CLINICAL STUDY

Recurrence of differentiated thyroid cancer in the elderly

Christopher S Hollenbeak^{1,2,3}, Melissa M Boltz^{1,2}, Eric W Schaefer³, Brian D Saunders^{2,4} and David Goldenberg^{2,5}

¹Division of Outcomes Research and Quality, Department of Surgery and ²Department of Surgery, College of Medicine, The Pennsylvania State University, 500 University Drive, Hershey, Pennsylvania 17033, USA, ³Department of Public Health Sciences, College of Medicine, The Pennsylvania State University, 600 Centerview Drive, Hershey, Pennsylvania 17033, USA, ⁴Division of General Surgery and Surgical Oncology and ⁵Division of Otolaryngology, Department of Surgery, College of Medicine, The Pennsylvania State University, 500 University Drive, Hershey, Pennsylvania 17033, USA

(Correspondence should be addressed to C S Hollenbeak who is now at Department of Surgery, College of Medicine, The Pennsylvania State University, 600 Centerview Drive, A210, Hershey, Pennsylvania 17033, USA; Email: chollenbeak@psu.edu)

Abstract

Objective: Data from the Surveillance Epidemiology and End Results Medicare-linked database were used to estimate the incidence of and risk factors associated with recurrent thyroid cancer, and to assess the impact of recurrence on mortality following diagnosis, controlling for mortality as a competing risk.

Design: We identified 2883 patients over 65 years of age diagnosed with a single, primary well-differentiated thyroid cancer between 1995 and 2007. A recurrence was considered if the patient had evidence of I-131 therapy, imaging for metastatic thyroid carcinoma, or complete thyroidectomy beyond 6 months of diagnosis. Competing risk regressions were performed using Cox proportional hazards models with 1- and 2-year landmarks.

Results: Recurrence was observed in 1117 (39%) of the 2883 patients in the cohort. Age, stage, and treatment status were significant risk factors for developing recurrent disease ($P < 0.0001$). Patients with recurrent disease had a higher risk of all-cause mortality within 10 years of diagnosis than patients with no recurrence at 1- and 2-year landmarks. Patients with follicular histology and a recurrence were less likely to die from cancer (hazard ratio 0.54; $P = 0.03$) than patients with no recurrence.

Conclusions: The rate of recurrence of well-differentiated thyroid carcinomas in this sample of elderly patients was 39%. Extent of disease and older age negatively impacted the risk of recurrence from differentiated thyroid cancer. In these data, patients with follicular histology and a recurrence were less likely to die, suggesting that mortality and recurrence are competing risks. These data should be taken into account with individualized treatment strategies for elderly patients with recurrent malignant thyroid disease.

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Introduction

The incidence of well-differentiated thyroid cancer for all ages in the USA has more than doubled since the early 1970s with the median time of diagnosis being 50 years of age. Between 1996 and 2005, the incidence rose annually by 5.8% among men and 7.1% among women, a more rapid increase than any other cancer site. Although the incidence is rising steadily, thyroid cancer is still relatively uncommon as only 45 000 cases are diagnosed per year (1).

Prognosis for well-differentiated thyroid cancer remains excellent, and its associated mortality has not changed in the past 35 years over all ages. In the 1990s, well-differentiated (papillary and follicular) thyroid cancer had an expected 10-year survival of 90% or greater, exclusive of other causes of mortality. Even patients with distant metastatic disease live many years

before succumbing to their disease or dying of other causes. The literature suggests that ~55% of patients who present with pulmonary metastases and thyroid cancer survive at least 10 years (1, 2).

Recurrence of thyroid cancer is not unusual, and the literature suggests that it has an impact on mortality. Coburn *et al.* (2) suggested that patients who develop recurrent disease after curative treatment do not fare as well as those with no recurrence, with 50–60% eventually dying of the disease. The ability to detect recurrent disease has improved in recent years. In the past, surveillance to detect persistent or recurrent differentiated thyroid carcinoma did not include sensitive serum thyroglobulin assays or neck ultrasonography by experienced technicians. Therefore, many patients appeared to be cured by initial therapy of total thyroidectomy with or without lymph node dissection and radioactive iodine (I-131) ablation

therapy to the remnant tissue only to have recurrent disease found years later (3).

