Management of Active Surveillance-Eligible Prostate Cancer during Pretransplantation Workup of Patients with Kidney Failure: A Simulation Study

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Abstract

Background and objectives The general rule that every active malignancy is an absolute contraindication for kidney transplantation is challenged by kidney failure patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup. Interdisciplinary treatment teams therefore often face the challenge of balancing the benefits of early kidney transplantation and the risk of metastatic progression. Hence, we compared the quality-adjusted life expectancy of different management strategies in kidney failure patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup.

Design, setting, participants, & measurements A discrete event simulation model was developed on the basis of a systematic literature search, clinical guidelines, and expert opinion. After model validation and calibration, we simulated four management strategies in a hypothetical cohort of 100,000 patients: Definitive treatment (surgery or radiation therapy) and listing after a waiting period of 2 years, definitive treatment and immediate listing, active surveillance and listing after a waiting period of 2 years, and active surveillance and immediate listing. Individual patient results (quality-adjusted life years; QALYs) were aggregated into strategy-specific means (± SEs).

Results Active surveillance and immediate listing yielded the highest amount of quality-adjusted life expectancy (6.97 ± 0.01 QALYs) followed by definitive treatment and immediate listing (6.75 ± 0.01 QALYs). These two strategies involving immediate listing not only outperformed those incorporating a waiting period of 2 years (definitive treatment: 6.32 ± 0.01 QALYs; active surveillance: 6.59 ± 0.01 QALYs) but also yielded a higher proportion of successfully performed transplantations (72% and 74% versus 56% and 59%), with less time on hemodialysis on average (4.02 and 3.81 years versus 4.80 and 4.65 years).

Conclusions Among kidney failure patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup, the active surveillance and immediate listing strategy outperformed the alternative management strategies from a quality of life expectancy perspective, followed by definitive treatment and immediate listing.

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Introduction

Despite the growing body of retrospective evidence that metastatic progression of low-risk prostate cancer under immunosuppressive therapy is very unlikely (1,2), most transplantation guidelines still insist on the rule that every active malignancy is an absolute contraindication for kidney transplantation (3). In order to proceed to an active listing status, patients with kidney failure have to undergo definitive treatment by either radical prostatectomy or radiation therapy, which exposes them to significant treatment-related harms. However, such a management strategy for low-risk prostate cancer (Gleason score ≤ 6, prostate-specific antigen <10 ng/ml, and a tumor that is either nonpalpable or only palpable in less than one half of one lobe of the prostate) (4) does not reflect current treatment strategies for low-risk prostate cancer patients without kidney failure. Most clinical guidelines recommend active surveillance for patients with low-volume, low-risk prostate cancer and consider definitive treatment to be an overtreatment that is usually recommended for selected patients with a relatively high risk of metastatic progression (5).

Therefore, kidney failure patients diagnosed with active surveillance-eligible prostate cancer during the pretransplantation workup clinically challenge their interdisciplinary treatment teams because the benefits of early kidney transplantation have to be weighed against the risks of metastatic progression. In a recently published survey among transplantation centers in the United States, more than two thirds of the respondents allowed active surveillance in transplantation candidates (6). Unfortunately, there

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is neither randomized controlled evidence available to guide practice nor can we expect such studies in the future due to feasibility constraints. In situations like this, a decision analysis is a valid option to address questions not answered by clinical trials, and to assess complex balances of benefit and harm including quality of life (7). Hence, we used a simulation approach to compare the quality-adjusted life expectancy of different management strategies in kidney failure patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup. Quality-adjusted life expectancy is a well established measure used in medical decision analysis that includes both the quantity and quality of life lived.

