Survival outcomes for patients with surgically induced end-stage renal disease

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Abstract

Introduction: While medically induced end-stage renal disease (m-ESRD) has been well-studied, outcomes in patients with surgically induced ESRD (s-ESRD) are unknown. We sought to quantitatively compare the non-oncological outcomes for s-ESRD and m-ESRD in a large population-based cohort.
Methods: Medicare patients >65 years old initiating hemodialysis were identified using the U.S. Renal Data System database (2000–2012). Metastatic cancer, prior transplant history, and nephrectomy for polycystic kidney disease were exclusion criteria. Patients were classified as having s-ESRD or m-ESRD based on hospital and physician claims for nephrectomy within a year preceding the onset of maintenance hemodialysis. Outcomes included non-cancer mortality (NCM), overall survival (OS), cardiovascular event (CVE), and renal transplantation. Time-to-event analyses were performed using Kaplan-Meier and cumulative incidence curves, and multivariable Cox and Fine-and-Grey regression models.
Results: The cohort included 312 612 patients, of whom 1648 (0.53%) had s-ESRD. Compared to m-ESRD patients, s-ESRD patients had a significantly lower five-year cumulative incidence of NCM (68% vs. 80%; $p<0.001$) and CVE (62% vs. 68%; $p<0.001$), with a correspondingly higher probability of OS (22% vs. 17%; $p<0.001$) and rate of renal transplantation (3.6% vs.

2.0%; p<0.001). On multivariable analyses, s-ESRD remained associated with lower risks of NCM (p<0.001) and CVE (p<0.001), improved OS (p<0.001), and higher chance of renal transplantation (p<0.001).
Conclusions: While outcomes for s-ESRD appear more favorable than m-ESRD, s-ESRD is still associated with a substantial risk of NCM and CVE, and a low incidence of renal transplantation in Medicare patients >65 years old. These non-oncological outcomes are worth considering in patients potentially facing postoperative ESRD.

Introduction

Dialysis for end-stage renal disease (ESRD) is associated with significant morbidity and risk of mortality. Despite improvements over time, estimated 3-year survival on hemodialysis is 57%, a striking difference from the estimated 97% 3-year survival in age and sex-matched controls in the general population.[1] In order to avoid dialysis, nephron-sparing surgery is recommended for patients with bilateral renal tumors and for patients with a tumor in a solitary kidney.[2,3] Furthermore, there is an increasing drive to perform nephron-sparing surgery in all patients in order to maximize post-operative renal function. The benefit of renal preservation is realized beyond facilitation of uremic toxin clearance as reductions in in glomerular filtration rate (GFR) are associated with increased risk of hospitalization, cardiovascular events, and death.[4,5]

Interestingly, relatively recent data suggests that not all etiologies of chronic kidney disease (CKD) are the same. Conditions leading to intrinsic renal dysfunction either abruptly or over time are deemed medically-induced. In contrast, surgically-induced CKD appears to have a lower risk of progressive renal decline and mortality compared to patients with medically-induced CKD.[6,7]

Medically-induced ESRD (m-ESRD), representing that largest subset of the ESRD population, comprises the basis for reports on survival outcomes in dialysis studies.[8] Thus, survival outcomes of patients with surgically-induced ESRD (s-ESRD), and how these outcomes differ from patients with medically-induced ESRD, remain poorly characterized. There are several instances when surgeons need to balance adequate oncologic control against nephron-sparing. As such, we sought to characterize and quantitatively compare the non-oncologic outcomes for s-ESRD to m-ESRD in a large population-based cohort.

Methods

Design and participants

The United States Renal Data System (USRDS) is a national data system funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that collects data on patients with CKD and ESRD. The data originate from the Centers for Medicare and Medicaid Services (CMS), the Organ Procurement and Transplantation Network (OPTN), the Centers for Disease

Control and Prevention (CDC), the ESRD Networks, the USRDS Special Studies, and the U.S. Census. Data have been collected on both Medicare enrollees and other patients of all ages since 1995, when the Medical Evidence Report forms (CMS-2728) became mandatory for providers to complete for all ESRD patients.[9,10]

Using the USRDS, we completed a retrospective cohort study of patients 66 years of age or older who initiated maintenance hemodialysis, defined as at least 90 days, between 1/1/2000 and 12/31/2012. We included only patients who started with center hemodialysis and had Medicare as their primary coverage from the start of their dialysis. To allow uniform assessment of co-morbidities, we further restricted the cohort to those with Medicare coverage for the 12 months preceding the onset of hemodialysis. Patients with renal transplantation prior to the start of dialysis or a history of metastatic cancer were excluded. In the s-ESRD group, patients with a history of polycystic kidney disease were also excluded because we were unable to determine if ESRD preceded a nephrectomy that was done in preparation for renal transplantation (Supplementary Fig. 1).

Exposure, covariates, and outcomes

To classify patients as having s-ESRD, we adapted an externally validated claims-based algorithm for identifying patients who underwent renal cancer surgery.[11] S-ESRD patients had an inpatient claim for kidney cancer surgery identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD- 9-CM) procedure codes and an associated ICD-9 diagnosis code for a renal or upper tract urothelial neoplasm within 12 months before initiating chronic hemodialysis (Appendix). Patients not satisfying this definition were classified as having m-ESRD.

