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Prostate Cancer Outcomes Following Solid-Organ Transplantation: A SEER-Medicare Analysis

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Abstract

Background: Immunosuppressive regimens associated with organ transplantation increase the risk of developing cancer. Transplant candidates and recipients with prostate cancer are often treated, even if low-risk features would ordinarily justify active surveillance.
Methods: Using SEER-Medicare, we identified 163 676 men aged 66 years and older diagnosed with nonmetastatic prostate cancer. History of solid organ transplant was identified using diagnosis or procedure codes. A propensity score-matched cohort was identified by matching transplanted men to nontransplanted controls by age, race, region, year, T-stage, grade, comorbidity, and cancer therapy. Fine-Gray competing risk models assessed associations between transplant status and prostate cancer-specific mortality (PCSM) and overall mortality (OM).
Results: We identified 620 men (0.4%) with transplant up to 10 years before (n = 320) or 5 years after (n = 300) prostate cancer diagnosis and matched them to 3100 men. At 10 years, OM was 55.7% and PCSM was 6.0% in the transplant cohort compared with 42.4% ($P < .001$) and 7.6% ($P = .70$) in the nontransplant cohort, respectively. Adjusted models showed no difference in PCSM for transplanted men (hazard ratio = 0.88, 95% confidence interval = 0.61 to 1.27, $P = .70$) or differences by prostate cancer therapy. Among 334 transplanted men with T1-2N0, well or moderately differentiated "low-risk" prostate cancer, PCSM was similar for treated and untreated men (hazard ratio = 0.92, 95% confidence interval = 0.47 to 1.81).
Conclusions: Among men aged 66 years and older with prostate cancer, an organ transplant is associated with higher OM but no observable difference in PCSM. These findings suggest men with prostate cancer and previous or future organ transplantation should be managed per usual standards of care, including consideration of active surveillance for low-risk cancer characteristics.

Immunosuppression, whether acquired or iatrogenic, is associated with an increased risk of developing solid tumors (1). Consequently, candidates for solid organ transplantation commonly undergo screening for certain cancers, and patients who are posttransplant may be subject to more rigorous screening, treatment, or posttreatment surveillance related to heightened concerns for cancer progression (2). Prostate cancer, commonly diagnosed after prostate-specific antigen (PSA) screening, can therefore present a clinical challenge for patients who are pre-transplant or posttransplant, especially because of the wide heterogeneity in disease characteristics and risk of progression. Healthy patients with low-risk prostate cancer are ideal candidates for active surveillance, whereas those with high-risk cancers have a 20%–40% risk of cancer mortality at 15 years after local therapy (3,4).

There are no widely accepted guidelines regarding prostate cancer screening or treatment in the transplant population, and practice patterns widely vary (5). Most studies evaluating prostate cancer outcome following previous transplant include very

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small cohorts treated with a single modality of local therapy (6–11). Larger population-based studies suggest immunosuppression does not increase the incidence of prostate cancer (2,12–14); however, no population-based studies to our knowledge have assessed whether immunosuppression alters the likelihood of dying from prostate cancer. To obtain a large sample size with increased power, we studied men in the Surveillance, Epidemiology, and End Results (SEER)-Medicare population who had prostate cancer diagnosed before or after solid organ transplantation. Our hypothesis was that immunosuppression following transplantation would not adversely influence the rate of prostate cancer mortality compared with men without a history of transplantation. Our secondary aim was to compare outcomes by therapies for transplant and nontransplant patients.

Methods

Patients and Study Design

SEER data include 18 population-based registries, representing approximately 28% of the US population. SEER-Medicare links this registry to Medicare health-care claims data of US residents at least age 65 years. We used SEER data 1991–2013 and Medicare data 1991–2011 to identify 383 470 men aged 65 years and older with no history of malignancy or other subsequent malignancy (Supplementary Figure 1 available online). Data were obtained from the National Cancer Institute for the men diagnosed 1991–2003 with a subsequent custom data request to add men diagnosed 2004–2011. The National Cancer Institute provided a single SEER Patient Entitlement and Diagnosis Summary File data file for 1991–2011 cases. Because our study spanned multiple SEER-Medicare linkages, we adjusted patient identifiers as recommended by SEER-Medicare to link the two file releases.

