Prostate Cancer Screening and Management in Solid Organ Transplant Candidates and Recipients

Ezequiel Becher, MD, Alex Wang, Herbert Lepor, MD
Department of Urology, NYU Langone Health, New York, NY

The number of solid organ transplantations is increasing worldwide. Major medical advances have allowed for incremented survival in this population, which, because approximately 50% of recipients are over age 50 years, makes for an increasingly older population of transplant survivors. This article discusses controversies and current guidelines related to prostate cancer (PCa) screening, detection, and treatment for men in the general population. The relevant literature is reviewed in order to provide insights on how to optimize PCa screening, detection, and treatment pre– and post–solid organ transplantation. There is compelling evidence that immunosuppression does not increase the risk for the development or progression of PCa following solid organ transplantation. Therefore, PCa screening, detection, or treatment should not be influenced by the impact of immunosuppression on the biology of the disease. Prostate-specific antigen (PSA) appears to be as reliable for PCa screening of transplant candidates and recipients as it is for the general population. There is no consensus on how or when it should be implemented. Evidence is also equivocal as to the suggested waiting time between treatment and transplantation. Surgery and radiation therapy appear to be safe and provide good outcomes for managing PCa in solid organ transplant candidates and recipients. However, certain precautions should be taken with this vulnerable population, especially for kidney transplant patients given the pelvic location of the renal graft. Partial gland ablation of PCa should be considered in appropriate candidates.

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The number of recipients of solid organ transplants is increasing worldwide. Of the 767,534 solid organ transplants performed in the United States from 1988 through 2018, 59%, 22%, and 10% were of the kidney, liver, and heart, respectively.[1] Due to advances in immune suppression, surgical technique, and general medical care, both the half-life of transplanted organs and the life expectancy for solid organ recipients has markedly increased.[2,3]

As of June 2019, the Organ Procurement and Transplantation Network (OPTN) reports that the proportion of kidney, liver, and heart recipients

over age 50 years in the United States are 47.8%, 59.4%, and 57.4%, respectively.[4] Therefore, men who are candidates for, or who have undergone kidney, heart, or liver transplantations will likely have to address issues related to prostate cancer (PCa) screening, detection, and management.

Do Men Die From, or With, PCa?

The average age of men diagnosed with PCa is approximately 65 years.[5] About 33% of men between the ages of 60 to 70 years will harbor PCa,[6] and approximately 3% will die of the disease.[7] Therefore, the majority of PCa are indolent and are best undiagnosed and untreated. Despite these reassuring statistics, PCa is the second-most lethal cancer for men in the United States.[5] The challenge for the urology community is to develop screening, detection, and treatment paradigms that subjects only those men with potentially lethal disease to biopsy and treatment.

Today, most men with low-risk PCa are managed with active surveillance (AS). Of the men randomized to AS in the ProtecT trial, only 6.1% and 1.5% developed metastasis or died of their disease, respectively, at 10 years.[8] Of men with intermediate- and high-risk PCa undergoing radical prostatectomy (RP) in a contemporary series, only 1% and 7.4%, respectively, died of their disease 10 years after their RP.[9] The mean survival for men presenting with systemic metastasis undergoing androgen deprivation therapy (ADT) is approximately 42 months.[10] Therefore, for men with any risk PCa without demonstrable metastasis, and concomitant end-stage kidney, liver, or heart disease, solid organ transplantation is likely to significantly improve both quality of life and overall survival due to the mortality related to the primary organ failure.

Despite level 1 evidence, screening, detection, and treatment of PCa remains highly controversial. Unfortunately, there is a paucity of literature addressing screening, detection, and management of PCa in candidates undergoing evaluation for or following solid organ transplantation. It is imperative for the urologist to provide guidance to the transplant team regarding PCa diagnosis and treatment because management decisions are often dictated by local policy and not national guidelines.

Current Status of PCa Screening in the General Population

Prostate-specific antigen (PSA) screening gained widespread acceptance in the 1990s[11] and the aggressive treatment of screening-detected PCa has been justified by the subsequent 40% decline in PCa mortality.[12] It was therefore surprising that in May 2012, the United States Preventive Services Task Force (USPSTF) released an updated recommendation statement in which PCa screening was given a Grade D recommendation, indicating with moderate-high certainty that the benefits of PCa screening did not outweigh the risks.[13] This recommendation was based primarily on results from two randomized, controlled trials: the Prostate, Lung, Colon, and Ovarian (PLCO)[14] trial, which failed to show any survival advantage of PCa screening, and the European Randomized Study for of Screening for PCa (ERSPC),[15] which showed only a modest survival advantage. A significant criticism of standard of care raised by the USPSTF was the presumed harms from treating low-risk PCa with immediate curative intent. The USPSTF recommendation met with significant criticism from multiple organizations, including the American Urological Association (AUA) and Society of Urologic Oncology (SUO). A subsequent analysis of the PLCO study demonstrated major contamination because approximately 90% of men randomized to the control arm underwent PSA screening.[16] The increasing acceptance of AS by the urology community and recognition of the flawed study design of PLCO lead the USPSTF to give PSA screening a C recommendation, indicating that the decision to screen men between the ages of 55 and 69 years should be individualized considering the harms and benefits of PCa screening.[17]