Baseline co-morbidities were identified using ICD-9-CM codes through the USRDS claims data for the 12 months preceding the initiation of chronic dialysis.

The primary outcome of interest was non-cancer mortality (NCM), using the date of death on the CMS-2728 form. Data on cause of death has been previously validated.[10,12] In the main analysis, patients with an unknown cause of death were counted as non-cancer deaths. A sensitivity analysis was performed excluding patients with an unknown cause of death in order to ensure this a-priori decision did not introduce bias.

Secondary outcomes were overall survival (OS), occurrence of a cardiovascular event (CVE; including acute myocardial infarction, cerebrovascular accident, sudden cardiac death, and peripheral vascular event; see Appendix), hospitalization (any cause), and receipt of a renal transplant. These outcomes were identified using USRDS medical claims data including ICD-9-CM procedures and Current Procedural Terminology (CPT). Hospitalizations were identified using inpatient claims data. Outcomes were assessed starting from 90 days after the initiation of hemodialysis to avoid the inclusion of patients requiring temporary hemodialysis. Patients were followed until death or censorship due to loss to follow-up or receipt of a renal transplant (except in the analysis where renal transplant was the outcome of interest).

Statistical analysis

Kaplan-Meier curves were used to plot the estimated survival function for up to 10 years of follow-up and multivariable Cox proportional hazards models were performed to compare OS between groups. Cumulative incidence curves and multivariable Fine-and-Grey competing risks models were used to compare the remainder of the outcomes between groups. Multivariable models were adjusted for age at first ESRD service (5-yr groups), gender, race, Charlson comorbidity index, and history of myocardial infarction, cerebrovascular disease, diabetes (type I and II), hypertension, and dyslipidemia. A conditional frailty model was used to assess recurrent hospitalizations, using random effects to model hospitalizations as multiple non-independent events for each patient. All assumptions for models were verified and multicollinearity was assessed (Variance Inflation Factor<10).

In order to test our a-priori decision to use a 12 months interval from surgery to dialysis for inclusion in the s-ESRD group, we performed a sensitivity analysis using a tighter time interval whereby we excluded those whose interval from surgery to dialysis was greater than 2 months.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and p-values <0.05 were considered statistically significant.

Results

The final cohort included 312,612 patients, of whom 1,648 (0.53%) had s-ESRD (Supplementary Fig. 1). Patient demographics and baseline co-morbidities are summarized in Table 1. Mean age for patients with s-ESRD and m-ESRD was 74.4 years (SD=5.7) and 75.9 years (SD=6.5), respectively, and median Charlson co-morbidity index was 8 (range:1-15) and 7 (range:0-17), respectively. Notably, patients in the m-ESRD group were more likely to have a history of myocardial infarction (26.2% vs. 22.5%), cerebrovascular disease (36.4% vs. 33.9%), and diabetes (71.0% vs. 57.1%), while patients with s-ESRD were more likely to have a history of kidney cancer (89.3% vs. 3.5%) or other cancer (33.1% vs. 16.2%)(Table 1). Median time from surgery to dialysis in the s-ESRD group was 18 days (IQR 4,151). The median follow-up among those alive at last follow-up was 2.8 years (IQR 1.5,4.8) and 2.3 years (IQR 1.2,4.0) in the s-ESRD and m-ESRD groups, respectively.

Survival outcomes

There were a total of 274,769 deaths recorded, of which 9,115 were cancer-related deaths and 210,090 were non-cancer deaths, while 54,745 patients had an unknown cause of death. OS at 1, 5, and 10 years from the initiation of maintenance dialysis was 79%, 22%, and 3%, respectively, in the s-ESRD group versus 74%, 17%, and 1%, respectively, in the m-ESRD group (Fig. 1a). In the multivariable Cox regression analysis (Table 2), s-ESRD was associated with improved OS (HR=0.76;95%CI 0.72-0.80;p<0.001) compared to m-ESRD, after adjusting for age, race,

Charlson co-morbidity index, and history of myocardial infarction, cerebrovascular disease, diabetes, hypertension, and dyslipidemia.

Meanwhile, the cumulative incidence of non-cancer mortality at 1, 5, and 10 years from the initiation of maintenance dialysis was 18%, 68%, and 86%, respectively, in the s-ESRD group and 25%, 80%, and 95%, respectively, in the m-ESRD group (Fig. 1b). At the same time, the cumulative incidences of cancer mortality at 1, 5, and 10 years were 3%, 10%, and 11%, respectively, in the s-ESRD group and 1%, 3%, and 3%, respectively, in the m-ESRD group **(Fig. 1b).** In the multivariable competing risks analyses (Table 2), s-ESRD versus m-ESRD was associated with a lower risk of non-cancer mortality (HR=0.62;95%CI 0.59-0.67;p<0.001). A sensitivity analysis excluding patients with an unknown cause of death did not meaningfully alter findings (data not shown).

Cardiovascular events

During follow-up, there were 209,984 patients who had a CVE. The cumulative incidence of having a CVE at 1, 5, and 10-years from the initiation of maintenance dialysis was 35%, 62%, and 66%, respectively, in the s-ESRD group, and 41%, 68%, and 71%, respectively, in the m-ESRD group (Fig. 2a). In the multivariable competing risks analyses (Table 2), s-ESRD versus m-ESRD remained associated with a lower risk of having a CVE (HR=0.85;95%CI 0.80-0.91;p<0.001).