Although most cases of thyroid cancer are diagnosed before 55 years of age (American Cancer Society. Thyroid cancer. Available from URL: <http://www.cancer.org/Cancer/ThyroidCancer/DetailedGuide/thyroid-cancer-key-statistics> (accessed April 29, 2011)), it does occur frequently among elderly patients over 65 years of age at an incidence of ~20%. Furthermore, the implications for recurrent disease may be very different in the elderly population than among younger patients. Older patients are at greater risk of other health conditions to which they may succumb, lessening the health burden of the recurrent thyroid cancer. Assessing the rate of recurrence of thyroid cancer and the impact of thyroid cancer recurrence on mortality is made more challenging by the fact that recurrence and mortality are competing risks. Patients who die will not recur, and a recurrence suggests that patients survived long enough for the event to happen. This must be accounted for in any analysis of thyroid cancer recurrence and its impact. The objective of this study was to use data from the Surveillance Epidemiology and End Results (SEER) (4) Medicare-linked database to study recurrent well-differentiated thyroid cancer in the elderly. We identified risk factors associated with recurrent thyroid cancer of well-differentiated histology among elderly Medicare patients, and assessed the impact of recurrence on a 5-year survival after controlling for patient-, disease-, and treatment-related variables, as well as competing risks with mortality.

Materials and methods

Data

Data for this study were from the SEER-Medicare-linked database of the National Cancer Institute (NCI) (4). The SEER program is a national tumor registry that collects data on ~26% of the US population, and reports cancer incidence and survival in the USA (National Cancer Institute. Surveillance Epidemiology and End Results. Available from URL: <http://seer.cancer.gov/> (accessed April 29, 2011)). The SEER-Medicare-linked database contains the subset of Medicare enrollees in the SEER registry. It then links these patients to all Medicare claims records. Thus, using the Medicare billing claims data, it is possible to identify specific types of resource utilization in the combined SEER-Medicare data. We exploit this feature of the data in order to identify recurrent thyroid cancer based on utilization of specific procedures commonly used to diagnose and treat recurrent disease.

Our analysis was limited to elderly adult Medicare enrollees (65 years and older) diagnosed with a single, unifocal primary thyroid cancer (papillary or follicular

between 1995 and 2007. Data from the SEER registry included demographics (age, gender, race/ethnicity, location of residence), stage at diagnosis (local, regional, distant, unstaged), therapy (surgical intervention, radioisotope therapy with surgery, chemotherapy), and survival (duration from diagnosis until death). We also included only patients who survived at least through the first year so that recurrence could be possible. The final analysis data set contained 2883 patients.

Recurrence definition

Recurrence of disease is not recorded as such in the SEER registry (American Thyroid Association. ICD-9 codes recommended to Medicare by the ATA. Available from URL: <http://www.thyroid.org/professionals/advocacy/icd9.html> (accessed April 1, 2010)). Therefore, we identified recurrence through billing records for procedures that are not commonly used except in such cases. Billing codes included a combination of International Classification of Diseases 9th Version, Clinical Modification (ICD9-CM), Current Procedural Terminology (CPT) codes and Healthcare Common procedure Coding System (HCPCS) codes. Patients were classified as having recurrent thyroid cancer if they were undergoing injection of I-131 (ICD9-CM 92.28), therapeutic I-131 injection (HCPCS A9530) with thyroid uptake on nuclear imaging (CPT 78000), thyroid carcinoma nuclear medicine imaging for metastasis (CPT 78015), had thyroid carcinoma metastases imaging whole-body nuclear imaging (CPT 78018) or with additional studies (CPT 78016), total or complete thyroidectomy (CPT 60240), thyroid lobectomy (CPT 60220), subtotal or partial thyroidectomy (CPT 60271), subtotal or total thyroidectomy for malignancy with limited neck dissection (CPT 60252), thyroidectomy with radical neck dissection (CPT 60254), thyroidectomy substernal with sternal split (CPT 60270), or modified radical neck dissection (CPT 38724), more than 6 months after their initial diagnosis date and procedure (total or hemithyroidectomy and/or I-131 therapy). While we recognize that this algorithm cannot perfectly capture recurrent disease, these are procedures that are very infrequently received among thyroid cancer patients except in the case of recurrent disease.