Materials and Methods

We developed a discrete event simulation model in the statistical programming environment R (R Core Team, Vienna, Austria) by using the *simmer* package, which is specifically designed for the implementation of discrete event simulations in R (8). Discrete event simulation is a flexible and efficient modeling technique capable of representing complex behavior within patients, and can be used for a broad range of clinical problems (9). It is characterized by time progression in discrete intervals (*e.g.*, 12 hours, 751 days, or 5 years) and mutually exclusive events (*e.g.*, stroke, hospitalization, or death) (9). Model development, validation, and calibration followed the methodology described by Caro *et al.* (10) and was further in adherence with the guidelines published by the Society of Medical Decision Making (9). A more in-depth description of the model (influence diagram, assumptions, event logic, input sources, validation, and calibration) can be found in the Supplemental Material (Supplemental Figures 1 and 2 and Supplemental Tables 1-7).

Simulation Setting and Strategies

The simulated model cohort comprised men 50–75 years old with stage 4 or 5 CKD who were diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup. The patients were assumed to be already on hemodialysis or the initiation of hemodialysis was expected to occur within the following 18 months.

On the basis of a systematic literature review, clinical guidelines, and expert opinion, we defined four management strategies as described in Table 1: A, definitive treatment and listing after a waiting period of 2 years; B, definitive treatment and immediate listing; C, active surveillance and listing after a waiting period of 2 years; and D, active surveillance and immediate listing. Strategy A reflects the recommendation of most current practice guidelines (11) and was used as the reference management strategy. Our model allowed for both deceased-donor and living-donor transplantation. We restricted the definitive treatment options to radical prostatectomy and external beam radiation therapy, the two most established and investigated definitive modalities for localized prostate cancer, and assumed an equal utilization of the two modalities. Among patients within the active surveillance strategies, we further assumed an upper age limit for access to definitive treatment in case of upstaging. Therefore, patients older than 75 years at the time of upstaging were managed by a watchful waiting approach (5). Because sufficiently granular model input could not be identified, brachytherapy and peritoneal dialysis were not considered as definitive a treatment option and kidney replacement therapy, respectively, although they both represent well accepted modalities.

Simulation Logic

Simulated events were start/end of definitive treatment, biochemical recurrence, start of hemodialysis, transplantation, symptomatic metastatic progression, death (prostate cancer-related), and death (other causes). The simulation logic is visualized in Figure 1. Kidney failure patients enter

Table 1. Definition of the simulated management strategies

Strategy	Description
A	**Definitive treatment and listing after a waiting period of 2 yr**
	Treatment by radical prostatectomy or radiation therapy
	Active listing 2 yr after completion of definitive treatment
	No listing in the event of biochemical recurrence or if the patient reaches an age of 75 yr
B	**Definitive treatment and immediate listing**
	Treatment by radical prostatectomy or radiation therapy
	Immediate active listing after completion of definitive treatment
	No listing in the event of biochemical recurrence or if the patient reaches an age of 75 yr
C	**Active surveillance and listing after a waiting period of 2 yr**
	Active listing 2 yr after initiation of active surveillance
	No listing in the event definitive treatment becomes indicated or if the patient reaches an age of 75 yr
	Immediate active listing after completion of definitive treatment in patients younger than 75 yr
	No listing in the event of biochemical recurrence
	WW approach in case definitive treatment is indicated after the patient reaches an age of 75 yr
D	**Active surveillance and immediate listing**
	Immediate active listing
	No listing in the event definitive treatment becomes indicated or if the patient reaches an age of 75 yr
	Immediate active listing after completion of definitive treatment in patients younger than 75 yr
	No listing in the event of biochemical recurrence
	WW approach in case definitive treatment is indicated after the patient reaches an age of 75 yr

WW, watchful waiting.