Hospitalizations

During follow-up, 1521 patients in the s-ESRD group were hospitalized a median of 4 times (IQR 2,8) and 282,701 patients in the m-ESRD group were hospitalized a median of 4 times (IQR 2,7). The cumulative incidence of ever being hospitalized at 6 months, 1 year, and 5 years from the initiation of maintenance dialysis was 52%, 69%, and 93%, respectively, in the s-ESRD group, and 51%, 68%, and 92%, respectively, in the m-ESRD group (Fig. 2b). In the multivariable competing risks analyses (Table 2), there was no significant difference in the risk of ever being hospitalized between s-ESRD and m-ESRD (HR=0.99;95%CI 0.94-1.04;p=0.77). However, in the frailty model analysis allowing for recurrent events, s-ESRD was associated with a lower risk of hospitalizations during follow-up (HR=0.89; 95%CI 0.86-0.92;p<0.001).

Renal transplantation

During follow-up, 6,402 patients underwent renal transplantation. The cumulative incidence of renal transplantation at 5 and 10 years from the initiation of maintenance dialysis was 3.6% and 4.0%, respectively, in the s-ESRD group, and 2.0% and 2.1%, respectively in the m-ESRD group (Fig. 2c). In the multivariable competing risks analyses (Table 2), s-ESRD versus m-ESRD was associated with a greater chance of receiving a renal transplant (HR=1.63; 95%CI 1.26-2.10; p<0.001).

Sensitivity analysis

In the sensitivity analysis that only included patients in the s-ESRD if they initiated dialysis within 2 months of surgery, effect estimates from the multivariable models were not meaningfully different (Supplementary Table 1).

Discussion

S-ESRD is associated with longer OS, a lower risk of non-cancer mortality, a lower risk of CVE, a lower rate of recurring hospitalizations (although the risk of ever being hospitalized was not significantly different), and a greater chance of receiving a renal transplant when compared to m-ESRD. However, outcomes are still poor with s-ESRD, with a 78% probability of mortality, a 68% probability of non-cancer mortality that surpasses the cancer-mortality risk, and only a 4% probability of renal transplant at 5 years.

These data have important implications for patients with a renal tumor in a solitary functioning kidney and prognostication for individuals facing ESRD after surgical intervention. Assuming nephron sparing is not possible, realistic expectations should be set, including the low likelihood of transplantation. Of note, the low probability of transplantation is consistent with our institutional series where only 4/27 patients (15%) surgically rendered anephric were able to receive a renal transplant.[13]

Strengths of this study include its size, the population-based design, which enhances the generalizability of these findings, and the relative completeness of follow-up, with the majority of patients being followed until death.

While the adverse effects of diminished renal function were initially established in a population with largely medical etiologies of CKD,[4,5] it has been confirmed that nephrectomy-induced CKD is also associated with increased risk of subsequent cardiovascular morbidity and mortality,[14,15] as well as all-cause mortality.[14,16]

Notably, however, differences between surgical and medical CKD have been described.[6,7] Lane et al.[6] found a slower rate of GFR decline (0.7% vs. 4.7%) in the surgical CKD group versus medical CKD group. This makes intuitive sense given the one-time surgical insult versus the ongoing insult of the medical comorbidities on renal function.[17] Given that the most common cause of CKD and ESRD is diabetes, outcomes in medical CKD are likely worsened by the end-organ effects of this systemic disease.

Moreover, survival outcomes in patients with surgically-induced CKD more closely approximate those of patients without CKD rather than those with medical-surgical CKD.[6] Specifically, Lane et al.[6] reported that non-cancer mortality at 5 years was 6% in patients without CKD, 9% in patients with surgical CKD, and 20% in patients with medical-surgical CKD. These data are consistent with the European Organisation for Research and Treatment of Cancer (EORTC)-30904 randomized trial comparing survival outcomes between radical and partial nephrectomy.[18] Despite superior renal function outcomes after partial nephrectomy,[19] this did not translate into a survival benefit.

On the other hand, one study[20] suggests that it may in part depend on the new postoperative baseline eGFR that is achieved. Lane et al.[20] reported that a postoperative baseline eGFR less than 45ml/min/1.73m^2 was associated with a greater risk of progressive renal decline, perhaps due to hyperfiltration injury,[21,22] and all-cause mortality.

The data in the present study represent the extreme situation whereby postoperative ESRD is surgically induced. Consistent with this notion, we found poor survival outcomes in the s-ESRD group, albeit slightly superior to the m-ESRD group.

Similarly, outcomes differences exist within the m-ESRD populations. O'Shaughnessy et al.[23] recently showed variations in CVE rates between those with glomerulonephritis-induced and diabetes-ESRD. The risk of CVE was substantially higher for diabetes-ESRD (adjusted HR = 2.97, 95% CI 2.77–3.20) compared to IgA nephropathy. This difference may be due to the multi-system effects and duration of the underlying medical causes of ESRD in the m-ESRD group, particularly in diabetes.[24,25] However, in our study, the observed survival difference between s-ESRD and m-ESRD was preserved after adjusting for diabetes and other important clinical factors.

