Screening for renal cancer in recipients of kidney transplants

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Abstract

Background. Renal cancer is the most common solid organ cancer in the kidney transplant population with an excess risk ~5-fold greater than the general population. It is uncertain whether routine screening for renal cancer is cost-effective. The aim of our study is to estimate the costs and health benefits of ultrasonographic (US) screening for renal cancer in the kidney transplant population.

Methods. A Markov model was developed to compare the costs and benefits in a cohort of kidney transplant recipients ($n = 1000$, aged 18–69 years), who underwent annual and biennial US screening for renal cancer, compared with a cohort that did not.

Results. For recipients of kidney transplants aged 18–69 years, the incremental cost-effectiveness ratio (ICER) for routine US screening ranged from $252 100/LYS for biennial screening to $320 988/LYS for annual screening. A total of two and one cancer deaths were averted in the annually and biennially screened population, with a relative cancer-specific mortality reduction by 25% and 12.5%, respectively. Using a series of sensitivity analyses, the ICER was most sensitive to the costs and test specificity of ultrasonography, prevalence of disease, and the risk of graft failure in the screened population.

Conclusions. Routine screening for renal cancer may reduce the risk of cancer-related deaths in recipients of kidney transplants. Uncertainties, however, exist in the model’s influential variables including the risk of graft failure among those who received contrast-enhanced diagnostic computer tomography. Given the available evidence, routine screening for renal cancers may not be cost-effective for recipients of kidney transplants.

Keywords: cost-effectiveness; kidney transplantation; renal cancer; screening

Introduction

Compared with the general population, cancer risk is increased by at least 2-fold in kidney transplant recipients and is their second most common cause of death [1,2]. Renal cancer is the most common solid organ cancer in people with end-stage kidney disease (ESKD) with an excess risk of at least 5–10-fold greater than the age- and gender-matched general population, and a significant cause of mortality and morbidity [3,4]. At least one in four dies in the first year after cancer diagnosis, with a 5-year cancer survival rate of <20% [5].

Early detection and treatment of renal cancer through routine screening of kidney transplant recipients are a plausible means to prevent the development of advanced-stage cancer which has an unfavourable prognosis. General population screening for cancers such as breast, colorectal and cervical cancer is now standard practice and is effective in reducing cancer-specific mortality [6–10]; however, screening for renal cancer is not recommended in the general population. In the ESKD population, the benefits of routine screening for renal cancer are even less certain. This is predominantly because their kidneys are structurally different (as a result of congenital abnormality and/or intrinsic renal disease), thus adding to the complexity of test result interpretation. Although there is a body of literature assessing the incidence/prevalence of renal cancer in recipients of kidney transplants [11–16], few studies have estimated the test performance characteristics (sensitivity and specificity) of ultrasonographic screening and the treatment effectiveness for renal cancer in the ESKD and transplant populations [17–20].

The current recommendations for screening for renal cancer in the kidney transplantation population are contradictory. The American Society of Transplantation and the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Care of the Kidney Transplant Recipient found no evidence to support routine screening for renal cancers in recipients of kidney transplants and did not recommend screening using ultrasonography in average-risk transplant recipients [21,22]; guidelines from the European Association of Urology recommended annual screening of the native and the graft kidneys using ultrasonography for people who are at high risk but did not specify or define the high-risk populations [23]. The most reliable method to ascertain the benefits and harms of screening would ideally
come from randomized controlled trials (RCT) of screening compared with no screening. However, given the paucity of trial-based data and the low feasibility of adequately powered trials, estimates of costs and effects of screening derived from analytical modelling are the most effective method to inform decision makers about the possible benefits, harms, costs and uncertainties of screening for renal cancer in this setting. The aims of this study are firstly to estimate the health benefits and costs of routine annual and biennial screening using ultrasonography of the native kidneys in recipients of kidney transplants, and secondly to determine the influential and uncertain variables in screening for renal cancer to help inform future research priorities.

Materials and methods

Using a broad healthcare funder perspective, a Markov model was developed to simulate the lifetime costs and health outcomes of a hypothetical cohort of kidney transplant recipients.

