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Octreotide Long-Acting Repeatable among Elderly Patients with Neuroendocrine Tumors: A Survival Analysis of SEER-Medicare Data

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Abstract

Background: Octreotide long-acting repeatable (LAR) is approved in the United States for the management of carcinoid syndromes among patients with neuroendocrine tumors (NET). The objective of our study is to evaluate the impact of octreotide LAR on overall survival (OS), as it has not been established.

Methods: NET patients of 65 years and older diagnosed between January 1999 and December 2009 were identified from the SEER-Medicare database. We compared the OS of NET patients who started octreotide LAR within 12 months of diagnosis with those who did not receive it during the same period. We conducted Kaplan–Meier estimations and Cox proportional hazard models to examine the association between octreotide LAR and OS.

Results: Among 1,176 distant stage patients, 233 (20%) received octreotide LAR within 12 months of diagnosis, compared with 2% (96 in 5,764) of local/regional stage patients. Median OS for patients who started octreotide LAR within 12 months was 35.22 months [95% confidence interval (CI), 27.96–47.77], longer than those who did not receive it (19.15 months; 95% CI, 16.36–22.80; $P < 0.0001$). Multivariate analysis showed that octreotide LAR was associated with significant survival improvement for distant stage patients (HR, 0.68; $P < 0.001$) and in the subgroups with (HR, 0.65; P, 0.003) and without (HR, 0.55; P, 0.002) carcinoid syndrome. No survival benefit was found among local/regional stage patients.

Conclusion: This population-based study suggests potential survival benefits of octreotide LAR among elderly distant stage NET patients, both with or without carcinoid syndrome.

Impact: The study provides population-based evidence of a positive association between octreotide LAR and overall survival among elderly distant stage NET patients. *Cancer Epidemiol Biomarkers Prev; 24(11); 1656–65. ©2015 AACR.*

Introduction

The incidence of neuroendocrine tumors (NET) has been on the rise in the United States, increasing from 1.09 per 100,000 in 1973 to 5.25 per 100,000 in 2004 (1). Although well-differentiated NETs have a more indolent course than adenocarcinoma of corresponding primary site, they are nonetheless incurable when metastases are present. NETs are often classified by functional status. Although the majority of NETs are nonfunctional, functional tumors secrete serotonin and other hormonal peptides that bring additional symptom burdens. For example, pancreatic NETs can secrete gastrin, glucagon, insulin, and vasoactive intestinal peptide and cause symptoms related to acid hypersecretion, glucose metabolism, and diarrhea. Midgut NETs, including those arising from jejunum, ileum, appendix, and proximal large bowel, are more likely to secrete serotonin and bioactive substances that lead to the classic carcinoid syndrome with flushing and diarrhea. Because of the hepatic inactivation of these hormones, hormonal symptoms from midgut NETs usually only occur in the setting of distant metastases. In contrast, foregut carcinoid tumors of lung and thymus can cause atypical carcinoid syndrome with flushing in the absence of distant metastasis (2).

Although somatostatin analogues are widely approved and recommended for the control of hormonal syndrome from NETs, treatment options for oncologic control remain limited. Recent phase III clinical trials have led to the approval of mammalian target of rapamycin inhibitor, everolimus, and vascular endothelial growth factor receptor inhibitor, sunitinib, for the therapy of advanced pancreatic NETs (3–5). Lanreotide became the first therapy approved by the FDA for the treatment of pancreatic and gastrointestinal neuroendocrine tumors to improve progression-free survival in December, 2014. Since the initial approval of octreotide in 1988, many have speculated that somatostatin analogue has antiproliferative effect. Recently, two placebo-controlled studies (PROMID and CLARINET) have demonstrated that somatostatin analogues delay time to progression in patients with advanced NETs (6, 7). The impact of somatostatin analogues on overall survival, however, has been more difficult to assess in clinical trials. Because of the longer survival experienced by these patients, prospective studies evaluating overall survival will require thousands of patients and long follow-up. The wide availability of somatostatin analogues will also mean that the study will likely be confounded by crossover whether on study or off study. Such challenges make it nearly impossible to establish overall survival benefits using traditional clinical trials. Therefore, observational study is a feasible alternative because of the large number of patients in the data, long follow-up time, and

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information on other treatments that can be captured in the data and adjusted in the analyses.

The objectives of our current study are to evaluate the effect of octreotide LAR on overall survival among patients with NET with and without carcinoid syndrome using population-based data and also investigate the impacts of tumor characteristics, other treatments patients received, sociodemographic factors on survival. We limited this study to elderly patients because the data source we employed provides reasonably reliable information on patients 65 years of age and older.

Materials and Methods

Data source

We used the Surveillance, Epidemiology, and End Results (SEER) registry data from the NCI linked with Medicare claims data. The SEER registries collect information on tumor characteristics, demographic, and cause of death information for persons diagnosed with cancer in the United States; the registries cover approximately 28% of the U.S. population. The linkage to Medicare claims data adds information on neighborhood socioeconomic status (SES), and date of death, and allows the ascertainment of treatments received by patients as well as their comorbidity through the use of International Classification of Disease 9th Revision (ICD-9), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes in Medicare claims. The SEER-Medicare data are widely used in the literature and considered demographically representative (8).

