Screening for acquired cystic kidney disease: A decision analytic perspective

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Screening for acquired cystic kidney disease: A decision analytic perspective. Acquired cystic kidney disease (ACKD) increases the risk of renal malignancy, and many authors suggest routine screening of dialysis patients for ACKD and renal tumors. However, they have defined neither the target population, the optimal screening strategy, the magnitude of its benefit, nor its risk. We used decision analysis to evaluate strategies of performing either computed tomography (CT) or ultrasound every three years on all dialysis patients and annually on patients found to have cysts. We compared these strategies to a strategy of seeking cysts and cancer only if these are clinically suspected. The baseline analysis shows that both CT and ultrasound may decrease cancer deaths by half for patients with a life expectancy of 25 years. Screening for ACKD offers these patients as much as a 1.6 year gain in life expectancy. However, for the majority of patients beginning renal replacement therapy, age or comorbid disease substantially limits life expectancy. For such patients, the gain in life expectancy from an ACKD screening program is measured in days. Sensitivity analyses show that the benefit of screening depends on the rate of malignant transformation, which needs better definition. The gain in life expectancy does not appear to be large enough to justify an ACKD screening program for the entire ESRD population. However, for the youngest and healthiest patients, a screening program would be of benefit. The magnitude of this benefit is uncertain, because the analysis was consistently biased in favor of the screening strategies.

Acquired cystic kidney disease (ACKD) is a common, and worrisome, complication of end-stage renal disease (ESRD). Although most cysts remain silent, ACKD can cause flank pain, spontaneous hemorrhage and hematuria [1–3]. Its most feared consequence, however, is renal cancer [4–7]. Several authors have recommended CT or ultrasound surveillance of asymptomatic dialysis patients after three years of renal failure and every one to three years thereafter [4–6, 8–13]. However, neither the basis of these recommendations nor their potential consequences have been elaborated [14].

We used decision analysis to examine the consequences of CT or ultrasound screening for ACKD and cancer. To represent the natural history of ACKD-related cancer, we constructed a tumor growth model. Using data on renal cell carcinoma, we estimated the relationship between tumor size, clinical stage and patient survival. For each strategy, we calculated the number of deaths

from ACKD-related cancer, the number of deaths from surgical treatment, and patient life expectancy. Our analysis shows that the benefit of screening for ACKD is much more limited than generally presumed.

Methods

Decision analysis explicates the logic of a choice among alternate strategies [15]. To analyze a decision, one defines possible strategies, describes plausible and important clinical events associated with each strategy, and specifies the probability of each event. One estimates the value of each possible state of health resulting from each strategy, and calculates the average expected value of pursuing each strategy. The axioms of decision analysis dictate that the strategy with the greatest expected value is preferred. We describe the structure of this analysis in general below. The **Appendix** presents the decision model, the tumor growth model, probabilities and calculations in detail.

The decision model

Figure 1 shows the decision model, which compares three strategies. The square decision node on the left in Figure 1A represents the choice among the strategies. Under the no screening strategy, no screening for ACKD is performed. However, patients who develop symptomatic cysts and/or cancer undergo CT imaging. Under the CT screening strategy, CT screening occurs after three years of dialysis. Patients found to have cysts undergo annual CT thereafter, and the entire population undergoes CT every three years. Screening tests may or may not correctly identify cysts and cancer. The ultrasound (US) screening strategy follows the same scheme, but substitutes ultrasound for CT.

After the initial choice among strategies, a Markov state transition model determines the prognosis by simulating recurrent chance events [16–20]. The use of Markov models is well established in the medical literature in general, and in particular in the study of renal disease and renal failure [21–26]. Patients' states of health are represented as states of the Markov process. They are shown as branches emanating from the Markov node, a rectangle with circles connected by an arrow. All three strategies lead to the same Markov states. However, under the no screening strategy, the upper six Markov states lead to the no screening subtree, represented by a diamond, while under CT screening and US screening, these upper six Markov states lead to the screening subtree. Subtrees are cascades of chance events, represented by
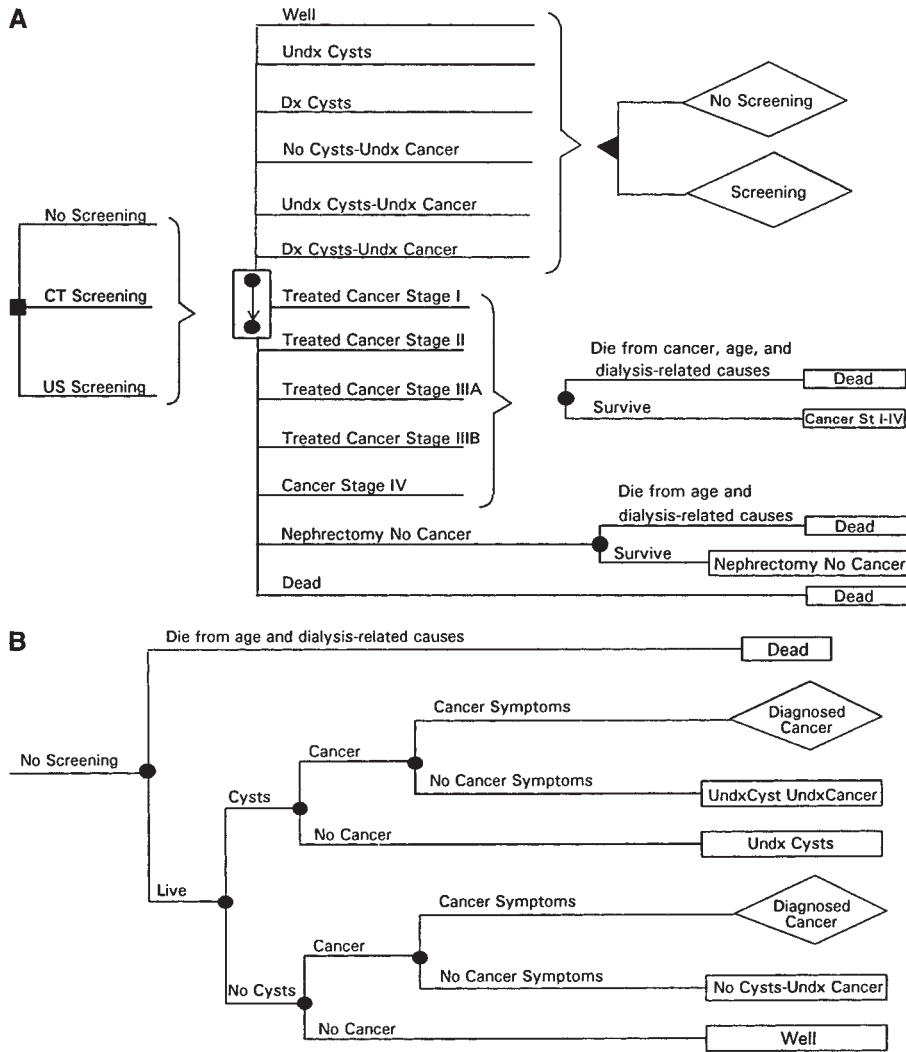
A

B

Fig. 1. A. *The choice among strategies and the Markov model.* **B**. The no screening subtree. **C**. The screening subtree. **D**. The diagnosed cancer subtree.

solid circular nodes, occurring within one cycle of the Markov process. Figure 1 B and C shows the no screening and screening subtrees, respectively. Each subtree contains the diagnosed cancer subtree, which is shown in Figure 1D. The next six states lead to chance nodes, denoted by solid circles. The terminal nodes, shown as rectangles, are states of health at the end of a single cycle of the Markov process.

