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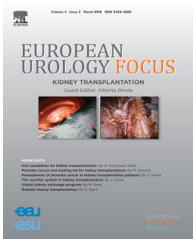

Prostate Cancer

Low-risk Prostate Cancer Prior to or After Kidney Transplantation

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Abstract

Context: Organ transplantation requires immunosuppression, which was regarded as a risk factor for tumor induction and tumor progression in all types of malignancy. Until recently, any form of active neoplasia was, therefore, regarded as contraindicative to organ transplantation. However, there is growing evidence that the increased tumor risk by immunosuppression is restricted to particular subgroups of malignancy, whereas others such as prostate cancer (PCa) are not negatively influenced.
Objective: To compare life expectancy (LE) under various low-risk situations of PCa (untreated low-risk primary tumor, slowly progressing asymptomatic biochemical recurrence after curative treatment) with LE under renal replacement therapy. To discuss the question whether or not low-risk untreated or incurable situations of PCa must be regarded contraindicative to kidney transplantation (KT) or to transplantation of other organs.
Evidence acquisition: A systematic literature search was conducted using PubMed to identify original and review articles regarding PCa risk after KT as well as the natural history of untreated and treated situations of PCa. Articles published between 1991 and 2018 were reviewed and selected with the consensus of all the authors.
Evidence synthesis: No evidence could be found that KT and immunosuppression are associated with an increased PCa-related risk, neither in incidence nor in aggressiveness.
Conclusions: Screening for and treatment of PCa in applicants for KT or in patients after KT should be performed in an individualized manner on the basis of lifetime risk calculations. In particular, untreated or incurable low-risk manifestations (presumed LE >10 yr) of PCa cannot be regarded as strictly contraindicative against KT.
Patient summary: For prostate cancer, even when left untreated, a number of low-risk situations can be defined which are associated with a life expectancy (LE) of 15 yr and more. The LE of elderly patients suffering from end-stage renal failure often does not significantly exceed 15 yr even after kidney transplantation (KT). When remaining on dialysis, however, their further LE is significantly reduced and often far below 15 yr. To the best of the presently available knowledge, KT does not worsen or accelerate the course of untreated low-risk prostate cancer. Even in the presence of untreated low-risk prostate cancer, patients with end-stage renal failure must, therefore, be expected to significantly benefit from KT.

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1. Introduction

Over the past decades, the mean age of patients listed for and treated by kidney transplantation (KT) for end-stage renal failure has significantly increased. In France, the ratio of patients >65 yr on the waiting list increased from 2.5% (1996–1999), 5.2% (2000–2003), 8.4% (2004–2007) to 12.4% (2008–2011) [1]. In the elderly male population,

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the question that gains importance is how to handle prostate cancer (PCa) or PCa risk. Until a few years ago, both chronic uremia and immunosuppression were described as predictors of an increased general cancer risk including PCa [2–4]. Consequently, any neoplasia was regarded as contraindication for organ transplantation. Contemporary studies, however, do not find an enhanced PCa incidence under renal replacement therapy (RRT) [5]. Older case series describing an increased incidence of PCa after KT [6] must be presumed to be biased by more intense screening of a transplant population as compared to the general population. The same may hold true for older publications describing similar trends [7]. For this review, available guidelines for KT were analyzed as well as outcome data of PCa diagnosed after KT. Furthermore, long-term survival data of patients after KT were critically compared with the long-term oncological risk of PCa under various treatment strategies.

2. Evidence acquisition

A systematic literature search was conducted using PubMed to identify original articles and review articles describing life expectancy (LE) of patients under RRT. In a similar way, publications describing untreated or treated natural history of low-risk PCa categories were selected. Low-risk PCa category was defined as any form of disease that is associated with a high probability (>75%) of survival beyond 10 yr. Articles published between 1991 and 2018 were reviewed and selected with the consensus of all the authors.

3. Evidence synthesis

3.1. Principal considerations and historic background

European Association of Urology (EAU) guidelines published in 2005 [8] defined any form of active neoplasia as a contraindication against KT, which would preclude every man harboring PCa from KT. In-between, the PCa prevention trial [9] made evident that PCa can be biopsy-detected even in a significant fraction of men who are completely unsuspicious for PCa. Strict adherence to the 2005 guideline recommendation would, therefore, require a rigorous biopsy-based screening protocol for every man asking for KT. Such a biopsy program has never been established. A significant proportion of elderly men undergoing KT must, therefore, be assumed to harbor subclinical PCa. If immunosuppression would stimulate PCa progression, these men would bear a high risk of developing symptomatic PCa. In spite of the increasing age of transplant recipients, no trend towards an increased PCa incidence, morbidity, or mortality, compared with the general population, has been described so far, suggesting that the natural course of PCa remains unaffected by KT and immunosuppression.

Actual guideline recommendations describing PCa risk, PCa screening, or PCa treatment of men suffering from end-stage renal failure and applying to get listed for KT are often lacking or exclusively focusing onto the necessary relapse-free time interval after curative treatment as a sufficient proof of eradicated tumor activity. Recommendations concerning the necessary waiting time after curative treatment of PCa are heterogeneous and vary from 1 to >5 yr. Dahle et al [10] analyzed the influence of different waiting times on the risk of post-KT tumor progression and found a waiting time of 1 yr, as recommended in Norway, not associated with an increased risk of PCa progression. In the most actual EAU guideline published in 2017, oncological aspects during KT preparation remain unmentioned [11]. An update, based on actual systematic reviews [12] is announced for the 2019 version. Gin et al [13] tried to collect information about the attitude of kidney transplant centers in the USA: they received answers from 65 of 195 programs (33% response rate). A routine prostate-specific antigen (PSA) screening program was performed by 89% of programs and 71% had set guidelines for PCa screening. The most common age to start screening was 50 yr and 79% of the programs had no upper age limit defined. Of the replying centers, 45% regarded definitive treatment of PCa mandatory before proceeding to transplantation. Active surveillance, however, was regarded as viable option by 67% of the responders.

3.2. Actual review data

More recent publications argue towards a more liberal strategy regarding PCa and PCa risk in potential candidates for KT. The review by Boissier et al [12] analyses the general cancer risk after KT and concludes that the natural course of PCa is unaffected by immunosuppression. Similarly, Hibberd et al [14] had described in 2013 that immunosuppression increased the cancer risk in a total of four cancer groups, particularly in those of viral origin. The course of PCa was again described as unaffected by immunosuppression, similar to other more recent publications [15]. The impression that PCa does not interfere with the immune system is corroborated by negative studies of checkpoint-inhibition [16,17] as well as by the principle observation that T-cell infiltration in PCa is less frequent and less intense than in other neoplasias that could be defined as susceptible to T-cell based immunotherapy [18–20].

In a recent review describing outcome of PCa treatment after KT, Marra et al [21] summarized data from 27 retrospective studies describing a total of 241 patients, most frequently treated by surgery (186/241). With follow-up times from 1 to 120 mo, cancer-specific and overall survival exceeded 95%. The majority of the patients described had low-risk and organ-confined PCA. Open as well as laparoscopic and robot-assisted approaches had been used for prostatectomy. Functional results as well as complication rates or handling of immunosuppression or antibiotics had been less frequently reported. Lethal complications or graft losses have not been described so far. Another case series with 20 PCa diagnosed after KT was published by Carvalho et al [22]. The relatively low incidence of 1.1% was explained by PCa screening prior to KT. Of 20 patients, 17 underwent prostatectomy and two developed bone metastases. In summary, outcomes of PCa treatment seemed encouraging