Study cohort

Our study cohort included 6,940 elderly cancer patients who were diagnosed with NET between July 1st, 1999, and December 31st, 2009, and followed up until December 31st, 2011, in terms of survival information. The latest claims date available in the SEER-Medicare data at the time of this research was December 31st, 2010. We identified NET patients using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes: 8150, 8151, 8152, 8153, 8154, 8155, 8156, 8157, 8240, 8241, 8242, 8243, 8244, 8245, 8246, and 8249. We excluded patients with unknown stage, histologic grade 3, 4, or unknown, or missing values for covariates, as well as those younger than 65 years old at diagnosis. We also excluded patients who enrolled in Health Maintenance Organizations (HMOs) or without continuous Medicare Parts A and B enrollment so as to ensure the completeness of medical claims to identify octreotide LAR use and other treatments received by patients. Table 1 provides a detailed flowchart for the inclusion and exclusion criteria of our study cohort.

Explanatory variables

We conducted multivariate analyses to examine the association between octreotide LAR and overall survival. Key explanatory variables included the use of octreotide LAR and the presence of carcinoid syndrome. We identified octreotide use via HCPCS codes (J-2353 and J-2352). Patients with these codes in their Medicare claims within 12 months of the NET diagnosis were considered users of octreotide LAR.

The carcinoid syndromes considered in this article were defined as the conditions approved for octreotide LAR: flushing, diarrhea, or carcinoid syndrome (functional NETs). They were identified using ICD-9 codes: flushing (782.62), diarrhea (564.5, 787.91), and carcinoid syndrome (259.2). The presence of carcinoid syndrome is defined as having at least 2 claims for flushing, diarrhea, or carcinoid syndrome: (i) with the earliest one before the start of octreotide LAR treatment for those who received treatment within 12 months of diagnosis; or (ii) within the 12 months of diagnosis for those who did not receive treatment within 12 months of diagnosis.

Other explanatory variables in our multivariate analyses were demographics, neighborhood SES, comorbidity scores, tumor characteristics, and other treatments received. The demographic information included age (65–69, 70–74, 75–79, $\geq$ 80), gender (male vs. female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics, or all others), region (Northeast, West, Midwest, South), and urban/rural status (metropolitan vs. nonmetropolitan). The neighborhood SES included three variables in terms of quartiles: median household income, percent living in poverty, and percent with at least 4 years of college education. We used the Deyo–Romano-modified Charlson comorbidity score, which is a commonly adopted measure for comorbidities in studies using claims data, such as the SEER-Medicare data (9–12). The comorbidity score was derived from Medicare Provider Analysis and Review, Outpatient and Carriers claims files during the 12 months preceding diagnosis and categorized into three groups: zero, one, or at least two.

Tumor characteristics included tumor size, histologic grade, primary cancer site, and year of diagnosis. We categorized tumor size into four groups: <1 cm, 1–2 cm, >2 cm, and unknown. The histologic grade was classified into three categories: grade 1, grade 2, and unspecified (either grade 1 or 2). We classified primary cancer sites into six categories: larynx, bronchus, lung, trachea, and other respiratory organs; cecum and appendix; colon; small intestine; pancreas; and all others.

Other treatments were characterized by four binary variables (yes/no) indicating whether a patient received resection of primary tumor within 6 months of cancer diagnosis; resection of liver

Table 1. Flow chart for study sample construction

Step	Criteria	Number of patients included	Number of patients excluded
1	All patients diagnosed with NETs during 1999–2009	28,420	
2	Exclude if patients had histologic grade 3, 4, or unknown	19,314	9,106
3	Exclude if patients were younger than 65 in age at diagnosis	12,483	6,831
4	Exclude if patients had unknown stage of cancer	10,742	1,741
5	Exclude if the data were reported based on autopsy or death certificate	10,659	83
6	Exclude if patients enrolled in HMO or did not have continuous Part A and B enrollment within 12 months of the NET diagnosis, unless the patients died and had continuous Part A and B enrollment and no HMO enrollment till death	7,393	3,266
7.	Exclude if patients started octreotide treatment after 12 months of diagnosis	7,055	338
8	Exclude if patients had missing information on covariates	6,940	115

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Table 2. Description of the study sample by stage of NET and whether octreotide treatment was received