For each of the three different strategies, each member of a cohort begins in a particular state of health and is followed over time. The passage of time is modelled as a series of cycles. In the baseline analysis, the cycles are one year long. During each cycle, each cohort member may remain in the same state of health or move to another. The process of moving from one state of health to another is represented by the subtrees and by subsequent chance nodes. The probability of moving to another state of health is derived from the literature and from expert opinion. The process continues until all members of the cohort have died. All members of the cohort who are alive in a given year contribute to the overall survival of the cohort. Thus, the simulation predicts the life expectancy of the cohort.

The **Appendix** gives a detailed account of the Markov state transitions. Briefly, all patients begin either in the well state or in the undiagnosed cysts state. During each annual Markov cycle,

patients may die, with deaths occurring at a rate determined by patient age on reaching ESRD. During each cycle, survivors may develop ACKD, cysts may undergo malignant transformation, patients free of ACKD may develop renal cancer, symptoms may make cancer clinically evident, and surgical treatment of localized cancer may result in death. Cancers which become clinically evident are evaluated and treated within the same cycle.

Patients who are thought to have Robson stage I–III cancer undergo bilateral radical nephrectomy. Patients who have stage IV cancer receive supportive treatment, but no specific therapy for the malignancy. Those surgical survivors who actually had cancer, and all stage IV patients, are assigned a cancer stage-specific excess mortality rate. A few patients who survive bilateral nephrectomy did not have cancer. Their screening tests were falsely positive for malignancy. They are henceforth protected against developing cysts and cancer.

The tumor growth model

To represent the natural history of renal cell cancer, we constructed a Gompertzian tumor growth model, an exponential process limited by a progressive decrease in the growth rate as tumor size increases [20, 72] (**Appendix**). Tumor doubling time allows calculation of cell count, cell count predicts tumor mass,
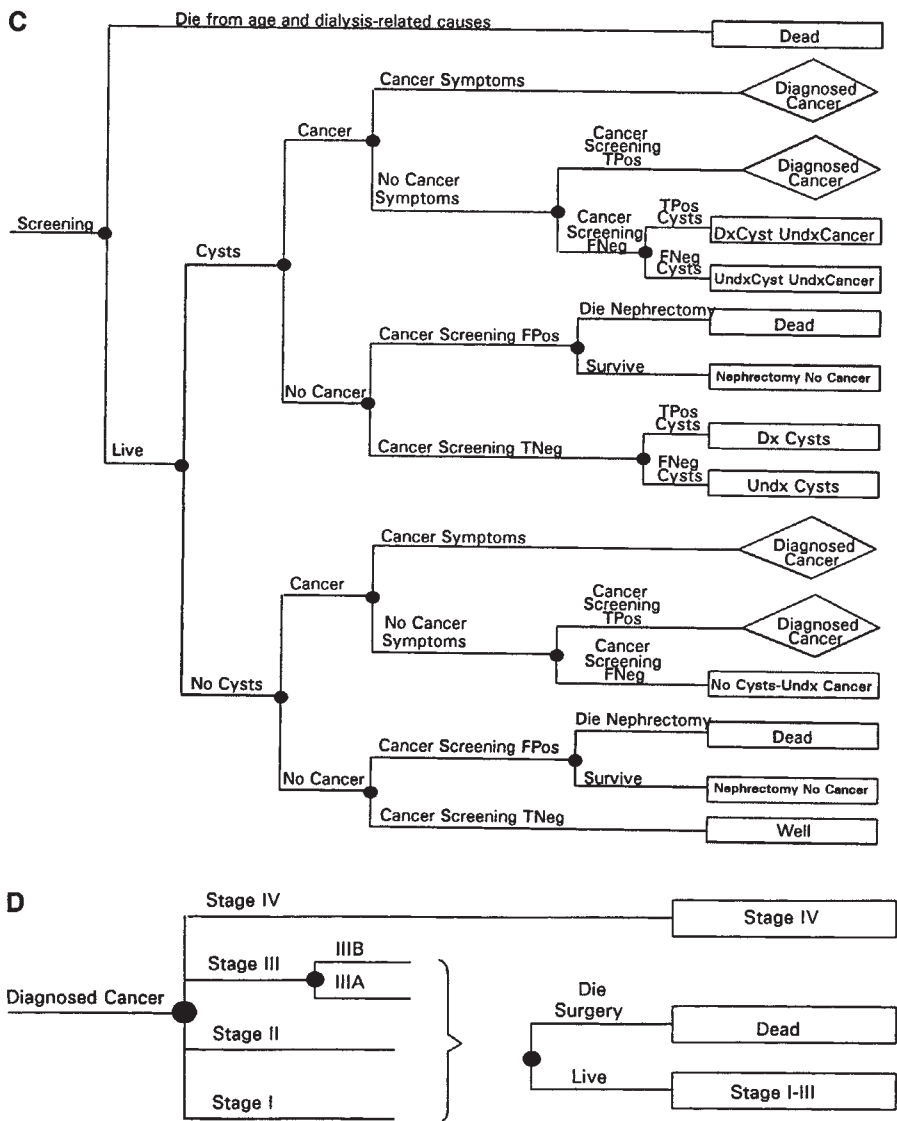
C

D

Fig. 1. *Continued.*

and tumor mass predicts tumor size at any point in time. Tumor size determines both staging and the probability that the tumor will be detected during any cycle of the model.

Utilities

This analysis considers outcomes from the patient's perspective. We measure the number of deaths from cancer and from surgery, and as years of survival. A patient's survival is the sum of the number of years lived in each different state. We do not apply quality adjustments to account for the short-term morbidity of procedures or the long-term morbidity associated with cysts or with cancer in various stages. Such adjustment could easily be incorporated into the model. However, the effect of ACKD or renal cell cancer on the quality of life in ESRD has not been characterized well enough to make such adjustments reliable. Nor does this analysis consider cost, although costs could be added for the purpose of computing cost-effectiveness from the payor's perspective.

Assumptions and sources of bias

The absence of published information required assumptions on several points, and assumptions can bias a decision model. To avoid overlooking a benefit of screening, we chose our assumptions so as to achieve a consistent bias in favor of the screening strategies. Our assumptions are as follows:

1. Renal cell cancers in dialysis patients, whether ACKD-related or not, behave like renal cell carcinomas in patients who are not uremic.

2. Renal cell cancer growth is an exponential process.

3. CT and US examinations have no complications. This assumption biases the analysis in favor of the screening strategies.

4. The specificity of CT and US in detecting cysts is 100%. This assumption biases the analysis in favor of the screening strategies.

