University, Kutahya, Turkey

Cite as: Kartal IG, Alkıs O, Sevim M, Sonmez OY, Telli S, Aras B. Our experience with radical prostatectomy and extended pelvic lymph node dissection in the treatment of clinical stage T3 prostate cancer and its possible advantages. Grand J Urol 2022;2(2):47-52.

Submission date: 01 January 2022 **Acceptance date:** 01 March 2022 **Online First:** 10 March 2022 **Publication date:** 20 May 2022

Corresponding Author: Okan Alkis / Kutahya Health Science University, Department of Urology, Kutahya, Turkey / okanalks@hotmail.com / ORCID ID: 0000-0001-6116-9588

Abstract

Objective: To evaluate the impact of radical prostatectomy (RP) and extended pelvic lymph node dissection (EPLND) on the disease process in terms of oncological outcomes and quality of life in the treatment of clinical stage cT3N0M0 prostate cancer (PCa).
Materials and Methods: The data of patients with cT3N0M0 who had undergone open radical prostatectomy and extended pelvic lymph node dissection in our clinic between January 2015 and March 2021 were analyzed retrospectively. Preoperative and postoperative data were compared in terms of oncological and functional outcomes. Biochemical recurrence was accepted as detection of PSA >0.2 ng/ml on consecutive measurements and biochemical disease-free survival time was calculated.
Results: The mean age of 23 operated patients who met the study criteria, was 66.8±7.4 years. In the pathological staging, the organ-confined disease was detected in 10 (43.4%) patients. Surgical margin positivity was observed in 6 (26.2%), while lymph node positivity in 3 (13.1%) patients. Biochemical recurrence was detected in 7 (30.2%) patients during a mean follow-up period of 33.6±22.9 months. The mean biochemical disease-free survival time was 48.4±6.3 months. In the evaluations of the patients at the postoperative 6th months, a 3.2±2.2-point decrease was found in the International Prostate Symptom Score (IPSS) (p=0.001) and a 13.1±5.0 point decrease in the International Index of Erectile Function (IIEF) score (p=<0.001).
Conclusion: Radical prostatectomy and extended pelvic lymph node dissection applied in the treatment of locally advanced prostate cancer is seem to be an effective and safe treatment method in terms of oncological and functional outcomes.

Keywords: prostatectomy, lymph node excision, disease-free survival, prostate-specific antigen

Öz

Amaç: Klinik evre cT3N0M0 prostat kanserinde tedavisinde radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonun hastalık seyrini nasıl etkilediğinin onkolojik sonuçlar ve yaşam kalitesi açısından değerlendirilmesi.
Gereçler ve Yöntemler: Kliniğimizde Ocak 2015 ve Mart 2021 arası klinik evresi cT3N0M0 olup açık radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonu uygulanan prostat kanser hastalarının verileri retrospektif olarak incelendi. Preoperatif ve postoperatif veriler karşılaştırıldı. Biyokimyasal nüks PSA'nın ardışık ölçümlerde >0,2 ng/ml saptanması olarak kabul edildi ve biyokimyasal nüksüz sağkalım süresi hesaplandı.
Bulgular: Çalışma kriterlerine uygun olup opere edilen 23 hastanın yaş ortalaması 66,8±7,4 yıldı. Patolojik evrelemede 10 (%43,4) hastada organa sınırlı hastalık saptandı. Cerrahi sınır pozitifliği 6 (%26,2) hastada görülürken, 3 (%13,1) hastada lenf nodu pozitifliği bulundu. Ortalama 33,6±22,9 aylık takip süresinde 7 (%30,2) hastada biyokimyasal nüks tespit edildi. Biyokimyasal nüksüz sağkalım süresi ortalama 48,4±6,3 ay olarak saptandı. Hastaların operasyon sonrası 6. ayda yapılan değerlendirmelerinde uluslararası prostat semptom skorunda (IPSS) 3,2±2,2 puan azalma (p=0,001) ve uluslararası cinsel işlev indeksi skorunda (IIEF) 13,1±5,0 puanlık düşüş (p=<0,001) saptandı.
Sonuç: Lokal ileri evre prostat kanserinin tedavisinde uygulanan radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonu onkolojik ve fonksiyonel açıdan etkili ve güvenli bir tedavi yöntemi gibi gözükmektedir.