Structure of the model

The structure of the model is outlined in Figure 1, and details of the structure of the model are provided in Appendix 1. In short, we first structured the model to include all the potential consequences of the natural history of renal cancer and transplantation (Table 1). We then populated the model using the best available evidence and finally assessed the uncertainties around model assumptions and parameter estimates using one-way and multiway sensitivity analyses. In the absence of randomized controlled trial evidence of screening for renal cancer, data of health benefits, harms and costs were extrapolated from published observational studies in the transplant and dialysis population, and where not available, using published data from the general population (Table 2).

Sensitivity analyses

Uncertainties existed in the model’s parameter estimates and structure. Using a series of one- and two-way sensitivity analyses, we tested the robustness of the results to the uncertainties surrounding the model’s estimates. The baseline participation rate of screening renal cancers was assumed to be 70%. Given that transplant recipients were subjected to intense monitoring by their treating physicians, a higher than the expected participation rate in screening trials [24,25] was assumed in recipients of kidney transplants. The expected participation rate was then varied between low and high values of 40–100%. Other variables such as the prevalence of disease (in the high-risk population, such as those with prior history of renal cancer, acquired cystic disease and analgesic nephropathy), the probability of graft failure, the estimates of screening test accuracy (test specificity and sensitivity), discount rates for costs and benefits, the cancer stage-specific distribution, and the probability of survival with renal cancer were also extensively assessed in the sensitivity analysis.

Scenario analyses

We modelled two different scenarios for screening renal cancer in the transplant population. The first scenario (base-case analysis) assumed recipients with failed kidney transplant who returned to dialysis and were continued to be screened either annually or biennially. The second scenario assumed all transplant recipients with failed kidney transplants who returned to dialysis and did not continue routine screening for renal cancer.

Model outcomes

The model’s outcomes include the average and incremental health outcomes (in life-years saved) and costs of screening for renal cancers in renal transplant recipients, the number of renal cancers averted from early detection, and the absolute and relative cancer-specific mortality reduction from screening for renal cancers. The incremental costs and benefits were calculated according to this formula:

\[
\text{ICER} = \frac{\text{Costs}_\text{New} - \text{Costs}_\text{Comparator}}{\text{Effectiveness}_\text{New} - \text{Effectiveness}_\text{Comparator}}
\]

Future costs and outcomes were discounted at an annual rate of 5%. The discount rate was also tested in the sensitivity analyses within the accepted rates by most funding agencies [26–28]. In this model, we used a half-cycle correction to minimize overestimation of the expected outcomes at the end of the analysis. TreeAge Pro 2008 and Excel were used to develop the decision-analytic model [29].
**Results**

**Base-case analysis**

Tables 3 and 4 show the results of the base-case analysis of the no screening, annual screening or biennial screening arms. Assuming a screening participation rate of 70%, the incremental benefit of annual screening compared with no screening was 0.004 life-years saved (LYS), and the incremental benefit of biennial screening compared with no screening was 0.003 LYS. The incremental cost of annual screening compared with no screening arm...
screening was $1300. The incremental cost of biennial screening compared with no screening was $900. The incremental costs-effectiveness ratio (ICER) of annual screening compared with no screening was $320 988/L YS, and the ICER of biennial screening compared with no screening was $252 100/L YS. Over the entire screening period, there were six deaths from renal cancer per 1000 transplant recipients in the annual screening arm, compared with seven and eight deaths from renal cancer per 1000 transplant recipients in the biennial screening and no screening arms, respectively. Compared with no screening, the relative risk reduction of death from renal cancer for annual screening was 25%, and 12.5% for biennial screening, with an absolute risk reduction of death from renal cancer of only 0.2% for annual screening and 0.1% for biennial screening.

