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The Role of Radical Prostatectomy in the Treatment of Patients with High-Risk Prostate Cancer

Yüksek Riskli Prostat Kanserli Hastaların Tedavisinde Radikal Prostatektominin Rolü

Barış Kuzgunbay, Özgür Yaycıoğlu

Başkent University Faculty of Medicine, Department of Urology, Adana, Turkey

ABSTRACT

High-risk prostate cancer (PCa), which is defined as PSA >20 ng/mL or Gleason Score (GS) >7 or ≥cT3a, accounts for up to 40% of newly diagnosed cases and carries a significant risk of progression and death. However, the best management approach for patients with high-risk PCa is still under debate. Recently, radical prostatectomy (RP) with extended lymphadenectomy (LND) has become popular for the treatment of high-risk PCa with good prognosis in selected patients in the context of multimodal approach. However, decision should be made after all treatments have been discussed by a multidisciplinary team and the patient should be informed about the likelihood of a multimodal approach. On the other hand, necessity of sufficient surgical expertise for RP to keep the level of morbidity acceptable in high-risk PCa patients should be kept in mind.

Key Words

Prostate cancer, high-risk patient, radical prostatectomy

ÖZET

Yüksek riskli prostat kanseri, PSA >20 ng/mL veya Gleason Score (GS) >7 veya ≥cT3a olarak tarif edilmekte, yeni tanı konulan olguların %40'ına kadarında görülebilmekte, hastalığın ilerlemesi ve hastalığa bağlı ölüm açısından da belirgin risk taşımaktadır. Bununla beraber yüksek riskli prostat kanseri olan hastaların en iyi hangi tedavi yöntemi ile tedavi edilebileceği hala tartışmalı bir konudur. Son zamanlarda, yüksek riskli prostat kanserli hastaların tedavisinde multimodal tedavinin bir parçası olarak genişletilmiş lenfadenektomi ile birlikte radikal prostatektomi, seçilmiş olgularda iyi prognoz ile popüler hale gelmektedir. Bununla beraber, multidisipliner bir takım tarafından tüm tedavi yöntemleri tartışıldıktan sonra karar verilmeli ve multimodal bir tedavi almasının gerekebileceği hastaya anlatılmalıdır. Ayrıca, yüksek riskli prostat kanseri hastalarında cerrahiye bağlı morbiditeyi makul düzeylerde tutabilmek için radikal prostatektomi konusunda yeterli cerrahi deneyimin gerekliliği akılda tutulmalıdır.

Anahtar Kelimeler

Prostat kanseri, yüksek riskli hasta, radikal prostatektomi

Introduction

High-risk prostate cancer (PCa) accounts for up to 40% of newly diagnosed cases and carries a significant risk of progression and death (1). There are various definitions for high-risk clinically localized PCa; the European Association of Urology (EAU) guidelines use the D'Amico risk-group classification to define high-risk PCa as PSA >20 ng/mL, or Gleason Score (GS) >7, or ≥cT3a (2,3). In the absence of high-level evidence, the best management approach for patients with high-risk PCa is still under debate. Main treatment options are radical prostatectomy (RP) or radiotherapy. It is generally accepted that multimodality treatment should be the standard for these patients. This usually means surgery followed by radiotherapy (RT) or RT with concurrent androgen deprivation therapy (ADT). Even though these two primary options have not been compared in a randomized prospective trial, RT was usually the favored approach by many centers. However, in recent years, favorable outcomes reported with RP in high-risk PCa patients have caused increased interest in surgery as a part of multimodality treatment (4). A web-based survey study exploring the preferences in the management of patients with newly diagnosed high-risk PCa among urologists practicing in Europe reported that 60% of the urologists preferred RP with extended lymphadenectomy (LND) initially as a part of multimodal treatment (5). Indeed, the EAU guidelines offers RP as a first step in selected patients with a low tumor volume provided that the tumor is not fixed to the pelvic wall or that there is no invasion of the urethral

Correspondence
Barış Kuzgunbay MD, Başkent University Faculty of Medicine, Department of Urology, Adana, Turkey
E-mail: kuzgunbay33@yahoo.com **Received:** 10.08.2015 **Accepted:** 12.08.2015

sphincter, with extended LND due to the fact that estimated risk for positive lymph nodes is 15-40% (6). LND should include at least the removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. With this template, 75% of all anatomical landing sites are cleared.