Anahtar kelimeler: prostatektomi, lenf nodu eksizyonu, hastalıksız sağkalım, prostat spesifik antijen

ORCID ID: **I.G. Kartal** 0000-0002-2313-3522 **O.Y. Sonmez** 0000-0003-1538-867X **B. Aras** 0000-0002-7020-8830
M. Sevim 0000-0002-7571-7669 **S. Telli** 0000-0001-8045-5205

Introduction

Clinical stage cT3N0M0 prostate cancer is defined within the high-risk prostate cancer group in the European Association of Urology (EAU) and American Urological Association (AUA) guidelines [1]. External beam radiotherapy (EBRT), radical prostatectomy (RP), brachytherapy, focal treatment methods, androgen deprivation therapy (ADT), or combinations of these schemes constitute high-risk prostate cancer treatment protocols [2,3]. However, discussions remain for the treatment methods to be applied in high-risk prostate cancer. Clinical stage T3N0M0 prostate cancer can be defined as the most localized group within the definition of high-risk prostate cancer. Therefore, it can be suggested that this group would benefit most from local treatments.

RP is increasingly preferred in the treatment of high-risk prostate cancer. Although there are no consistent results in the literature, still some studies have reported serious advantages of RP in cancer-specific survival [4]. It has been suggested that surgery can be used as a monotherapy, as well as to avoid potential side effects of ADT and EBRT [5]. In our study we aimed to evaluate the impact of RP and extended pelvic lymph node dissection on the course of the disease in terms of its oncological outcomes and quality of life in the treatment of cT3N0M0 stage cancers with the hypothesis of whether we can be protected from the side effects of systemic treatments.

Materials and Methods

Study Design and Cohort

The study was approved by the Ethical Committee of Kutahya Health Science University (approval date and number: 2021/31761). Written informed consent was obtained from all patients. The data of the patients with cT3N0M0 stage PCa who underwent open RP and extended pelvic lymph node dissection in our clinic between January 2015 and March 2021 were analyzed retrospectively. Clinical stage T3N0M0 was defined as presence of extracapsular invasion or seminal vesicle invasion without lymph node metastases and distant metastases after preoperative evaluation with digital rectal examination (DRM) and imaging methods. Contrast-enhanced abdominal computed tomography (CT)/magnetic resonance imaging (MRI) and whole-body bone scintigraphy were routinely performed after prostate biopsy. Histological grading was done according to the International Society of Urological Pathology (ISUP) grading system [6]. Patients with a diagnosis of metastatic disease at the time of diagnosis, with less than 6- month follow-up, receiving neoadjuvant RT or ADT, or with insufficient data were excluded from the study. Post-treatment follow-up was performed with prostate-specific antigen (PSA) level monitoring and digital rectal examination at 3,6 and 12 months, and every 6 months until 3 years and then annually, according to European Association of Urology (EAU) guidelines [7].

The patients' age, preoperative PSA level (ng/ml), biopsy ISUP grades, preoperative and postoperative International Prostate Symptom Scores (IPSS), and International Index of Erectile Function (IIEF-5) scores were recorded. Preoperative and postoperative IPSS and IIEF-5 scores were compared to evaluate functional outcomes. Postprostatectomy incontinence has been defined as any urinary leakage complained by patients at the end of one year.

All patients underwent open retropubic RP and bilateral extended pelvic lymph node dissection. The nerve-sparing method was not preferred in patients.

Biochemical recurrence was considered as detection of PSA> 0.2 ng/ml on consecutive measurements [8]. Except for biochemical recurrence, adjuvant treatment was applied to patients with positive surgical margins and positive lymph nodes. Biochemical disease-free survival times were calculated to evaluate the success of oncological treatment.

Statistical Analysis

Statistical analyzes were performed using SPSS version 20 (SPSS Inc., Chicago, IL). The relevant variables were analyzed using visual (histograms) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed data, and medians and interquartile range (IQR) values for the non normally distributed data and ordinal variables. The Mann-Whitney U test was used for comparisons between two groups for parameters without normal, and Student's t-test for parameters with normal distribution. A Kaplan–Meier survival curve was plotted to determine biochemical disease-free survival (BDFS).