	Distant stage NET ($N = 1,176$)			Local and regional stage NET ($N = 5,764$)		
	Without octreotide treatment *N* (%)	With octreotide treatment *N* (%)	*P*	Without octreotide treatment *N* (%)	With octreotide treatment *N* (%)	*P*
Carcinoid syndrome			<0.0001			<0.0001
No	718 (76.14%)	57 (24.46%)		5,000 (88.21%)	25 (26.04%)	
Yes	225 (23.86%)	176 (75.54%)		668 (11.79%)	71 (73.96%)	
Age, y			0.0154			0.6322
65–69	223 (23.65%)	60 (25.75%)		1,600 (28.23%)	29 (30.21%)	
70–74	242 (25.66%)	73 (31.33%)		1,426 (25.16%)	27 (28.13%)	
75–79	217 (23.01%)	59 (25.32%)		1,259 (22.21%)	22 (22.92%)	
≥80	261 (27.68%)	41 (17.60%)		1,383 (24.40%)	18 (18.75%)	
Gender			0.0079			0.9175
Male	390 (41.36%)	119 (51.07%)		2,397 (42.29%)	40 (41.67%)	
Female	553 (58.64%)	114 (48.93%)		3,271 (57.71%)	56 (58.33%)	
Race/ethnicity			0.5024			0.5583
Non-Hispanic white	788 (83.56%)	202 (86.70%)		4,443 (78.39%)	76 (79.17%)	
Non-Hispanic black	90 (9.54%)	18 (7.73%)		647 (11.41%)	Masked[a]	
Hispanic or others	65 (6.89%)	13 (5.58%)		578 (10.20%)	Masked[a]	
Region			0.0205			0.0416
Northeast	158 (16.76%)	55 (23.61%)		1,063 (18.75%)	29 (30.21%)	
Midwest	150 (15.91%)	46 (19.74%)		910 (16.06%)	12 (12.50%)	
South	226 (23.97%)	46 (19.74%)		1,391 (24.54%)	20 (20.83%)	
West	409 (43.37%)	86 (36.91%)		2,304 (40.65%)	35 (36.46%)	
Urban/rural status			0.1298			0.3990
Metropolitan	833 (88.34%)	214 (91.85%)		5,082 (89.66%)	Masked[a]	
Nonmetropolitan	110 (11.66%)	19 (8.15%)		586 (10.34%)	Masked[a]	
Census tract median income in quartile			0.0101			0.1984
First quartile	253 (26.83%)	42 (18.03%)		1,420 (25.05%)	21 (21.88%)	
Second quartile	221 (23.44%)	72 (30.90%)		1,419 (25.04%)	22 (22.92%)	
Third quartile	240 (25.45%)	54 (23.18%)		1,421 (25.07%)	20 (20.83%)	
Fourth quartile	229 (24.28%)	65 (27.90%)		1,408 (24.84%)	33 (34.38%)	
Census tract % below poverty level in quartile			0.0482			0.5578
First quartile	223 (23.65%)	71 (30.47%)		1,422 (25.09%)	22 (22.92%)	
Second quartile	237 (25.13%)	57 (24.46%)		1,408 (24.84%)	30 (31.25%)	
Third quartile	234 (24.81%)	61 (26.18%)		1,421 (25.07%)	22 (22.92%)	
Fourth quartile	249 (26.41%)	44 (18.88%)		1,417 (25.00%)	22 (22.92%)	
Census tract % college in quartile			0.0668			0.1598
First quartile	249 (26.41%)	45 (19.31%)		1,411 (24.89%)	30 (31.25%)	
Second quartile	230 (24.39%)	64 (27.47%)		1,423 (25.11%)	18 (18.75%)	
Third quartile	225 (23.86%)	69 (29.61%)		1,422 (25.09%)	19 (19.79%)	
Fourth quartile	239 (25.34%)	55 (23.61%)		1,412 (24.91%)	29 (30.21%)	
Comorbidity score			0.5263			0.6872
0	606 (64.26%)	161 (69.10%)		3,413 (60.22%)	60 (62.50%)	
1	155 (16.44%)	35 (15.02%)		990 (17.47%)	16 (16.67%)	
≥2	110 (11.66%)	21 (9.01%)		788 (13.90%)	Masked[a]	
Unknown	72 (7.64%)	16 (6.87%)		477 (8.42%)	Masked[a]	
Tumor size			0.9576			0.0005
<1 cm	28 (2.97%)	Masked[a]		1,220 (21.52%)	Masked[a]	
1–2 cm	120 (12.73%)	Masked[a]		1,390 (24.52%)	Masked[a]	
>2 cm	426 (45.17%)	102 (43.78%)		1,445 (25.49%)	38 (39.58%)	
Unknown	369 (39.13%)	95 (40.77%)		1,613 (28.46%)	27 (28.13%)	
Histology grade			<0.0001			0.3429
Grade 1	705 (74.76%)	207 (88.84%)		4,960 (87.51%)	Masked[a]	
Grade 2	160 (16.97%)	Masked[a]		470 (8.29%)	Masked[a]	
Unspecified (either grade 1 or 2)	78 (8.27%)	Masked[a]		238 (4.20%)	Masked[a]	
Primary site			<0.0001			<0.0001
Larynx, bronchus, lung, trachea, and other respiratory organs	262 (27.78%)	16 (6.87%)		1,508 (26.61%)	14 (14.58%)	
Cecum and appendix	81 (8.59%)	18 (7.73%)		347 (6.12%)	Masked[a]	
Colon	81 (8.59%)	20 (8.58%)		1,123 (19.81%)	Masked[a]	
Small intestine	309 (32.77%)	109 (46.78%)		1,788 (31.55%)	42 (43.75%)	
Pancreas	119 (12.62%)	40 (17.17%)		192 (3.39%)	Masked[a]	
Others	91 (9.65%)	30 (12.88%)		710 (12.53%)	20 (20.83%)	
Resection of primary tumor			0.3420			0.0011
No	464 (49.20%)	123 (52.79%)		900 (15.88%)	28 (29.17%)	
Yes	479 (50.80%)	110 (47.21%)		4,768 (84.12%)	68 (70.83%)	

(Continued on the following page)

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Table 2. Description of the study sample by stage of NET and whether octreotide treatment was received (Cont'd)

