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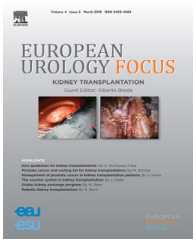


Prostate Cancer

# 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

and did not appear to be inferior to PCa treatment in the general population, again corroborating the impression that KT and/or immunosuppression do not stimulate PCa growth or aggressiveness.

According to the best available evidence, it therefore seems adequate to inform patients concerned that KT as well as immunosuppression is unlikely to increase PCa-related risks. The decision for or against listing should, therefore, best be based on a reasonable balance between the LE after transplantation and the potential life-limiting effect of PCa under various conditions or treatment strategies.

#### 3.2.1. LE under RRT

Chantrel et al [23] analyzed the life-time benefit by KT in comparison to the general population and in comparison to RRT by dialysis: at age 30 yr, a woman under dialysis has a further LE of 24 yr, which is increased to 41 yr by KT (gain of lifetime of 17 yr [41.5%]), which, however, does not reach the LE of the general population (55 yr). Furthermore, 9-yr survival rates under dialysis are strongly age-dependent. For age groups 20–44, 45–64, 65–74, and 75–84 yr, they are calculated as 85.7%, 55.4%, 24.7%, and 10.6%, respectively. Comparison of LE under dialysis versus KT is problematic because both groups must be assumed to differ in comorbidity: diabetes, one cardiovascular comorbidity, and two cardiovascular comorbidities under dialysis reduce the 9-yr survival rates by 17.3%, 25.9%, and 39.4%, respectively. LE for males after transplantation (vs dialysis/vs general population) for age groups 55, 60, 65, 70, and 75 yr was calculated as 20.8 (8.9/26.2), 17.2 (7.1/22.2), 14.1 (6.0/18.4), 11.2 (5.0/14.8), and 9.2 (4.2/11.3) yr, respectively. Thus, age and risk groups can be defined, for whom KT is associated with a significant gain in LE on one hand, and for whom the lifetime risk of untreated or incurable low-risk categories of PCa is marginal or negligible on the other hand.

#### 3.2.2. LE with low-risk PCa

Natural course of disease in low-risk PCa can best be studied in trials comparing active curative treatment with no curative treatment (watchful waiting, WW) such as SPCG-4 [24]. After 18 yr of follow-up, PCa-related death had been observed in 11/118 patients after prostatectomy (10.2%) and in 20/131 patients under WW (14.0%). For clinical interpretation of such studies, occurrence of metastases must be regarded as the more reliable endpoint because of the drastic reduction of quality of life that precedes tumor-related death by years. Metastasis rates after prostatectomy and WW were 15/118 (13.6%) versus 35/131 (24.2%), respectively ($p = 0.006$). The data indicate on one hand that many patients with low-risk PCA do not benefit from curative treatment, which held in particular true for older patients aged >65 yr in this trial. On the other hand, curative treatment significantly reduced the metastasis risk after 18 yr of follow-up. When interpreting these data, further LE and competing mortality become important covariables requiring consideration: in the WW-arm of SPCT-4, 65/131 low-risk patients had died independently of PCa, indicating a relatively high risk of PCa metastases in the 66 remainders with a proven LE of more than 18 yr. In patients with a high remaining LE, the risk of metastases under expectant management may, therefore, exceed 50% even in the low-risk population. SPCT-4 patients have been recruited prior to 2000. Since then, the general LE has seen a dramatic increase. The ratio of tumor-related to tumor-unrelated deaths could, therefore, be dramatically different if the trial would be repeated in a contemporary population with identical chronological age.

Whether or not active surveillance (AS) can overcome the tumor-related risks associated with WW is unproven. Recent data are rather discouraging: the only randomized trial comparing AS with primary active treatment ("PROTECT") found clinical progression (112/545; 20.5%) and metastases (33/545; 6%) after AS more than double as frequent when compared to primary active treatment [25]. More than 50% of AS patients had secondary curative interventions. With follow-up times of not more than 10 yr, these results must still be regarded as preliminary and should be interpreted with caution; however, on the long run, they will rather worsen and certainly not improve. Within the Gothenburg subtrial of the European PCa screening study ERSPC, patients with low-risk tumors under AS were reported to have an estimated 15-yr failure rate of 27% [26]. As only a small minority of the patients had an observed survival of 15 yr, the failure rate might again substantially increase in the future. But even on the basis of the present data, the authors conclude that AS can only be regarded as sufficiently safe in very low risk, but in low-risk PCa, as soon as the host must be regarded as having a long remaining LE. The results raise doubts that AS, at least under the presently evaluated conditions, will turn out to be oncologically equieffective to primary prostatectomy or superior to WW.