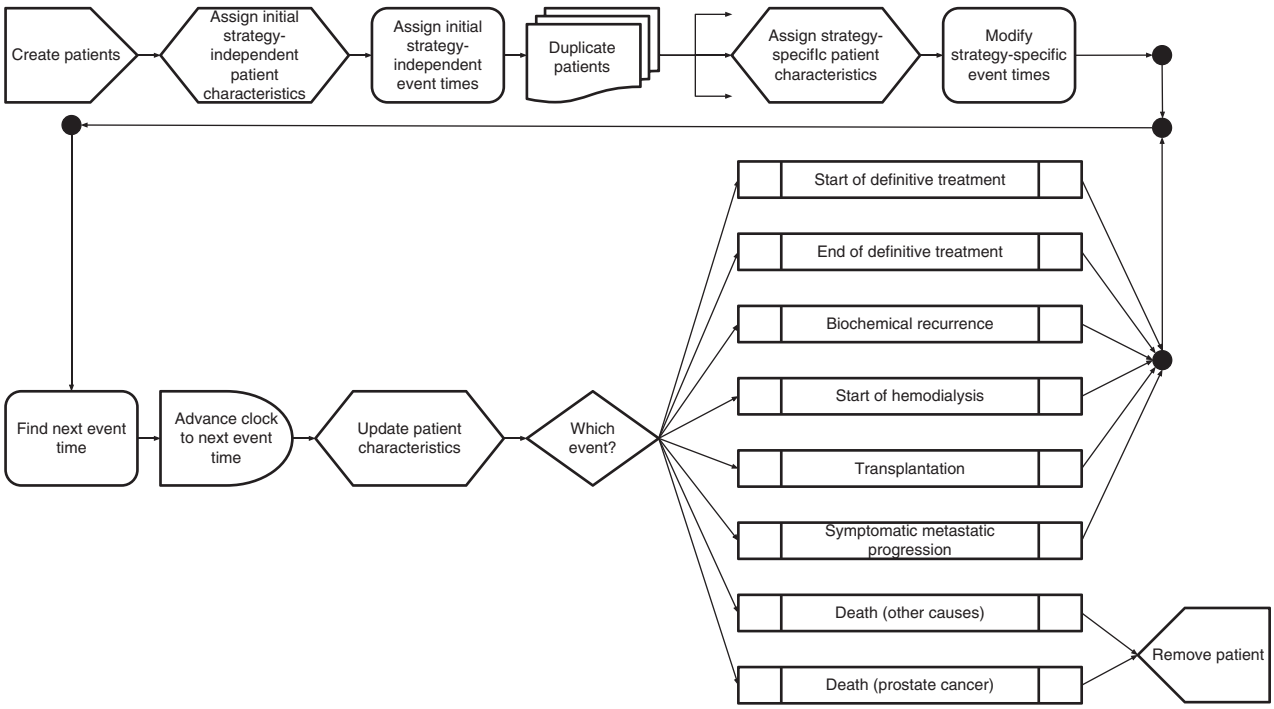

Figure 1. | **Simulation logic describing the mechanics of the model.**

the model after diagnosis of active surveillance-eligible prostate cancer during pretransplantation workup. The next step assigns individual characteristics such as age or current kidney failure management to each patient. The model then samples strategy-independent event times for each patient (under consideration of individual characteristics) before the patient is cloned for each of the four strategies. The latter step not only represents the modeling equivalent to randomization in a randomized controlled trial but also decreases nuisance variance. After cloning, the four copies receive strategy-specific modifications of their characteristics and event times before the simulation clock starts to run.

During the actual simulation, a patient always experiences the event that occurs next in time. Each event has an associated event logic that might include actions like the modification of patient characteristics or the resampling of event times. The experience of a death event leads to the removal of the corresponding patient. By weighting each health state in the clinical path of an individual with different utility values [ranging from 0 (death) to 1 (perfect health); see Table 2)], each patient acquires a distinct amount of quality-adjusted life expectancy (depending on the individual event order). The design of the model structure is on the basis of urological and nephrological guidelines, clinical reasoning, and expert opinion. More details (including the event logic) can be found in the Supplemental Material (Supplemental Figure 1 and Supplemental Table 1).

Model Input

The model required three types of input parameters: event times, probabilities, and health state utility values. All input parameters were obtained through literature review or expert opinion. We sampled event times on the basis of uniform or Weibull distributions. Weibull distribution parameters were estimated by fitting parametric survival models to reconstructed patient-level data, as described by Guyot *et al.* (12) and Ishak *et al.* (13). Background mortality was derived from mortality and life expectancy statistics published by Eurostat, the statistical office of the European Union (14). On the basis of prior literature (1,2), we assumed that the immunosuppression associated with the receipt of a kidney transplant does not modify prostate cancer-specific event times (*e.g.*, time to biochemical recurrence). A detailed list of all input sources as well as an in-depth description of the methodology we used to derive input parameters can be found in the Supplemental Material (Supplemental Tables 2-4).