	Distant stage NET ($N = 1,176$)			Local and regional stage NET ($N = 5,764$)		
	Without octreotide treatment *N* (%)	With octreotide treatment *N* (%)	*P*	Without octreotide treatment *N* (%)	With octreotide treatment *N* (%)	*P*
Resection of liver metastases			<0.0001			0.0021
No	908 (96.29%)	201 (86.27%)		5,655 (99.77%)	Masked[a]	
Yes	35 (3.71%)	32 (13.73%)		13 (0.23%)	Masked[a]	
Chemotherapy			<0.0001			<0.0001
No	806 (85.47%)	130 (55.79%)		5,351 (94.41%)	55 (57.29%)	
Yes	137 (14.53%)	103 (44.21%)		317 (5.59%)	41 (42.71%)	
Radiotherapy			0.2294			0.4405
No	851 (90.24%)	204 (87.55%)		5,426 (95.73%)	Masked[a]	
Yes	92 (9.76%)	29 (12.45%)		242 (4.27%)	Masked[a]	
Year of diagnosis			0.0419			0.1689
1999–2003	374 (39.66%)	75 (32.19%)		2,181 (38.48%)	30 (31.25%)	
2004–2007	569 (60.34%)	158 (67.81%)		3,487 (61.52%)	66 (68.75%)	

[a]Masked per SEER-Medicare user agreement for confidentiality.

metastases, radiation, and chemotherapy, respectively, within 12 months of diagnosis.

Statistical analyses

We used both Kaplan–Meier estimation and Cox proportional hazard model to evaluate the association between octreotide LAR use and overall survival. The log-rank test, HRs, and corresponding 95% confidence intervals (CI) were reported for overall survival.

We performed separate analyses for NET patients at distant stage and those at local/regional stage. We explored the association among patients with and without syndrome by using the presence of syndrome as a covariate in the Cox proportional hazard model for the whole group and also conducting subgroup analyses for patients with and without syndrome. We conducted subgroup analyses because the current FDA-approved indication of octreotide LAR is for managing carcinoid syndrome and secretory syndromes associated with VIPoma (13). However, some clinicians prescribe octreotide LAR for patients without carcinoid syndrome (i.e., off-label prescription) for antineoplastic effect. Thus, the subgroup analysis would allow us to explore whether the association differs between on- and off-label uses of octreotide LAR.

We conducted a sensitivity analysis that uses propensity score matching method for the distant stage patients so as to deal with possible selection issues. The propensity score for receiving octreotide LAR treatment was estimated using a logistic regression and all the covariates were included.

The primary objective of the study of the study was to assess the effect of octreotide LAR therapy on overall survival in multivariate model adjusted for covariates.

All statistical analyses were conducted in SAS 9.3 (SAS Institute). The Institutional Review Board at The University of Texas MD Anderson Cancer Center exempted this study for approval because all patients in the database had been deidentified.

Results

Table 2 presents the descriptive statistics of the study cohort by stage and also whether the patients received octreotide LAR treatment. Some numbers and percentages are masked in this table because of data confidentiality requirement by the SEER-Medicare database. Of 1,176 elderly distant stage patients, 233 (20%) received octreotide LAR within 12 months of diagnosis. Among the 233 distant stage patients who received octreotide LAR treatment within 12 months of diagnosis, 176 (76%) had a diagnosis in Medicare claims, indicating the presence of carcinoid syndrome before the start of treatment, whereas among the 943 distant stage patients who did not receive octreotide LAR treatment, 225 (24%) had carcinoid syndrome within 12 months of diagnosis. The bivariate analysis suggested that there were statistically significant differences in the use of octreotide LAR by the presence of carcinoid syndrome ($P < 0.001$).

Of the 5,764 elderly local/regional patients, only 96 (2%) received octreotide LAR within 12 months of diagnosis. Among these 96 patients, 71 (74%) had carcinoid syndrome before the start of octreotide treatment, whereas carcinoid syndrome was observed in 668 (12%) of the 5,668 local–regional stage patients who did not receive octreotide LAR treatment. The bivariate analysis again finds statistically significant difference in the use of octreotide LAR by the presence carcinoid syndrome ($P < 0.001$).

For elderly distant stage NET patients, unadjusted Kaplan–Meier estimation (Fig. 1A) suggested that those who received octreotide LAR treatment within 12 months of diagnosis had better survival ($P < 0.0001$). The median overall survival of patients who received octreotide LAR treatment was 35.22 months (95% CI, 27.96–47.77), compared with 19.15 months (95% CI, 16.36–22.80) for patients who did not receive octreotide. Further, the unadjusted Kaplan–Meier estimations for the subgroups with and without syndrome (Fig. 1B and C) also showed better survival for patients with octreotide LAR treatment in each subgroup.

Table 3 provides the results from the multivariate Cox proportional hazard model for the distant stage patients. The main analysis showed that octreotide LAR was significantly positively associated with overall survival for these patients (HR, 0.68; $P < 0.001$). Significantly positive association was also found between overall survival and female gender, being non-Hispanic black, living in rural area, having resection of primary tumor, and having resection of liver metastases, whereas significantly negative association was found with older age, living in less educated neighborhoods, higher comorbidities scores, having histologic grade 2 or unspecified (compared with grade 1), and having primary cancer site in cecum and appendix, colon, pancreas, and others (compared with larynx, bronchus, lung, and trachea).