Prostate cancers were identified based on *International Classification of Diseases, Ninth Edition – Clinical Manifestations* (15) diagnosis codes reported in the SEER excluded patients with noninvasive (n = 114, 0.03%) or metastatic prostate cancer (n = 37 371, 9.8%). Cancer cases were identified in Medicare data using ICD-9 185.x, with a corresponding SEER diagnosis within 2 months. Men were enrolled in Medicare Parts A and B more than 1 year before and after the index date. We excluded Medicare enrollees in managed care during the 2-year interval (n = 89 591, 23.4%), those without the required enrollment interval in Medicare Parts A and B (n = 35 929, 9.4%), men diagnosed in 2011 (n = 11 631, 3.0%), and men with prostate cancer diagnosis more than 60 days before or following the SEER diagnosis date (n = 43 068, 11.2%). We also excluded men with treatment before the index diagnosis date (n = 968, 0.3%) and those with brachytherapy claims following prostatectomy (n = 22, 0.01%). We excluded men who had transplants more than 10 years before cancer diagnosis (n < 11) or more than 5 years following cancer diagnosis (n = 166, 0.04%). After these exclusions, 163 676 men (41.3%) aged 66 years and older remained (Supplementary Figure 1 available online).

Covariates

Transplant covariate data were extracted from Medicare claims data using diagnosis or procedure codes for kidney, heart, lung, liver, pancreas, and intestine transplants (Supplementary Table 1, available online). For men with multiple transplants, the timing of the earliest transplant was used. We computed years from cancer diagnosis date to first transplant date.

Patient-level covariates included T-stage, N-stage, grade, age, race, geographic region, year of diagnosis, and Charlson comorbidity index, which was computed from Medicare claims (excluding cancers). Primary definitive treatments were identified by Medicare claims the first 12 months following index diagnosis. Local therapy included surgery and radiation therapy. Surgery was classified as prostatectomy alone or with any other treatment occurring within 12 months. Radiation therapy included external beam radiation therapy (EBRT) alone, EBRT with hormone therapy or orchiectomy (ADT), EBRT with brachytherapy, and brachytherapy alone. Men who had EBRT and hormonal therapy or orchiectomy within 6 months with at least one treatment within 12 months were considered to have had EBRT and ADT. Patients receiving "primary hormonal therapy" included ADT without radiation or prostatectomy. Patients without any claims for prostate cancer treatment during the first year were classified as having no therapy.

Outcomes

The primary outcomes were prostate cancer-specific mortality (PCSM), other cause mortality, and overall mortality (OM) as coded by SEER as of December 31, 2013. Although we had up to 22 years of follow-up mortality data, we ascertained status and cause of death as of the date 10 years following cancer diagnosis.

Statistical Analysis

Baseline characteristics of the transplant and nontransplant groups were compared using the χ^2 test. All tests were two-sided, and a P value of less than .05 was considered statistically significant. We constructed propensity score-matched cohorts to account for differences in baseline characteristics. Because men with transplants before cancer diagnosis are clinically distinct from men transplanted postcancer diagnosis, the transplant patients were split into two cohorts by transplant timing and matched separately. Propensity scores were computed using two logistic regressions with dependent variables of prior or posttransplant vs nontransplant and independent variables of region, age group, race or ethnicity, year (grouped), T-stage, grade, Charlson comorbidity (0, 1, ≥2), and initial therapy (local, primary hormonal, none). Patients in both cohorts were matched 1:5 – initial transplant before cancer diagnosis (n = 320) with matched controls (n = 1600); initial transplant from the date of cancer diagnosis up to 5 years later (n = 300) with matched controls (n = 1500). Patients were matched using a greedy algorithm and maximum allowed caliper distance of 0.1. The cohorts were recombined for analysis. Covariate balance was assessed by postmatch standardized difference, with less than 10% indicating a similar distribution (16).

Fine-Gray's subdistribution hazard models for competing risks were used to assess associations between mortality, transplant, and cancer therapy for 10-year survival for PCSM, competing cause of mortality, and OM from the date of prostate cancer diagnosis (17). There were no competing risks in the OM models. To address our two aims, we modeled main effects or transplant × initial therapy, controlling for age group, Charlson score, grade, T-stage, and year. Timing of first transplant was modeled as a time-dependent variable. Kaplan-Meier plots and Fine-Gray models were used to assess in greater detail the

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effects of transplant timing on mortality. In a subgroup analysis, we also compared local therapy and primary hormonal therapy to no therapy for transplanted men with "low-risk" cancer characteristics (T1-2N0) and well- or moderately differentiated tumors. Adequacy of the proportional hazards assumption was tested using Kaplan-Meier curves for survival functions. All analyses used SAS 9.4 (Cary, NC, 2014).

