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Objectives

To examine, using competing risks regression, differences in cancer-specific mortality (CSM) that might distinguish between local tumour ablation (LTA) and observation (OBS) for patients with kidney cancer.

Patients and Methods

The study focused on 1 860 patients with cT1a kidney cancer treated with either LTA or OBS between 2000 and 2009 in the Surveillance Epidemiology and End Results-Medicare database. Propensity-score matching was used. The study outcome was CSM. Multivariable competing risks regression analyses, adjusting for other-cause mortality as well as patient (including comorbidities) and tumour characteristics, were fitted.

Results

Overall, fewer patients underwent LTA than OBS (30 vs 70%; n = 553 vs n = 1 307). Compared with patients in the OBS group, those in the LTA group were younger (median age 77 vs 78 years; $P < 0.001$), more likely to be white (84 vs 78%; $P = 0.005$), more frequently married (59 vs 52%; $P = 0.02$) and more frequently of high socio-economic status (54 vs 45%; $P = 0.001$). After propensity-score matching, 553 patients who underwent LTA and 553 who underwent OBS remained for subsequent analyses. The mean standardized differences of patient characteristics between the two groups were <10%, indicating a high degree of similarity. After LTA or OBS, the 5-year CSM estimates from Poisson regression-derived smoothed plots were 3.5 and 9.1%, respectively. In multivariable competing risks regression analyses, LTA use was found to have a protective effect on CSM (hazard ratio 0.47 [95% confidence interval 0.25–0.89]; $P = 0.02$).

Conclusions

After adjustment for comorbidity and tumour characteristics in elderly patients with kidney cancer, LTA was associated with a clinically and statistically significant protective effect on CSM, compared with OBS. This advantage of LTA deserves consideration when obtaining informed consent.

Keywords

local tumour ablation, observation, non-surgical management, oncological outcomes, kidney cancer, elderly patients

Introduction

Patients diagnosed with a small renal mass are frequently frail and elderly [1,2], and their age and comorbidities may undermine their selection for surgical treatment. Local tumour ablation (LTA) and observation (OBS) therefore represent attractive treatment alternatives in such patients [1,2]. Notably, to date, no study has directly compared the

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cancer-specific mortality (CSM) outcomes that are associated with these two alternative management options. To address this, we examined the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which is particularly well suited for the study of cancer control outcomes in the elderly, and permits the detailed assessment of comorbidity and other-cause mortality (OCM). We used competing risks regression methodology to examine the main endpoint, namely CSM, after accounting for OCM. We hypothesized that LTA may be associated with a small, albeit significant, advantage relative to OBS, with regard to CSM.

Methods

Study Source

We used the 2000–2009 SEER-Medicare-linked database, with follow-up updated until 31 December 2011. The SEER registries identify 28% of all cancer cases in the USA. Medicare insures ~97% of all US citizens aged ≥65 years. Linkage to the SEER database is complete for ~93% of cases [3].

Study Population

Patients with a primary diagnosis of T1a N0 M0, unilateral kidney cancer between 2000 and 2009 were abstracted. Primary treatment was assessed during the first 6 months from diagnosis using an established claims-based algorithm [4] for treatment identification. LTA was defined according to ablative procedure-specific claims [5] (Table S1), while OBS was defined as absence of any kidney cancer-specific procedure claims. To ensure the evaluation of active follow-up cases, kidney cancer diagnoses that appeared only on death certificates were excluded. Patients treated with partial nephrectomy (PN) or radical nephrectomy (RN) were also excluded. This resulted in a cohort of 1 860 patients.

Study Design

The study was retrospective, observational and population-based, comparing CSM in patients managed with either LTA or OBS for T1a N0 M0 kidney cancer.