One-way sensitivity analysis

Annual screening. The model was most sensitive to changes in the following variables for annual screening: prevalence of renal cancer, probability of graft failure and return to dialysis, and the cost and test specificity of ultrasonography. Figure 2A shows the change in the ICER over the plausible range of estimates tested in the sensitivity analyses for annual screening compared with no screening. There were substantial uncertainties surrounding each of these variables on the overall ICER. If a willingness-to-pay (or the cost-effectiveness) threshold was set at the recommended ratio of $100 000/L YS [30], annual screening for renal cancer does not appear to be good value for money, unless the annual probability of renal graft failure was <2% (the average rate of graft failure is between 2%

Table 2. Total and incremental costs and benefits of screening renal cell carcinoma

<table>
<thead>
<tr>
<th>Screening strategies</th>
<th>Total benefits (LYS)</th>
<th>Total costs ($)</th>
<th>Incremental benefits (LYS)</th>
<th>Incremental cost ($)</th>
<th>Incremental cost-effectiveness ratio ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screen</td>
<td>13 64193</td>
<td>301 700</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual</td>
<td>13 64598</td>
<td>303 000</td>
<td>0.00405</td>
<td>1300</td>
<td>320 988</td>
</tr>
<tr>
<td>Biennial</td>
<td>13 64550</td>
<td>302 600</td>
<td>0.00357</td>
<td>900</td>
<td>252 100</td>
</tr>
</tbody>
</table>

All screening strategies (annual or biennial) were compared with no screening.
Table 4. Marginal costs and benefits of screening renal cell carcinoma (expanding from biennial to annual screening)

<table>
<thead>
<tr>
<th>Screening strategies</th>
<th>Total benefits (LYS)</th>
<th>Total costs ($)</th>
<th>Average cost-effectiveness ratio ($/LYS)</th>
<th>Marginal costs ($)</th>
<th>Marginal benefits (LYS)</th>
<th>Marginal cost-effectiveness ratio ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual</td>
<td>13.64598</td>
<td>303 000</td>
<td>22 204</td>
<td>400</td>
<td>0.000488</td>
<td>833 333</td>
</tr>
<tr>
<td>Biennial</td>
<td>13.64550</td>
<td>302 600</td>
<td>22 175</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

and 4% ([31,32]) and the disease prevalence rate was at least five times greater than the expected prevalence rate in the transplant population.

**Biennial screening.** A similar range of influential variables was found in the biennial screening arm. Figure 2B shows the change in ICER over the plausible range of estimates tested in the sensitivity analyses for biennial screening compared with no screening. Similar to the annual screening arm, uncertainties exist surrounding each of the influential variables on the overall ICER. Again, using a willingness-to-pay threshold of $100 000/lys, screening renal cancer biennially may not be cost-effective unless the disease prevalence is at least 3.5 times greater than the expected disease prevalence in the transplant population and the biennial probability of renal graft failure is <5.5%.

**Two-way sensitivity analyses**

A series of two-way sensitivity analyses were performed to assess the combined effects between the influential variables within the model. Figure 3 shows the effect of varying disease prevalence in combination with other influential variables in the model; these results suggest that disease prevalence was the single most important variable that determines the overall cost-effectiveness of screening renal cancer in recipients of kidney transplants. For example, even with the 100% test specificity, screening for renal cancer was not cost-effective unless the relative disease prevalence was at least 2.5 times greater than the expected age-specific disease prevalence of renal cancer in the transplant population.

**Screening in the high-risk population.** Table 5 summarizes the costs and benefits of annual and biennial screening for renal cancer using ultrasonography in the high-risk kidney transplant population. For example, among people with a family history of renal cancer, biennial screening saves ~5.7 days of life compared with no screening, with the overall ICER of <$70 000/lys.

**Scenario analysis**

Scenario analysis was conducted to assess the health outcomes if routine screening was not continued after graft failure and return to dialysis. The total costs of annual and biennial screening were $302 700 and $302 400. The total benefits (in life-years saved) were 13.6474 and 13.6454 LYS. The incremental benefits of annual screening compared with no screening were 0.0035 LYS, and the incremental benefits of biennial screening compared with no screening were 0.0056 LYS. The incremental costs of annual screening compared with no screening were $700, and the incremental costs of biennial screening compared with no screening were $700. The ICER for annual screening compared with no screening was $178 571/ LYS, and the ICER for biennial screening compared with no screening was $200 000/LYS.