Results

A total of 163 676 patients met the study selection criteria (Table 1), which included 620 (0.4%) transplanted men and 163 056 (99.6%) without transplants. Transplanted patients were younger, more likely to be nonwhite, live in the West vs the Midwest and South, and have multiple comorbidities and shorter follow-up after prostate cancer diagnosis. The 620 transplanted men (median follow-up, 5.5 years) were matched to 3100 nontransplanted men (median follow-up, 6.4 years). Our final study cohort included 3720 men aged a mean of 73.3 years. Postmatch baseline distributions of age, race or ethnicity, region, year of diagnosis, T-stage, N-stage, grade, comorbidity, and therapy group were similar between groups (Supplementary Table 2 available online; all P values $>.05$). In the analytic sample, 366 (59.0%) transplanted men and 1898 (61.2%) nontransplanted men received local therapy. Another 112 (18.1%) and 471 (15.2%) men, respectively, received primary hormonal therapy, and 142 (22.9%) and 731 (23.6%) men in each cohort had no therapy or active surveillance (Supplementary Table 2 available online).

Organ transplant occurred before prostate cancer diagnosis in 320 (51.6%) men and after diagnosis in 300 (48.4%) men; 11.8% (n = 73) had multiple organ transplants (Table 2). Kidney was the most commonly transplanted organ both before and after prostate cancer diagnosis. Since approximately one-half of the men had initial transplants before cancer diagnosis, the time interval from cancer diagnosis to first transplant was normally distributed with a mean of −0.43 (SD = 3.20) years (Supplementary Figure 2 available online).

Among the transplanted men, 37 (6.0%) died of prostate cancer, 308 (49.7%) died of other causes, and 345 (55.6%) died overall (Table 3). In bivariate analyses using χ^2 tests, 10-year PCSM did not differ by transplant status (6.0% vs 7.6%, $P = .17$), but 10-year OM was higher in transplanted men (55.7% vs 42.4%, $P < .001$) from other causes.

To address the main question of whether transplant (or immunosuppression) affects mortality in prostate cancer patients, we conducted adjusted Fine-Gray models for 10-year mortality outcomes. Although the propensity score-matched cohorts were balanced and did not require adjustment for potential confounding factors, model fit improved by adjusting for these covariates. Table 3 shows the subhazard ratios associated with transplant for PCSM, other causes of death, and OM. The PCSM model showed transplanted men had the same risk of dying from prostate cancer as nontransplanted men (hazard ratio [HR] = 0.88, 95% confidence interval [CI] = 0.61 to 1.27, $P = .70$). Examining the effect of transplant on cohorts defined by therapy groups, transplant did not affect the risk of PCSM for any therapy group. In accord with the raw counts, after adjustment, transplanted patients had an 83% increased risk of dying from other causes. For OM, transplant patients had a 65% higher risk of dying than nontransplanted men (HR = 1.65, 95% CI = 1.45 to 1.88, $P < .01$). Transplant was associated with elevated risk of OM for men who had local therapy (HR = 1.77, 95% CI = 1.47 to 2.13) and no therapy (HR = 2.04, 95% CI = 1.61 to 2.59) but not for those who had primary hormonal therapy (HR = 1.18, 95% CI = 0.92 to 1.52). Figure 1 graphically depicts the findings of Table 3 by plots of the adjusted cumulative incidence functions for PCSM and OM by transplant group overall and for each therapy group. Analyses with additional detail for different local therapies are shown in Supplementary Tables 5 and 6 (available online).

Repeating the analyses for 334 men with "low-risk" features of prostate cancer, we did not observe any differences by transplant for PCSM (HR = 0.92, 95% CI = 0.47 to 1.81), and the patterns for other cause and OM followed those of the full cohort (Table 4). We did not observe differences in PCSM by therapy; men who had no therapy for their prostate cancer had similar PCSM to treated men (HR = 0.86, 95% CI = 0.21 to 3.54).

To examine the differences in outcomes by relative timing of cancer diagnosis and transplant, we explored the data using Kaplan-Meier survival plots. Supplementary Figure 3 (available online) shows plots for CSS and OS, including the nontransplant group for visual reference. We did not find differences in survival by transplant timing. We also repeated the Fine-Gray analyses from Table 3 testing for difference between prior and posttransplant and running models separately for the prior transplant (n = 1600) and posttransplant (n = 1500) cohorts and their respective matched samples. For the overall outcomes, hazard ratios were slightly lower in the prior transplant group and slightly higher in the posttransplant group (Supplementary Table 3 available online). However, the conclusions about differences compared with nontransplanted men did not differ from those drawn from Table 3, for the overall group, or when analyzed according to prostate cancer therapy received (Supplementary Table 4 available online). All proportional hazards assumptions were met.