5. Cysts develop at a constant rate and undergo malignant transformation at a constant rate.

6. Neither cysts nor cancers are discovered incidentally in the investigation of symptoms unrelated to cancer. Since the opportunity for incidental diagnosis under the no screening strategy

Table 1. Rates and probabilities for baseline and sensitivity analyses

Variable	Baseline value	Literature range
	%	
ACKD development		
Prevalence at ESRD	13	15–70
Annual incidence after ESRD	7	
Annual cancer incidence		
in presence of ACKD	0.9	0.5–7
in absence of ACKD	0.2	
Annual renal cancer mortality rates		
Stage I	1	0.5–3
Stage II	4.5	4–10
Stage III A	10	9–27
Stage III B	28	25–35
Stage IV	50	35–60
Probability of perioperative	2	0.5–6
mortality		
Test characteristics		
Sensitivity		
renal mass < 3 cm in diameter		
CT	94	80–100
ultrasound	80	50–100
renal mass > 3 cm in diameter		
CT	100	80–100
ultrasound	100	80–100
renal cysts		
CT	100	50–100
ultrasound	60	30–100
Specificity		
renal masses, all sizes		
CT	100	90–100
ultrasound	100	90–100
cysts		
CT	100	90–100
ultrasound	100	90–100

Fig. 2. *Life expectancy of ESRD patients as reported by the USRDS in 1993.*

would diminish the benefit of screening, this assumption biases the analysis in favor of the screening strategies.
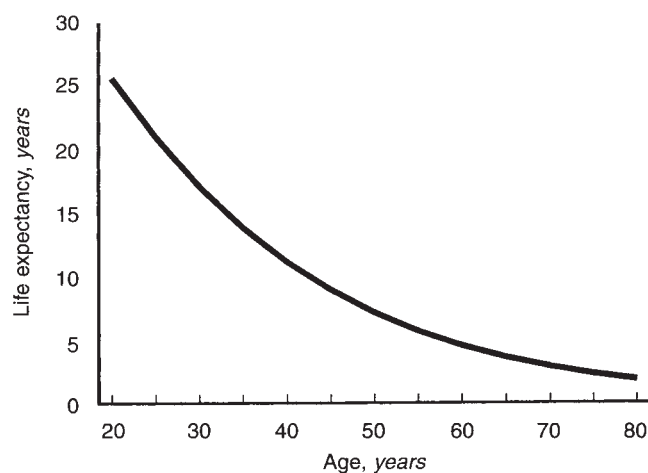
7. The probability that a renal cancer is in any given clinical stage is a linear function of the size of the tumor at that time. The mean diameter of tumors less than 5 cm in diameter at diagnosis is 2.5 cm, and the mean diameter of tumors greater than 5 cm in diameter is 10 cm. The **Appendix** shows how these assumptions allow estimation of stage distribution from data published on tumor size and stage at diagnosis.

8. Bilateral nephrectomy mortality is low and constant across different dialysis populations and across different age groups. This assumption biases the analysis in favor of the screening strategies.

Summary of the data employed

Probabilities and rates used in the baseline analysis. Table 1 and Figure 2 show the probabilities and rates used in the baseline analysis. The Appendix explains these values.

Epidemiology of ACKD. ACKD is a bilateral condition, reported in nearly every disease causing progressive renal insufficiency, and found equally in patients treated by hemodialysis and by peritoneal dialysis [4–9]. The disease can antedate the institution of renal replacement therapy, and ACKD and ACKD-related tumors can occur after transplantation [27]. Blacks appear to be more commonly affected than Caucasians. Age at renal failure does not appear to predispose to ACKD. Although one study found that male sex predisposed to ACKD [86], other authors

found no difference between the sexes [4]. Cyclosporine has been reported to accelerate the development of cysts in the native kidneys of the recipients of cardiac as well as of renal allografts [28, 29].

Estimates of the prevalence of ACKD in the dialysis population range between 35% and 95%. A linear regression which we performed on prevalence data in a review including 800 dialysis patients [4] suggests that 13% of patients have ACKD when they start dialysis. The probability that cysts are present increases by 7% every year; the regression has an r^2 of 0.78.

Incidence of renal cancer in ACKD. In various studies, the cumulative incidence of malignant transformation in ACKD ranges from less than 1% to 7% [4–9, 30–34]. In our baseline analysis, we used the midpoint of a recent textbook estimate of the cumulative incidence of renal carcinoma among ACKD: 3 to 6% of patients with ACKD will develop cancer after a mean time on dialysis of five years [35]. This implies an incidence of 0.9 cancers per hundred patient-years.

Incidence of renal cancer in dialysis patients free of ACKD. Dialysis patients free of ACKD are also at substantial risk of developing renal carcinoma [36]. However, few of the studies describing this relationship provide sufficient information to calculate the rate at which the cancers appear. Glicklich et al have summarized 22 radiologic studies which specified the mean time since ESRD [31]. Among 647 chronic dialysis patients, renal neoplasms were found in four (0.6%). The mean follow-up was 3.4 years; we calculate the renal cancer incidence to have been 0.2 cancers per hundred patient-years.

Renal cancer: Clinical staging and mortality. Cancer classification and survival data are taken from a non-uremic population with clear cell renal carcinoma, because this histology predominates among ACKD-related cancers [37]. We used the classification introduced by Robson et al and modified by Flocks and Kadesky, which determines four clinical stages with different prognoses [38].

Risks of nephrectomy. Published operative mortality rates for patients who undergo radical nephrectomy for renal cancer without metastasis range from 0.5 to 6% [39–42]. However, mortality may reach 10% among patients with metastatic disease [43]. A recent review found the mean mortality in series of ESRD

patients undergoing general surgery to be 3.9% [44]. In our baseline analysis, we used a perioperative mortality of 2%.

Imaging procedures. CT is considered more sensitive than ultrasound in the diagnosis of ACKD, but both techniques appear to be very accurate [45–49]. We found reports neither of CT or US specificity in the diagnosis of cysts, nor of the sensitivity or the specificity of either test in the diagnosis of renal cancer in the presence of ACKD. We used information about healthy kidneys to estimate test sensitivity for renal cancer. In our initial analysis, we assumed that tests for cysts and renal cancer have perfect specificity [50–52].

End-stage renal disease-related mortality. We used information from the United States Renal Data System (USRDS) to estimate average excess mortality in ESRD [53, 84]. The Appendix describes these calculations in detail. Age at ESRD and the cause of ESRD significantly affect mortality rates among chronic dialysis patients [54, 55]. Figure 2 shows the average life expectancy of patients aged 20 to 80 who have survived the first 90 days of renal replacement therapy. For a 20-year-old patient beginning treatment for end-stage renal disease, average life expectancy is 25 years, while it is only five years for a 58-year-old patient, and 1.8 years for an 80-year-old [53]. We express our results as the benefit of a screening program for incident ESRD patients at these three ages. The median age of incident ESRD patients in the United States between 1988 and 1991 was 62 years [56]. Therefore, the five-year life expectancy of the hypothetical 58-year-old patient exceeds the life expectancy of more than half the incident ESRD population.

Results

Baseline analyses

The three panels of Figure 3 show results of the baseline analyses for the entire range of life expectancies shown in Figure 2. For each strategy, Figure 3A shows the number of cancer deaths in a hypothetical cohort of 10,000 patients, and Figure 3B shows the number of nephrectomy deaths. Figure 3C shows the gain in life expectancy if CT screening or US screening is used rather than no screening.

For example, Figure 3A shows that in a hypothetical cohort of 10,000 20-year-old patients, with a life expectancy of 25 years, treated according to the no screening strategy, 1337 will die of cancer. CT screening decreases cancer deaths to 705. Using US screening decreases cancer deaths to 785. However, Figure 3B shows that the decrease in cancer deaths occurs at the cost of an increase in surgical deaths, from 2 with no screening to 30 with US screening and 33 with CT screening. The 2 surgical deaths with no screening occur in patients whose cancers are discovered because of symptoms.

Figure 3 A and B also shows that among 10,000 58-year-old patients, with a life expectancy of five years, CT screening would be associated with 41 deaths from cancer and 4 surgical deaths. Using US screening would be associated with 52 deaths from cancer and 3 surgical deaths, and no screening would be associated with 82 deaths from cancer and less than 1 surgical death.