Results

The mean age of 23 patients operated on at cT3N0M0 PCa stage was 66.8±7.4 years, and none of the patients aged over 80 years. Preoperative PSA was >20 ng/ml in 13 (56.5%) patients. Neoadjuvant therapy was not given to any patient. The median ISUP grade in transrectal needle biopsy was 3 (1-5). In the pathological staging, organ-confined disease (pT2 without lymph node metastasis) was detected in 10 (43.4%) patients, while specimen-confined disease (pT3N0 without positive surgical margin or lymph node metastasis) in 7 (30.4%) patients. Surgical margin positivity was observed in 6 (26.2%), and lymph node

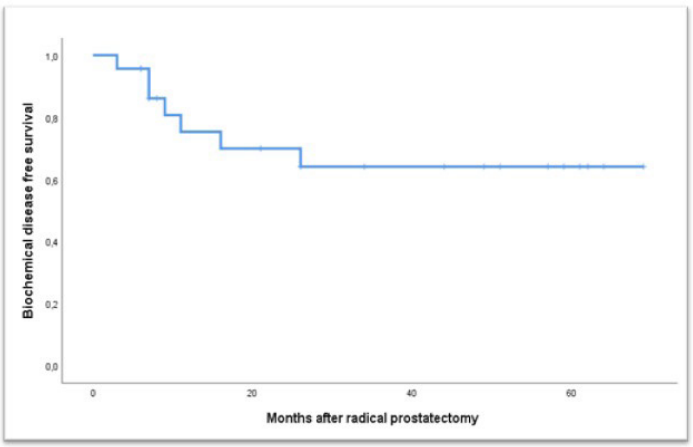

Figure 1. Biochemical disease-free survival curve after radical prostatectomy and extended pelvic lymph node dissection in patients with cT3N0M0 prostate cancer

Table 1. Demographic, oncological, and quality of life data of the study group

	N =23
Age (month) (mean ± ss)	66,8±7,4
PSA level, preoperative (mean ± ss)	21,8±15,7
PSA level, preoperative (n) (%)	
PSA<10 ng/ml	6 (26,1%)
PSA 10-20 ng/ml	4 (17,4%)
PSA> 20 ng/ml	13 (56,5%)
Pathologic stage (n) (%)	
pT2a	3 (13,1%)
pT2b	3 (13,1%)
pT2c	4 (17,4%)
pT3a	6 (26,2%)
pT3b	7 (30,2%)
pT4	-
Surgical margin positivity (n) (%)	6 (26,2%)
Lymph node involvement (n) (%)	3 (13,1%)
Biopsy ISUP grade (median)	3 (1-5)
Pathologic (specimen) ISUP grade (median)	3 (1-5)
Biochemical recurrence (n) (%)	7 (30,2%)
Biochemical disease-free survival time (month) (mean ± ss)	48,4±6,3
Follow-up time (month) (mean ± ss)	33,6±22,9
IPSS, preoperative (mean ± ss)	11,9±3,5
IPSS, postoperative (6^{th} month) (mean ± ss)	8,6±2,0
IIEF-5, preoperative (mean ± ss)	20,6±3,2
IIEF-5, postoperative (6^{th} month) (mean ± ss)	7,4±4,8
Length of hospital stay (day) (mean ± ss)	4,8±2,3
Complication (n)	
Incontinence	2
Stricture	3
Epididymitis	1
Blood transfusion	5
Wound infection	1

PSA: prostate specific antigen; ISUP: international society of urological pathology; RT: radiotherapy; ADT: androgen deprivation therapy; IPSS; international prostate symptom score; IIEF: international index of erectile function; ss: standard deviation

positivity was detected in 3 (13.1%) patients. Except for one patient, PSA level was below 0.2 ng/ml in the first measurement after RP in all patients. Biochemical recurrence was detected in 7 (30.2%) patients during a mean follow-up period of 33.6±22.9 months. Biochemical disease-free survival time was determined to be 48.4±6.3 months [within 95% confidence interval (CI) 36.5–61.4] (**Figure 1**). No death was observed during the follow-up period. Adjuvant therapy was given to 6 patients as RT and ADT. As salvage treatment, ADT and RT were applied to one, and only ADT to six patients.

The mean hospital stay of the patients was 4.8±2.3 days. Post-RP complications being more than one in some patients were as strictures (n: 3), epididymitis (n: 1), wound infection (n:1), and requirement for blood transfusion (n: 5). While 2 (8.6%) patients had stress urinary incontinence at the end of one year, at 6th postoperative months an average of 3.2±2.2-point decrease in the IPSS (p=0.001) and 13.1±5.0-point decrease in the IIEF-5 scores were detected (p=<0,001) **(Table 1).**

Discussion

With the increase in PSA measurements and the widespread use of screening, prostate cancer is mostly diagnosed in local stages. Although the proportion of patients with prostate cancer diagnosed at stage cT3 is decreasing, the course of the disease may be aggressive at this stage and require complicated treatments [9,10]. Traditionally, urologists preferred EBRT and ADT in the cT3 stage, but in recent years, it has been shown that the option of RP plays an important role in this stage [11]. It has been understood that RP can be used safely with oncological and functional results in patients with stage cT3, as shown in our study in parallel with the literature.