Covariates

Covariates consisted of age at diagnosis, gender, race (classified as white vs black vs other), marital status (classified as married vs unmarried vs unknown), socio-economic status (SES), a composite variable of income, education and poverty levels [6] and classified as high vs low, population density (urban vs rural), year of diagnosis, Charlson comorbidity index (CCI) derived from Klabunde's modification [7], tumour size and tumour histology (classified as clear-cell RCC vs non-clear cell RCC, namely papillary or chromophobe vs other/unknown) [8].

Outcomes

The main outcome of the study was CSM, defined as death from kidney cancer (CODPUB domain = 59). Death from any other cause was considered a competing cause of death. The duration of follow-up was measured as the interval between kidney cancer diagnosis and the Medicare date of death or last follow-up.

Statistical Analyses

Statistical analyses and reporting and interpretation of the results were conducted according to established guidelines [9], and consisted of four steps. First, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Mann–Whitney and chi-squared tests were used to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively. Second, with the aim of controlling for measurable baseline difference among patients undergoing LTA and those undergoing OBS, adjustment was performed using 1:1 propensity-score matching [10]. Propensity scores were computed using a logistic regression model with the dependent variable defined as the odds of receiving LTA vs OBS and the independent variables as age at diagnosis, gender, race, marital status, SES, population density, year of diagnosis, baseline CCI and tumour size. Subsequently, covariate balance between the matched groups was examined [11]. Third, estimates of 5-year CSM rates in the post-propensity-score-matched cohort were plotted using a smoothed Poisson regression method. Finally, a multivariable competing risks regression [12] model testing the effect of LTA vs OBS on CSM was fitted. In addition to adjustment for OCM, the model also controlled for age, tumour size, CCI and tumour histology.

All statistical tests were performed using an RStudio [13] software environment for statistical computing and graphics (Version 0.98). All tests were two-sided with P values <0.05 taken to indicate statistical significance.

Results

Baseline Characteristics

Overall, 1 860 patients were included in the study (Table 1). Most patients were managed with OBS (70%; n = 1 307), while fewer patients (30%; n = 553) were treated with LTA. Patients treated with LTA were younger (median age 77 vs 78 years; P < 0.001), more likely to be white (84 vs 78%; P = 0.005), more likely to be married (59 vs 52%; P = 0.02) and more frequently of high SES (54 vs 45%; P = 0.001).

Table 1 Descriptive characteristics of 1 860 patients treated with local tumour ablation (n = 553) or observation (n = 533) for T1a kidney cancer, who were included in the Surveillance, Epidemiology, and End Results-Medicare database, 2000–2009.

Variable	Before propensity-score matching			After propensity-score matching		
	LTA (n = 553)	OBS (n = 1 307)	P	LTA (n = 553)	OBS (n = 553)	P*
Age, years						
Median	77	78	<0.001	77	76	0.6
IQR	71–82	72–84		71–82	71–84	
Gender, *n* (%)						
Male	308 (56)	778 (60)	0.1	308 (56)	322 (58)	0.4
Female	245 (44)	529 (40)		245 (44)	231 (42)	
Race, *n* (%)						
White	463 (84)	1 022 (78)	0.005	463 (84)	452 (82)	0.7
Black	45 (8)	175 (14)		45 (8)	52 (9)	
Other	45 (8)	110 (8)		45 (8)	49 (9)	
Marital status, *n* (%)						
Married	325 (59)	677 (52)	0.02	325 (59)	315 (57)	0.8
Unmarried	206 (37)	568 (43)		206 (37)	214 (39)	
Unknown	22 (4)	62 (5)		22 (4)	24 (4)	
SES, *n* (%)						
High	297 (54)	593 (45)	0.001	297 (54)	283 (51)	0.4
Low	256 (46)	714 (55)		256 (46)	270 (49)	
Population density, *n* (%)						
Urban	480 (87)	1 086 (83)	0.053	480 (87)	476 (86)	0.8
Rural	73 (13)	221 (17)		73 (13)	77 (14)	
Year of diagnosis*,†, *n* (%)						
2000–2004	34 (6)	530 (41)	<0.001	34 (6)	43 (8)	0.5
2005–2007	237 (43)	493 (37)		237 (43)	237 (43)	
2008–2009	282 (51)	284 (22)		282 (51)	273 (49)	
CCI, *n* (%)						
Median	2.1	2.1	0.08	2.1	2.1	0.4
IQR	1.4–4.5	0–4.5		1.4–4.5	0–4.8	
Tumour size, mm						
Median	27	28	0.06	27	27	0.9
IQR	20–32	20–35		20–32	20–33	