**Discussion**

Despite the increased risk of renal cancer and the improved life expectancy after transplantation relative to remaining on dialysis, routine screening (annual and biennial) using ultrasonography in this population does not appear good value for money using the current data. Annual and biennial screening for renal cancer achieved very small gains in life expectancy, with <1.5 days of life saved, and at relatively high costs. At best, compared with no screening, the absolute gain in survival is only two deaths from renal cancer avoided per 1000 recipients if screened annually for 62 years, and one death from renal cancer avoided per 1000 recipients if screened biennially over the same time frame, with ICERs of >$300 000/lys for annual screening and >$200 000/lys for biennial screening. If the screening interval was reduced from 2 to 1 year, there was an increase in the overall and marginal costs of screening. However, the health benefits achieved (total and incremental) through more frequent screening are trivial, with the marginal cost-effectiveness ratio of annual screening compared with biennial screening exceeding $800 000/lys.

Using decision-analytic modelling, we have provided the first step in formulating a decision about whether a programme of screening for renal cancer is effective and feasible in the kidney transplant population. In addition, we have also identified a list of important and influential factors that have the greatest impact on the cost-effectiveness ratio. In contrast to many well-established screening programmes, such as colorectal, breast and cervical cancer screening, the optimal screening strategies and the mortality benefits of routine screening for renal cancer have not yet been established in the general or transplant population. In particular, the screening test accuracy, the natural history of renal cancer, the extent of benefits of detecting small and incidental lesions, and the effectiveness of treatment using newer therapies such as the mTOR inhibitors and the tyrosine kinase inhibitors are all uncertain.

The accuracy of ultrasonography is an important determinant of screening efficiency, but is uncertain in recipients of kidney transplants. Not only is ultrasonography operator-dependent, but its performance also varies with the size and morphology of the patient, the kidneys and the tumour [33,34]. In the general population, observational
**A) Comparing annual screening with no screening**

- **Graft Failure**
- **Test specificity**
- **Costs of ultrasound**
- **Relative disease prevalence**

**B) Comparing biennial screening with no screening**

- **Graft failure**
- **Test specificity**
- **Costs of ultrasound**
- **Relative disease prevalence**

<table>
<thead>
<tr>
<th>Influential variables</th>
<th>Annual screening compared with no screening</th>
<th>Biennial screening compared with no screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of graft failure</td>
<td>0.031 (between 0.02 and 0.04)</td>
<td>0.058 (between 0.057 and 0.062)</td>
</tr>
<tr>
<td>Test specificity of ultrasound</td>
<td>0.90 (between 1.0 and 0.5)</td>
<td>0.90 (between 1.0 and 0.5)</td>
</tr>
<tr>
<td>Costs of ultrasound</td>
<td>$120 (between $60 and $200)</td>
<td>$120 (between $60 and $200)</td>
</tr>
<tr>
<td>Relative disease prevalence</td>
<td>1.0 (between 5.0 and 0.8)</td>
<td>1.0 (between 5.0 and 0.8)</td>
</tr>
</tbody>
</table>

*The black vertical lines represent the ICER of annual and biennial screening (compared with no screening) at base-case, $320,988/LYS for annual screening and $252,100/LYS for biennial screening.

**Fig. 2.** One-way sensitivity analyses assessing the influential variables in the model. The black vertical lines represent the ICER of annual and biennial screening (compared with no screening) at base-case, $320,988/LYS for annual screening and $252,100/LYS for biennial screening.
Fig. 3. Two-way sensitivity analysis between influential variables in the biennial screening model.

Table 5. Total and incremental costs and benefits of screening renal cell carcinoma in the high-risk kidney transplant population