Figure 3C shows how the screening strategies change life expectancy. For 20-year-old patients with a life expectancy of 25 years, both CT screening and US screening increase life expectancy by about 1.6 years compared to no screening, a prolongation of approximately 6%. For 58-year-old patients with a life expect-
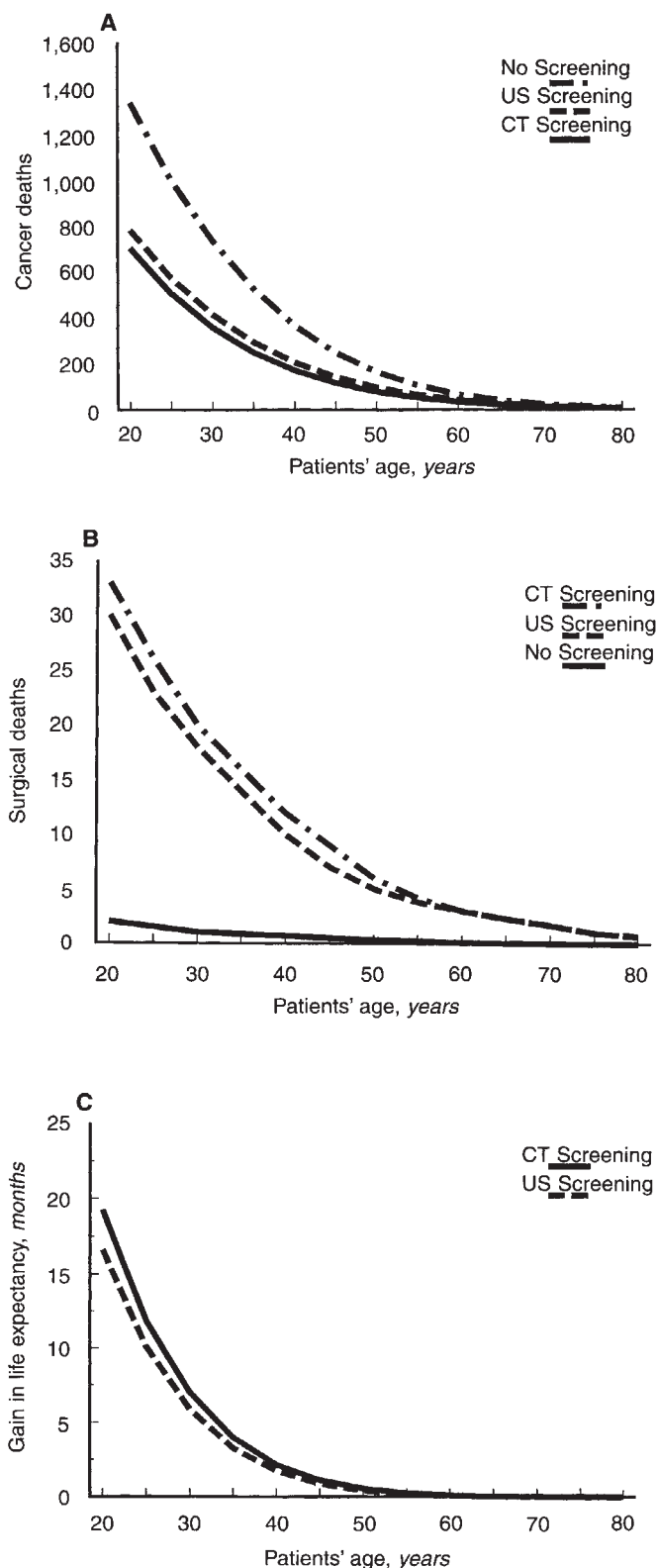

Fig. 3. A. *Number of cancer deaths predicted for the three strategies as a function of age in a cohort of 10,000 patients.* **B.** Number of surgical deaths predicted for the three strategies as a function of age in a cohort of 10,000 patients. **C.** Gain in life expectancy (in months) from either screening strategy, compared to no screening, as a function of age (in years).

ancy of five years, CT and US screenings prolong average life expectancy by 4 or 5 days, an 0.3% prolongation.

If all deaths could be expected to occur at the same time, tabulation of deaths would be a reasonable measure by which to compare strategies. However, surgical deaths occur early and cancer deaths occur late. By contrast, life expectancy offers a common denominator which allows a weighted combination of the impact of early and late deaths, whether caused by tumor, surgery or other medical problems. It is a more comprehensive measure by which to compare strategies, and the standard metric in studies exploring cancer screening strategies [57–61]. We base subsequent sensitivity analysis and our conclusions on life expectancy.

Sensitivity analysis

In sensitivity analysis (Fig. 4), we vary the value of parameters over a wide range to determine (1) changes in life expectancy associated with each strategy and (2) whether the ranking of strategies changes. Because the two screening strategies have similar outcomes, we display comparisons of no screening and CT screening only. The last three sensitivity analyses described in the text are not shown in Figures. These are analyses on CT specificity, frequency of screening, and renal cell carcinoma doubling time.

Annual rate of cyst development. Figure 4A shows the gain in life expectancy associated with CT screening for different age groups over a range of cyst development rates from half the baseline (3.5%) to more than double the baseline rate (15%). CT screening remains the preferred strategy for all age groups. The gain in life expectancy remains roughly the same for different cyst development rates. Even if the rate of cyst development were 15%, more than twice the baseline rate, and even if the higher rate is applied to 20-year-old patients with an underlying life expectancy of 25 years, the gain in life expectancy attributable to CT screening would increase only by about one month compared to the baseline calculations at a 7% cyst development rate, or by less than 0.5% of life expectancy.

Cancer incidence. Figure 4B shows the effect of varying the estimate of cancer incidence in ACKD. Screening is the preferred strategy for all rates examined. The younger the patients and the longer their life expectancy, the greater the sensitivity of the analysis to the cancer incidence estimate. If cancer incidence is 0.5% per year, lower than the baseline, the gain provided by CT screening ranges from less than 2 hours to 12 months, depending on life expectancy. If cancer incidence is higher (7% per year), the gain provided by CT screening may reach five years for the 20-year-old patients whose life expectancy is 25 years.

Nephrectomy mortality. In the baseline analysis, we used a single low value of 2% for perioperative mortality across different age groups. Since surgical mortality increases with age, this assumption biases the analysis in favor of the screening strategies. Figure 4C shows that the life expectancy gain is relatively insensitive to plausible changes in the estimate of nephrectomy mortality. Reducing the estimate of nephrectomy mortality to 1% has little effect.

Specificity of CT as a test for cancer. In our baseline analysis, we assume that neither CT or US is ever falsely positive; both are assigned a specificity of 100%. This assumption strongly biases the analysis in favor of screening. We examined the effect of a 10% false positive rate of CT as a test for cancer in the presence of

cysts. Under these circumstances, screening would actually shorten survival for those patients aged 64 and older, or almost half the incident ESRD population. False-positive CT scans would prompt incorrect cancer diagnoses, which would occasion unnecessary surgery, sometimes resulting in deaths. This loss of life would overwhelm the reduction in cancer mortality for those aged 64 years and older.

Frequency of screening. Increasing the frequency of screening should increase its benefit by revealing cancer at an earlier stage. We performed sensitivity analysis on the screening frequency. If dialysis patients undergo annual CT screening for cysts, and those found to have cysts undergo CT screening for cancer every six months, the gain provided by CT screening compared to no screening almost doubles for 20-year-old patients with a 25 year life expectancy, from 1.6 years or approximately 6% prolongation to 2.6 years or approximately 11% prolongation of life. For 58-year-old patients with a life expectancy of five years, the higher screening frequency has a negligible impact.