Statistical analysis

Statistical analysis was designed to identify risk factors for recurrent thyroid cancer in the SEER population, and to estimate the impact of recurrence on cancer-specific mortality, controlling for other patient and disease characteristics that may also impact survival. Summary statistics for patient characteristics, cancer stage, histology, and treatment, stratified by recurrence, are presented using χ^2 and Wilcoxon tests to test for differences between groups. Time to recurrence

was defined as the time from the date of diagnosis to the date of the first recurrence treatment code at least 6 months after diagnosis. Patients who were alive and free from recurrence at their last follow-up were censored. Death prior to recurrence is a competing risk that must be accounted for in the analysis. Traditional Kaplan–Meier survival method is not appropriate as the method assumes that censored individuals remain at risk for recurrence. This is violated for patients who die prior to recurrence. Therefore, cumulative incidence curves were used to estimate the time to recurrence curves in the presence of the competing risk of death.

As an alternative, we used a landmark Kaplan–Meier analysis at 1 and 2 years. In this analysis, only patients that are alive at the landmark are included in the analysis. Patients who have recurred prior to the landmark are classified as having recurrence, and patients who have not recurred prior to the landmark are classified in a comparison group, even if recurrence occurred after the landmark. Kaplan–Meier curves were created for these groups beginning at the time of the landmark. One limitation to the landmark approach is that we must select a landmark before conducting the data analysis and patient data are explicitly excluded in the estimation of the survival curves. In addition, the interpretation is conditional on the time point chosen.

Multivariate analysis of survival was also performed using a Cox proportional hazards model with a time-varying covariate. In this model, all patients are initially grouped as 'no recurrence' at baseline. Once a recurrence is observed, the patient group status is changed to 'recurrence' at the time (month) of recurrence. Comparisons of recurrence vs non-recurrence were based only on those time points that have both recurrent and non-recurrent patients. The multivariable model includes adjustments for baseline patient characteristics. All statistical analyses were performed using SAS software (version 9.2; Cary, NC, USA). All tests were two-sided and statistical significance was defined as a P value <0.05 .

Results

Recurrence

Using data from the SEER database, 2883 patients were identified with either primary papillary or follicular thyroid cancer (FTC) between 1995 and 2007. Of this group, 1117 patients developed recurrence at some point according to our measure (38.7%, average length of follow-up was 5 years). Characteristics of the patients stratified by recurrence are presented in Table 1, which shows that these groups were similar in demographic characteristics such as gender ($P=0.57$), race ($P=0.33$), and urbanicity ($P=0.56$). The groups were

Table 1 Characteristics of the patient cohort stratified by recurrence.

Variables	No recurrence <i>n</i> =1757	Recurrence <i>n</i> =1126	<i>P</i> value
Age at diagnosis (years)			<0.0001
Mean (s.d.)	74.6 (6.53)	72.8 (5.46)	
Median	74	72	
Range	66.0–99.0	66.0–94.0	
Age at diagnosis (group)			<0.0001
66–69 years	492 (28%)	398 (35.3%)	
70–74 years	469 (26.7%)	334 (29.7%)	
75–79 years	404 (23%)	238 (21.1%)	
80+ years	392 (22.3%)	156 (13.9%)	
Sex			0.7231
Female	1273 (72.5%)	809 (71.8%)	
Male	484 (27.5%)	317 (28.2%)	
Race			0.3311
White	1373 (78.1%)	897 (79.7%)	
Non-white	384 (21.9%)	229 (20.3%)	
Urban/rural code			0.6012
Big metro	1051 (59.8%)	658 (58.4%)	
Metro/urban	558 (31.8%)	362 (32.1%)	
Less urban/rural	148 (8.4%)	106 (9.4%)	
Historic stage			<0.0001
Localized	1073 (61.1%)	493 (43.8%)	
Regional	424 (24.1%)	500 (44.4%)	
Distant	195 (11.1%)	104 (9.2%)	
Unstaged	65 (3.7%)	29 (2.6%)	
Histology			0.1541
Papillary	1539 (87.6%)	1006 (89.3%)	
Follicular	218 (12.4%)	120 (10.7%)	
Treatment			<0.0001
None	161 (9.2%)	24 (2.1%)	
Surgery only	1062 (60.4%)	368 (32.7%)	
Surgery and radioisotopes	383 (21.8%)	598 (53.1%)	
Other (chemo, non-radioisotope radiation)	151 (8.6%)	136 (12.1%)	