Validation and Calibration

We used an iterative and multidimensional approach to ensure the validity of our model. First, we consulted with content experts at all stages of model development to ensure face validity (*e.g.*, correctness of clinical paths, plausibility of outcomes, required complexity, *etc*.). Second, formal verification of the whole model and its submodules was conducted to detect potential inconsistencies and/or coding errors. Third, we performed external validation and quantitatively verified if patient outcomes predicted by the model matched observed outcomes reported in literature. Fourth and last, outcome mismatches detected during external validation were addressed by model calibration. We therefore calibrated several input parameters either manually (low-complexity problems) or by more advanced optimization techniques (*e.g.*, Latin hypercube sampling

Table 2. Health state utility values and their plausibility ranges

Health state	Utility (base)	Plausibility range	Reference
Health states associated with prostate cancer			
Postoperative recovery phase after radical prostatectomy	0.67	0.56–0.90[a]	Stewart *et al.* (25)
Delivery of radiation therapy	0.73	0.71–0.91[a]	Stewart *et al.* (25)
Adverse effects of definitive treatment			
Erectile dysfunction	0.89	0.86–1.00[a]	Stewart *et al.* (25)
Urinary incontinence	0.83	0.78–0.98[a]	Stewart *et al.* (25)
Urinary incontinence and erectile dysfunction	0.79	0.76–0.96[a]	Stewart *et al.* (25)
Bowel dysfunction	0.71	0.61–0.90[a]	Stewart *et al.* (25)
Urinary incontinence and bowel dysfunction	0.70	0.66–0.88[a]	Stewart *et al.* (25)
Bowel dysfunction and erectile dysfunction	0.57	0.41–0.76[a]	Stewart *et al.* (25)
Urinary incontinence, erectile dysfunction, and bowel dysfunction	0.45	0.17–0.78[a]	Stewart *et al.* (25)
Biochemical recurrence	0.67	0.56–0.84[a]	Stewart *et al.* (25)
Symptomatic metastatic progression	0.25	0.01–0.52[a]	Stewart *et al.* (25)
Health states associated with kidney failure			
Conservative management	0.900	0.700–1.000[b]	Hogan *et al.* (26)
Management by transplantation	0.775	0.675–0.875[b]	Hogan *et al.* (26)
Management by hemodialysis	0.525	0.450–0.600[b]	Hogan *et al.* (26)

In the event a patient experienced two or more health states at the same time (*e.g.*, delivery of radiation therapy and conservative kidney failure management), the current health state utility value was always determined by the state with the lowest value.
[a]Interquartile range.
[b]Range used in sensitivity analyses of the reference study.

combined with weighted goodness-of-fit measures for more complex problems). A detailed description of the external validation and calibration approach can be found in the Supplemental Material (Supplemental Figure 2 and Supplemental Tables 5-7).

Outcomes

Primary outcomes included undiscounted and discounted (3% per year) quality-adjusted life years (QALYs). By discounting QALYs it is possible to account for time preference, specifically the preference to acquire QALYs earlier than later. Individual patient results were aggregated into strategy-specific means (± Monte-Carlo SEM). Secondary outcomes were proportion of transplanted patients, proportion of pre-emptive transplantations, time spent on hemodialysis (years), proportion of patients who underwent definitive treatment, proportion of patients who died from prostate cancer, and crude survival (years). In addition, we performed subgroup analyses among different age strata (*i.e.*, younger than 60 years, younger than 70 years, and 70 years and older) and among different types of definitive treatment (*i.e.*, radical prostatectomy versus external beam radiation therapy).