Renal cell carcinoma doubling time. Varying tumor doubling time from its baseline value (50 days) to lower (25 days) or higher values (75 days) changes survival slightly, but does not affect the ranking of strategies or substantially change the gains provided by screening.

Discussion

Regular screening for ACKD and ensuing malignancies among dialysis patients should reduce the number of deaths from renal cancer. This gain would be achieved at the cost of an increased number of surgical deaths. Our analysis shows the magnitude of those two effects, and how they jointly affect life expectancy. We have applied our model to patients beginning dialysis over a wide range of ages, with corresponding variability in life expectancies.

For twenty-year-old patients beginning dialysis, with an average life expectancy of twenty-five years, both CT and US screenings increase life expectancy by about 1.6 years compared to no screening, a prolongation of approximately 6%. By way of comparison, one analysis of coronary heart disease showed that cessation of tobacco use would be expected to lengthen a 35-year-old's life by 2.3 years [62]. Regular breast cancer screening may prolong the life of a 50-year-old woman by 2 months [61]. Strategies to screen for colorectal cancer have been estimated to prolong the survival of an asymptomatic 50-year-old man at average risk by 31 to 88 days [58]. Strategies to screen for cervical cancer have been estimated to prolong the survival of an asymptomatic average-risk woman by 94 to 99 days [57]. It is standard practice to recommend that patients stop using tobacco, and to screen for colorectal, cervical and breast cancers. When the screening tests are applied to the youngest adult ESRD patients, the benefit of the screening ACKD screening programs which we explored appears to be comparable to the benefit of these established interventions.

However, the results of this analysis would not support a policy of screening all dialysis patients for ACKD. The benefit of screening, as Figure 3C shows, depends critically on life expectancy. For 58-year-old patients, beginning dialysis treatment with a life expectancy of five years, CT screening and US screening prolong average life expectancy by 4 or 5 days, a 0.3% prolongation. For yet older patients, the absolute and relative gains are even smaller. It has not been established what absolute or relative gain should be considered an important gain in life expectancy
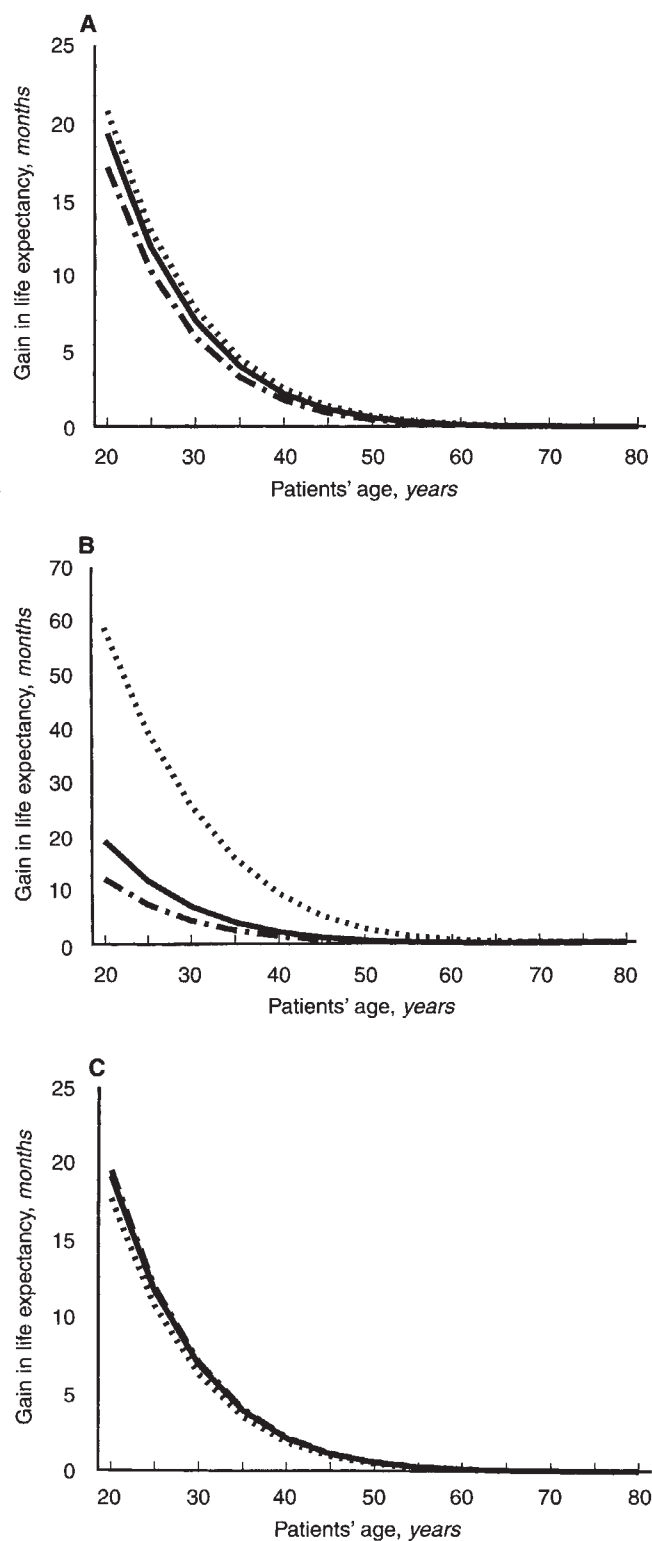
Fig. 4. A *Gain in life expectancy (in months) from CT screening compared to no screening as a function of age (in years);* effect of cyst development rates of 3.5% (– – –), 7% (—), and 15% (- - -). **B.** Gain in life expectancy (in months) from CT screening compared to no screening as a function of age (in years); effect cancer incidence of 0.5% (– - –), 0.9% (—) and 7% (- - -). **C.** Gain in life expectancy (in months) from CT screening compared to no screening as a function of age (in years); effect of surgical mortality rates of 1% (– – –), 2% (—) and 6% (- - -).

[60, 63]. However, we think it unlikely that most patients would consider a gain of a few days important. In this context, it is important to bear in mind our model's consistent analytic bias in favor of the screening strategies; the estimates of benefit calculated from this model represent upper bounds.

Since the median age of patients beginning dialysis in the United States is now 62 years [56], this analysis implies that for more than half of the incident ESRD population, screening of asymptomatic individuals for ACKD is unlikely to be of benefit. As in the general population, some individuals beginning dialysis treatment are much healthier than others of the same age, and can be expected to survive much longer. Important prognostic factors include the cause of renal failure, the burden of coexistent diseases [64–66], treatment-related variables [67–70], and perhaps general health and function [71]. It is obvious that not all 20-year-olds beginning dialysis have a life expectancy of 25 years. For some, burdened with diabetes, it is much shorter [54]. For others it must therefore be longer. Conversely, there must be some patients in their late 50's and 60's who are otherwise so healthy that their life expectancy is substantially longer than the mean, and they might derive benefit from screening. Finally, there are all the patients in the middle, those beginning dialysis treatment in their fourth, fifth and early sixth decades. Will these patients benefit from screening? What is their physiologic age? Development of instruments to predict survival from readily available clinical data will be essential in the application of this model to clinical practice.