also similar in terms of histology ($P=0.19$). There were, however, characteristics that were suggestive of risk factors for recurrence, which include age, stage, and treatment (all $P<0.0001$). Regional disease was present in 44% of the recurrence group and in only 24% of the control group. In addition, only 32% of the recurrence group received single modality surgery while 61% of patients who did not experience recurrence had single modality surgery. Moreover, while 53% of the recurrence group had surgery and radioisotope therapy (I-131) as part of their initial treatment, only 22% of the non-recurrence group had the same treatment, indicating that I-131 is a marker of more aggressive disease.

The overall cumulative incidence for recurrence in the presence of the competing risk of death, as well as cumulative incidence stratified by histology, is presented in Fig. 1. In Fig. 1A, B and C, a majority of thyroid cancer recurrence occurred within the first 2 years of diagnosis. After the first 2 years of diagnosis, the probability of developing recurrent thyroid cancer within 10 years never exceeded 45%.

Figure 1 Univariable cumulative incidence curve for recurrence in the presence of competing risk of death and cumulative incidence curves stratified by histology. (A) All patients, (B) papillary and (C) follicular.

All-cause mortality

Of the 2883 patients diagnosed with thyroid cancer, 662 (23%) patients died. Thyroid cancer represented the cause of death in 273 (41.2%) of those patients or 9% of the patients overall. Figure 2a presents 10-year all-cause mortality stratified by recurrent disease status at a landmark of 1 year. Without controlling for other

factors, patients who had a disease recurrence had a higher risk of all-cause mortality within 10 years of diagnosis than patients with no recurrence; however, this was not statistically significant ($P=0.65$). A similar trend was observed at a landmark of 2 years ($P=0.99$; Fig. 2b).

Figure 3 presents 10-year all-cause mortality stratified by recurrent disease and histology. Interestingly, patients with follicular cancer and disease recurrence (Fig. 3C and D) had a lower risk of all-cause mortality within 10 years of diagnosis than patients with no recurrence at both 1-year ($P=0.61$) and 2-year ($P=0.09$) landmarks, but this was not statistically significant.

Table 2 presents the results of a Cox proportional hazards regression of all-cause mortality fit separately for papillary and FTC. Recurrence is estimated as a time-varying covariate. Among patients with papillary thyroid cancer (PTC) and controlling for other covariates, patients who had thyroid cancer recurrence were more likely to die (hazard ratio (HR) 1.13; $P=0.27$) than patients with no recurrence, but this was not statistically significant. Other factors also contributed

Figure 2 Kaplan-Meier curves for recurrence status at landmarks of (a) 1 and (b) 2 years.

Figure 3 Kaplan–Meier curves for recurrence status for each histology at landmarks of (A and C) 1 and (B and D) 2 years.

to all-cause mortality with the papillary group. For example, patients (HR 1.50; $P < 0.001$) with regional (HR 1.68; $P < 0.001$) or distant (HR 4.52; $P < 0.001$) thyroid disease had a significantly increased risk of all-cause related death. In addition, patients who had treatment other than surgery or I-131 therapy (HR 1.99; $P < 0.001$) or no treatment at all (HR 4.39; $P < 0.001$) had an increased all-cause mortality risk. I-131 therapy in conjunction with surgery was a protective factor (HR 0.77; $P = 0.024$) when assessing mortality from all causes.

Unlike papillary cancer, recurrence in patients with follicular cancer was protective against all-cause mortality (HR 0.54; $P = 0.03$). The only significant risks of all-cause mortality in patients with follicular cancer were older age and stage of disease. Distant disease increased mortality by 593% ($P < 0.001$). As with PTC, patients with FTC who underwent surgery and I-131 therapy were 31% less likely to die ($P = 0.21$).

Discussion

Thyroid cancer is the most common malignancy of the endocrine system. There were 44 670 cases diagnosed in the USA in 2010. Well-differentiated tumors (papillary or follicular) are highly treatable and usually curable. Medullary or anaplastic tumors are much less common, more aggressive, metastasize early, and have a much poorer prognosis. Factors such as age, sex, size of the tumor, stage of disease, presence of extrathyroidal spread, and completeness of resection have been found to significantly influence prognosis and outcomes (5, 6).