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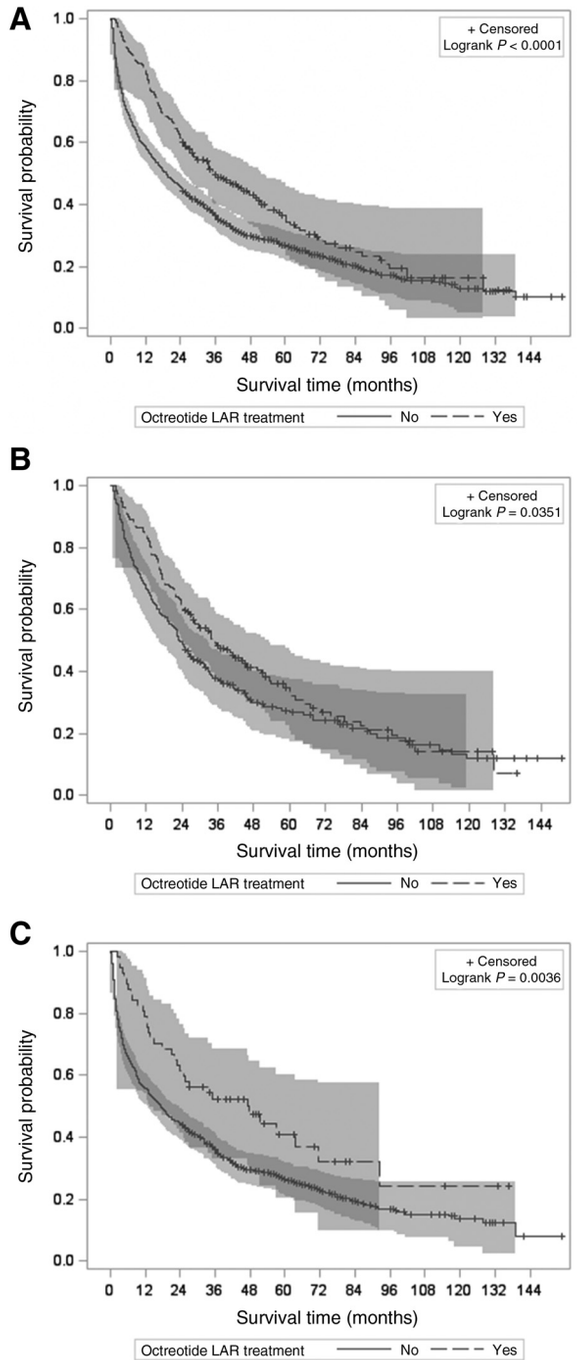

Figure 1.
A, unadjusted Kaplan–Meier curves with 95% Hall–Wellner Bands for distant stage patients. B, unadjusted Kaplan–Meier curves with 95% Hall–Wellner Bands for distant stage patients with carcinoid syndrome. C, unadjusted Kaplan–Meier curves with 95% Hall–Wellner Bands for distant stage patients without carcinoid syndrome.

The subgroup analysis for the distant stage patients with carcinoid syndrome showed a positive association between octreotide LAR and overall survival (HR, 0.65; $P < 0.001$). Resection of primary tumor is also associated with better overall survival. Characteristics associated with worse survival included older age, living in Midwest region, having primary site in colon, cecum and appendix, and having chemotherapy and radiotherapy. The subgroup analysis for distant stage patients without carcinoid syndrome similarly showed a positive association between octreotide LAR use and overall survival (HR, 0.55; *P*, 0.002). For this subgroup, being non-Hispanic black, having resection of primary tumor and resection of liver metastases were associated with better overall survival, whereas older age, more comorbidities, histologic grade being 2 or unspecified, having primary site in cecum and appendix, colon, pancreas, and others were associated with worse survival. Notice that although the point estimate of HR for this subgroup is lower than that for the group with carcinoid syndrome, the 95% CIs for the HRs of these two subgroups overlap. Further, the purpose of the analyses is not to compare the two subgroups. It is very likely that the patient and provider characteristics differ between the two subgroups in ways that were not captured by the observational data.

For the local/regional stage patients, the unadjusted Kaplan–Meier estimation (Fig. 2) showed that those without octreotide LAR treatment have longer survival than those with the treatment ($P = 0.003$). The median overall survival of patients who received octreotide LAR treatment was 64.85 months (95% CI, 55.92–77.93), compared with 104.97 months (95% CI, 98.96–108.55) for those who did not. However, the above pattern was no longer observed in the multivariate analyses. Table 4 showed that the association between octreotide LAR use and overall survival was not statistically significant in the main analysis (HR, 1.25; *P*, 0.142) as well as the two subgroup analyses (with carcinoid syndrome: HR, 1.24; *P*, 0.281; without carcinoid syndrome: HR, 1.26; *P*, 0.393).

As a robustness check for the survival benefit we observe from the distant stage patients, we also conducted a propensity score matching analysis. We used nearest neighbor algorithm and examined the standardized differences of baseline covariates in original and matched samples. Then we used Cox proportional hazard model stratified by octreotide LAR treatment. The results are consistent with what we find in the main analyses. Octreotide LAR treatment is significantly associated with better survival for distant stage NET patients (HR, 0.63; 95% CI, 0.45–0.88). Such significant association is also found in both the subsample with carcinoid syndrome (HR, 0.48; 95% CI, 0.32–0.72) and in the subsample without carcinoid syndrome (HR, 0.41; 95% CI, 0.21–0.81). Given the small sample size, we also conducted a 1:2 matching for the subsample without carcinoid syndrome. The significant association is robust with HR of 0.51 (95% CI, 0.29–0.89).