Sensitivity analysis identifies the rate of cancer development as one factor which could have a major effect on the decision to screen young and otherwise healthy patients. At the baseline value for cancer development of 0.9% per year, CT screening lengthens the life expectancy of 20-year-olds by about 1.6 years, or about 6%. Figure 4B shows that if the rate of cancer development were 7% per year, an almost tenfold increase over our baseline estimate, a screening program would increase the life expectancy of such young and otherwise healthy patients by almost five years, about a 28% gain in life expectancy compared to no screening. Figure 4B also shows that even such a dramatic change in the cancer incidence estimate would not substantially change the benefit of screening to patients beginning dialysis after their mid fifties. However, it would materially increase the benefit to patients in their fourth and fifth decades. More accurate measurement of the rate at which cancer develops in ACKD is thus essential to decision making in the care of those ESRD patients who have the longest life expectancy.

This analysis also shows that for patients with the shortest life expectancy, the false positive rate of CT or US as a test for cancer in the presence of ACKD becomes important. There may be considerable disagreement over the desirability of a strategy which yields a very small gain in life expectancy. On the other hand, a strategy which slightly shortens survival is unlikely to be attractive. Using the baseline assumption of no false positive tests for cancer, screening prolonged survival, if only slightly, for all ages. However, if the false positive rate of CT as a test for cancer in the presence of ACKD were 10%, screening would shorten survival for patients aged 64 and older. We found no published data regarding the specificity of imaging procedures as tests for cancer in kidneys distorted by ACKD. However, a false positive rate of 10% in routine clinical practice would not be implausible in the context of published CT and US test characteristics for

other clinical entities [20]. Under those circumstances, screening would actually shorten the average survival of almost half of incident ESRD patients in the United States.

In summary, this analysis does not support a policy of routine screening of the entire ESRD population for acquired cystic kidney disease and renal malignancy. The two variables which are most important in the decision are overall life expectancy and cancer incidence. Improved methods for predicting life expectancy and more precise estimates of cancer incidence should allow better definition of subgroups likely to benefit from screening. Screening for acquired cystic kidney disease and cancer appears to offer substantial benefit only among those patients having the longest life expectancy. However, for most of the incident ESRD population, any benefit would be negligible.

Appendix

This appendix explains (1) the structure of the decision tree and Markov model, (2) the tumor growth model, and (3) data used in the analysis.

I. The decision tree and the Markov model

The thirteen states of health (Fig. 1A) used in the Markov model are described below: (1) well is the initial state for those dialysis patients who do not have ACKD, and the state to which those who have not suffered any adverse events return; (2) undx cysts is a state for dialysis patients with undiagnosed ACKD who do not have renal cell cancer; (3) dx cysts is the corresponding state for patients with diagnosed ACKD; (4) no cysts-undx cancer is a state for patients without ACKD who have developed undiagnosed cancer; (5) undx cysts-undx cancer is a state for dialysis patients with undiagnosed ACKD, and undiagnosed cancer. The undiagnosed cancer will increase in size from one time cycle (1 year) to another according to the tumor growth model. To represent 30 years of follow-up, we created 30 undx cysts-undx cancer states. During each of the 30 years, tumor size is different. (6) Dx cysts-undx cancer is the corresponding state for patients with diagnosed ACKD. Undiagnosed cancer increases in size as described above, and there are also 30 dx cysts-undx cancer states. (7) Treated cancer stage i, treated cancer stage ii, treated cancer stage iiia, and treated cancer stage iiib are states for dialysis patients with diagnosed and surgically treated renal cancer stage I to IIIB. (8) Cancer stage iv is the corresponding state for patients with diagnosed renal cancer stage IV. These patients receive supportive therapy only (see *Assumptions*). (9) Nephrectomy-no cancer is a state for dialysis patients in whom an incorrect diagnosis of renal cancer was made, and who have survived unnecessary nephrectomy. (10) Dead contains patients who have died from any cause.

Under all three strategies, 87% of patients enter the Markov model in the well state, and 13% enter in the undx cysts state. A logical expression denoted by a solid triangle determines whether the screening or no screening subtree in Figure 1A is followed.

In the no screening subtree (Fig. 1B), the first circular node represents the probability of death from age or dialysis-related causes. This probability recurs in each cycle over the entire simulation. Patients who die move to the dead state. In the same cycle, survivors may develop cysts or remain well. Patients may develop cancer whether or not they have ACKD. Patients with cancer may become symptomatic; the diagnosis of cancer is made, and patients enter the diagnosed cancer subtree. At the end of the
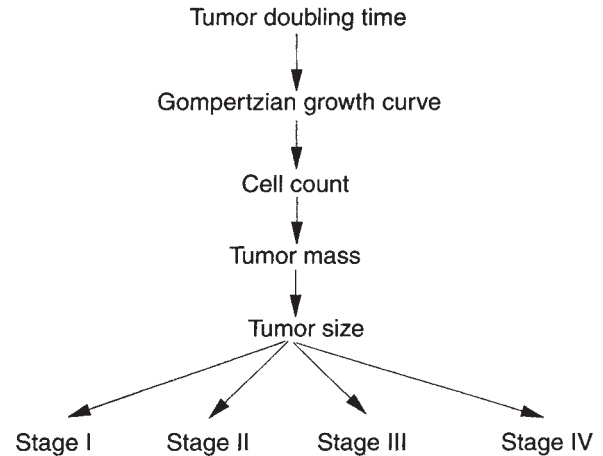
cycle, patients who have developed neither cysts nor cancer return to the well state. Patients without cysts who have developed asymptomatic cancer move or return to the no cysts - undx cancer state. Patients with cysts but without cancer move or return to the undx cysts state. Patients with cysts and undiagnosed cancer move or return to the undx cysts - undx cancer state.

In the screening subtree (Fig. 1C), all patients undergo regular screening by CT or ultrasound. As in the no screening subtree, they may die from age and dialysis-related causes, or may survive. Survivors may develop cysts. Whether or not they have ACKD, all patients may develop cancer. Symptomatic cancer will lead patients to the diagnosed cancer subtree as above. In the absence of cancer symptoms, classification of patients with cysts and cancer (cancer screening tpos and cancer screening fneg) depends upon the sensitivity of the imaging procedure. For patients with cysts but without cancer, classification (cancer screening fpos and cancer screening tneg) depends upon the specificity of the test. Patients falsely diagnosed as having cancer are subjected to the risk of surgical mortality. Survivors move to the nephrectomy-no cancer state. Patients correctly classified as free of cancer move into the dx cysts and undx cysts states depending on the sensitivity of the imaging procedure for cysts. We assume that no false positive diagnoses of cysts are made (see *Assumptions*).

In the diagnosed cancer subtree (Fig. 1D), patients are classified by tumor size as being in one of the states, stages i to iv (see *The tumor growth model and clinical staging*). Patients in stages i to iii have surgery (see *Assumptions*). If they survive surgery, or are in stage iv, they move to treated cancer stage i, treated cancer stage ii, treated cancer stage iii or cancer stage iv, where prognosis is determined by the clinical stage.

II. The tumor growth model and clinical staging

To simulate the natural history of renal cancer, we constructed a tumor growth model which applies Gompertzian kinetics to the tumor doubling time (Fig. 5) [72, 73]. Doubling times have been calculated for many tumors and range from more than 160 days for carcinoma of the esophagus to less than 15 days for embryonal carcinoma of the testis [73]. For clear cell carcinoma of the kidney, tumor doubling time has been estimated to be 50 days [74].

Tumor doubling time
↓
Gompertzian growth curve
↓
Cell count
↓
Tumor mass
↓
Tumor size

Stage I   Stage II   Stage III   Stage IV

Fig. 5. *The model of tumor growth on which clinical stage assignments at diagnosis are based.*

Table 2. Prevalence of clinical stages at diagnosis and size distribution for different clinical stages

Stage	I	II	III	IV
Prevalence of tumor stage at time of diagnosis %	25	15	29	31
Prevalence of tumors < 5 cm in diameter %	67	31	25	20
Prevalence of tumors > 5 cm in diameter %	33	69	75	80

Data are from [83].