Probabilistic Sensitivity Analysis

Because the final selection of the preferred management strategy might be strongly driven by the health state utility values used in our model, we further compared the best and the second-best management strategy in a probabilistic sensitivity analysis. By sampling each of the 14 health state utility values from a plausibility range reported in literature, we created 10,000 distinct parameter sets. To maintain clinical validity within each parameter set (*e.g.*, $\text{utility}_{\text{hemodialysis}} < \text{utility}_{\text{conservative kidney failure management}}$), we used an ordered sampling approach as proposed by Ren *et al.* (15). Each of the 10,000 clinically valid parameter sets was then used to compare the best and second-best management strategies in a population of 10,000 patients requiring 10,000 × 10,000 patient-level simulations. The result of the probabilistic sensitivity analysis was then reported both graphically and numerically (percentage of parameter sets in favor of the best strategy).

Results

Quality-Adjusted Life Expectancy

After ascertaining model validity, we simulated the four management strategies among 100,000 kidney failure patients who were diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup. Figure 2 compares the mean QALYs ± Monte Carlo SEM (undiscounted: QALYs; discounted: dQALYs) between the four strategies. Strategy D (active surveillance and immediate listing) was the preferred strategy from a integrative health care perspective because it yielded on average the highest amount of quality-adjusted life expectancy, 6.97 ± 0.01 QALYs and 5.74 ± 0.01 dQALYs, followed by definitive treatment and immediate listing (strategy B) with 6.75 ± 0.01 QALYs and 5.56 ± 0.01 dQALYs. Apparently, these two strategies markedly outperformed those incorporating a mandatory uneventful waiting period of 2 years (strategy A: 6.32 ± 0.01 QALYs and 5.21 ± 0.01 dQALYs; strategy C: 6.59 ± 0.01 QALYs and 5.43 ± 0.01 dQALYs). When we assessed the effect of age and type of definitive treatment on quality-adjusted life expectancy, we did not observe any changes in the overall order of the preferred strategies (Supplemental Figures 3 and 4).

Secondary Outcomes

As shown in Table 3, the superiority of the strategies involving no waiting period (B and D versus A and C) was