Discussion

This population-based study used the SEER-Medicare data to examine the association between the use of octreotide LAR and overall survival among elderly patients with NET. This study is the first in the literature to examine the survival benefits among patients without carcinoid syndrome (14). Our analyses suggest that there might be survival benefits associated with octreotide LAR use in distant stage patients, both with and without carcinoid syndrome. The finding of statistically significant survival benefits among those without carcinoid syndrome is especially interesting. This finding is consistent with the findings from two placebo-controlled phase III studies (6, 7). Both the PROMID and CLARINET studies

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Table 3. Cox proportional hazard model for overall survival of distant stage patients

	Whole group				Subgroup with carcinoid syndrome				Subgroup without carcinoid syndrome			
	HR	95% HR confidence limits		*P*	HR	95% HR confidence limits		*P*	HR	95% HR confidence limits		*P*
Treatment												
Without octreotide LAR	1				1				1			
With octreotide LAR	0.682	0.554	0.840	0.0003	0.647	0.486	0.861	0.0028	0.553	0.381	0.803	0.0019
Carcinoid syndrome												
No	1											
Yes	0.952	0.810	1.119	0.5512								
Age, y												
65–69	1				1				1			
70–74	1.240	1.008	1.524	0.0413	1.381	0.960	1.987	0.0822	1.210	0.935	1.565	0.1473
75–79	1.492	1.203	1.852	0.0003	1.315	0.893	1.935	0.1651	1.537	1.181	2.001	0.0014
≥80	1.941	1.572	2.397	<0.0001	2.232	1.503	3.314	<0.0001	1.958	1.513	2.533	<0.0001
Gender												
Male	1				1				1			
Female	0.838	0.727	0.965	0.0143	0.849	0.655	1.100	0.2153	0.864	0.725	1.030	0.1029
Race/ethnicity												
Non-Hispanic white	1				1				1			
Non-Hispanic black	0.731	0.568	0.941	0.0151	0.785	0.485	1.272	0.3259	0.704	0.518	0.958	0.0257
Hispanic or Others	0.819	0.604	1.112	0.2004	0.848	0.476	1.511	0.5757	0.856	0.589	1.244	0.4143
Region												
Northeast	1				1				1			
West	1.064	0.836	1.354	0.6118	0.992	0.642	1.532	0.9706	1.066	0.788	1.442	0.6788
Midwest	1.224	0.961	1.558	0.1012	1.986	1.263	3.122	0.0030	1.037	0.770	1.396	0.8129
South	0.899	0.733	1.102	0.3044	0.957	0.663	1.381	0.8132	0.858	0.664	1.109	0.2432
Urban/rural status												
Metropolitan	1				1				1			
Nonmetropolitan	0.759	0.593	0.971	0.0284	0.713	0.446	1.142	0.1591	0.823	0.609	1.113	0.2063
Census tract median income in quartile												
First quartile	0.925	0.650	1.315	0.6625	0.827	0.446	1.532	0.5458	0.885	0.563	1.390	0.5960
Second quartile	0.741	0.548	1.001	0.0510	0.770	0.457	1.296	0.3247	0.735	0.508	1.062	0.1008
Third quartile	0.808	0.640	1.022	0.0752	0.855	0.547	1.338	0.4937	0.852	0.645	1.126	0.2611
Fourth quartile	1				1				1			
Census tract % below poverty level in quartile												
First quartile	1				1				1			
Second quartile	1.038	0.836	1.289	0.7334	0.958	0.644	1.425	0.8314	1.064	0.816	1.386	0.6482
Third quartile	1.061	0.810	1.390	0.6658	0.909	0.573	1.443	0.6850	1.157	0.823	1.627	0.4011
Fourth quartile	1.209	0.871	1.680	0.2568	0.929	0.533	1.620	0.7952	1.389	0.902	2.138	0.1356
Census tract % college in quartile												
First quartile	1.319	1.007	1.726	0.0440	1.593	0.971	2.613	0.0653	1.247	0.894	1.738	0.1930
Second quartile	1.450	1.130	1.861	0.0035	1.693	1.061	2.701	0.0272	1.360	1.004	1.842	0.0473
Third quartile	1.273	1.027	1.579	0.0275	1.245	0.826	1.876	0.2944	1.202	0.931	1.552	0.1574
Fourth quartile	1				1				1			
Comorbidity score												
0	1				1				1			
1	1.192	0.986	1.442	0.0698	1.393	0.991	1.957	0.0560	1.108	0.872	1.407	0.4036
≥2	1.557	1.253	1.935	<0.0001	1.790	1.194	2.684	0.0049	1.481	1.139	1.925	0.0034
	1.394	1.060	1.832	0.0173	1.411	0.852	2.336	0.1814	1.398	0.994	1.966	0.0545
Tumor size												
<1 cm	1				1				1			
1–2 cm	0.959	0.587	1.566	0.8673	0.702	0.259	1.904	0.4864	1.086	0.609	1.936	0.7802
>2 cm	1.097	0.694	1.734	0.6919	1.130	0.443	2.882	0.7984	1.123	0.656	1.920	0.6729
Unknown	1.269	0.800	2.014	0.3119	1.249	0.487	3.199	0.6435	1.328	0.772	2.283	0.3054
Histology grade												
Grade 1	1				1				1			
Grade 2	1.215	1.006	1.468	0.0431	0.996	0.656	1.511	0.9839	1.310	1.051	1.632	0.0161
Unspecified (either grade 1 or 2)	1.627	1.224	2.163	0.0008	1.555	0.713	3.392	0.2676	1.666	1.215	2.285	0.0015
Primary site												
Larynx, bronchus, lung, trachea, and other respiratory organs	1				1				1			
Cecum and appendix	1.626	1.204	2.195	0.0015	1.857	1.013	3.405	0.0454	1.689	1.175	2.428	0.0046
Colon	2.144	1.639	2.805	<0.0001	2.161	1.203	3.880	0.0099	2.049	1.494	2.811	<0.0001
Small intestine	1.095	0.878	1.367	0.4203	1.185	0.737	1.904	0.4838	1.145	0.880	1.489	0.3123
Pancreas	1.413	1.111	1.796	0.0048	1.123	0.686	1.838	0.6436	1.745	1.301	2.342	0.0002
Others	1.314	1.021	1.691	0.0339	1.437	0.854	2.418	0.1724	1.408	1.030	1.926	0.0322