*CCI, Charlson comorbidity index; IQR, interquartile range; LTA, local tumour ablation; OBS, observation; SES, socio-economic status. Data presented as frequencies and percentages unless otherwise specified. Frequency <11 cases masked for protection of patient confidentiality reasons, as per National Cancer Institute regulations. *All standard mean differences were <10%. †Grouped as categorical variable in the table for clarity purpose but computed in propensity-score matching as continuous variable.*

Overall, 497, 203 and 1 160 patients had clear-cell, non-clear cell (papillary or chromophobe) or other/unknown tumour histology, respectively. The median follow-up was 30 months among survivors.

After 1:1 ratio propensity-score matching for all covariates, 553 patients in the LTA group and 553 in the OBS group remained. The mean standardized differences of patient characteristics between the two groups were <10%, indicating a high degree of similarity in the distribution of all the covariates computed in the propensity-score matching in both groups. All subsequent analyses were based on the post-propensity-score matched cohort.

Survival

Overall, in the post-propensity-score-matched cohort, 200 deaths were recorded. Of those, 43 deaths were from kidney cancer and 157 were from other causes. The smoothed Poisson regression-derived 5-year CSM rates were 3.5 and 9.1% for LTA and OBS, respectively. These estimates result in a 5.6% absolute CSM difference. This difference in turn indicates that the use of OBS instead of LTA in 18 patients may contribute to one potentially avoidable cancer-specific death.

Prediction of Cancer-Specific Mortality

In multivariable competing risks regression analyses that adjust for OCM and covariates (Table 2), LTA exerted a protective effect on CSM relative to OBS (hazard ratio [HR] 0.47 [95% CI 0.25–0.89]; P = 0.02).

Discussion

Local tumour ablation and OBS are non-surgical options for the management of patients diagnosed with T1a N0 M0 kidney cancer [1,2]. We sought to examine the difference in CSM between LTA and OBS. Our hypothesis stated that a small, albeit significant, reduction in CSM might distinguish LTA from OBS. To test this hypothesis, we used the most contemporary version of the SEER-Medicare database (2000–2009), which represents the largest North American repository of oncological data.

Table 2 Competing risks regression analysis predicting cancer-specific mortality in 1 860 patients treated with local tumour ablation (n = 553) or observation (n = 533) for T1a kidney cancer, who were included in the Surveillance, Epidemiology, and End Results-Medicare database, 2000–2009.

Predictors	Multivariable competing risks regression predicting cancer-specific mortality	
	HR (95% CI)	P
Treatment		
Observation	1.00 (Reference)	–
Local tumour ablation	0.47 (0.25–0.89)	0.02
Age, years	1.05 (1.01–1.09)	0.02
Tumour size, mm	1.04 (1–1.08)	0.048
CCI	1.14 (1.03–1.27)	0.01
Histology		
Clear-cell RCC	1.00 (Ref.)	–
Non-clear-cell RCC	1.89 (0.66–5.41)	0.2
Other/Unknown	1.38 (0.67–2.84)	0.4

CCI, Charlson comorbidity index; HR, hazard ratio.