There are several limitations worth mentioning. First, in order to use a Medicare claims-based definition for s-ESRD, we were limited to analyzing patients >65 years old and it is unknown how our findings apply to younger patients. We considered using the cause of ESRD data provided on the CMS-2728 form in order to classify s-ESRD versus m-ESRD status, but this field did not demonstrate satisfactory validity when compared to the claims-based standard (data not shown). Second, we did not have data on the indication for nephrectomy or disease severity, although 89% of patients in the s-ESRD group had a kidney cancer diagnosis. Third, we were unable to differentiate the specific site of fatal cancer. Given the low rates of background cancer mortality in the m-ESRD group, it is likely that most cancer mortalities in the s-ESRD were related to kidney cancer or upper tract urothelial cancer. Fourth, we did not have access to a comparison group who underwent nephrectomy but did not develop ESRD. Finally, we did not have preoperative renal function data or data on whether patients had a solitary kidney. As such, we cannot rule out the presence of concurrent medical renal disease in the s-ESRD group. However, if present, this would bias the results towards the null by making the groups more similar, and therefore our estimates are likely on the conservative side.

Conclusions

Surgically-induced ESRD is associated with a more favorable OS, lower risks of non-cancer mortality, CVE, and hospitalizations, and a greater chance of receiving a renal transplant compared relatively to m-ESRD in Medicare patients >65 years old. However, the outcomes are still poor with s-ESRD, with the non-cancer mortality risk eclipsing the cancer-related mortality risk. These non-oncologic outcomes are worth considering in patients potentially facing s-ESRD.

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Figures and Tables

Fig. 1. Comparison of ***(A)*** overall survival; ***(B)*** non-cancer mortality, and cancer-related mortality between patients with surgically and medically-induced end-stage renal disease. m-ESRD: medically-induced end-stage renal disease; s-ESRD: surgically induced end-stage renal disease.

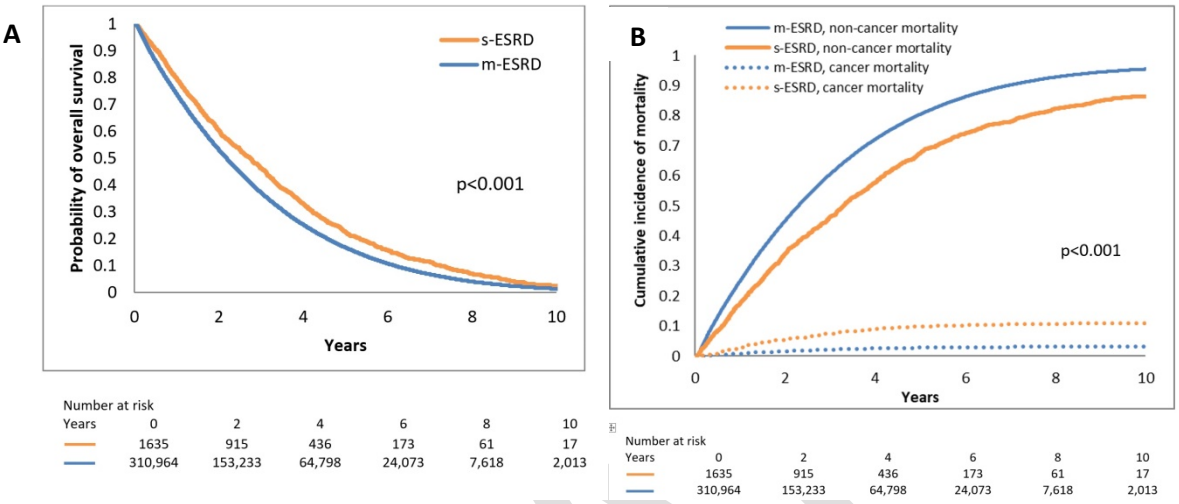


Fig. 2. Cumulative incidence of ***(A)*** cardiovascular events; ***(B)*** hospitalization; and ***(C)*** renal transplantation. Counts <11 suppressed as per USRDS policy. m-ESRD: medically-induced end-stage renal disease; s-ESRD: surgically induced end-stage renal disease.