Current practices for early detection of PCa have been outlined extensively by the AUA and the National Comprehensive Cancer Network (NCCN). The AUA PCa screening recommendation is age dependent.[18] In men age 40 years or younger, the AUA recommends against screening for PCa due to the low incidence of disease. In men between ages 40 and 54 years with low-average risk, the AUA also recommends against screening due to lack of level 1 evidence. Men younger than 55 years at high risk for PCa (eg, black men or those with a family history of metastatic or lethal adenocarcinomas), or men between ages 55 and 69 years should consult with their urologist and establish a more personalized plan. This involves weighing benefits of the early detection of potentially malignant PCa against the risks of unnecessary biopsy and treatment. In the end, the choice to undergo PCa screening should involve shared decision making and be aligned with the patient's values and desires. The AUA doesn't recommend routine PSA screening for men older than 70 years or those

with less than a 10- to 15-year life expectancy. The NCCN recommends starting discussion of the risks and benefits of PCa screening with men age 45 years and, if the option of screening is decided upon, screening is performed via PSA and digital rectal examination (DRE) until the patient is age 75 years.[19]

Today, the goal of PCa screening is to maximize the detection of "clinically significant" PCa and to minimize the detection of "clinically insignificant" disease in men with life expectancies of more than 10 years.

Immunosuppression and PCa: Implications for Screening, Detection, and Treatment

The success of solid organ transplantation mandates immunosuppression. If immunosuppression exhibits an adverse impact on the biology of PCa, it would follow that the intensity of PCa screening, detecting, and treating prior to and after transplantation should be higher than in the general population.

The immune system plays a key role in protecting the host from developing cancer.[20] Modulating the immune system is playing an increasing role in treating various malignancies. The effectiveness of immunotherapy appears to be related to the mutational load of the primary disease.[21] PCa appears to have a low level of mutation, which may explain the ineffectiveness of immunotherapy in this disease.[22]

Immunosuppression appears to explain the increased overall rate of developing solid malignancies following transplantation. The influence of immune suppression on developing malignancy appears to be organ dependent. Engels and colleagues compared the observed incidence of various malignancies across 175,732 patients who received a solid organ transplant captured by both the United States Scientific Registry of Transplant Recipients and 13 cancer registries. Significantly higher rates of malignancy were observed for melanoma, bladder cancer, and kidney cancer (Table 1).[23] These tumors are known to be associated with a high mutational load and are effectively treated with immunotherapy. The development of PCa was not increased in men who received a prior solid organ transplant.

A meta-analysis by Shang and colleagues reported an overall increased risk of cancer amongst renal transplant recipients. The risk of PCa was not greater than the general population.[24]

A recent systematic review by Boissier and colleagues[25] examined recurrence rates and overall survival in men who underwent treatment for a urologic malignancy prior to renal transplantation. Men treated for low- or intermediate-risk PCa did not have increased risk of recurrence after renal transplantation. Another study by Taborelli and colleagues reported on rates of malignancies in a cohort of 2832 liver transplant recipients. They observed an increased risk of non–virus-related malignancies (head and neck, esophagus, and adrenal) that does not translate to an increase in PCa risk.[26]

There have been several advances in immunotherapy regimens following solid organ transplantation. mTOR inhibitors have been shown to be equally effective at preventing tissue rejection and are better tolerated than cyclosporine and tacrolimus.[27,28] mTOR inhibitors have also been shown to be effective anti-cancer agents. Therefore, based on tolerability and cancer risk, mTOR inhibitors are becoming the preferred immunotherapy agent to reduce the development of malignancies.[29,30] The observation that sirolimus reduces PSA levels by 50% must be considered in screening and management of PCa.[31]

There is no evidence that the immunosuppression increases the risk for the development or progression of PCa following solid organ transplantation. Therefore, PSA screening, detection, or treatment of PCa should not be influenced by the impact of immunosuppression on the biology of the disease.

