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Original Scientific Paper

MANAGEMENT OF PROSTATE CANCER IN KIDNEY TRANSPLANT RECIPIENTS

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SUMMARY – Kidney transplantation is the treatment of choice in eligible patients with end-stage kidney disease. Prostate cancer (PC) is the second most common cancer in men worldwide. The prevalence of chronic kidney disease worldwide is 13.4%. The management of localized PC in these patients is challenging due to immunosuppressive therapy and pelvic graft localization. High graft and recipient survival rates have resulted in higher numbers of these patients in our everyday practice. A retrospective analysis of male patients who had undergone kidney transplantation at our center between 2002 and 2022 and were diagnosed and treated for PC was performed. We analyzed the incidence, treatment methods, and follow-up of PC patients in this population. A total of 1079 male patients were transplanted. PC was diagnosed in 12 patients (8 after and 4 before transplantation). The incidence of PC was 1.11%. Radical prostatectomy was performed in 11 patients, and one patient was treated with radical radiotherapy. Eleven patients had stable graft function; 1 graftectomy was performed, unrelated to PC. Three patients were indicated for salvage radiotherapy, one is in process for prostate-specific membrane antigen positron emission tomography (PSMA PET CT), and 7 patients are in follow-up and without recurrence. Radical prostatectomy is a safe treatment method for localized PC in kidney transplant recipients, which does not impair graft function and survival.

Key words: *Prostate cancer; Kidney transplantation; Radical prostatectomy*

Introduction

Kidney transplantation is the treatment of choice in eligible patients with end-stage chronic kidney disease[1]. The worldwide prevalence of chronic kidney disease is estimated at 13.4%, with 4,902 to 7,083 million patients requiring renal replacement therapy[2]. Prostate cancer (PC), with approximately 1,4 million cases in 2020, was the second most common cancer in men[3]. Immunosuppressive therapy increases the incidence of malignancies in renal transplant recipients. However, if we look at PC particularly, there is no clear clinical evidence that these drugs increase or decrease PC risk, although several studies have reported a slight rise in the incidence of PC in this population[4]. Malignancies, as a result of the increasing age of recipients and overall better graft survival, are currently one of the leading causes of death in renal transplant recipients[5]. Treatment of localized PC in renal transplant recipients, regardless of the patient risk group, is an imperative due to immunosuppressive therapy and also a challenge due to the pelvic placement of renal

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graft. Increasing age of recipients, rise in the number of transplantations performed, better overall patient and graft survival, combined with modern, effective immunosuppressive therapy lead to longer life expectancy, which consequentially leads to a rise in the incidence of PC in this population. All of these factors might contribute to a higher incidence of these patients in our everyday practice; thus, urologists dealing with uro-oncology and transplant medicine have to be familiar with this clinical situation.

The aim of this study was to analyze the incidence, treatment methods, and follow-up of PC in renal transplant recipients in our center.

Patients and Methods

A retrospective study included male patients who had been treated with kidney transplantation and diagnosed and treated for PC at the Department of Urology, Zagreb University Hospital Center during the 2002-2022 period. We analyzed patient medical records, treatment methods, follow-up of PC patients, and the incidence of PC in this population. A descriptive statistical analysis of acquired data was performed. The study was conducted in accordance with valid ethical principles.

Results

From January 2002 until January 2022, 1079 male patients had kidney transplantation and 12 had prostate cancer. Four of them had cancer before and the remaining eight after kidney transplantation. The median age at the time of transplantation was 59.5 (40-73) years. Immunosuppressive therapy included calcineurin inhibitors (cyclosporine or tacrolimus), antimetabolites (mycophenolic acid, azathioprine) and corticosteroids; basiliximab was used in induction when indicated.

Median age at the time of diagnosis of PC was 60 (55-75) years, with an initial median prostate-specific antigen (PSA) level of 6.51 (1.19-12.88) ng/mL. Biopsy Gleason score (GS) was predominantly 3+3=6 (8 patients), three patients had a GS 3+4=7, and one had a GS 4+3=7. Patients were then divided into risk groups according to the European Association of Urologists guidelines on PC: 10 patients were in the low risk group, and two were in the intermediate-risk group.

Radical prostatectomy (RP) was performed in 11 cases, and one patient received radical radiotherapy. Lymph node dissection was not performed to avoid graft loss and to preserve iliac vessels for potential future transplantations. Histopathologic results were as follows: 4 patients had GS 6(3+3), 4 had GS 7 (3+4), 1 had GS 7 (4+3),1 had GS 8(4+4) and 1 had GS9(4+5), while GS upstaging was found in 54.5% of the patients. The pT staging was as follows: pT1a (1 patient); pT2a (3 patients); pT2c (6 patients); and pT3a (1 patient). Three patients developed biochemical relapse and had salvage radiotherapy, one of these patients is planned for prostate-specific membrane antigen positron emission tomography (PSMA PET CT) to evaluate the possible further disease progression.