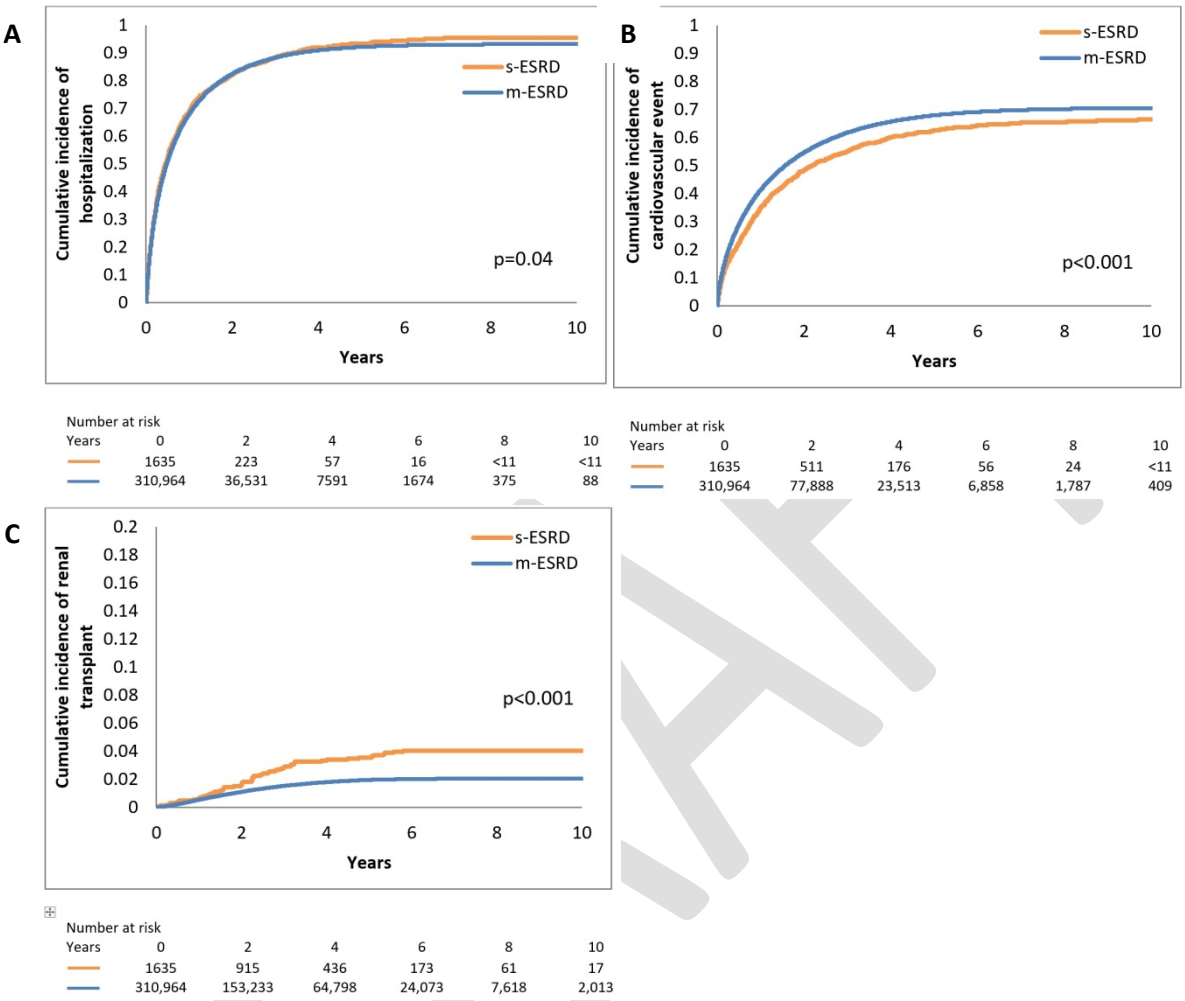


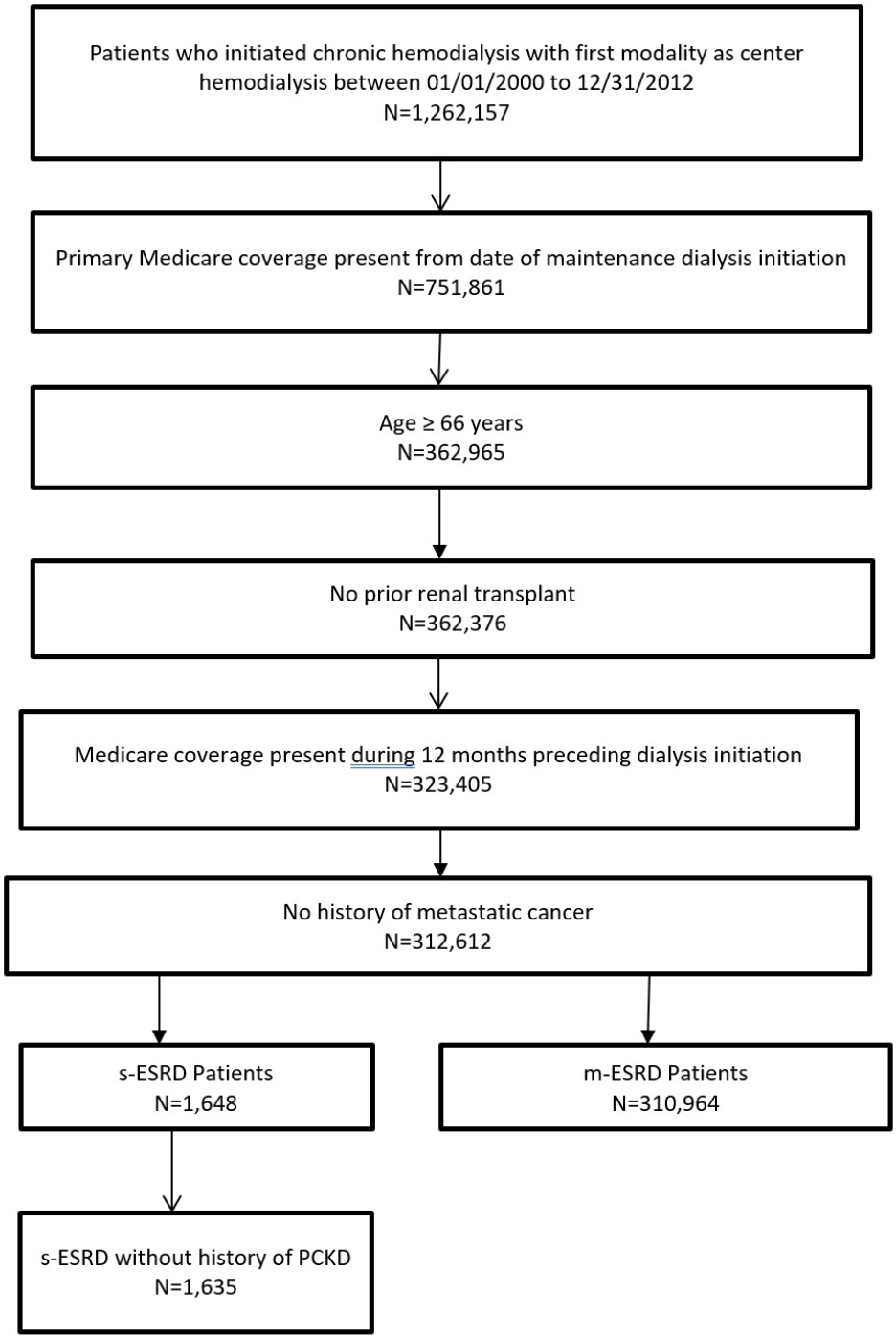
Table 1. Cohort characteristics		
	s-ESRD (n=1635)	m-ESRD (=310 964)
Age at first ESRD service, mean (SD)	74.4 (5.7)	75.9 (6.5)
65–69	394 (24.1%)	61 973 (19.9%)
70–74	494 (30.2%)	79 656 (25.6%)
75–79	429 (26.2%)	76 735 (24.7%)
80–84	235 (14.4%)	58 512 (18.8%)
85 plus	83 (5.1%)	34 088 (11.0%)
Gender		
Male	1011 (61.8%)	159 346 (51.2%)
Female	624 (38.2%)	151 566 (48.7%)
Missing	0 (0.0%)	52 (<0.1%)
Race		
Native American	12 (0.7%)	2637 (0.8%)
Asian	17 (1.0%)	11 235 (3.6%)
Black	271 (16.6%)	68 221 (21.9%)
White	1332 (81.5%)	22 7162 (73.1%)
Missing	0 (0.0%)	26 (<0.1%)
Other	<11 (<0.7%)*	1683 (0.5%)
Charlson score		
Median (range)	8 (1–15)	7 (0–17)
Specific comorbidities		
Myocardial infarction	368 (22.5%)	81 432 (26.2%)
Cerebrovascular disease	555 (33.9%)	113 047 (36.4%)
Diabetes	934 (57.1%)	220 933 (71.0%)
Diabetes with organ damage	689 (42.1%)	178 013 (57.2%)
History of hypertension	1564 (95.7%)	295 757 (95.1%)
Dyslipidemia	963 (58.9%)	174 618 (56.2%)
Other cancer	542 (33.1%)	50 332 (16.2%)
Kidney cancer	1460 (89.3%)	10 820 (3.5%)