Discussion

In this SEER-Medicare study, we examined the effects of solid organ transplant and cancer therapy on PCSM and OM. Using a propensity score-matched cohort, we did not identify meaningful differences in prostate cancer mortality in men with transplant history whether the transplant took place before or after the prostate cancer diagnosis. We did not observe differences in cancer mortality by cancer therapy. In the transplant cohort, local therapy was associated with a similar reduction in risk of prostate cancer-specific and OM as that of nontransplanted men. In transplanted men with "low-risk" cancer, prostate cancer mortality was uncommon (≤5%) and initial management with "no therapy" was not associated with any observable compromise in cancer mortality. Finally, in transplanted men, primary hormonal therapy was not associated with a reduction in cancer mortality compared with no therapy and may not be a preferred treatment option for localized disease, similar to the nontransplant setting (18). Overall, our findings suggest local therapy (radical prostatectomy or radiation therapy) or active surveillance may be justifiable in this population, as suited to individual patient risk factors and comorbidity and per usual standards of care.

Many studies have evaluated how prior transplant and accompanying immunosuppression may influence incidence of new cancers and outcome of treated cancers. Evidence supports an increased incidence of cancer in the transplanted patient, with cancer mortality identified as the third-leading cause of death (12). Several solid-organ cancers are at increased risk

Table 1. Patient and therapy characteristics in prostate cancer patients aged 66 years and older: SEER-Medicare 1992–2010

Characteristic	Transplant (N = 620) No. (%)	No Transplant (N = 163 056) No. (%)	Total (N = 163 676) No. (%)	P*
Age group, y				.03
66–74	392 (63.2)	95 210 (58.4)	95 602 (58.4)	
75–84	200 (32.3)	57 979 (35.6)	58 179 (35.6)	
>84	28 (4.5)	9867 (6.1)	9895 (6.1)	
Mean (SD)	73.3 (5.7)	74.1 (5.9)	74.1 (5.9)	<.001
Race or ethnicity				<.001
White, non-Hispanic	458 (73.9)	136 501 (83.7)	136 959 (83.7)	
Black, non-Hispanic	107 (17.3)	15 582 (9.6)	15 689 (9.6)	
Other or unknown	55 (8.9)	10 973 (6.7)	11 028 (6.7)	
Region				<.001
Northeast	109 (17.6)	30 859 (18.9)	30 968 (18.9)	
Midwest	86 (13.9)	28 414 (17.4)	28 500 (17.4)	
South	84 (13.6)	31 886 (19.6)	31 970 (19.5)	
West	341 (55.0)	71 897 (44.1)	72 238 (44.1)	
Year of diagnosis				.23
1992–1999	135 (21.8)	35 197 (21.6)	35 332 (21.6)	
2000–2003	169 (27.3)	39 874 (24.5)	40 043 (24.5)	
2004–2007	154 (24.8)	45 792 (28.1)	45 946 (28.1)	
2008–2010	162 (26.1)	42 193 (25.9)	42 355 (25.9)	
Charlson comorbidities				<.001
0	200 (32.3)	105 399 (64.6)	105 599 (64.5)	
1	121 (19.5)	35 412 (21.7)	35 533 (21.7)	
≥2	299 (48.2)	22 245 (13.6)	22 544 (13.8)	
Mean (SD)	1.76 (1.75)	0.59 (1.04)	0.60 (1.04)	<.001
T-stage				.47
T1	285 (46.0)	70 441 (43.2)	70 726 (43.2)	
T2	276 (44.5)	77 008 (47.2)	77 284 (47.2)	
T3	>16 (>2.6)†	<4411 (<2.7)	4427 (2.7)	
T4	<11 (<1.8)	>3666 (>2.2)	3677 (2.3)	
Unknown	32 (5.2)	7530 (4.6)	7562 (4.6)	
N-stage				.77
No lymph nodes	503 (81.1)	132 924 (81.5)	133 427 (81.5)	
Any lymph nodes	<11 (<1.8)	>2005 (>1.2)	2016 (1.2)	
Unknown	>106 (>17.1)	<28 127 (<17.3)	28 233 (17.3)	
Grade				1.00
Well differentiated	31 (5.0)	8101 (5.0)	8132 (5.0)	
Moderately differentiated	330 (53.2)	86 423 (53.0)	86 753 (53.0)	
Poorly differentiated	236 (38.1)	62 521 (38.3)	62 757 (38.3)	
Unknown	23 (3.7)	6011 (3.7)	6034 (3.7)	
Therapy group				.07
Local therapy	366 (59.0)	103 510 (63.5)	103 876 (63.5)	
Primary hormonal therapy	112 (18.1)	25 619 (15.7)	25 731 (15.7)	
No therapy	142 (22.9)	33 927 (20.8)	34 069 (20.8)	
Therapies				.05
Prostatectomy	98 (15.8)	30 937 (19.0)	31 035 (19.0)	
EBRT alone	97 (15.7)	22 435 (13.8)	22 532 (13.8)	
EBRT and ADT	74 (11.9)	21 709 (13.3)	21 783 (13.3)	
EBRT and brachytherapy	42 (6.8)	14 620 (9.0)	14 662 (9.0)	
Brachytherapy alone	55 (8.9)	13 809 (8.5)	13 864 (8.5)	
Primary hormonal therapy	112 (18.1)	25 619 (15.7)	25 731 (15.7)	
No therapy	142 (22.9)	33 927 (20.8)	34 069 (20.8)	
Prostatectomy with EBRT	<11 (<1.8)	>2200 (>1.3)	2211 (1.4)	.63