Despite progress in imaging modalities and validated nomograms, 13-27% of patients with stage cT3 were determined as having organ-confined disease in their final pathology (upgrading) [12]. Considering the importance of correct staging in any oncological condition, one of the most important advantages of RP is that it provides accurate pathological staging. Thus, patients with the pathologically organ-confined disease can be diagnosed and other treatments with high morbidity are not required. In this context, a multicenter study conducted in T3N0 patients indicated that there was no difference between 2-year and 5-year biochemical recurrence-free survival rates between adjuvant RT and salvage RT, and therefore there was no need for applying routine adjuvant RT to T3N0M0 patients. It was also shown that RP can be used as monotherapy in T3N0M0 patients [13].

Extended pelvic lymph node dissection should be performed during RP in the surgery of locally advanced prostate cancer. For this purpose, lymph nodes between the external iliac and hypogastric veins, including the hypogastric and obturator lymph nodes, the internal iliac nodes, and nodes above and below the obturator nerve should be removed completely [14]. Thus, with lymph node dissection performed during RP, it is possible to detect micrometastases that cannot be detected by imaging methods. EAU guidelines emphasize that lymph node dissection after RP may provide a survival advantage in microscopic lymph node-positive patients [15]. The rate of regional lymph node metastasis in high-risk prostate cancer patients who underwent RP ranges from 17% to 31% according to the series [16]. These outcomes show the extra benefit of extended pelvic lymph node dissection, which can be performed with RP. A 10-year cancer-specific survival was reported with ADT in 84% of the patients who had positive lymph nodes and had undergone radical prostatectomy [17]. Studies reporting that removing multiple lymph nodes provide longer cancer-specific survival times have shown the advantage of removing lymph nodes in RP [18].

The EAU Guideline increased the level of evidence supporting RP for high-risk prostate cancer from 3 to 2a in 2013 and has suggested the grade of recommendation as grade A in 2016 [19]. Ward et al. reported 5,10,15-year cancer-specific survival rates as 95%, 90%, and 79%, respectively, in patients with T3 prostate cancer, whose biochemical recurrence value was accepted as PSA ≥0.4 ng/mL [20]. A survival advantage of radical prostatectomy over other treatment protocols has been also reported. A recently published observational study of 13,985 patients under 65 years of age demonstrated that RP as monotherapy in high-risk localized prostate cancer is advantageous in overall survival compared to the combination of EBRT and brachytherapy [21]. In another study evaluating the cT3N0 patient group, as in our study, Bandini et al., reported that 10-year cancer-specific mortality and mortality rates due to other causes were statistically significantly lower in the RP group than in EBRT [22].

Along with the advantage of being used as a monotherapy, if additional treatment is required after surgery, RP also guides the selection of the treatment of these patients. Follow-up of the patients together with detection of biochemical recurrence after radical prostatectomy is easier when compared to RT [23,24]. Besides, there is an opportunity to monitor the patients regardless of the condition of the disease and it also allows the opportunity to treat them when necessary. For instance, patients can be protected from the possible side effects of RT with salvage RT in case of need, and any difference between adjuvant RT and salvage RT has not been shown in some studies [25]. More effective treatment is provided by adding ADT in patients with positive lymph nodes [26].

It is stated that the morbidity of RP in cT3 disease is not different from the organ-confined disease [27]. In addition, such conditions as persistent gross hematuria, bladder outlet obstruction, pelvic pain, and ureteral obstruction can also be treated with RP. A recent study has demonstrated a significant improvement in IPSS (decrease from 9 to 5) and an increase in Qmax in patients with locally advanced prostate cancer at 12-month follow-up after RP [28]. In terms of morbidity, it can be said that RP is reliable. In a Canadian cohort study, Nam et al., showed that EBRT had higher rates of disease-related complications than RP. The same study reported that RP was associated with fewer hospital admissions, secondary malignancies, requirements for rectal-anal procedures, and open surgery compared to RT during a 5-year follow-up [29]. Similarly, no major surgery-related complications were observed in our study, and a significant improvement was noticed in the voiding functions of the patients.