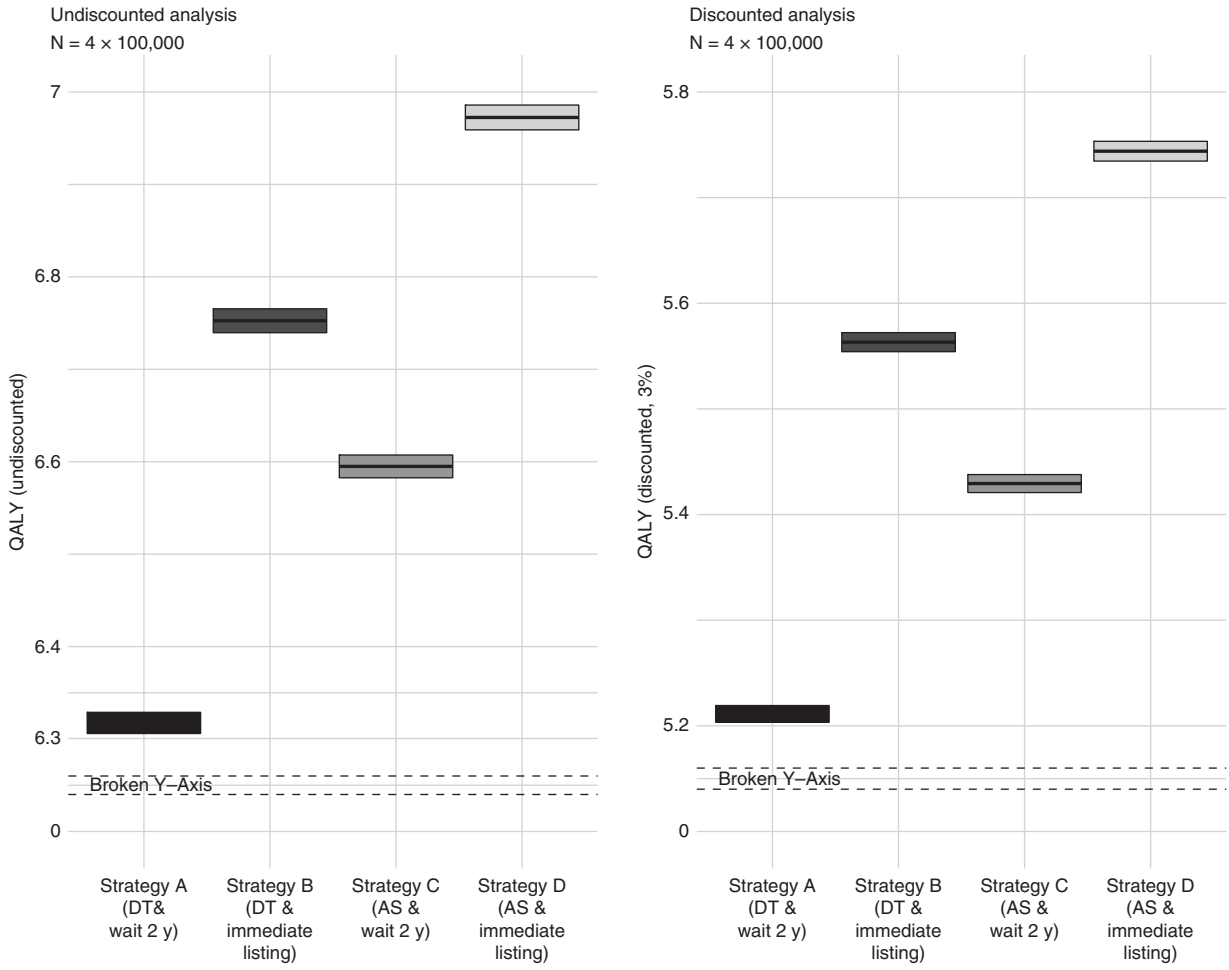

Figure 2. | **Mean quality-adjusted life expectancy of each strategy.** The boxes with the central horizontal line represent means ± Monte Carlo SEMs. Each of the four strategies was simulated among a cohort of 100,000 patients. AS, active surveillance; DT, definitive treatment; QALY, quality-adjusted life years; y, years.

also reflected in a higher percentage of successfully performed kidney transplantations (72% and 74% versus 56% and 59%), a higher percentage of pre-emptive kidney transplantations (40% and 45% versus 9% and 11%), and on average less time spent on hemodialysis (4.02 years and 3.81 years versus 4.80 years and 4.65 years). Among the strategies involving active surveillance, 38% (C) and 37% (D) of the patients ultimately received definitive treatment. In comparison to the strategies involving immediate definitive treatment (A and B), strategies C and D showed a slightly higher proportion of patients who died from prostate cancer (2% and 2% versus 1% and 1%). Despite this aspect, the raw mean survival time remained virtually unaffected (11.0 years and 10.8 years versus 10.9 years and 10.8 years). In addition, as observed for quality-adjusted life expectancy, age and type of definitive treatment did not change the overall order of the preferred strategies when it comes to secondary outcomes (Supplemental Tables 8 and 9).

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis between the best (D: active surveillance and immediate listing) and the

Table 3. Secondary outcomes

Strategy	Proportion who underwent transplantation (%)	Proportion who underwent pre-emptive transplantation (%)	Mean time spent on hemodialysis (yr)	Proportion who underwent definitive treatment (%)	Proportion who died from prostate cancer (%)	Mean survival (yr)
A	56	9	4.8	100	1	11.0
B	73	40	4.0	100	1	10.8
C	59	11	4.7	38	2	10.9
D	74	45	3.8	37	2	10.8

second-best (B: definitive treatment and immediate listing) strategy, which accounted for the uncertainty associated with the health state utility values, confirmed the superiority of strategy D (active surveillance and immediate listing) in 99.6% of the 10,000 parameter sets (Figure 3).