TABLE 1

Risk of Non–infection-related Malignancies in US Transplant Recipients

Organ	Observed	Expected	SIR (95%CI)
Lung	1344	682.8	1.97 (1.86-2.08)
Prostate	1039	1126.9	0.92 (0.87-0.98)
Kidney	752	161.8	4.65 (4.32-4.99)
Colon/rectum	627	504.9	1.24 (1.15-1.34)
Breast	481	567.9	0.85 (0.77-0.93)
Melanoma	381	160.3	2.38 (2.14-2.63)
Bladder	225	148.1	1.52 (1.33-1.73)

CI, confidence interval; SIR, standardized incidence ratio.
Data from Engels EA et al.[23]

PSA Screening in Candidates for Solid Organ Transplantation

There are no specific PCa screening guidelines for men who are candidates for solid organ transplantation or for those who have undergone solid organ transplantation. The American Society of Transplantation recommends that all men age 50 years or older with a life expectancy >10 years who are candidates for a renal transplantation should undergo PCa screening.[32] Therefore, the same principles guiding PCa screening in the general population are recommended for the transplant population. The mean survival following solid organ transplantation taken from a retrospective analysis of patients registered on the United Network for Organ Sharing (UNOS) is shown in Table 2. In general, candidates for kidney, liver, heart, and pancreas transplantation should follow general population PSA screening recommendations, as most will have a life expectancy exceeding 10 years.

Vitiello and colleagues reviewed compliance with PSA screening at a single high-volume transplant institution.[33] Overall, there was poor compliance with screening recommendations because only 63.6% of patients followed PSA screening recommendations. Of the men between the ages of 55 and 59 years, only 24.7% underwent PSA screening whereas 34.9% of men younger than 55 years and 4.1% of men older than 69 years underwent PSA screening. One limitation of this study is that comorbidities and, therefore, life expectancy may have appropriately influenced the decision to undergo screening.

Another study by Gin and colleagues[34] surveyed the major transplant centers in the United States and revealed that even though 89% of the programs routinely screen for PCa prior to renal transplantation, only 71% of them had established guidelines for PSA screening. A major limitation of this study is the poor response rate because only one-third of the surveyed centers responded.

TABLE 2

Mean Survival Following Solid Organ Transplantation in the United States

Organ Transplanted	Mean Survival (y)
Kidney	12.4
Liver	11.6
Heart	9.5
Lung	5.2
Pancreas	13.2
Intestine	5.1

Data from Rana A et al.[2]

Is PSA a Reliable Screening Test for PCa in Candidates for Solid Organ Transplantation?

PSA Values in End-stage Renal Disease (ESRD)

In patients with ESRD, one must consider if PSA is a reliable screening tool for aggressive PCa. Based on cohort and case-control studies, men with ESRD have PSA levels similar to age-matched controls.[35] Under most conditions, the kidney filters proteins less than 60 kDa. Because the majority of serum PSA is complexed to α-1-antichymotrypsin or α-2-macroglobulin (cPSA), the molecular weight is about 90 kDa. Therefore, PSA should remain a useful tool for PCa screening in patients with ESRD.[36] With regards to patients on hemodialysis (HD), most studies have shown no clinically significant difference in PSA before and after HD.[37] Both hematocrit and PSA values may increase by 10% immediately post-HD due to a hemoconcentration mechanism.[38] Therefore, if PSA is slightly elevated consideration should be to obtain the PSA prior to HD. In one small study, PSA values were slightly lower than controls in men on continuous peritoneal dialysis. There is no consensus in the literature whether free PSA (fPSA) is affected by ESRD, although a study by Bruun and colleagues showed that fPSA tends to be increased in this population.[39,40]

PSA Values in Liver Failure

Several investigators have provided compelling evidence that the liver is the site of PSA metabolism. Agha and colleagues observed a statistically significant difference in PSA concentration between the infrahepatic and suprahepatic vena cava, whereas no significant difference was observed between the pulmonary and renal circulation.[41] Kilik and colleagues subsequently reported that a total PSA (tPSA), fPSA, and cPSA were all decreased across the hepatic circulation, whereas only fPSA was decreased across the renal circulation.[42] The liver has a reasonable reserve to metabolize the relatively small quantities of PSA in the serum.[43] PSA levels appears to be influenced by the severity of liver disease because serum PSA levels are lower in cirrhotic patients compared with the general population.[44] Therefore, serum PSA measurement may not be a sensitive tool to reliably screen for PCa in men with severe liver failure. Ideally, the impact of liver failure on PSA would be

best defined by measuring serum PSA values before and after liver transplantation.