There are some limitations of our study. Due to the

retrospective and single-center design of the study, it may be overly selective in patients recommended for RP. However, despite the limited number of patients, our study can be also a guide in terms of the general quality of life of the patients after RP together with evaluation of its oncological and functional outcomes. Another limitation is that clinical staging is performed with digital rectal examination and conventional imaging methods with a lower staging sensitivity. However, with the introduction of advanced imaging methods into the guidelines and the increase in the use of these methods, more reliable data will be collected using our prospectively designed data.

Conclusion

In the treatment of locally advanced prostate cancer, RP and extended pelvic lymph node dissection seem to have advantages such as accurate pathological staging, applicability of lymph node dissection, relatively higher survival rates, improvement in voiding functions, and convenience for the use of adjuvant treatments. To increase the level of evidence, randomized controlled studies compared with other treatment modalities are needed.

Ethics Committee Approval: The study was approved by the Ethical Committee of Kutahya Health Science University (approval date and number: 13.12.2021-31761).
Informed Consent: An informed consent was obtained from all the patients for research.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept- I.G.K., O.A., M.S., O.Y.S.; Design- I.G.K., O.A., M.S., O.Y.S.; Supervision- I.G.K., S.T., B.A.; Resources- I.G.K., O.A., M.S., B.A.; Materials- I.G.K., O.A., M.S., B.A.; Data Collection and/or Processing- O.A., M.S., O.Y.S.; Analysis and/or Interpretation- I.G.K., O.A., S.T.; Literature Search- I.G.K., O.A., M.S.; Writing Manuscript- I.G.K., M.S., S.T.; Critical Review- I.G.K., S.T., B.A.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Roy CSD, Sachdeva A, Kandaswamy GV, Rai BP. The role of surgery in high risk and advanced prostate cancer: A narrative review. Turk J Urol 2021;47(Supp.1):S56-S64. https://doi.org/10.5152/tud.2020.20475.

[2] Marvaso G, Corrao G, Zaffaroni M, Pepa M, Augugliaro M, Volpe S, et al. Therapeutic Sequences in the Treatment of High-Risk Prostate Cancer: Paving the Way Towards Multimodal Tailored Approaches. Front Oncol 2021;11:732766. https://doi.org/10.3389/fonc.2021.732766.

[3] Karacetin D. Current Approaches in Prostate Cancer Radiotherapy. Grand J Urol 2021;1:22-5. https://doi.org/10.5222/gju.2021.54264.

[4] Wilkins LJ, Tosoian JJ, Sundi D, Ross AE, Grimberg D, Klein EA, et al. Surgical management of high-risk, localized prostate cancer. Nat Rev Urol 2020;17:679-90. https://doi.org/10.1038/s41585-020-00384-7.

[5] Vernooij RW, Lancee M, Cleves A, Dahm P, Bangma CH, Aben KK (2020) Radical prostatectomy versus deferred treatment for localised prostate cancer. Cochrane Database Syst Rev 2020;6:CD006590. https://doi.org/10.1002/14651858.CD006590.pub3.

[6] van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol 2020;44:e87-e99. https://doi.org/10.1097/PAS.0000000000001497.

[7] Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol 2021;79:263-82. https://doi.org/10.1016/j.eururo.2020.09.046.

[8] Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, Eton DT, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177:540-5. https://doi.org/10.1016/j.juro.2006.10.097.

[9] Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007;51:121-8; discussion 128-9. https://doi.org/10.1016/j.eururo.2006.05.024.

[10] Adsan O. Focal Ablation Therapies in Prostate Cancer. Grand J Urol 2021;1:128-32 https://doi.org/10.5222/gju.2021.87598.

[11] Guy DE, Chen H, Boldt RG, Chin J, Rodrigues G. Characterizing Surgical and Radiotherapy Outcomes in Non-metastatic High-Risk Prostate Cancer: A Systematic Review and Meta-Analysis. Cureus 2021;13:e17400. https://doi.org/10.7759/cureus.17400.

[12] Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2011;59:572-83. https://doi.org/10.1016/j.eururo.2011.01.025.

[13] Smith JA. Commentary on "Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: Results of a match-controlled multi-institutional analysis".