The surgical treatment of clinical stage T3 or locally advanced PCa has traditionally been discouraged due to increased risk of positive surgical margins (33.5-66%) and lymph node metastases and/or distant relapse (7.9-49%) (7,8). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage RT or ADT (9,10). However, RP may provide excellent tumor control in selected patients with cT3 disease, with 5-, 10- and 15-year cancer specific survival (CSS) ranging between 90% and 99%, 85% and 92% and 62% and 84%, respectively (1,9,10,11,12). Even in patients with cT4 disease who underwent RP, CSS has been found to be 88-92% at 5 years and 92% at 10 years (13,14). These survival rates, which are similar to that with RT combined with adjuvant ADT, show that RP is superior to RT alone (15). Even though more than half of the patients received adjuvant ADT and/or RT in most of the presented studies, the high CSS suggests that local cancer control by RP remains especially important in men with locally advanced disease, since local recurrence after RT carries risks of complications, such as urinary obstruction and hematuria that have detrimental effects on the patients' quality of life. Another advantage of RP as primary treatment in high-risk PCa is the ability for accurate pathologic staging. It has been shown that overstaging in cT3 PCa occurs in 13-27% of cases (9,10). Accurate staging guides the secondary treatment decisions, thereby help identify patients who do need post surgical RT and avoid unnecessary toxicities caused by radiotherapy. Additionally, it should be kept in mind that since pathologic staging is not always available, a considerable number of patients receive unnecessary long-term ADT when treated by primary radiotherapy. However, RP for clinical T3-4 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. Increased overall surgical experience contributes to decreased operative morbidity and improves functional results after RP for clinical T3 cancer (9,12). It has been shown that continence can be preserved in most cases, and in selected cases, potency can also be preserved (13). A study comparing the results of RP in patients with localized and T3-4 PCa did not report any significant difference in surgical morbidity except for blood transfusion, operative time, and lymphoceles, which showed a higher rate in patients with advanced disease (16).

Patients with high-grade PCa (GS 8-10) and confined to the prostate at histopathological examination have a good prognosis after RP. Several studies have demonstrated good outcomes after RP in the context of a multimodal approach for patients with a biopsy GS >8; the CSS rate at 5-, 10- and 15-year follow-up was 96%, 84-88% and 66%, respectively (17,1). However, recent studies have reported a rate of 31-45% downgrading to GS <7 in the RP specimen in men with biopsy GS 8-10 indicating a better biochemically progression free survival (BPFS) probability (18,19). Therefore, these patients may benefit most from RP as potentially curative resection. It has also been reported that health status and age of the patient are also important factors influencing prostatectomy outcomes in high-risk patients. It has been shown that in very high-risk patients (cT3b/4) overall cancer-specific mortality (CSM) rates were low; for healthy men, CSM was independent of age, supporting RP even for older men and, less healthy group had a higher risk of dying from other causes while having low risk of CSM (20). Patients with PSA >20 ng/mL and clinically organ-confined tumors have good prognosis after RP monotherapy with a PSA failure rate of 44-50% at 5 years; a CSS rate of 90% and 85% at 10 and 15 years after RP (21,22,23). However, these studies demonstrated lowered CSS rates and higher PSA failure rates in the presence of concomitant cT3 stage and/or biopsy GS 8-10. In a recent study, it has been proven that CSS rate after RP decreases as the initial PSA value increases; ten-year CSS rate was 80%, 85% and 91% in patients with PSA a level of >100 ng/mL, 50.1-100 ng/mL and 20.1-50 ng/mL, respectively. However, RP may be an option as a part of a multimodal treatment strategy in selected patients with PCa since CSS remains relatively high even in those with PSA levels >100 ng/mL (24). The role of adjuvant vs. salvage RT is the subject of ongoing studies. There are also clinical studies on delivery of RT in the neoadjuvant setting for patients with high-risk PCa (25,26).

Traditionally, positive lymph node (LN) status has been considered a systemic disease state, thus, positive LN diagnosis during pelvic LND has potentially lead to the abandonment of RP in PCa among urologists until a retrospective study from Munich comparing the results of LN-positive patients with and without RP demonstrated that with RP, relative survival of patients at 5 and 10 years was 95% and 86%, respectively and, without RP, it was 70% and 40%, respectively (27). Nevertheless, the combination of RP and early adjuvant ADT in LN-positive PCa has been shown to achieve a 10-year CSS rate of 60-86% supporting the role of RP as an important component of multimodal strategies for LN-positive PCa (27,28,29,30,31,32). Additionally, it has been reported that patients with 2 or less positive nodes had significantly better CSS at 15-year follow-up compared to patients with more than 2 positive nodes (84% vs. 62%) indicating the lower incidence of tumor progression in patients with fewer positive lymph nodes and in those with microscopic invasion only (33). In another study, it was demonstrated that median CSS at 10 years in patients with ≤2 or ≥3 positive nodes removed was 78.6% and 33.4%, respectively (30). These results make it unclear whether early adjuvant ADT should still be used in the present era of increased detection of microscopic involvement as a result of more frequently performed extended LND. The benefits should be judged against the side effects of long-term ADT. Follow-up of PSA and delaying the initiation of ADT in patients with rising PSA is therefore an acceptable option in selected cases with ≤2 microscopically involved lymph nodes in an extended node dissection (6).