<table>
<thead>
<tr>
<th>High-risk populations</th>
<th>Screening strategies</th>
<th>Total benefits (LYS)</th>
<th>Total costs ($)</th>
<th>Incremental benefits (LYS)</th>
<th>Incremental costs ($)</th>
<th>Incremental cost-effectiveness ratio (ICER) ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior history of renal cancer</td>
<td>No screening</td>
<td>13.57948</td>
<td>300 008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual</td>
<td>13.59719</td>
<td>301 568</td>
<td>0.01771</td>
<td>1560</td>
<td>88 085</td>
</tr>
<tr>
<td></td>
<td>Biennial</td>
<td>13.59518</td>
<td>301 018</td>
<td>0.01570</td>
<td>1010</td>
<td>64 331</td>
</tr>
<tr>
<td>Familial or hereditary disease such as tuberous sclerosis</td>
<td>No screening</td>
<td>13.59883</td>
<td>300 530</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual</td>
<td>13.61278</td>
<td>301 931</td>
<td>0.01395</td>
<td>1401</td>
<td>100 430</td>
</tr>
<tr>
<td></td>
<td>Biennial</td>
<td>13.61077</td>
<td>301 460</td>
<td>0.01197</td>
<td>930</td>
<td>77 694</td>
</tr>
<tr>
<td>History of analgesic nephropathy</td>
<td>No screening</td>
<td>13.58538</td>
<td>300 167</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual</td>
<td>13.60193</td>
<td>301 679</td>
<td>0.0165</td>
<td>1512</td>
<td>91 636</td>
</tr>
<tr>
<td></td>
<td>Biennial</td>
<td>13.59993</td>
<td>301 153</td>
<td>0.0145</td>
<td>986</td>
<td>68 000</td>
</tr>
<tr>
<td>Acquired cystic kidney disease</td>
<td>No screening</td>
<td>13.55289</td>
<td>299 291</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual</td>
<td>13.57571</td>
<td>301 069</td>
<td>0.02282</td>
<td>1778</td>
<td>77 914</td>
</tr>
<tr>
<td></td>
<td>Biennial</td>
<td>13.57368</td>
<td>300 411</td>
<td>0.02079</td>
<td>1120</td>
<td>53 872</td>
</tr>
</tbody>
</table>

All screening strategies (annual or biennial) were compared with no screening.
studies have reported lower test sensitivity and specificity among smaller tumours (lesions <3 cm) even with modern techniques of harmonic imaging and ultrasound contrast [47,48]. The difficulties associated with ultrasonographic screening in people with CKD include the effect of multi-cystic diseases and small scarred native kidneys on the overall test accuracy and poor reliability in differentiating small hyperechoic renal cancers from lesions such as adenomas and angiomyolipomas. Information and evidence to address these issues are lacking. The detection of an equivocal solid lesion is followed by a reference standard such as the contrast-enhanced computer tomography. Unnecessary use of the intravenous contrast-enhanced imaging can lead to unwanted complications of contrast-induced nephropathy and increased risk of graft failure, particularly among those with reduced renal function (eGFR <30 mL/min) [35], and is one of the major influential factors on the overall cost-effectiveness ratio in our model.

In general, malignant lesions are more aggressive in people with kidney transplants compared with cancers in the general population. The extent of the aggressiveness is dependent upon the immunosuppressive state of the recipients. Previous studies have reported substantial variability in the natural growth rates of small and incidentally detected renal cancers in the general population, varying between 0.08 and 17.34 cm³ annually, and are dependent upon the histological grading of the tumour [36]. The impact of long-term immunosuppression upon the growth rates of these small tumours is uncertain and will be difficult to measure because recipients are likely to be treated surgically, regardless of their tumour size, immediately after diagnosis. In the absence of data from recipients of kidney transplants, we assumed that the rates of cancer growth are comparable with that in the general population. The benefits and cost-effectiveness of routine screening may be more favourable if we had confirmed accurate data of the expected increased rates of cancer development (due to the effect of long-term immunosuppression use) in the transplant population.

As expected, disease prevalence is the most influential determinant on cost-effectiveness in this setting. The greater the disease burden within the target population, the greater the number of diseased individuals who may benefit from the early detection and effective treatment of the disease share the costs of screening. Even though our results may not support a policy of population screening for renal cancer among the average-risk kidney transplant recipients, routine biennial screening may be a good use of our healthcare dollars if we target screening among the higher-risk population, such as those with a history of acquired cystic disease, a family history of renal cancer or a familial syndrome of kidney cancer such as von Hippel–Lindau syndrome. The findings from our analyses had shown that if the relative prevalence of disease is four times greater than the expected (adjusted for age and gender), the ICER for biennial screening improves from a baseline of >$200 000/LYS to <$100 000/LYS.