*Counts <11 suppressed as per USRDS policy. For all comparisons between s-ESRD vs. m-ESRD groups, p<0.001, except history of hypertension (p=0.31) and dyslipidemia (p=0.03). m-ESRD: medically induced end-stage renal disease; s-ESRD: surgically induced end-stage renal disease.

Table 2. Multivariable-adjusted comparisons of outcomes between patients with surgically vs. medically induced end-stage renal disease		
Outcome	**Multivariable-adjusted effect estimates for s-ESRD vs. m-ESRD**	
No competing risks	**HR (95% CI)**	**p**
Overall survival	0.76 (0.72-0.80)	<0.001
Hospitalization risk*	0.89 (0.86-0.92)	<0.001
Competing risks analyses	**Sub-distributional HR (95% CI)**	**p**
Non-cancer mortality	0.62 (0.59–0.67)	<0.001
Cardiovascular event	0.85 (0.80–0.91)	<0.001
Hospitalization (first occurrence)	0.99 (0.94–1.04)	0.77
Renal transplantation event	1.63 (1.26–2.10)	<0.001

A Cox proportional hazards model was used to evaluate overall survival, a frailty model was used to evaluate hospitalization risk in a recurrent event analysis, and Fine-and-Grey competing risks models (sub-distributional) were used to evaluate time to non-cancer mortality, time to first cardiovascular events, time to first hospitalization, and time to transplant in the setting of competing risks. Multivariable models adjusted for age, race, Charlson comorbidity index, and history of myocardial infarction, cerebrovascular disease, diabetes, hypertension, and dyslipidemia. CI: confidence interval; HR: hazard ratio; m-ESRD: medically induced end-stage renal disease; s-ESRD: surgically induced end-stage renal disease.

Supplementary Fig. 1. Study flow diagram. m-ESRD: medically induced end-stage renal disease; PCKD: polycystic kidney disease; s-ESRD: surgically induced end-stage renal disease;



Supplementary Table 1. Sensitivity analysis excluding patients from the surgical end-stage renal disease group with interval from surgery to dialysis greater than 2 months		
Outcome	**Multivariable-adjusted effect estimates for s-ESRD vs. m-ESRD**	
No competing risks	**HR (95% CI)**	**p**
Overall survival	0.74 (0.70–0.80)	<0.001
Hospitalization risk*	0.87 (0.84–0.90)	<0.001
Competing risks analyses	**Sub-distributional HR (95% CI)**	**p**
Non-cancer mortality	0.60 (0.55–0.65)	<0.001
Cardiovascular event	0.83 (0.77–0.90)	<0.001
Hospitalization (first occurrence)	1.02 (0.96–1.09)	0.55
Renal transplantation event	1.56 (1.14–2.14)	0.006