The Gompertz equation for the number of tumor cells is of the form:

$$Cellcount(t) = e^{\left(\left(\log\left[\frac{V_m}{N_0}\right]\right)*[1 - e^{(\ rate*t)}]\right)}$$

where *Cellcount* is the number of cells at time t. This number is a function of the number of tumor cells when t approaches infinity, also called the plateau size (V_M), and a function of the number of tumor cells at time zero (N_0). V_M is a constant, set to 10^{12}, this number of cells representing a volume of 1,000 cm^3 and a mass of 1 kg. N_0 is calculated by setting *cellcount* to 10^{12} as t approaches infinity, yielding 2.34×10^{-16}. The rate is based on the threshold of clinical detectability and is calculated to be 6.67×10^{-7} for a tumor doubling time of 50 days [75].

We calculate the volume that corresponds to a given number of cells with the formula: *Volume = Cellcount × 10⁻⁹*, since 10^9 cells correspond to a volume of 1 cm^3. Tumor diameter in centimeters is calculated from the tumor volume through the formula for the volume of a sphere: *diameter = (6 x Volume/π)*$^{1/3}$. The model thus uses doubling time to predict tumor size at any calendar time. From size we predict clinical stage and hence prognosis.

Tumor size has been used to predict clinical staging in breast and lung cancer [76–78]. For renal cancer, a relationship between the size of the primary tumor and clinical stages has also been suggested. Bell found that tumors smaller than 3 cm in diameter have the lowest incidence of metastases (5%) [79]. Kay showed that patient survival is inversely related to tumor size [80]. Fuhrman et al confirmed the relationship between metastases and size: 48% of patients with tumors less than 5 cm had metastases, and 60% with tumors larger than 5 cm [81]. Recently, Hermanek et al published data on 872 cases of surgically treated renal cell carcinoma [82]. They found a significant relationship between tumor size and macroscopic venous invasion. Macroscopic venous invasion was not found in patients with tumors less than 2.5 cm in diameter, but was found in 9% of those with tumors between 2.5 cm and 5 cm, in 26% of those with tumors between 5 and 7.5 cm, in 46% of those with tumors between 7.5 cm and 10 cm, and in 64% of those with tumors greater than 10 cm. Tumor size and perinephric invasion also correlated.

Golimbu et al studied prognostic factors in a large cohort of patients with renal cell carcinoma [83]. He found that the proportion of tumors larger than 5 cm in diameter increased with the stage of the disease. Stage IV tumors were larger than 5 cm in 80% of cases, but 67% of stage I tumors were smaller than 5 cm in diameter. Table 2 shows the distribution of clinical stages at diagnosis and the size distribution for different clinical stages. Knowing the distribution of clinical stages at diagnosis from the same study, we used Bayesian revision to calculate the probability that a patient whose tumor is less than 5 cm in diameter is in each of the four different stages; we performed the same calculation for a patient whose tumor is greater than 5 cm in diameter [15]. We assumed that the mean size of tumors smaller than 5 cm was 2.5 cm, and that the mean size of tumors larger that 5 cm was 10 cm. We assumed that the probability that a tumor is in any given clinical stage is a linear function of size. Using linear regression, we could then predict the stage distribution for any tumor size. Figure 6 shows this distribution. For example, the model predicts that 68% of patients with a 2.5 cm tumor will have limited disease (stage I or II), and that 32% will have more extensive disease (stages III and IV).

III. Probabilities used in the baseline analysis

Mortality rates. ESRD mortality was calculated from the most recent data available from the USRDS [53]. Five year survival data from day 91 to 5 years + 90 days for patients aged 5 to 84 years at the time of ESRD were used to calculate age-specific mortality rates using the declining exponential approximation of life expectancy (the DEALE) [84]. The DEALE allows calculation of the average annual mortality rate as *−(ln S) ÷ t*, where *t* is time at which the survival *S* is measured. Linear regression on age of the logarithmic transformation of the mortality rates showed that

$$\mu = e^{((age * 0.05) - 4.3)}$$

where μ is the annual mortality rate (the inverse of the life expectancy) and *age* is the age at which the patient reached ESRD. This regression has an r^2 of 0.98.

Rate of cyst development. The correlation between the prevalence of cysts and the duration of ESRD has been confirmed in various series, both imaging and autopsy [3, 6, 11, 12, 45]. Matson reviewed the current prevalence of ACKD among 800 dialysis patients studied by CT or US [4]. The mean time since ESRD was 4.8 years. We performed a simple linear regression on Matson's data to calculate the annual increase in the prevalence of cysts to be 7%. Figure 7 shows this relationship. According to this model, one would predict that 13% of patients have cysts when dialysis therapy is begun.

Probability that cysts will be diagnosed. The probability that ACKD will be correctly diagnosed or excluded depends on the test used. In the normal kidney, contrast-enhanced CT with a thin section technique produces excellent resolution of renal contour and is sensitive enough to detect cysts as small as 0.3 to 0.5 cm in diameter [85]. In ACKD, although cysts are multiple and may attain sizes of 2.5 cm to 3 cm, most are less than 0.5 cm in maximal dimension. Moreover, in patients with end-stage renal disease, the kidneys are often fibrotic, inhomogeneous, and shrunken. However, these morphologic changes do not appear to affect CT accuracy in detecting cysts, which is reported to be 100% [86].

In contrast to CT, ultrasound has difficulty resolving cysts less than 1 cm in a small fibrotic kidney [87]. This difference is important, because most cysts in ACKD are 0.5 cm or less in size. In the one blinded prospective study which compared CT and US in renal imaging of long-term dialysis patients, ACKD was diagnosed in 59% of patients by CT. Among patients with ACKD by CT, US detected cysts in only ⅓ of individuals [88]. However, this is a small series, and no "gold standard" was used. In our baseline analysis, we used a sensitivity of 60% for US and 100% for CT. Specificity is assumed to be perfect for both procedures.
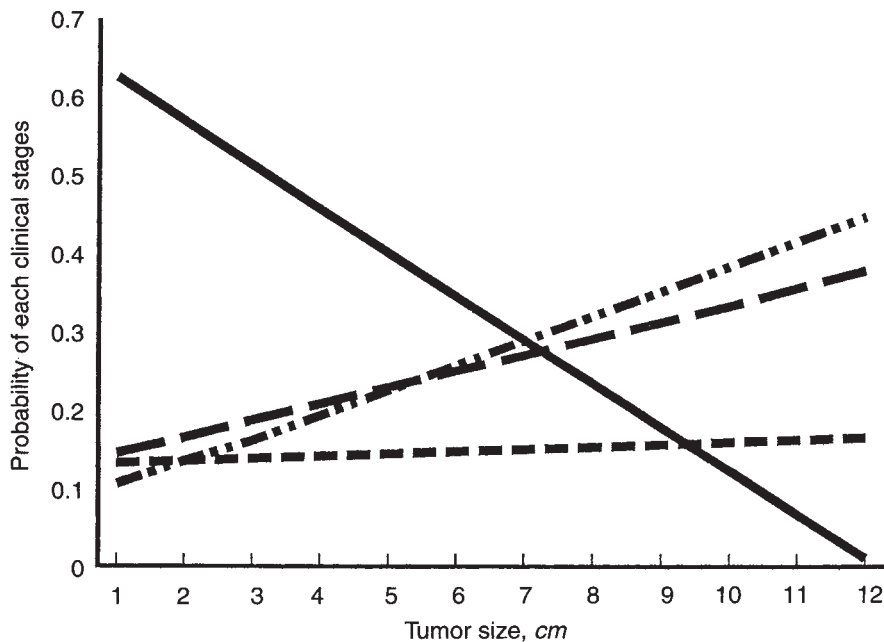
Fig. 6. *Linear regression on results of Bayesian revision to calculate stage distribution given tumor size.* Symbols are: (—) Stage I; (- - -) Stage II; (– –) Stage III; (– - -) Stage IV.
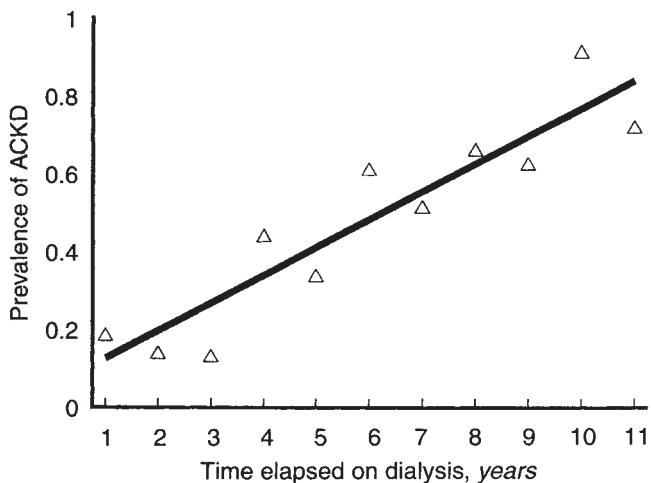