The impact of shortened life expectancy on the overall benefits of population cancer screening in people with CKD, in particular among those on dialysis, is a concern for some clinicians and decision makers because the average expected survival for some on dialysis (or with end-stage kidney disease) is shorter than the time lived to develop cancer [31,32]. The impact of life expectancy on the benefits, costs and harms of screening renal cancer among those on dialysis has been assessed extensively in our scenario analyses. Findings from our model suggest that limiting routine screening to those with longer life expectancy will improve the overall cost-effectiveness ratio of screening, but the incremental gains are small, saving less than half a day of life in the entire screening period.

There are a number of other potential limitations in the study. First, the estimates of survival benefits and probabilities of a favourable stage shift from routine screening were extrapolated from prospective and retrospective observational studies in the transplant and non-transplant populations, and are subjected to potential selection, measurement and analytical bias. For some, a carefully designed and well-conducted randomized controlled trial of screening for renal cancer may seem unreasonable and impractical, but the decision to implement a population-based screening programme on asymptomatic individual relies on convincing evidence of screening benefits and treatment effectiveness. Well-conducted primary studies on the benefits/harms of early detection and treatment effectiveness of renal cancer in the transplant population should undoubtedly be future research priorities. Prospective studies assessing the screening test accuracy of ultrasonographic screening and the treatment benefits of renal cancer in all transplant recipients may not be feasible, but a study that limits to the high-risk population such as those with a family history of renal cancer and with underlying acquired cystic disease is potentially achievable. Second, we have not taken into account the implication and potential harms and costs of over-detection and inconsequential disease in our model. Screening can sometimes lead to the detection of inconsequential disease, a disease state that is detected by screening that would not contribute to poor outcomes if it remained undetected. Early detection of disease that would not eventually present clinically in individuals can lead to harms for the individual (and potentially unnecessary costs) because it would lead to treatment, often invasive, and of no significant clinical benefits. Third, we have only considered screening in the native kidneys and not in the transplanted kidneys. Approximately 10–13% of renal cancers in the kidney transplant population occur in the renal graft [31]. The test accuracy of the ultrasonography and the overall cost-effectiveness of screening may be different if we had included cancers in the transplanted kidneys. Given the paucity of data of benefits and harms of screening renal cancer in the transplant population, a deterministic rather than a probabilistic model was used to handle the uncertainties within the model’s parameter estimates. A probabilistic model has the advantage of estimating the joint effects of all the parameter’s uncertainties over a designated time frame, and allowing the estimation of uncertainties surrounding the mean cost-effectiveness ratios. Finally, outcomes are measures in life-years saved rather than adjusted life-years, which may better estimate...
the overall survival and quality of life of people with cancer and kidney disease.

Conclusions

In summary, screening for renal cancer in the kidney transplant population may not provide valuable benefits to patients, but targeted screening among those with underlying risk factors may be a better use of the limited healthcare resource. Using decision-analytic modelling, we have integrated the best available evidence to inform policy makers and clinicians about the effectiveness and uncertainties of routine screening for renal cancer in transplant recipients. Better information about the screening test characteristics of ultrasonography for renal cancers, and the clinical health outcomes and benefits after the implementation of routine screening are needed before it can be routinely recommended in recipients of kidney transplants.

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Appendix 1

Structure of the model

The model compared the health outcomes, in life-years saved (LYS), and healthcare costs, of no screening, annual screening and biennial screening in a hypothetical cohort of transplant recipients \((n = 1000)\) aged 18–69 years. Similar to other established population screening programmes [1], an upper age limit was set at 70 years because of the expected diminishing marginal benefits from screening older populations [2]. Individuals’ progression through the model was based upon age-specific transition probabilities (annual and biennial) through mutually exclusive health states of renal cancer over time. The age range included in the model was chosen to reflect the actual age range of recipients of kidney transplants in Australia and New Zealand [3]. The entire lifetime of the cohort of transplant recipients was modelled, whereby each individual was at risk of allograft graft failure and subsequently returned to dialysis at the end of each cycle (annual and biennial). The model assumed the population cohort was transplanted once only: all recipients with failed first transplant were managed subsequently on dialysis until death.