*Two-sided chi-square test. ADT = hormonal therapy or orchiectomy; EBRT = electron beam radiation therapy; SEER = Surveillance, Epidemiology, and End Results.
†Suppressed, subgroup N less than 11.

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Table 2. Transplant procedures in prostate cancer patients aged 66 years and older and patient mortality: SEER-Medicare 1992–2010*

Characteristic	No. (%)	Cancer-specific mortality at 10 y No. (%)	OM at 10 y No. (%)
Total	620 (100.0)	37 (6.0)	345 (55.7)
Transplant before prostate cancer diagnosis			
Patients (n = 363 transplants)	320 (100.0)	16 (5.0)	168 (52.5)
Transplants	363 (100.0)		
Kidney	189 (59.1)	<11 (<5.8)†	95 (50.3)
Heart	98 (30.6)	<11 (<11.2)	54 (55.1)
Lung	>13 (>3.6)	<11 (<45.8)	—†
Liver	42 (13.1)	<11 (<26.2)	21 (50.0)
Pancreas	<11 (<3.0)	0 (0.0)	—
Intestines	<11 (<3.0)	0 (0.0)	—
Transplant after prostate cancer diagnosis			
Patients (n = 345 transplants)	335 (100.0)	24 (7.2)	190 (56.7)
Transplants	345 (100.0)		
Kidney	172 (51.3)	<11 (<6.4)	89 (51.7)
Heart	65 (19.4)	<11 (<16.9)	31 (47.7)
Lung	28 (8.4)	<11 (<39.3)	15 (53.6)
Liver	63 (18.8)	<11 (<17.5)	52 (82.5)
Pancreas	<11 (<3.3)	—	—
Intestines	<11 (<3.3)	0 (0.0)	—
Transplants per patient, no.			
1	547 (88.2)	>27 (>4.9)	313 (57.2)
>1	73 (11.8)	<11 (<5.5)	32 (43.8)
Before prostate cancer diagnosis	>27 (>4.4)	—	>13 (>48.0)
After prostate cancer diagnosis	<11 (<1.8)	0 (0.0)	—
Before and after cancer diagnosis	35 (5.7)	<11 (<31.4)	13 (37.1)
Timing of transplant relative to cancer diagnosis			
5–10 y before	65 (10.5)	<11 (<16.9)	29 (44.6)
5 y before PCa diagnosis	255 (41.1)	<19 (<7.5)	140 (54.9)
PCa diagnosis to 1 y after	76 (12.3)	<11 (<14.5)	47 (61.8)
1–5 y after	224 (36.1)	16 (7.2)	129 (57.6)

*Sums exceed 100% because some men had multiple transplants before and/or after prostate cancer diagnosis. dx = diagnosis; OM = overall mortality; PCa = prostate cancer; SEER = Surveillance, Epidemiology, and End Results.
†Suppressed, subgroup less than 11.