Well-differentiated thyroid carcinoma (WDTC) is associated with good outcomes in the majority of patients. In prior series, the recurrence rates for WDTC have been reported to be 20–30% (2, 7). The overall rate of recurrence for WDTC in our series of elderly Medicare patients was 39%, which is 10 percentage points above the range of prior studies. As with other studies, recurrence in our study had a significantly negative impact on patient outcomes, but only for patients with papillary disease. In one study, 50–60% of patients with differentiated thyroid cancer who recurred eventually died of their disease (2).

Since many studies are based on single institutional series, and because PTC is overwhelmingly more common than FTC, many studies combine the two types of WDTC together in their findings. Previous reports suggest that the rate of recurrence for PTC is ~25% (8), while the rate of recurrence for FTC is ~18% (9). Rates of recurrence in this study were not similar. Of the patients who developed a recurrence, 89.3% had PTC and 10.7% had FTC. We found those with FTC had a decreased risk for developing thyroid cancer recurrence when compared with those with PTC.

The risks of metastasis and recurrence have been summarized by the American Joint Committee

Table 2 Multivariable Cox model fit separately for papillary and follicular thyroid cancer.

	Papillary		Follicular	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, 5-year increase	1.46 (1.32–1.61)	<0.001	1.24 (1.01–1.51)	0.04
Sex				
Male	1.05 (0.80–1.39)	0.72	0.87 (0.52–1.46)	0.6
Female	Reference		Reference	
Race				
White	Reference		Reference	
Non-white	0.86 (0.62–1.18)	0.35	0.89 (0.52–1.52)	0.66
Urban/rural code				
Big metro	Reference		Reference	
Urban/metro	0.97 (0.72–1.30)	0.84	1.01 (0.59–1.73)	0.98
Rural	1.34 (0.89–2.01)	0.17	1.86 (0.87–3.99)	0.11
Historic stage				
Localized	Reference		Reference	
Regional	4.90 (3.20–7.51)	<0.001	3.18 (1.19–8.45)	0.02
Distant	16.97 (10.79–26.71)	<0.001	17.78 (7.04–44.89)	<0.001
Unstaged	0.76 (0.32–1.82)	0.54	1.24 (0.14–10.84)	0.85
Number of comorbidities				
0	Reference		Reference	
≥ 1	1.10 (0.79–1.53)	0.58	0.79 (0.43–1.46)	0.46
Treatment				
Surgery	Reference		Reference	
Surgery and radioisotopes	0.98 (0.67–1.44)	0.93	0.55 (0.24–1.26)	0.16
Other	3.47 (2.38–5.06)	<0.001	1.18 (0.60–2.33)	0.63
None	7.98 (5.03–12.68)	<0.001	1.76 (0.85–3.65)	0.13
Recurrence				
Yes	1.96 (1.40–2.73)	<0.001	0.58 (0.27–1.25)	0.16
No	Reference		Reference	

HR, hazard ratio.

on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN) (NCCN and AJCC/IUCC thyroid carcinoma practice guidelines. Available from URL: http://www.nccn.org/physician_gls/fguidelines.html 2003) (accessed November 5, 2011)) and are related to both patient- and tumor-related factors. Sex is considered as an independent risk factor in well-differentiated thyroid cancer, with males typically having a more aggressive disease course. In our study, 71.8% of females as opposed to 28.2% of males developed recurrent disease, which was not a statistically significant difference from those with no recurrence. Age has also been considered as an important factor for well-differentiated thyroid cancer. For patients below the age of 40 years, mortality rate at the time of diagnosis is low and increases progressively after the age of 40 years. Patients who are older than 65 years, when compared with patients younger than 40 years, often develop locally aggressive tumors and have clinical recurrences (10). We, too, found similar evidence that older age significantly impacts outcome for WDTC.