Fig. 7. *Linear regression of ACKD prevalence on time elapsed since ESRD, as reported by Matson [4].*

Probability that cancer will develop

Several authors have compiled series of dialysis patients in an attempt to estimate the incidence of ACKD and carcinoma [5, 32, 33]. Gehrig et al combined data from 9 autopsy studies of 330 patients with ACKD and a mean dialysis time of 3.7 years [6]. A total of 26 patients had some evidence of renal neoplasms. Adenocarcinoma, when defined as a tumor greater than 2 to 3 cm in diameter, was present in only four patients, with metastases in two. The 22 tumors accounting for the difference were small benign papillary adenomas. This study yields an estimated 0.3/100 patient-years incidence of adenocarcinoma in ACKD. MacDougall et al found three cases of autopsy-proven renal adenocarcinoma in their 185 chronic dialysis patients over a six year period, representing an incidence of 0.27/100 patient-years [34]. Matson

and Cohen found four well-documented cases of renal carcinoma in 289 patients with ACKD followed for a mean of 4.8 years. (4 is the sum of the numerators of their Fig. 1). This represents an incidence of 0.28/100 patient-years [4]. In our baseline analysis, we used an estimate of 0.9 cancers/100 patient-years derived from an expert's opinion [35]. It is higher than other reported estimates, and represents another bias in favor of screening.

Detection of renal cancer by screening. The probability that cancer will be diagnosed depends on tumor size, and on the sensitivity of the imaging procedure used. Tumor size depends on time (see the growth model above), and sensitivity depends on tumor size. Our model considered 1 cm to be the threshold of detectability, allowing no tumors smaller than that threshold to be detected by CT or US.

CT is more sensitive than US in detecting masses in a normal kidney. Recent studies found US to have 80% sensitivity and CT 94% sensitivity in detecting pathologically proved renal cell carcinoma 3 cm or less in size [50, 51, 52]. A blinded study compared US and CT in detecting renal masses in normal-sized functioning kidneys, and found that US identified 60% of CT-detected lesions between 1 and 2 cm, 82% of CT-detected lesions between 2 and 3 cm, and 85% of lesions 3 cm or more in diameter [52]. Thus, CT is very sensitive in detecting renal masses and has some margin of superiority over US. Unfortunately, no published data confirm this superiority in patients with ACKD. In our model, we assumed that above 3 cm, both CT and US have perfect sensitivity.

There are no published data on the specificity of CT and US in detecting renal cancer in a multicystic kidney. However, patients with ACKD present a special problem: retention cysts or hemorrhagic cysts can be similar to hyperdense masses on CT, and can make distinction from renal tumors impossible. We found no reports of CT or US false-positive rates for renal cancer diagnosis. In our baseline analysis, we assumed that CT and US are never falsely positive.

Detection of renal cancer without screening

We assumed that some patients with cancer will become symptomatic and be diagnosed during each time period. To calculate this probability, we used data from 872 symptomatic patients who had not been screened and who presented with renal cell carcinoma [82]. These data provide a probability distribution of the size of the renal cancer at the time of presentation: 1% had tumors < 2.5 cm, 16% had tumors 2.5–5.0 cm, 27% had tumors 5–7.5 cm, 25% had tumors 7.5–10 cm, and 29% had tumors > 10 cm in diameter. Our model, which keeps track of the tumor size (see the growth model above), applies these proportions to determine the number of patients in whom cancer becomes clinically apparent over time.

Mortality rates: Diagnosed renal malignancy. Matson reviewed reports of renal cancer in dialysis and transplant patients and performed a life table analysis [4]. Although these data are subject to selection bias, they provide some insight into the natural history of ACKD-related cancer. The 35% five-year survival rate is close to that for renal cancer in a non-uremic population, for which a recent estimate of five-year survival is 42% [89].

In a non-uremic population, the prognosis of renal cell carcinoma depends on the size of the primary tumor and on the presence or absence of venous and lymph node involvement and metastasis [90, 91]. We employed the modified Robson classification [38]. Using this classification, the five-year survival for renal cell carcinoma with surgical treatment ranges between 67% and 95% for Stage I, and between 51% and 77% for Stage II [42, 92, 93, 94, 95]. For patients with Stage III, the five-year survival ranges from 42% to 58% without lymph node involvement (Stage III-A) and between 18% and 24% if lymph nodes are invaded (Stage III-B) [42, 45, 92]. For patients with metastatic disease, five-year survival remains between 0% and 18% [26, 27, 61, 96].

In our baseline analysis, we used data from a recent series including more than 800 patients with renal cancer treated with total nephrectomy [82]. Compared to comparably aged patients without cancer, the relative five-year survival is 92% for stage I, 77% for stage II, 58% for stage III A, 24% for stage III B, and 8% for stage IV. The annual disease specific excess mortality rate was calculated using the declining exponential approximation of life expectancy [84].

Mortality rates: Undiagnosed renal malignancy. Our model allows for the circumstance that patients may die of undiagnosed cancer. Using the average clinical stage distribution of renal cancer at diagnosis, we calculated a weighted average to obtain the excess mortality rate for undiagnosed renal cancer.

Surgical mortality. Radical nephrectomy became the treatment of choice for renal cancer when reports were published showing that it improved the surgical cure rate and survival compared to simple nephrectomy. Published overall perioperative mortality for patients undergoing nephrectomy for renal cancer ranges from 2% to 10% [40–43]. This wide variation is explained by the inclusion of patients with localized disease and of patients with distant metastasis for whom early mortality is higher. We found no perioperative mortality data on dialysis patients undergoing nephrectomy for cancer. In our baseline analysis, the value for perioperative mortality is 2%, and this value remains constant for different age and population subgroups. This baseline value is probably an underestimate, since age, diabetes mellitus and associated coronary artery disease raise dialysis patients' surgical mortality [97, 98, 99, 100, 101, 102].

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