If KT patients must be regarded as having LE that does not significantly exceed 15 yr, their risk associated with an untreated low-risk PCa may nevertheless be negligible: When excluded from the transplantation program, these patients are expected to lose significantly more years of life than by their untreated tumor. On the basis of pure lifetime calculations, low-risk PCa, even when left untreated, can therefore not be regarded as strictly contraindicative to a KT. However, patients need to be informed that an observational strategy is associated with a measurable oncological risk which will start to rise after year 10 and to gain significant dimensions after year 15. In case of low comorbidity and a presumed higher LE, the patients should, therefore, be recommended to undergo curative treatment of PCa prior to KT. All authors consent that surgery should be preferred to radiotherapy for two reasons:

1. Surgery avoids radiotherapy alterations in the operation field during and after transplantation.
2. After surgery, PSA is a more reliable surrogate parameter for post-treatment control and for estimation of long-term prognosis than after radiotherapy.

However, even patients with an uncured biochemical recurrence (BR) after prostatectomy may qualify for KT: Freedland et al [27] analyzed the fate of 379 patients with an untreated PSA recurrence after a prostatectomy

performed between 1982 und 2000. The series dates back to a time when clinical relevance and treatment options of BR were not well understood. Palliative androgen deprivation therapy (ADT) had only been recommended when distant or symptomatic metastases became obvious. In spite of treatment concepts which must be regarded as outdated from the actual point of view, median survival had not been reached after 16 yr of observation. The authors identified subgroups with a low or very low risk of PCa-specific mortality even after 15 yr: interval from surgery to BR >3 yr (PCa-specific mortality ~15%), Gleason score of the prostatectomy specimen ≤7 (PCa-specific mortality ~40%), and PSA-doubling time >9mo (PCa-specific mortality ~25%). Given the additional treatment options nowadays available for patients with BR, BR by its own must, therefore, not necessarily disqualify for a KT. A recent study analyzed the clinical course of prostatectomy patients with adverse pathology (Gleason score ≥8, pT3b, pT4, pN+ and/or Gleason 7 with positive margins). Patients had been treated for 2 yr with adjuvant ADT± Mitoxantron chemotherapy. Ten-yr overall survival rates in both arms turned out to be 86–87%, significantly higher than expected (50%) at the time of the protocol design [28]. Even in patients who are uncured by surgery alone from unfavorable disease, multimodal postoperative treatment can, therefore, prolong the LE to an extent that may allow qualification for KT listing.

## 4. Conclusions

To the best of our knowledge, there is no clear evidence that KT and immunosuppression are associated with an increased PCa-related risk, neither in incidence nor in aggressiveness. Screening for and treatment of PCa in applicants for KT or in patients after KT should, therefore, be performed in an individualized manner on the basis of lifetime risk calculations. In particular, untreated or even incurable low-risk manifestations of PCa cannot be regarded as strictly contraindicative against KT. The conclusions are not limited to KT and can presumably be generalized to transplantation of other organs as well. In particular for patients waiting for a liver or lung transplant, an organ replacement treatment comparable to dialysis is not available. The net loss in years of life, when excluded from transplantation because of low-risk PCa, would therefore be significantly higher than in KT aspirants, which even further reduces the relevance of low-risk PCa for the decision-making process. However, all available reviews describing PCa risk after transplantation are based on retrospective data with limited evidence. Patients undergoing any form of transplantation in the presence of active PCa should, therefore, carefully be observed. A centralized data collection would be desirable in order to gain more robust data about PCa risk after transplantation.

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*Study concept and design:* Stöckle.
*Acquisition of data:* Stöckle, Junker.
*Analysis and interpretation of data:* Stöckle, Junker, Fornara.
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