Briganti A, Wiegel T, Joniau S, Cozzarini C, Bianchi M, Sun M, Tombal B, Haustermans K, Budiharto T, Hinkelbein W, Di Muzio N, Karakiewicz PI, Montorsi F, Van Poppel H., Eur Urol 2012;62:472-87. Urol Oncol 2012;30:960. https://doi.org/10.1016/j.urolonc.2012.08.005.

[14] Gupta M, McCauley J, Farkas A, Gudeloglu A, Neuberger MM, Ho YY, et al. Clinical practice guidelines on prostate cancer: a critical appraisal. J Urol 2015;193:1153-8. https://doi.org/10.1016/j.juro.2014.10.105.

[15] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65:467-79. https://doi.org/10.1016/j.eururo.2013.11.002.

[16] Xylinas E, Dache A, Roupret M. Is radical prostatectomy a viable therapeutic option in clinically locally advanced (cT3) prostate cancer? BJU Int 2010:106:1596-1600. https://doi.org/10.1111/j.1464-410X.2010.09630.x.

[17] Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Predicting survival of patients with node-positive prostate cancer following multimodal treatment. Eur Urol 2014;65:554-62. https://doi.org/10.1016/j.eururo.2013.09.025.

[18] Fossati N, Parker WP, Karnes RJ, Colicchia M, Bossi A, Seisen T, et al. More Extensive Lymph Node Dissection at Radical Prostatectomy is Associated with Improved Outcomes with Salvage Radiotherapy for Rising Prostate-specific Antigen After Surgery: A Long-term, Multi-institutional Analysis. Eur Urol 2018;74:134-7. https://doi.org/10.1016/j.eururo.2018.02.024.

[19] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017;71:618-29. https://doi.org/10.1016/j.eururo.2016.08.003.

[20] Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005;95:751-6. https://doi.org/10.1111/j.1464-410X.2005.05394.x.

[21] Berg S, Cole AP, Krimphove MJ, Nabi J, Marchese M, Lipsitz SR, et al. Comparative Effectiveness of Radical Prostatectomy Versus External Beam Radiation Therapy Plus Brachytherapy in Patients with High-risk Localized Prostate Cancer. Eur Urol 2019;75:552-5. https://doi.org/10.1016/j.eururo.2018.10.032.

[22] Bandini M, Marchioni M, Preisser F, Zaffuto E, Tian Z, Tilki D,et al. Survival after radical prostatectomy or radiotherapy for locally advanced (cT3) prostate cancer. World J Urol 2018;36:1399-1407. https://doi.org/10.1007/s00345-018-2310-y.

[23] Chiang PH, Liu YY. Comparisons of oncological and functional outcomes among radical retropubic prostatectomy, high dose rate brachytherapy, cryoablation and high-intensity focused ultrasound for localized prostate cancer. Springerplus 2016;5:1905. https://doi.org/10.1186/s40064-016-3584-4.

[24] Aras B, Yerlikaya A. Bortezomib and etoposide combinations exert synergistic effects on the human prostate cancer cell line PC-3. Oncol Lett 2016;11:3179-84. https://doi.org/10.3892/ol.2016.4340.

[25] Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet 2020;396:1422-31. https://doi.org/10.1016/S0140-6736(20)31952-8.

[26] Marra G, Valerio M, Heidegger I, Tsaur I, Mathieu R, Ceci F, et al. Management of Patients with Node-positive Prostate Cancer at Radical Prostatectomy and Pelvic Lymph Node Dissection: A Systematic Review. Eur Urol Oncol 2020;3:565-81. https://doi.org/10.1016/j.euo.2020.08.005.

[27] Berglund RK, Jones JS, Ulchaker JC, Fergany A, Gill I, Kaouk J, et al. Radical prostatectomy as primary treatment modality for locally advanced prostate cancer: a prospective analysis. Urology 2006;67:1253-6. https://doi.org/10.1016/j.urology.2005.12.003.

[28] Papadopoulos G, Fragkoulis C, Stasinopoulos K, Stathouros G, Glykas I, Theocharis G, et al. Does radical prostatectomy result in lower urinary tract symptom improvement in high-risk and locally advanced prostate cancer? A Single-center experience. Urologia 2021;88:110-4. https://doi.org/10.1177/0391560320964611.

[29] Nam RK, Cheung P, Herschorn S, Saskin R, Su J, Klotz LH, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol 2014;15:223-31. https://doi.org/10.1016/S1470-2045(13)70606-5.