PCa Detection

Since the mid-1980s, the detection of PCa was based on systematic biopsy under transrectal ultrasound guidance. Most biopsy protocols obtain 12 tissue cores from various regions of the peripheral zone.[45] A limitation of this random systematic biopsy approach is detection of low-risk disease and failure to detect high-risk disease, especially in the transition zone. There is increasing evidence that multiparametric magnetic resonance imaging (mpMRI) reliably identifies aggressive PCa[46] and mpMRI fusion target biopsy increases the detection of aggressive disease over systematic biopsy.[47-49]

Treatment of clinically localized PCa involves a shared decision-making process balancing the risks of the disease and the treatment. Treatment options for clinically localized PCa include AS, external beam radiotherapy (EBRT), RP, and whole-gland ablation using cryotherapy, or high-intensity focused ultrasound (HIFU). The use of partial-gland ablation is gaining support in the urology community.[50]

At NYU Langone, PSA screening is mandatory for transplant candidates age 50 years or older with a life expectancy longer than 10 years. The initial PCa risk assessment is based on level of PSA, PSA velocity, PSA density, DRE, and family history. If the initial risk assessment is concerning for PCa, mpMRI (and, on occasion, biomarkers) are obtained to better define the risk of aggressive PCa. Patients with a Prostate Imaging Reporting and Data System (PI-RADS) score higher than 2 or a PI-RADS score equal to 2 with elevated biomarkers are advised to undergo mpMRI fusion target biopsy with a bilateral systematic biopsy. Patients with a PI-RADS score equal to 1 associated with markedly elevated biomarkers are advised to undergo transperineal saturation biopsy.

Treatment of PCa in Pretransplant Patients

There are no well-established guidelines for managing clinically localized PCa diagnosed in candidates for solid organ transplantation. Central to treatment recommendations is whether the antirejection immunotherapy mandated following solid organ transplantation will adversely impact the biology of PCa and therefore require more aggressive treatment. The preponderance of data suggests that the rates of developing PCa are not increased following solid organ transplantation. Therefore, treatment decisions for PCa diagnosed pre- and post-transplantation should be influenced by established treatment guidelines for the general population. Factors influencing treatment decisions include life expectancy, comorbidities, complications, and impact on quality of life. The preponderance of PCa detected prior to solid organ transplantation are now usually managed with RP. Carvalho and colleagues reported on a large series of men undergoing renal transplantation in Portugal who were diagnosed with PCa prior to transplantation.[51] The mean age, serum PSA level, and distribution of Gleason scores for the 20 cases of PCa undergoing RP were comparable to the general population, indicating ESRD does not forebode a worse prognosis for PCa. Urologists should offer pelvic lymphadenectomy or radiation to the pelvic lymph nodes sparingly to minimize fibrosis of the iliac vessels that might increase the risk of technical challenges on a future transplantation.

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Wait Time Between Treatment and Transplantation

The current recommendations for timing of renal transplantation in men with newly diagnosed cancers derives from the Israel Penn International Transplant Tumor Registry (IPITTR), which suggests a 2-year disease-free period before receiving a kidney transplant.[52] The 2-year wait time independent of the malignant organ is arbitrary and lacks any validation. For example, it is unrealistic that the delay time should be similar for a man with low-risk PCa managed with AS and a man with metastatic pancreatic or lung cancer. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines challenged this recommendation, suggesting that patients with indolent tumors that were successfully treated can be immediate candidates for transplantation.[53]

Most of the recommendations for delaying solid organ transplantation for newly diagnosed cancers are based on small retrospective studies. Woodle and colleagues ran a retrospective analysis on the IPITTR and showed little to no increased risk of PCa-related death after transplantation regardless of the organ.[54] The limitation of this study is failure to report PSA values and Gleason scores. A slight increased risk of PCa mortality was observed in higher risk disease [American Joint Committee on Cancer (AJCC) stage III]. Because

there is a slight risk of PCa following definitive treatment, they recommend a cancer-free period of 5 years before kidney transplantation for patients with AJCC stage III disease. A 2- to 5-year wait for patients on hemodialysis is associated with high rates of mortality and increases surgical risks simply due to progressive ESRD.

Dahle and colleagues compared overall and cancer specific mortality and graft survival for renal transplant recipients with and without prior history of malignancy.[55] Although cancer-specific mortality was higher for the group with previous cancers, overall mortality and graft survival were not significantly different. The observation that history of PCa was not associated with increased overall or cancer-specific mortality is consistent with the report by Carvalho and colleagues.[51] Due to the protracted natural history of even high-risk PCa, prolonging waiting times for receiving a transplanted organ in men with PCa will likely have adverse impact on survival.