Discussion

Our discrete event simulation clearly suggests that, from an integrative health care perspective, active surveillance and immediate listing is the preferred management strategy in patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup. This result was also confirmed in a probabilistic sensitivity analysis that explored the uncertainty of the associated health state utility values. The difference of 1.41 QALY between the best strategy (active surveillance and immediate listing; 6.97 QALY) and the worst strategy (definitive treatment and listing after a waiting period of 2 years; 5.56 QALY) can be considered substantial, especially in light of the fact that incremental gains in quality-adjusted life expectancy are often much smaller (systematic review and meta analyses by Wisløff *et al.* (16): median of 0.06 QALY with a interquartile range from 0.01 to 0.32 QALY). Furthermore, our simulation demonstrates that immediate listing is crucial from a quality-adjusted life expectancy perspective, regardless of the final decision between definitive treatment and active surveillance. The same pattern of results could be observed in the analysis of our secondary outcomes: The performance of the strategies involving immediate listing was superior with regard to the proportion of transplanted patients and time spent on hemodialysis. However, the two strategies involving active surveillance showed a marginally higher proportion of patients who died from prostate cancer.

The finding that the cumulative time on hemodialysis can be considered the most important driver of the differences in QALYs between the simulated strategies is in line with the results of a recent meta-analysis conducted by Wyld *et al.* (17). The authors conclude that, among patients with kidney failure, treatment with dialysis in comparison to kidney transplantation is linked with a significant impairment in quality of life. On the basis of our observations, we not only advocate for the generous implementation of the active surveillance paradigm in the kidney failure population, but also for immediate listing regardless of the ultimate decision between active surveillance and definitive treatment. Such a policy is ideally accompanied by prospective data collection and close monitoring of any unexpected trends regarding prostate cancer biology after transplantation.

The implementation of an active surveillance approach in this population is currently hampered by two concerns: The first one relates to the belief that a post-transplant status might negatively interfere with definitive treatment. However, this fear is not supported by a recently published systematic review (18) showing that these patients can be managed with the same range of therapeutic options as the general population (19–22). The second concern involves the effect of immunosuppression on cancer progression. Although such an association has been demonstrated for

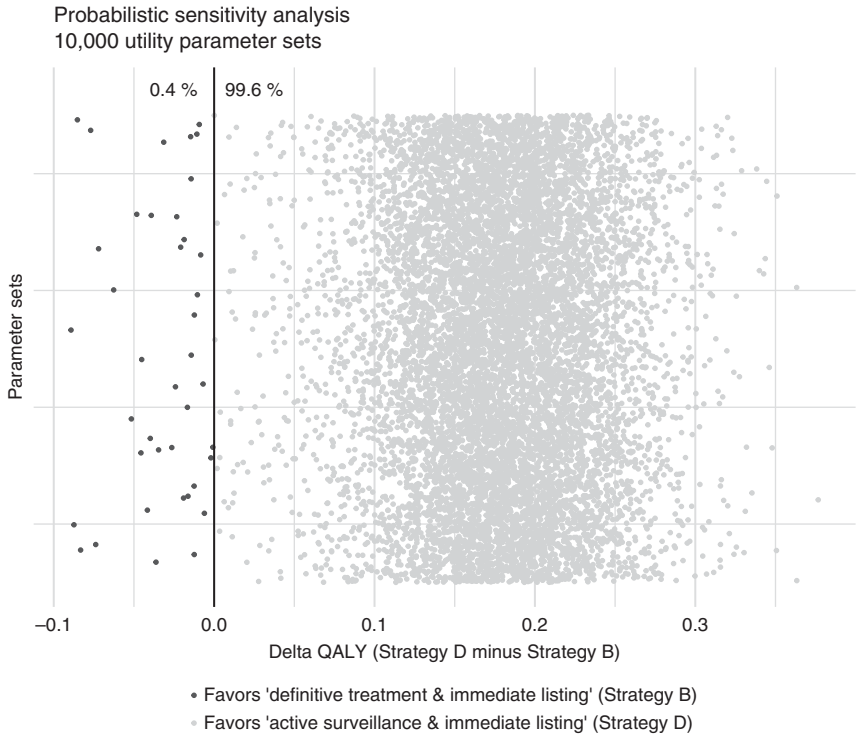

Figure 3. | Probabilistic sensitivity analysis between the best (D: active surveillance and immediate listing) and the second best (B: definitive treatment and immediate listing) strategy accounting for the uncertainty associated with the health state utility values. The scatter plot visualizes the incremental benefit of strategy D over strategy B (*x* axis) for each of the 10,000 parameter sets (*y* axis).

other malignancies such as urothelial cancer (23), there is currently no unambiguous evidence available that supports a harmful effect of immunosuppressive therapy on prostate cancer-related risks (2).