(Continued on the following page)

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Table 3. Cox proportional hazard model for overall survival of distant stage patients (Cont'd)

	Whole group				Subgroup with carcinoid syndrome				Subgroup without carcinoid syndrome			
	HR	95% HR confidence limits		P	HR	95% HR confidence limits		P	HR	95% HR confidence limits		P
Resection of primary tumor												
No	1				1				1			
Yes	0.546	0.458	0.651	<0.0001	0.551	0.391	0.777	0.0007	0.515	0.415	0.639	<0.0001
Resection of liver metastases												
No	1				1				1			
Yes	0.644	0.442	0.938	0.0219	0.675	0.388	1.176	0.1654	0.578	0.338	0.988	0.0449
Chemotherapy												
No	1				1				1			
Yes	1.117	0.936	1.333	0.2210	1.487	1.105	2.000	0.0088	0.960	0.755	1.220	0.7388
Radiotherapy												
No	1				1				1			
Yes	1.184	0.950	1.475	0.1337	1.649	1.077	2.524	0.0214	1.103	0.840	1.448	0.4823
Year of diagnosis												
1999–2003	1				1				1			
2004–2007	0.871	0.754	1.007	0.0616	0.835	0.629	1.109	0.2135	0.887	0.744	1.059	0.1845

demonstrated that somatostatin analogues delayed progression among patients with NETs. Although the molecular bases for its antineoplastic effect have not been fully elucidated, it is believed that the potential mechanisms include attenuating IGF1 levels, antiangiogenic effect, and regulation of protein phosphatases (15). It is possible that somatostatin analogues such as octreotide LAR mediate direct antiproliferative effect through G protein–coupled receptors. Importantly, despite the benefit in time-to-progression established in the PROMID and CLARINET clinical trials, they were not able to confirm an overall survival benefit due to the small sample size and possible crossover (6, 7). Our study thus provided the first peek into this issue. Since a prospective randomized trial to confirm these findings is not feasible, secondary data analyses might be the best evidence that we can provide. Confirmation with another database of European patients could add validity to our findings. It is also important to note that we did not find evidence supporting the use of octreotide LAR among local/regional stage patients suggesting there is limited role for octreotide LAR in the adjuvant setting after complete surgical resection. It is important that oncologists carefully select patients for octreotide LAR treatment based on tumor characteristics, such as stage and possibly progressiveness of the disease.

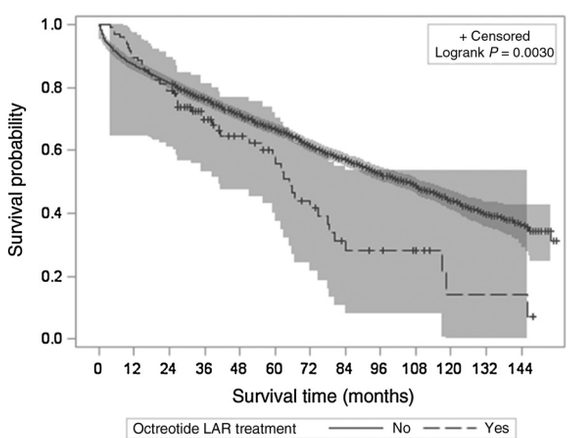

Figure 2.
Unadjusted Kaplan–Meier curves with 95% Hall–Wellner Bands for local/regional stage patients.

Results from our survival analysis showed that older age, higher comorbidity score, histologic grade, primary cancer site, and other treatments received were significantly associated with survival outcome. We also found that female and non-Hispanic black had better overall survival. The finding of longer survival among women is consistent with findings from a study using the SEER data that included NET patients of all ages (1). However, the finding that non-Hispanic black had better overall survival than non-Hispanic white was unexpected. We further explored the correlation between race and other covariates in our analyses and found that race was highly correlated with age in our sample, with the non-Hispanic black patients being much younger than non-Hispanic white. This is reasonably in line with another study (1) showing that the median age of black NET patients is 59, whereas the median age of white patients was 64. Such age differences may partially explain the pattern of reversed racial disparities observed in our study as age is a strong predictor of overall survival for cancer patients. The observation that patients with surgical resection had better survival should be taken with caution as surgery is usually performed in highly selected cases among patients with limited disease. For example, the number and size of liver metastases are likely to drive the decision for surgery but remains an unobserved covariate that cannot be accounted for in claims data. Whether surgery improves survival among patients with metastatic disease needs to be examined in a prospective study.