A Cox proportional hazards model was used to evaluate overall survival, a frailty model was used to evaluate hospitalization risk in a recurrent event analysis, and Fine-and-Grey competing risks models (sub-distributional) were used to evaluate time to non-cancer mortality, time to first cardiovascular events, time to first hospitalization, and time to transplant in the setting of competing risks. Multivariable models adjusted for age, race, Charlson co-morbidity index, and history of myocardial infarction, cerebrovascular disease, diabetes, hypertension, and dyslipidemia. CI: confidence interval; HR: hazard ratio; m-ESRD: medically induced end-stage renal disease; s-ESRD: surgically induced end-stage renal disease.

Appendix. Diagnostic and procedure codes used

Diagnostic codes for renal or upper tract tumor/cancer	
ICD-9-CM diagnostic codes used	**Description**
189.0	Malignant neoplasm of the kidney, except pelvis
223.0	Benign neoplasm of kidney, except pelvis
189.1	Malignant neoplasm of renal pelvis
189.2	Malignant neoplasm of ureter
Procedure codes	
ICD-9-CM procedure codes used	**Description**
55.4	Partial nephrectomy
55.5	Complete nephrectomy
55.51	Nephroureterectomy
55.52	Nephrectomy of remaining kidney
55.54	Bilateral nephrectomy
CPT codes	**Description**
50220	Nephrectomy, including partial ureterectomy, any open approach including rib resection;
50225	Nephrectomy, including partial ureterectomy, any open approach including rib resection; complicated because of previous surgery on same kidney
50230	Nephrectomy, including partial ureterectomy, any open approach including rib resection; radical, with regional lymphadenectomy and/or vena caval thrombectomy
50234	Nephrectomy with total ureterectomy and bladder cuff; through same incision
50236	Nephrectomy with total ureterectomy and bladder cuff; through separate incision
50240	Nephrectomy, partial
50543	Laparoscopy, surgical; partial nephrectomy
50545	Laparoscopy, surgical; radical nephrectomy (includes removal of Gerota's fascia and surrounding fatty tissue, removal of regional lymph nodes, and adrenalectomy)

50546	Laparoscopy, surgical; nephrectomy, including partial ureterectomy
50548	Laparoscopy, surgical; nephrectomy with total ureterectomy

ICD-9 codes for cardiac event outcomes	
ICD-9	**Code descriptions**
Myocardial infarction	
410	ACUTE MYOCARDIAL INFARCTION
410.0	ACUTE MYOCARDIAL INFARCTION OF ANTEROLATERAL WALL
410.00	ACUTE MYOCARDIAL INFARCTION OF ANTERIOLATERAL WALL, EPISODE OF CARE UNSPECIFIED
410.01	ACUTE MYOCARDIAL INFARCTION OF ANTERIOLATERAL WALL, INITIAL EPISODE OF CARE
410.02	ACUTE MYOCARDIAL INFARCTION OF ANTERIOLATERAL WALL, SUBSEQUENT EPISODE OF CARE
410.1	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL
410.10	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL, EPISODE OF CARE UNSPECIFIED
410.11	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL, INITIAL EPISODE OF CARE
410.12	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL, SUBSEQUENT EPISODE OF CARE
410.2	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL
410.20	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL, EPISODE OF CARE UNSPECIFIED
410.21	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL, INITIAL EPISODE OF CARE
410.22	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL, SUBSEQUENT EPISODE OF CARE
410.3	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL
410.30	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL, EPISODE OF CARE UNSPECIFIED
410.31	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL, INITIAL EPISODE OF CARE
410.32	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL, SUBSEQUENT OF EPISODE OF CARE
410.4	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL
410.40	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL, EPISODE OF CARE UNSPECIFIED
410.41	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL, INITIAL

	EPISODE OF CARE
410.42	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL, SUBSEQUENT EPISODE OF CARE
410.5	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL
410.50	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL, EPISODE OF CARE UNSPECIFIED
410.51	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL, INITIAL EPISODE OF CARE
410.52	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL, SUBSEQUENT EPISODE OF CARE
410.6	TRUE POSTERIOR WALL INFARCTION
410.60	ACUTE MYOCARDIAL INFARCTION OF TRUE POSTERIOR WALL, EPISODE OF CARE UNSPECIFIED
410.61	ACUTE MYOCARDIAL INFARCTION OF TRUE POSTERIOR WALL, INITIAL EPISODE OF CARE
410.62	ACUTE MYOCARDIAL INFARCTION OF TRUE POSTERIOR WALL, SUBSEQUENT EPISODE OF CARE
410.7	SUBENDOCARDIAL INFARCTION
410.70	ACUTE SUBENDOCARDIAL INFARCTION, EPISODE OF CARE UNSPECIFIED
410.71	ACUTE SUBENDOCARDIAL INFARCTION, INITIAL EPISODE OF CARE
410.72	ACUTE SUBENDOCARDIAL INFARCTION, SUBSEQUENT EPISODE OF CARE
410.8	ACUTE MYOCARDIAL INFARCTION OF OTHER SPECIFIED SITES
410.80	ACUTE MYOCARDIAL INFARCTION OF OTHER SPECIFIED SITES, EPISODE OF CARE UNSPECIFIED
410.81	ACUTE MYOCARDIAL INFARCTION OF OTHER SPECIFIED SITES, INITIAL EPISODE OF CARE
410.82	ACUTE MYOCARDIAL INFARCTION OF OTHER SPECIFIED SITES, SUBSEQUENT EPISODE OF CARE
410.9	ACUTE MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
410.90	ACUTE MYOCARDIAL INFARCTION OF UNSPECIFIED SITE, EPISODE OF CARE UNSPECIFIED
410.91	ACUTE MYOCARDIAL INFARCTION OF UNSPECIFIED SITE, INITIAL EPISODE OF CARE
410.92	ACUTE MYOCARDIAL INFARCTION OF UNSPECIFIED SITE, SUBSEQUENT EPISODE OF CARE
Hemorrhagic CVA	