To our knowledge, this is the first study that approaches this relevant and challenging clinical problem with a decision-analytic methodology. By developing a discrete event simulation model, a relatively novel technique in biomedical research that has its origins in the simulation of industrial systems, we were able to comprehensively explore and compare multiple potential strategies at the patient level. Efficient individual-level simulations of such a complex problem would not have been feasible with other modeling strategies, such as conventional decision trees or Markovian health-state transition models (24). An additional strength of our decision-analytic approach is the fact that it mitigates certain types of bias (mostly related to the "file drawer" effect), which are often prevalent in case series or individual patient data meta-analyses investigating relatively rare populations (such as kidney failure patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup). Last, we ascertained the validity of our model as rigorously as possible. We not only involved content experts at all stages of development to achieve face validity, but also externally validated and calibrated our simulation against sources that were not used to obtain the primary input parameters. In addition, we explored the uncertainty associated with the health state utility values by a probabilistic sensitivity analysis.

Nevertheless, this study has two important limitations. First, our findings are obviously not derived from a conventional study, but based on a simulation involving a cohort of hypothetical patients and numerous of input sources. To fulfill the crucial claims for validity and transparency, we followed strict methodology (9,10), used a meticulous validation framework (including external validation/calibration), and provide full model documentation in the Supplemental Material. Second, discrete event simulation requires a relatively high number of input parameters compared with other modeling strategies. Therefore, in the absence of sufficiently granular input sources, it was not feasible to incorporate additional clinical aspects such as kidney failure-specific patient characteristics (*e.g.*, diabetes mellitus), peritoneal dialysis, or brachytherapy into the simulation. Furthermore, although we always tried to derive our inputs from large multicentric North American or European cohorts to maintain a high level of external validity, it was unavoidable to derive certain parameters from smaller single-center studies and/or from other continents, which introduced a certain degree of heterogeneity into our source populations.

In conclusion, our decision-analytic work demonstrates that, among kidney failure patients diagnosed with active surveillance-eligible prostate cancer during pretransplantation workup, the strategy active surveillance and immediate listing outperforms the alternative management strategies from a quality of life expectancy perspective, followed by definitive treatment and immediate listing. The cumulative time on hemodialysis can be considered a more important driver of the differences in quality-adjusted life expectancy between the four strategies than the negligible higher rate of metastatic progression associated with active surveillance. This study can therefore be the basis for a change in practice and a motivation for prospective data collection in this specific kidney failure population.

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Disclosures

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14041119/-/DCSupplemental.

Supplemental Appendix.

Supplemental Figure 1. Influence Diagram.

Supplemental Figure 2. Scatter plot visualizing the goodness of fit of 1000 parameters sets used during the calibration process.

Supplemental Figure 3. Mean quality-adjusted life expectancy of each strategy stratified according to treatment modality (radical prostatectomy vs. radiation therapy).

Supplemental Figure 4. Mean quality-adjusted life expectancy of each strategy stratified by age group at start of simulation (younger than 60 years versus younger than 70 years versus 70 years and older).

Supplemental Table 1. Assumptions.

Supplemental Table 2. Time-to-event parameters.

Supplemental Table 3. Probabilities.

Supplemental Table 4. Health state utility values and their plausibility ranges.

Supplemental Table 5. Validation targets.

Supplemental Table 6. Deviation of prostate cancer-specific model output from results reported in literature.

Supplemental Table 7. Deviation of kidney failure-specific model output from results reported in literature.

Supplemental Table 8. Secondary outcomes stratified by treatment modality.

Supplemental Table 9. Secondary outcomes stratified by age group.

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