Our results confirmed our hypothesis and showed a larger-than-anticipated protective effect on CSM when LTA was used instead of OBS. The 5-year CSM estimates were 3.5% after LTA vs 9.1% after OBS. This difference in absolute estimates resulted in a number needed to harm of 18, when OBS was used instead of LTA, when CSM represented the endpoint of interest. Moreover, this difference translated into a relevant protective effect (HR 0.47 [95% CI 0.25–0.89]; P = 0.02) when LTA was compared with OBS, even after adjustment for OCM and various patient and tumour characteristics. These important observations are relevant with respect to clinical decision-making, when LTA is weighed against OBS, especially in the elderly.

To the best of our knowledge, the present study is the first direct comparison between the two treatment methods. Previously, several groups have reported on cancer control after LTA or OBS in selected non-comparative patient series. In the context of LTA, we observed a 5-year CSM of 0% in 104 patients with biopsy-proven kidney cancer treated with laparoscopic cryoablation [14] in an institutional study. Similarly, Lorber et al. [15] reported a 5-year CSM of 0% in an investigation of 103 radiofrequency ablation cases. Those reports originate from highly experienced tertiary care centres, however, and may not be representative of community practice. Moreover, they did not take into account OCM, which represents a key concept in elderly patients, and both these facts highlight the need for the present study.

Abouassaly et al. [16] studied 110 patients aged ≥75 years, who underwent OBS for renal masses of all sizes, with a median follow-up of 24 months, and reported a CSM of 0%. Similarly, Rosales et al. [17] reported on 223 renal masses in 212 patients, with a median follow-up of 35 months. The CSM rate reported in their study was 0.5%. In both studies, pathological diagnoses were unavailable in the majority of the patients. Consequently, both studies may have been critically contaminated by inclusion of individuals with benign lesions. The degree of contamination is substantially lower in the present study and may explain the discrepancy in observed CSM rates. It is also noteworthy that older patients, such as those included in the present study, have a higher risk of CSM. Additionally, loss to follow-up might be greater in institutional series than in the SEER database because of differences in referral patterns.

The present study contrasts with a study by Lane et al. [18]. In their retrospective institutional study of 537 patients, no difference was observed in CSM between active surveillance and nephron-sparing procedures, such as PN and LTA, and RN; however, these authors focused on patients aged ≥75 years. Moreover, there were significant differences in patient and tumour characteristics between the three comparison groups, and pathological confirmation of malignancy was not available in 94% of patients managed with active surveillance. This may have diluted the proportion of malignant histology to an unknown extent, similarly to the studies by Abouassaly et al. [16] and Rosales et al. [17], as previously discussed.

The present results corroborate the observed benefit of surgical management vs OBS, which was recently reported by Sun et al. [19] in a similar population of Medicare beneficiaries. Specifically, the absolute unadjusted CSM rates reported after PN (2.6%) and RN (4.5%) were similar to those observed after LTA in the present study (3.5%). This similarity corroborates the findings of several recent reports on the long-term efficacy of LTA, in which the latter performed similarly to PN [14,20–23]. The rates of OBS were also similar in both studies: 7.4% in the study by Sun et al. vs 9.1% in the present study. Moreover, the magnitude of the CSM benefit reported by Sun et al. after PN (HR 0.41) or RN (HR 0.47) relative to OBS was similar to that observed in the present study after LTA (HR 0.47) relative to OBS. Taken together, these findings further validate the results of the present study.

Interestingly, when sub-analyses focused on patients aged ≥75 years, Sun et al. [19] did not record any differences between surgical and non-surgical management, similarly to the study by Lane et al. [18] Unfortunately, we were not able to replicate such sub-analyses in the present study because of the limited number of CSM-specific deaths recorded in the overall population.

Even though we report a CSM benefit of LTA relative to OBS, it is important to state that the evaluation of the evaluation of oncological outcome alone is not sufficient to solve the clinical dilemma between LTA and OBS, as the decision should be based on cancer control and peri-operative morbidity considerations. A recent meta-analysis comparing the safety and efficacy of different types of LTA methods (cryoablation and radiofrequency) reported a complication rate of almost 20% [24]. It should be emphasized that complication rates may significantly differ between centres, LTA approach (open, laparoscopic, percutaneous) and LTA methods (cryoablation, radiofrequency ablation or other energy type). By contrast, the complication rate after OBS is null by definition.