Case series have been published on robot-assisted RP in high-risk patients with good surgical results. There has been concern about extended LND by robotic approach, but it has been suggested that with increased expertise, LND can be performed as effective as open surgery (34). In the future, the results of ongoing clinical trials on issues like the role of LND on oncologic outcomes and survival as well as neoadjuvant treatments such as chemotherapy, ADT, and radiotherapy, adjuvant vs. salvage RT with or without ADT will provide better insight for the role of RP in high-risk PCa patients (25,35,36).

In the context of the literature-based evidence that was presented above, the EAU guidelines offers RP with extended LND as a reasonable treatment option in selected patients with cT3a PCa, GS 8-10 or PSA

>20 while as an optional treatment in highly selected patients with cT3b-4N0 or any N1 PCa in the context of a multimodality approach (6). However, management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patient with regard to their own individual circumstances. Patient's life expectancy and comorbidity should be considered. The patient must be informed about the likelihood of a multimodal approach. On the other hand, it should be kept in mind that sufficient surgical expertise is essential to keep the level of morbidity acceptable in high-risk PCa patients.

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References

1. Yossepowitch O, Eggener SE, Serio AM, Carver BS, Bianco FJ Jr, Scardino PT, Eastham JA. Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. Eur Urol 2008;53:950-959.
2. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'amico risk group classification for predicting survival following radical prostatectomy. J Urol 2008;179:1354-1360.
3. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N; European Association of Urology. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65:124-137.
4. Stewart SB, Boorjian SA. Radical prostatectomy in high-risk and locally advanced prostate cancer: Mayo Clinic perspective. Urol Oncol 2015;33:235-244.
5. Surcel CI, Sooriakumaran P, Briganti A, De Visschere PJ, Fütterer JJ, Ghadjar P, Isbarn H, Ost P, Ploussard G, van den Bergh RC, van Oort IM, Yossepowitch O, Sedelaar JP, Giannarini G; Members of Prostate Cancer Working Group of Young Academic Urologists Working Party; Members of Young Urologists Office of European Association of Urology. Preferences in the management of high-risk prostate cancer among urologists in Europe: results of a web-based survey. BJU Int 2015;115:571-579.
6. Mottet N, Bastian PJ, Bellmunt J. Guidelines on Prostate Cancer, European Association of Urology 2014;59-61.
7. Fallon B, Williams RD. Current options in the management of clinical stage C prostatic carcinoma. Urol Clin North Am 1990;17:853-866.
8. Boccon-Gibod L, Bertaccini A, Bono AV, Dev Sarmah B, Höltl W, Mottet N, Tunn U, Zamboglou N. Management of locally advanced prostate cancer: a European Consensus. Int J Clin Pract 2003;57:187-194.
9. 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;95:751-756.
10. 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;51:121-128.
11. Van Poppel H, Vekemans K, Da Pozzo L, Bono A, Kliment J, Montironi R, Debois M, Collette L. Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). Eur J Cancer 2006;42:1062-1067.
12. Loeb S, Smith ND, Roehl KA, Catalona WJ. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology 2007;69:1170-1175.
13. Joniau S, Hsu CY, Gontero P, Spahn M, Van Poppel H. Radical prostatectomy in very high-risk localized prostate cancer: long-term outcomes and outcome predictors. Scand J Urol Nephrol 2012;46:164-171.
14. Johnstone PA, Ward KC, Goodman M, Assikis V, Petros JA. Radical prostatectomy for clinical T4 prostate cancer. Cancer 2006;106:2603-2609.
15. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Mattelaer J, Lopez Torecilla J, Pfeffer JR, Lino Cutajar C, Zurlo A, Pierart M. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002;360:103-106.
16. Gontero P, Marchioro G, Pisani R, Zaramella S, Sogni F, Kocjancic E, Mondaini N, Bonvini D, Tizzani A, Frea B. Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. Eur Urol 2007;51:922-929.
17. Stephenson AJ, Kattan MW, Eastham JA, Bianco FJ Jr, Yossepowitch O, Vickers AJ, Klein EA, Wood DP, Scardino PT. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 2009;27:4300-4305.
18. Donohue JF, Bianco F, Kuroiwa K, Vickers AJ, Wheeler TM, Scardino PT, Reuter VA, Eastham JA. Poorly differentiated prostate cancer treated with radical prostatectomy: long-term outcome and incidence of pathological downgrading. J Urol 2006;176:991-995.
19. Manoharan M, Bird VG, Kim SS, Civantos F, Soloway MS. Outcome after radical prostatectomy with a pretreatment prostate biopsy Gleason score >/=8. BJU Int 2003;92:539-544.
20. Moltzahn F, Karnes J, Gontero P, Kneitz B, Tombal B, Bader P, Briganti A, Montorsi F, Van Poppel H, Joniau S, Spahn M. Predicting prostate cancer-specific outcome after radical prostatectomy among men with very high-risk cT3b/4 PCa: a multi-institutional outcome study of 266 patients. Prostate Cancer Prostatic Dis 2015;18:31-37.
21. Yossepowitch O, Eggener SE, Bianco FJ Jr, Carver BS, Serio A, Scardino PT, Eastham JA. Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. J Urol 2007;178:493-499.
22. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Kaplan I, Beard CJ, Tomaszewski JE, Renshaw AA, Wein A, Coleman CN. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999;17:168-172.
23. Spahn M, Joniau S, Gontero P, Fieuws S, Marchioro G, Tombal B, Kneitz B, Hsu CY, Van Der Eeckt K, Bader P, Frohneberg D, Tizzani A, Van Poppel H. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. Eur Urol 2010;58:1-7.
24. Gontero P, Spahn M, Tombal B, Bader P, Hsu CY, Marchioro G, Frea B, Van Der Eeckt K, Kneitz B, Frohneberg D, Tizzani A, Van Poppel H, Joniau S. Is there a prostate-specific antigen upper limit for radical prostatectomy? BJU Int 2011;108:1093-1100.
25. Perez BA, Koontz BF. Radiotherapy before and after radical prostatectomy for high-risk and locally advanced prostate cancer. Urol Oncol 2015;33:226-234.
26. Gnanapragasam VJ, Payne H, Syndikus I, Kynaston H, Johnstone T. Primary radical therapy selection in high-risk non-metastatic prostate cancer. Clin Oncol (R Coll Radiol) 2015;27:136-144.
27. Engel J, Bastian PJ, Baur H, Beer V, Chaussy C, Gschwend JE, Oberneder R, Rothenberger KH, Stief CG, Hölzel D. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. Eur Urol 2010;57:754-761.

28. Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G, di'SantAgnese PA, Eastern Cooperative Oncology Group study EST 3886. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472-479.
29. Steuber T, Budaus L, Walz J, Zorn KC, Schlomm T, Chun F, Ahyai S, Fisch M, Sauter G, Huland H, Graefen M, Haese A. Radical prostatectomy improves progression-free and cancerspecific survival in men with lymph node positive prostate cancer in the prostate-specific antigen era: a confirmatory study. BJU Int 2011;107:1755-1761.
30. Schumacher MC, Burkhard FC, Thalmann GN, Fleischmann A, Studer UE. Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. Eur Urol 2008;54:344-352.
31. Briganti A, Karnes RJ, Da Pozzo LF, Cozzarini C, Capitanio U, Gallina A, Suardi N, Bianchi M, Tutolo M, Salonia A, Di Muzio N, Rigatti P, Montorsi F, Blute M. 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;59:832-840.
32. Da Pozzo LF, Cozzarini C, Briganti A, Suardi N, Salonia A, Bertini R, Gallina A, Bianchi M, Fantini GV, Bolognesi A, Fazio F, Montorsi F, Rigatti P. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. Eur Urol 2009;55:1003-1011.
33. Briganti A, Karnes JR, Da Pozzo LF, Cozzarini C, Gallina A, Suardi N, Bianchi M, Freschi M, Doglioni C, Fazio F, Rigatti P, Montorsi F, Blute ML. 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;55:261-270.
34. Harbin AC, Eun DD. The role of extended pelvic lymphadenectomy with radical prostatectomy for high-risk prostate cancer. Urol Oncol 2015;33:208-216.
35. Cha EK, Eastham JA. Chemotherapy and novel therapeutics before radical prostatectomy for high-risk clinically localized prostate cancer. Urol Oncol 2015;33:217-225.
36. Thalgott M, Horn T, Heck MM, Maurer T, Eiber M, Retz M, Autenrieth M, Herkommer K, Krause BJ, Gschwend JE, Treiber U, Kübler HR. Long-term results of a phase II study with neoadjuvant docetaxel chemotherapy and complete androgen blockade in locally advanced and high-risk prostate cancer. J Hematol Oncol 2014;7:20.