Table 3. Fine-Gray models testing the effect of transplant on 10-y PCSM and all-cause mortality among men with transplants and a nontransplant, propensity score-matched cohort,* men aged 66 years and older: SEER-Medicare 1992–2010

Outcome or therapy group	Transplant (N = 620)		No transplant (N = 3100)		Transplant vs no transplant	
	No. (%)	Therapy group HR (95% CI)	No. (%)	Therapy group HR (95% CI)	HR (95% CI)	P†
PCSM						
All patients	37 of 620 (6.0)	—	234 of 3100 (7.5)	—	0.88 (0.61 to 1.27)	.70
Therapy group X transplant						.14
Local therapy	16 of 366 (4.4)	0.54 (0.24 to 1.21)	85 of 1898 (4.5)	0.50 (0.35 to 0.72)	1.21 (0.70 to 2.09)	
Primary hormonal therapy	<11 of 112 (<9.8)‡	0.74 (0.30 to 1.81)	89 of 471 (18.9)	1.59 (1.12 to 2.25)	0.52 (0.26 to 1.03)	
No therapy	≥11 of 142 (≥7.8)	1.00 (Referent)	60 of 731 (8.2)	1.00 (Referent)	1.11 (0.57 to 2.16)	
Other mortality						
All patients	308 of 620 (49.7)	—	1079 of 3100 (34.8)	—	1.83 (1.60 to 2.10)	<.001
OM						
All patients	345 of 620 (55.6)	—	1313 of 3100 (42.4)	—	1.65 (1.45 to 1.88)	<.001
Therapy group X transplant						.005
Local therapy	158 of 366 (43.2)	0.49 (0.37 to 0.64)	556 of 1898 (29.3)	0.56 (0.49 to 0.64)	1.77 (1.47 to 2.14)	
Primary hormonal therapy	84 of 112 (75.0)	0.73 (0.54 to 1.00)	356 of 471 (75.6)	1.26 (1.08 to 1.47)	1.18 (0.92 to 1.52)	
No therapy	103 of 142 (72.5)	1.00 (Referent)	401 of 731 (54.9)	1.00 (Referent)	2.04 (1.61 to 2.59)	

*Separate Fine-Gray model for each mortality outcome. Adjusted for time-dependency of first transplant, age group, grade, T-stage, Charlson comorbidity, and year. CI = confidence interval; HR = hazard ratio; OM = overall mortality; PSCM = prostate cancer-specific mortality; SEER = Surveillance, Epidemiology, and End Results.
†Two-sided Wald χ^2 test.
‡Suppressed, subgroup less than 11.