Nonetheless, it is important to state that LTA results in acceptable peri-operative morbidity [25]. Moreover, LTA resulted in better peri-operative morbidity when compared with PN in another SEER-Medicare based observational study [26]. In consequence, it should be regarded as an attractive option in case of concern for peri-operative complications.

Despite its strengths related to its novelty and uniqueness, the present study has several limitations. First, it is based on a retrospective design. Ideally, LTA and OBS should be compared in a controlled fashion; however, as the first description of LTA for kidney cancer [27], such a randomized controlled trial has not been implemented yet and clinical decision-making lacks level 1 evidence-based recommendations. Hence, this important limitation is shared with all the available previous studies. It is noteworthy that the inherent risk of bias in population-based observational studies has been highlighted [28]. We attempted to partially compensate for this limitation by using propensity-score matching and competing risks regression to adjust to a maximum extent for any measurable difference between patients undergoing LTA and those undergoing OBS. Nonetheless, it is possible that there may be residual bias because of immeasurable differences between the two study cohorts.

Second, our definition of OBS includes patients who did not receive any primary treatment, regardless of their specific follow-up protocol. In this context, it cannot be directly compared with meticulous active surveillance protocols. In light of this, the important difference in terms of CSM-free survival observed between the LTA and OBS group might not be applicable to candidates for active surveillance protocols, where, in case of early progression, a timely treatment is administered, eventually attenuating the differences between the two cohorts with respect to CSM-specific survival [29].

Third, the present study is based on the SEER-Medicare cancer registry and, in consequence, the exclusion of individuals diagnosed with benign lesions might lead to the above-discussed overestimation of the benefit related to any type of active treatment vs non-interventional management. The lack of clinical information relative to clinical and radiological progression represents another limitation of the SEER-Medicare-based analyses.

Fourth, the median length of follow-up (30 months) is another limitation of the study; however, it is important to state that the limited life expectancy of the study population (median age at diagnosis 78 years) prevented the collection of an extended follow-up. Moreover, patients treated in a contemporary era (2000–2009) only were included. On the one hand, such inclusion criteria result in a more homogeneous cohort that reflects the current practice patterns, on the other, it shortens follow-up length.

Fifth, the hypothesis that the impact of treatment type (LTA vs OBS) was different by increasing patient age or tumour size was tested and rejected using interaction terms-adjusted models (all $P > 0.05$); however, given the relatively low number of CSM deaths recorded in the present study, it is possible that the results of this sub-analysis might be underpowered.

Finally, our outcome of interest (CSM) was defined using death certificate information, which might not be considered ideal; however, when death certificate information validity was examined in the specific context of cancer, the definition was deemed appropriate [30] and it is widely established in studies focusing on kidney cancer [31,32].

Despite the above-mentioned limitations, the present comparison of LTA vs OBS study represents a relevant reference point when considering either treatment method over competing management options.

In conclusion, after adjustment for patient and tumour characteristics in elderly patients diagnosed with T1a kidney cancer, LTA resulted associated with a clinically and statistically significant protective effect on CSM, compared with OBS. This advantage of LTA deserves consideration when obtaining patients' informed consent.

Conflict of Interest

None declared.

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Abbreviations: LTA, local tumour ablation; OBS, observation; CSM, cancer-specific mortality; SEER, Surveillance, Epidemiology, and End Results; OCM, other-cause mortality; PN, partial nephrectomy; RN, radical nephrectomy; SES, socio-economic status; CCI, Charlson comorbidity index; HR, hazard ratio.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 International classification of diseases, 9th revision, and current procedural terminology codes for treatment definitions.