The model was constructed with three arms to assess the relative costs and benefits of annual or biennial screening compared with no screening. Those who actually participated in routine screening could test positive or negative on ultrasonography for renal cancer, based on the prevalence of renal cancer and diagnostic characteristics of the ultrasonography test. A positive screen was defined as the presence of complex cystic (defined according to the Bosniak classification) or typical solid lesions on the native kidneys [4]. Transplant recipients with cancer who did not participate in screening could have their disease diagnosed clinically, or remain undiagnosed. All recipients with positive screening on ultrasound or on clinical suspicion of cancer were investigated further using contrast-enhanced computer tomography (CT) scans.

Transplant recipients diagnosed with renal cancer in their native kidneys were defined to have been treated based on the staging of the initial diagnosis. Recipients with early stage cancer were treated with curative surgical intervention (open or laparoscopic total nephrectomy). Recipients with aggressive disease associated with local lymph node extension and systemic metastases received cytokine therapy such as interferon-alpha-2a or newer oral tyrosine kinase inhibitors (sorafenib and sunitinib), and maintained on combination immunosuppressive therapy including mammalian target of rapamycin (mTOR) inhibitors (such as everolimus and sirolimus) and steroid therapy. Individuals with poor prognostic features did not receive any curative treatment, but instead received palliative chemotherapy and supportive therapy for symptomatic and pain control.

Recipients with early-stage disease who received treatment for their cancer could survive with cure, relapse after treatment, die from renal cancer or die from other causes. Recipients who had recurrent disease diagnosed had a chance of developing metastatic disease or could respond to treatment. Individuals with metastatic disease could survive that year with cancer, die from renal cancer or die from other causes. The standard maintenance immunosuppression for transplant recipients was changed from calcineurin inhibitor-based therapy to mTOR inhibitor-based immunosuppressive regimen after the diagnosis and/or treatment of renal cancer. Recipients in the annual screening arm with no cancer who remained alive at the end of 1 year cycled back to the annual screening decision node.

The biennial screening arm was similar to the annual screening arm but differed only in the cycle length (2 years instead of 1 year) and the transition probabilities (biennial probabilities rather than annual). In the annual screening arm, the cumulative benefits and costs were calculated after 62 annual cycles, and in the biennial screening arm, the cumulative benefits and costs were calculated after 31 biennial cycles, by which time all patients were deceased.

Input parameters for the model

Clinical data. A comprehensive literature search was conducted to obtain the age- and cancer-stage-dependent transition probabilities from relevant published literature in the transplant and non-transplant populations (Table 1). The included variables were age-specific participation rate, test sensitivity and specificity of US screening, stage-specific distribution of cancer in the screened (annual and biennial) and unscreened arms, probability of recurrence, and probability of complications from diagnostic investigations. The age-specific prevalence of renal cancer in transplant recipients and those who returned to dialysis after graft failure, the age- and stage-specific probability (annual and biennial) of survival and death from renal cancer,
and the age-specific mortality rates of death from other causes were sourced from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry 1995–2007. Given that screening for renal cancer is not routinely recommended for recipients of kidney transplant, we assumed that the rates of opportunistic screening among transplant recipients were minimal.

Cost data. Only direct healthcare costs were included in the analysis (Table 2). Unit costs of screening for renal cancer were obtained from the Australian Diagnosis Related Groups (AR-DRG) [5], the Medicare Benefits Schedule (MBS) [6], the Cancer Institute of NSW (CI NSW) [7] and the published data from trials of the intervention with mTOR and tyrosine kinase inhibitors for recipients with renal cancer [8–13]. The average Australian costs were then assigned to each of the disease health states, and all costs were subsequently updated to 2008 using the Medicare component of the Consumer Price Index (CPI) [14]. If the cost data for certain interventions and specified health states were unavailable in Australian dollars, costs from other high income countries with similar healthcare systems such as Canada and the UK were extrapolated and converted to the 2008 Australian dollar using purchasing power parities.

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