The median follow-up time of the patients was 56 (1-107) months. Eleven patients had a stable graft function, while one patient underwent graftectomy due to acute rejection, not related to PC treatment. The last median creatinine level was 140 (74-330) μmol/L, and the last recorded median PSA level was 0.03 (0.00-2.18) ng/mL.

Discussion

The incidence of PC in patients undergoing kidney transplantation at our center was 1.11%, which is consistent with other studies with the reported incidence ranging from 0.3% to 1.5%[6–9]. The reason for such a low incidence in our and other similar centers could be careful screening of these patients before kidney transplantation, which included PSA and digital rectal examination, but also their regular performance during follow-up after transplantation[10,11].

The preferred therapy for PC in our series was RP. This is consistent with the findings of a systematic review by Hevia *et al*. They found that 82% of patients that were treated with RP had oncologic outcomes that were comparable to non-transplanted population[4]. However, the presence of a functioning graft in the iliac fossa must be taken into consideration when planning treatment of localized PC. Surgical complications such as graft damage, ureteral damage or vascular injury can lead to graft loss, limb loss, and in some cases, to death of a patient. Lymph node dissection increases the risk of complications including vascular injury, but may also make subsequent kidney transplantation into the iliac fossa difficult or impossible. Thus, lymph node dissection should only be performed if indicated according to the current nomograms and guidelines[3,12]. Modifications have also been suggested in these patients, such as placing a retractor above the rectus muscle to avoid

unnecessary pressure on the graft and more cranial mobilization of the urinary bladder to avoid injury to the transplanted ureter[13].

Another treatment option of PC is radiotherapy. One should consider that the kidney is highly radiosensitive[13]. Radiotherapy can lead to radiation nephritis, ureteral anastomotic strictures, and, in combination with immunosuppressive therapy, to avascular necrosis of the femoral head[14,15].

A systematic review by Stöckle *et al*. showed that surgery should be preferred to radiotherapy for two reasons, i.e., to avoid radiotherapy changes in the operative field for future transplantation; and compared to post-radiation, post-surgical PSA is a more reliable follow-up parameter[16].

The use of long-term immunosuppressive therapy, among other factors, in solid organ transplant recipients increases the risk of malignancy 4 to 5 times[17]. Recent studies demonstrated that immunosuppression did not affect the clinical course of PC[18,19]. However, these were retrospective studies and their design could not avoid biases; therefore, until adequate level of evidence is available, we must approach each patient individually to assess their risk and best treatment options.

Conclusion

Radical prostatectomy is a safe method for the treatment of localized PC in kidney transplant recipients that does not impair graft function and survival when performed in experienced centers with experts in kidney transplantation and surgical oncology. It allows better postoperative monitoring of the disease by regular PSA determination than is the case after radical radiotherapy. RP without lymphadenectomy in patients with low-risk PC preserves the contralateral iliac fossa for the potential subsequent kidney transplantation.

References

1. Suthanthiran M, Strom TB. Renal transplantation. N Engl J Med. 1994;331(6):365-76. doi: 10.1056/NEJM199408113310606.
2. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Adv Exp Med Biol. 2019;1165:3-15. doi: 10.1007/978-981-13-8871-2_1. 981-13-8871-2_1
3. Mottet N, Bellmunt J, Briers E, van den Bergh RC, van Casteren N, Cornford P, *et al*. Guidelines on prostate cancer. Update. Eur Assoc Urol [Internet]. 2017;53(March):1-137. Available from: https://uroweb.org/guideline/prostate-cancer/#3
4. Hevia V, Boissier R, Rodríguez-Faba Ó, Fraser-Taylor C, Hassan-Zakri R, Lledo E, *et al*. Management of localised prostate cancer in kidney transplant patients: a systematic review from the EAU Guidelines on Renal Transplantation Panel. Eur Urol Focus. 2018;4(2):153-62. doi: 10.1016/j.euf.2018.05.010.
5. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29. doi: 10.3322/caac.21208.
6. Carvalho JA, Nunes P, Dinis PJ, Antunes H, Parada B, Marconi L, *et al*. Prostate cancer in renal transplant recipients: diagnosis and treatment. Transplant Proc [Internet]. 2017;49(4):809-12. doi: 10.1016/j.transproceed.2017.03.006.
7. Haroon UH, Davis NF, Mohan P, Little DM, Smyth G, Forde JC, *et al*. Incidence, management, and clinical outcomes of prostate cancer in kidney transplant recipients. Exp Clin Transplant. 2019;17(3):298-303. doi: 10.6002/ect.2018.0048.
8. Pettenati C, Jannot AS, Hurel S, Verkarre V, Kreis H, Housset M, *et al*. Prostate cancer characteristics and outcome in renal transplant recipients: results from a contemporary single center study. Clin Transplant. 2016;30(8):964-71. doi: 10.1111/ctr.12773.
9. Tsaur I, Karalis A, Probst M, Blaheta RA, Scheuermann EH, Gossmann J, *et al*. Development of urological cancers in renal transplant recipients: 30-year experience at the Frankfurt Transplant Center. Cancer Sci. 2010;101(11):2430-5. doi: 10.1111/j.1349-7006.2010.01676.x.
10. Gin GE, Pereira JF, Weinberg AD, Mehrazin R, Lerner SM, Sfakianos JP, *et al*. Prostate-specific antigen screening and prostate cancer treatment in renal transplantation candidates: a survey of U.S. transplantation centers. Urol Oncol Semin Orig Investig [Internet]. 2016;34(2):57.e9-57.e13. doi: 10.1016/j.urolonc.2015.08.020.
11. Tonkin-Crine S, Pruthi R, Taylor DM, Leydon GM, Calestani M, Oniscu GC, *et al*. Assessing consensus between UK renal clinicians on listing for kidney transplantation: a modified Delphi study. Transplant Direct. 2018;4(5):1-7. doi: 10.1097/TXD.0000000000000782.
12. Markić D, Oguić R, Krpina K, Vukelić I, Đorđević G, Žuža I, Španjol J. The role of lymphadenectomy in prostate cancer patients. Acta Clin Croat. 2019;58 (Suppl 1):24-35. doi: 10.20471/acc.2019.58.s2.05.
13. Heidenreich A, Pfister D, Thissen A, Piper C, Porres D. Radical retropubic and perineal prostatectomy for clinically localised prostate cancer in renal transplant recipients. Arab J Urol [Internet]. 2014;12(2):142-8. doi: 10.1016/j.aju.2014.01.004.
14. Mouzin M, Bachaud JM, Kamar N, Gamé X, Vaessen C, Rischmann P, *et al*. Three-dimensional conformal radiotherapy for localized prostate cancer in kidney transplant recipients. Transplantation. 2004;78(10):1496-500. doi: 10.1097/01.tp.0000137933.97259.e7.
15. Groth CG, Bäckman L, Morales JM, Calne R, Kreis H, Lang P, *et al*. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. Transplantation [Internet]. 1999 Apr 15;67(7):1036-42. doi: 10.1097/00007890-199904150-00017.
16. Stöckle M, Junker K, Fornara P. Low-risk prostate cancer prior to or after kidney transplantation. Eur Urol Focus [Internet]. 2018;4(2):148-52. doi: 10.1016/j.euf.2018.07.003.