Racial disparities in thyroid cancer have been reported. The incidence of thyroid cancer in African Americans is significantly lower than in white Americans. In fact, thyroid cancer is half as common in the African American population as in the white population (11). A number of studies have investigated racial disparities in incidence and outcome in thyroid

cancer (12). Mitchell *et al.* (13) found that although African American patients were more likely to harbor larger neoplasms, mortality and survival were not significantly different. Recently, Yu *et al.* (14) concluded that African American patients had a lower 5-year survival from PTC than other racial or ethnic groups, but not from other thyroid cancer histology. In the current study, only 20.3% of non-white patients developed recurrence compared with 79.7% of whites, but was not statistically significantly different from those with no recurrence.

Regional disease was present in 44% of the recurrence group and in only 24% of patients without recurrence ($P < 0.0001$). This may suggest that regional metastasis at diagnosis puts patients at higher risk for recurrence.

Postoperative I-131 therapy for well-differentiated thyroid cancer has been advocated for several reasons, which include treatment of possible residual disease, and ablation of residual thyroid tissue to allow more accurate follow-up of the patient with whole-body I-131 scans and serum thyroglobulin measurements. Radioiodine therapy in patients with differentiated thyroid cancer has resulted in decreased recurrences, regardless of whether patients had known residual disease (8) or no known residual disease (15). In our study, 53% of the recurrence group had received radioisotope therapy (I-131), while only 22% of the control (non-recurrent)

group ($P < 0.0001$) had undergone the I-131 treatment. It is not clear whether this difference represents actual practice in the elderly Medicare population or whether it represents a limitation of the data. In addition, use of I-131 therapy may indicate more advanced disease.

The most important departure from the literature in our findings was that patients who had FTC with recurrence were less likely to die from all causes than patients without a recurrence. There are several possible explanations for this finding. First, it may call into question the use of billing data to identify recurrence. However, the specific procedure codes we used to identify recurrence are rarely used outside the context of a recurrence. Furthermore, the fact that the rate of recurrence in the aggregate histologies was similar to previous studies lends face validity to our billing code proxy. The most likely explanation is that recurrence and mortality are competing risks that are more important in an older population. Some time is required for micrometastases to grow into full-blown recurrence. In a younger population where thyroid cancer is seen most often, it would be rare for a patient not to outlive the recurrence. However, in a study population whose average age is 73 years, this may not be the case. We suspect that many elderly patients in our population are not living long enough for recurrence to become a reality. Recurrence, then, in the elderly population becomes an indicator that a patient has survived longer. The longer survival observed among the population who recurred does not suggest that recurrence contributed to survival, but rather it is an indicator of a patient who would or who has survived longer independent of the recurrence.

The primary limitation of this study is the lack of a clinical variable in the SEER registry to indicate recurrence. We therefore relied on evidence from billing data of I-131, nuclear imaging for metastatic thyroid carcinoma, additional thyroid operations, or lymph node dissection beyond 6 months of diagnosis to suggest recurrence. While our proxy measure has face validity, as mentioned previously, there is still the chance that this measure missed patients who did not receive iodine treatment or who underwent no treatment or non-conventional treatment for their thyroid cancer. It may also have erroneously counted patients who underwent treatment for their primary cancer in a delayed fashion and did not actually have a recurrence. In addition, our analysis is unable to account for persistent disease beyond 6 months of diagnosis. However, given that thyroid cancer is a surgically treated disease, the likelihood of having persistent disease is low. Another limitation is that because our population is the elderly Medicare population, our results do not generalize to a younger population where thyroid cancer is more prevalent.

To our knowledge, this study represents the largest series of recurrent well-differentiated thyroid cancer in

the elderly Medicare population. We found an overall recurrence risk of 39% of the 2883 patients in the cohort. In this population, patients with regional disease and distant metastases were at greater risk for developing recurrent disease. Those with PTC were at greater risk for recurrence than those with FTC. Sex and racial difference impacted the chance of recurrence but were not statistically significant. Patients with FTC and recurrent disease had significantly longer survival, most likely suggesting a competing risk between recurrence and mortality. This may be important when considering treatment strategies for recurrent FTC in the elderly population. Additional research is needed in order to study the economic implications of recurrent thyroid cancer in the elderly.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Disclaimers: The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

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Author contribution statement

All authors contributed equally to the writing and revising of the manuscript. Dr C S Hollenbeak and Dr M M Boltz contributed to the study design. Mr E W Schaefer performed the statistical analysis. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

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