430	SUBARACHNOID HEMORRHAGE
431	INTRACEREBRAL HEMORRHAGE
432	OTHER AND UNSPECIFIED INTRACRANIAL HEMORRHAGE
432.0	NONTRAUMATIC EXTRADURAL HEMORRHAGE
432.1	SUBDURAL HEMORRHAGE
432.9	UNSPECIFIED INTRACRANIAL HEMORRHAGE
Ischemic CVA	
433	OCCLUSION AND STENOSIS OF PRECEREBRAL ARTERIES
433.0	OCCLUSION AND STENOSIS OF BASILAR ARTERY
433.00	OCCLUSION AND STENOSIS OF BASILAR ARTERY, WITHOUT MENTION OF CEREBRAL INFARCTION
433.01	OCCLUSION AND STENOSIS OF BASILAR ARTERY, WITH CEREBRAL INFARCTION
433.1	OCCLUSION AND STENOSIS OF CAROTID ARTERY
433.10	OCCLUSION AND STENOSIS OF CAROTID ARTERY
433.11	OCCLUSION AND STENOSIS OF CAROTID ARTERY, WITH CEREBRAL INFARCTION
433.2	OCCLUSION AND STENOSIS OF VERTEBRAL ARTERY
433.20	OCCLUSION AND STENOSIS OF VERTEBRAL ARTERY, WITHOUT MENTION OF CEREBRAL INFARCTION
433.21	OCCLUSION AND STENOSIS OF VERTEBRAL ARTERY, WITH CEREBRAL INFARCTION
433.3	OCCLUSION AND STENOSIS OF MULTIPLE AND BILATERAL PRECEREBRAL ARTERIES
433.30	OCCLUSION AND STENOSIS OF MULTIPLE AND BILATERAL ARTERIES, WITHOUT MENTION OF CEREBRAL INFARCTION
433.31	OCCLUSION AND STENOSIS OF MULTIPLE AND BILATERAL ARTERIES, WITH CEREBRAL INFARCTION
433.8	OCCLUSION AND STENOSIS OF OTHER SPECIFIED PRECEREBRAL ARTERY
433.80	OCCLUSION AND STENOSIS OF OTHER SPECIFIED PRECEREBRAL ARTERY, WITHOUT MENTION OF CEREBRAL INFARCTION
433.81	OCCLUSION AND STENOSIS OF OTHER SPECIFIED PRECEREBRAL ARTERY, WITH CEREBRAL INFARCTION
433.9	OCCLUSION AND STENOSIS OF UNSPECIFIED PRECEREBRAL ARTERY
433.90	OCCLUSION AND STENOSIS OF UNSPECIFIED PRECEREBRAL ARTERY, WITHOUT MENTION OF CEREBRAL INFARCTION
433.91	OCCLUSION AND STENOSIS OF UNSPECIFIED PRECEREBRAL ARTERY,

	WITH CEREBRAL INFARCTION
434	OCCLUSION OF CEREBRAL ARTERIES
434.0	CEREBRAL THROMBOSIS
434.00	CEREBRAL THROMBOSIS WITHOUT MENTION OF CEREBRAL INFARCTION
434.01	CEREBRAL THROMBOSIS WITH CEREBRAL INFARCTION
434.1	CEREBRAL EMBOLISM
434.10	CEREBRAL EMBOLISM WITHOUT MENTION OF CEREBRAL INFARCTION
434.11	CEREBRAL EMBOLISM WITH CEREBRAL INFARCTION
434.9	CEREBRAL ARTERY OCCLUSION, UNSPECIFIED
434.90	CEREBRAL ATERY OCCLUSION, UNSPECIFIED, WITHOUT MENTION OF CEREBRAL INFARCTS
434.91	CEREBRAL ARTERY OCCLUSION, UNSPECIFIED, WITH CEREBRAL INFARCTION
435	TRANSIENT CEREBRAL ISCHEMIA
435.0	BASILAR ARTERY SYNDROME
435.1	VERTEBRAL ARTERY SYNDROME
435.2	SUBCLAVIAN STEAL SYNDROME
435.3	VERTEBROBASILAR ARTERY SYNDROME
435.8	OTHER SPECIFIED TRANSIENT CEREBRAL ISCHEMIAS
435.9	UNSPECIFIED TRANSIENT CEREBRAL ISCHEMIA
436	ACUTE, BUT ILL-DEFINED, CEREBROVASCULAR DISEASE
Sudden cardiac death	
427.5	CARDIAC ARREST