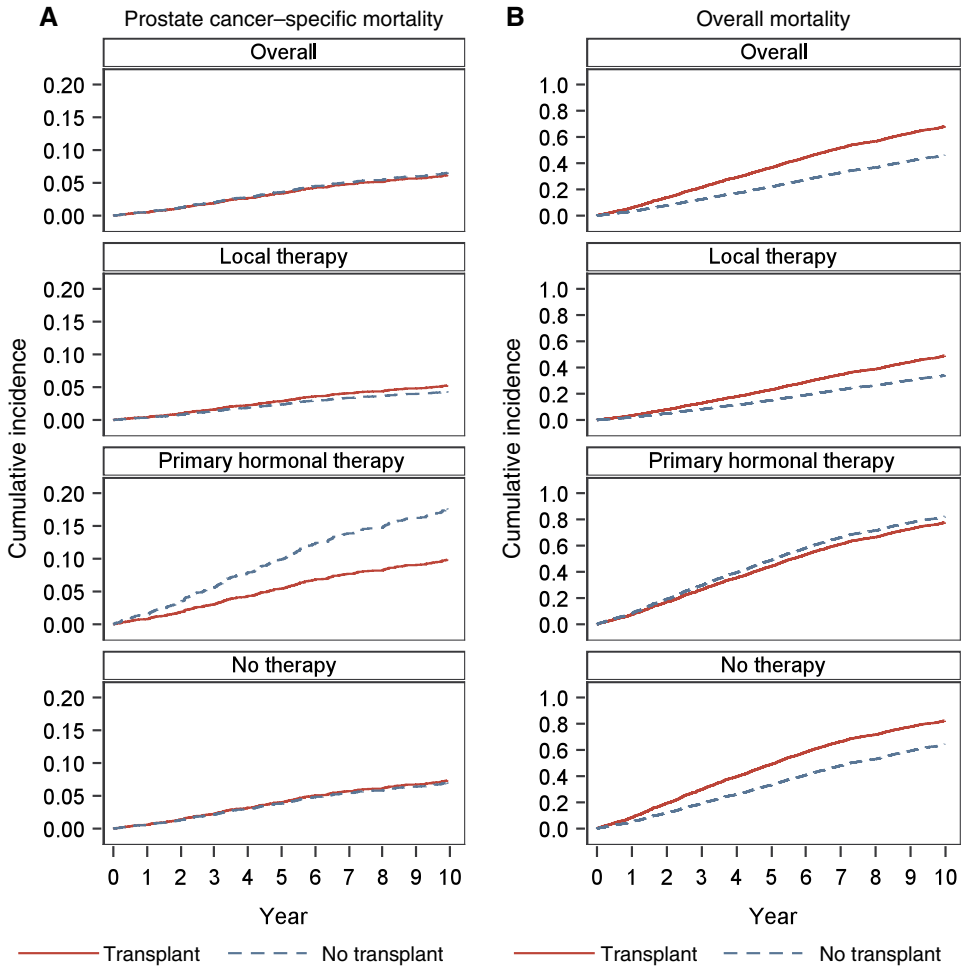

Figure 1. Adjusted Fine-Gray cumulative incidence functions for 10-year prostate cancer-specific mortality (PCSM) and overall mortality (OM) outcomes by initial therapy in men aged 66 years and older with transplants (N = 620) and propensity score-matched cohort without transplants (N = 3100): Surveillance, Epidemiology, and End Results-Medicare 1992–2010. Plots show predicted cumulative incidence functions for models of transplant cohort × initial therapy controlling for age group, Charlson score, grade, T-stage, and year. **A**) PCSM in the transplant and nontransplant cohorts shown for the overall cohort and by prostate cancer treatment type. **B**) OM in the transplant and nontransplant cohorts shown for the overall cohort and by prostate cancer treatment type.

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(13,19), with tumors with an infectious etiology such as squamous cell carcinomas of the skin, oropharynx, anus, or vulva, Kaposi sarcoma, and liver cancers at particular risk (20,21). Posttransplant cancers with the highest risk of mortality are lung, colon, melanoma, and liver cancer (2). Notably, prostate cancer has not been identified in population-based studies to have an increased incidence after transplant (2,13,21). In two recent meta-analyses of 241 (22) and 171 men (23), rates of prostate cancer recurrence after renal transplant did not appear to be different from nontransplanted men. However, the lack of robust controls and small sample sizes with no single study reviewed including more than 90 men led both sets of authors to remark that results should be interpreted with caution.

The lack of evidence on whether transplant history negatively influences prostate cancer outcomes has created uncertainty regarding prostate cancer screening as part of a routine workup for transplant candidacy and posttransplant surveillance. A meta-analysis reviewing 13 posttransplant cancer-screening guidelines was recently published, seven of which offered guidance on prostate cancer screening (24). Perhaps mirroring the controversy of PSA screening for prostate cancer in the general population, the recommendation for yearly PSA and digital rectal exam for men aged 50 years and older in transplanted men was supported by only three of the guidelines, and screening was discouraged in the remaining four. Our study results suggest it is reasonable to extrapolate normal screening guidelines for prostate cancer in the transplanted patient from the general population, as proposed by Breyer (25), because the natural history of prostate cancer progression and treatment outcomes do not appear to be different in the two populations.

The role of prostate cancer treatment as a prerequisite for organ transplant is debatable. Although transplant candidacy has historically required a waiting period to demonstrate no evidence of cancer, a uniform policy is difficult to apply in prostate cancer because there is such heterogeneity of risk (3). Guidelines from the European Association of Urology on renal transplantation in 2005 (26) deemed any active neoplasia a contraindication for transplantation; however, a guideline update in 2018 acknowledged that a waiting period after treatment of a

Table 4. Fine-Gray models testing the effects of therapy on 10-year PCSM and all-cause mortality among men with T1-2N0 prostate cancer, and well or moderately differentiated tumors comparing transplants and nontransplant propensity score-matched cohort,* men aged 66 years and older: SEER-Medicare 1992–2010