17. Engels EA, Pfeiffer RM, Fraumeni JF, Kasiske BL, Israni AK, Snyder JJ, *et al*. Spectrum of cancer risk among US solid organ transplant recipients. JAMA [Internet]. 2011 Nov 2;306(17):1891. doi: 10.1001/jama.2011.1592.
18. Hibberd AD, Trevillian PR, Wlodarczyk JH, Kemp DG, Stein AM, Gillies AHB, *et al*. Effect of immunosuppression for primary renal disease on the risk of cancer in subsequent renal transplantation: a population-based retrospective cohort study. Transplantation. 2013;95(1):122-7. doi: 10.1097/TP.0b013e3182782f59.
19. Hall EC, Pfeiffer RM, Segev DL, Engels EA. Cumulative incidence of cancer after solid organ transplantation. Cancer. 2013;119(12):2300-8. doi: 10.1002/cncr.28043.

Sažetak

LIJEČENJE KARCINOMA PROSTATE U BOLESNIKA S TRANSPLANTIRANIM BUBREGOM

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Transplantacija bubrega je metoda izbora za liječenja bolesnika u završnom stadiju kronične bubrežne bolesti. Učestalost kronične bubrežne bolesti u svijetu iznosi 13,4%. Karcinom prostate je drugi najčešći karcinom u muškaraca u svijetu. Liječenje lokaliziranog karcinoma prostate je izazovno zbog imunosupresivne terapije i lokalizacije grafta u zdjelici. Visoke stope preživljenja grafta i primatelja rezultirale su sve većom učestalošću karcinoma prostate u ovih bolesnika. Učinjena je retrospektivna analiza muških bolesnika u kojih je učinjena transplantacija bubrega u našem centru između 2002. i 2022. godine, a kojima je dijagnosticiran i liječen karcinom prostate. Analizirali smo incidenciju, metode liječenja i praćenje bolesnika s karcinomom prostate u ovoj populaciji. Ukupno je transplantirano 1079 muških bolesnika. Karcinom prostate dijagnosticiran je u 12 bolesnika (8 nakon i 4 prije transplantacije). Incidencija karcinoma prostate iznosila je 1,11%. Radikalna prostatektomija učinjena je u 11 bolesnika, a jedan bolesnik je liječen radikalnom radioterapijom. Stabilna funkcija presatka prati se u 11 bolesnika, a u jednog bolesnika je učinjena graftektomija, nevezano za karcinom prostate. U tri bolesnika indicirana je spasonosna radioterapija, u jednog je u tijeku *prostate-specific membrane antigen positron emission tomography* (PSMA PET CT), dok je 7 bolesnika u praćenju bez recidiva. Radikalna prostatektomija je sigurna metoda liječenja lokaliziranog karcinoma prostate u bolesnika s transplantacijom bubrega koja ne narušava funkciju i preživljenje grafta.

Ključne riječi: *Karcinom prostate; Transplantacija bubrega; Radikalna prostatektomija*