At NYU Langone, we do not recommend any wait time following definitive treatment for Gleason grade group 1 to 3 disease, assuming margins are not grossly involved with tumor or no evidence of multi–lymph node metastasis. For higher risk disease, we generally will wait 1 year and, if PSA is detectable, obtain a positron emission tomography (PET) to exclude regional or systemic metastasis. If the PSA is undetectable at 1 year, recommendations are made to proceed with organ transplantation.

Management of PCa After Transplantation

Hevia and colleagues reported a systematic review of 41 studies examining outcomes of men diagnosed with PCa following renal transplantation.[56] Of the 319 cases, 262 (82%), 30 (17%), and 20 (6%) were managed with RP, EBRT, or brachytherapy (BT), respectively. The observation that mean age, PSA, and distribution of Gleason score was like men undergoing RP in the general population is yet further evidence that immunotherapy does not adversely influence the biology of prostate cancer following solid organ transplantation (Table 3). RP can be performed either open or laparoscopically. Minimally invasive techniques to perform RP have been shown to be feasible and safe on the kidney transplant population.[57] In a systematic review by Zeng and colleagues, the complications categorized as Clavien I, II, III, and IV were 18 (6.9%), 11 (4.2%), 4 (1.5%), and 1 (0.4%), respectively, which are similar to surgical outcomes following open or robotic RP performed in the general population. Although long-term data is lacking, oncological control assessed by biochemical recurrence rates appear to parallel those seen in the general population when stratified according to baseline Gleason score.

There are several caveats that must be considered for RP or EBRT

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TABLE 3

Description of Demographic Data on Patients Included on the Systematic Review by Hevia V et al[56]

Mean age at diagnosis (y)	61.8 (47-79)
Mean baseline PSA (ng/mL)	8.45 (0.3-82)
Biopsy Gleason grade group (%)	
1	50.5
2	21.0
3	11.3
4	3.8
5	1.9
Unknown	11.6
Clinical T stage (%)	
cT1	33.2
cT2	28.9
cT3a	1.6
cT3b	0.3
Unknown	36.1

PSA, serum prostate-specific antigen level.

following renal transplantation. Performing an ipsilateral pelvic lymphadenectomy may be challenging due to the vascular anastomosis to the transplanted kidney. Avoiding injury to the transplanted vasculature and ureter is of paramount importance. One also must consider potential implications of contralateral pelvic lymphadenectomy if another kidney transplant should be required. Wound healing, especially in diabetic patients, may be further impaired by immunosuppression.

Radiation therapy may injure the transplanted kidney and ureter and the native bladder. Hevia and colleagues reported that EBRT had worse oncologic outcomes and a higher complication rate that RP following renal transplantation.[56] BT has been shown to be effective, safe, and feasible for renal transplant recipients.[58-60] However, a major limitation of the BT experience is that most cases were low risk and these cases would likely be managed with AS.

Heart and/or lung transplant recipients present with cardiovascular impairments that would require dedicated and specialized anesthesia and postoperative care team if RP is chosen as the treatment approach. Liver transplant recipients may present with metabolic abnormalities and coagulopathy that may complicate intraoperative and postoperative management.

Conclusions

There are no widely accepted guidelines on proper screening for PCa pre– and post–solid organ transplantation. However, several studies suggest that the same principles for PCa screening used in the general population can be applied to this population. Despite the lack of prospective level 1 evidence, solid organ transplantation appears to be safe immediately following recovery from proper management of low- or intermediate-risk PCa. There is no compelling evidence that immunosuppression adversely impacts the biology of PCa. ■

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MAIN POINTS

- The number of solid organ transplantations is increasing worldwide. Major medical advances have allowed for incremented survival in this population, which, because approximately 50% of recipients are over age 50 years, makes for an increasingly older population of transplant survivors.
- There is compelling evidence that immunosuppression does not increase the risk for the development or progression of prostate cancer (PCa) following solid organ transplantation. Therefore, PCa screening, detection, or treatment should not be influenced by the impact of immunosuppression on the biology of the disease.
- Prostate-specific antigen (PSA) appears to be as reliable for PCa screening of transplant candidates and recipients as it is for the general population. There is no consensus on how or when it should be implemented.
- Evidence is also equivocal as to the suggested waiting time between treatment and transplantation. Although it appears that an immediate transplantation following successful treatment of low- and intermediate-risk disease is safe.
- Surgery and radiation therapy appear to be safe and provide good outcomes for managing PCa in solid organ transplant candidates and recipients.
- Certain precautions should be taken with this vulnerable population, especially for kidney transplant patients given the pelvic location of the renal graft. Partial gland ablation of PCa should be considered in appropriate candidates.

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