Outcome or therapy group	Transplant (N = 334)		No transplant (N = 1684)		Transplant vs no transplant	
	No. (%)	Therapy group HR (95% CI)	No. (%)	Therapy group HR (95% CI)	HR (95% CI)	P†
PCSM						
All patients	11 (3.3)	—	62 (3.7)	—	0.92 (0.47 to 1.81)	.81
Therapy group X transplant						.28
Local therapy	<11 of 191 (<5.8)‡	1.00 (Referent)	25 of 1022 (2.5)	1.00 (Referent)	1.48 (0.61 to 3.58)	—
Primary hormonal therapy	<11 of 45 (<24.4)	0.65 (0.08 to 5.46)	21 of 181 (11.6)	3.96 (2.00 to 7.85)	0.24 (0.03 to 1.90)	—
No therapy	<11 of 98 (<11.2)	0.86 (0.21 to 3.54)	16 of 481 (3.3)	1.21 (0.61 to 2.38)	1.05 (0.30 to 3.71)	—
Other mortality						
All patients	181 (54.2)	—	606 (36.0)	—	2.01 (1.62 to 2.41)	<.001
OM						
All patients	192 (57.5)	—	668 (39.7)	—	1.93 (1.62 to 2.30)	<.001
Therapy group X transplant						.07
Local therapy	90 of 191 (47.1)	1.00 (Referent)	291 of 1022 (28.5)	1.00 (Referent)	2.13 (1.67 to 2.72)	—
Primary hormonal therapy	30 of 45 (66.7)	1.34 (0.88 to 2.03)	133 of 181 (73.5)	2.25 (1.81 to 2.79)	1.27 (0.85 to 1.88)	—
No therapy	72 of 98 (73.5)	1.62 (1.13 to 2.33)	244 of 481 (50.7)	1.65 (1.38 to 1.98)	2.09 (1.53 to 2.85)	—

*Separate Fine-Gray model for each mortality outcome. Adjusted for time-dependency of first transplant, age group, grade, T-stage, Charlson comorbidity, and year. CI = confidence interval; HR = hazard ratio; OM = overall mortality; PSCM = prostate cancer-specific mortality; SEER = Surveillance, Epidemiology, and End Results.
†Two-sided Wald χ^2 test.
‡Suppressed, subgroup less than 11.

low-risk prostate cancer may not be justified (27). In a survey of 90 American transplant surgeons, 89% routinely performed PSA screening before renal transplant, 45% required treatment of a newly diagnosed prostate cancer before transplant, and 73% indicated a variable waiting time following treatment dependent on the stage and risk of cancer (5). As proposed by the International Society for Heart and Lung Transplantation, transplant after a cancer diagnosis would ideally occur in collaboration with oncology specialists at a time when the risk of cancer recurrence is felt to be low and not necessarily at an absolute time point (28). At our institution, after a multidisciplinary discussion, many men on active surveillance for low-risk prostate cancer are risk assessed for transplant, ultimately leading to transplant listing and solid organ transplantation in most cases. Conversely, men with a previous organ transplant and newly diagnosed low-risk prostate cancer are given all management options, including active surveillance.

Our study has limitations. Despite conducting an analysis for 18 years, we identified only 620 men with a history both of transplant and prostate cancer, likely due to our reliance on diagnosis codes and the cohort being restricted to men over age 65 years. The modest number of patients and events in our study limits the power to identify potential associations. As a sensitivity analysis, we queried IBM MarketScan Research Databases (IBM Watson Health) from 2003 to 2015. Among 160 million individuals with employer-based health insurance, the percentage of men aged 66 years and older with both diagnoses was approximately 0.5%, similar to our study observation. Given that younger men do not present with more advanced prostate cancer at diagnosis (29) and may experience lower rates of cancer progression with surveillance (30) or local therapy (29), it may be unlikely that differences in our conclusions would exist in transplanted men younger than 66 years, but such a conclusion would require analysis of the corresponding data. We were unable to apply the more widely accepted NCCN definition of "low-risk" prostate cancer in our study, because of limitations in the availability of Gleason score and PSA data in SEER-Medicare. Defining low risk by T1–T2 stage and well–moderate differentiation is a reasonable compromise that still identifies a cohort of men considered appropriate for active surveillance, which follows a similar approach to other SEER-Medicare studies (31). Finally, the lack of transplant-specific data including immunosuppression regimens and graft survival is limiting as transplant physicians tailor immunosuppressive therapy to each patient. This potential variation in transplant immunosuppression that may be necessary in the setting of a new cancer diagnosis can have negative reciprocal consequences on graft and patient survival.

In conclusion, among men aged 66 years and older with prostate cancer in the United States, an organ transplant is associated with higher OM but no observable difference in PCSM. These findings suggest management of men with prostate cancer and previous or future organ transplantation should proceed per usual standards of care, including consideration of active surveillance for men with low-risk cancer characteristics.

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