In terms of the utilization pattern of octreotide LAR among elderly NET patients, our data showed that 44% of distant stage NET patients with carcinoid syndrome received octreotide LAR treatment within 12 months of diagnosis, compared with less than 10% of elderly local/regional stage NET patients with carcinoid syndrome. Because octreotide LAR is the only FDA-approved drug on the market for the management of carcinoid syndrome among patients with functional NETs, this observation raised a concern that carcinoid syndrome was not well managed for these patients.

For elderly NET patients without carcinoid syndrome, we found that about 7% of those at distant stage received octreotide LAR although the drug was indicated for the control of carcinoid syndrome. Among patients at local/regional stage, the percentage of off-label use of octreotide LAR was much lower (around 0.5%). The above pattern indicates that some physicians may have prescribed octreotide LAR for distant stage patients for

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Table 4. Cox proportional hazard model for overall survival of local/regional stage patients

	Whole group				Subgroup with carcinoid syndrome				Subgroup without carcinoid syndrome			
	HR	95% HR confidence limits		*P*	HR	95% HR confidence limits		*P*	HR	95% HR confidence limits		*P*
Treatment												
Without octreotide LAR	1				1				1			
With octreotide LAR	1.253	0.928	1.692	0.1415	1.244	0.836	1.852	0.2814	1.263	0.739	2.156	0.3929
Carcinoid syndrome												
No	1											
Yes	0.973	0.861	1.100	0.6660								
Age, y												
65–69	1				1				1			
70–74	1.239	1.086	1.413	0.0014	1.026	0.713	1.476	0.8903	1.282	1.112	1.478	0.0006
75–79	1.759	1.546	2.000	<0.0001	1.691	1.198	2.387	0.0028	1.758	1.529	2.021	<0.0001
≥80	2.937	2.602	3.315	<0.0001	2.731	1.967	3.793	<0.0001	2.963	2.598	3.379	<0.0001
Gender												
Male	1				1				1			
Female	0.732	0.674	0.795	<0.0001	0.803	0.632	1.019	0.0714	0.711	0.651	0.777	<0.0001
Race/ethnicity												
Non-Hispanic white	1				1				1			
Non-Hispanic black	1.065	0.928	1.222	0.3679	1.668	1.158	2.404	0.0060	0.994	0.857	1.154	0.9412
Hispanic or Others	0.744	0.633	0.876	0.0004	1.084	0.653	1.799	0.7549	0.705	0.593	0.838	<0.0001
Region												
Northeast	1				1				1			
Midwest	1.040	0.904	1.196	0.5864	1.001	0.694	1.444	0.9956	1.038	0.891	1.209	0.6292
South	1.210	1.057	1.384	0.0056	1.501	1.028	2.190	0.0353	1.167	1.009	1.349	0.0370
West	1.126	0.997	1.272	0.0567	1.274	0.901	1.801	0.1700	1.107	0.971	1.263	0.1289
Urban/rural status												
Metropolitan	1				1				1			
Nonmetropolitan	0.968	0.839	1.118	0.6602	1.205	0.802	1.811	0.3689	0.936	0.802	1.092	0.3987
Census tract median income in quartile												
First quartile	1.020	0.825	1.262	0.8543	1.016	0.556	1.856	0.9592	0.990	0.786	1.246	0.9319
Second quartile	1.069	0.898	1.272	0.4550	1.259	0.787	2.014	0.3370	1.022	0.845	1.236	0.8229
Third quartile	1.047	0.908	1.206	0.5296	1.237	0.836	1.830	0.2865	0.993	0.851	1.159	0.9311
Fourth quartile	1				1				1			
Census tract % below poverty level in quartile												
First quartile	1				1				1			
Second quartile	1.012	0.888	1.152	0.8605	1.122	0.784	1.606	0.5276	1.009	0.877	1.161	0.8996
Third quartile	0.946	0.809	1.107	0.4897	0.997	0.653	1.521	0.9884	0.936	0.789	1.11	0.4457
Fourth quartile	0.908	0.745	1.108	0.3434	0.782	0.452	1.350	0.3772	0.938	0.756	1.164	0.5628
Census tract % college in quartile												
First quartile	1.339	1.139	1.575	0.0004	1.120	0.694	1.808	0.6428	1.408	1.184	1.675	0.0001
Second quartile	1.238	1.071	1.430	0.0039	1.166	0.786	1.728	0.4456	1.287	1.1	1.506	0.0016
Third quartile	1.076	0.945	1.224	0.2698	0.895	0.624	1.282	0.5439	1.124	0.978	1.292	0.1001
Fourth quartile	1				1				1			
Comorbidity score												
0	1				1				1			
1	1.432	1.288	1.591	<0.0001	1.350	0.999	1.826	0.0511	1.460	1.303	1.636	<0.0001
≥2	2.399	2.163	2.662	<0.0001	2.173	1.598	2.953	<0.0001	2.448	2.190	2.738	<0.0001
Unknown	0.914	0.755	1.105	0.3522	1.294	0.813	2.059	0.2772	0.845	0.684	1.044	0.1180
Tumor size												
<1 cm	1				1				1			
1–2 cm	0.967	0.851	1.098	0.6016	0.942	0.630	1.408	0.7700	0.977	0.854	1.118	0.7404
>2 cm	1.102	0.972	1.249	0.1295	1.119	0.749	1.673	0.5818	1.102	0.965	1.259	0.1503
Unknown	1.069	0.947	1.205	0.2799	1.422	0.953	2.121	0.0844	1.044	0.920	1.186	0.5036
Histology grade												
Grade 1	1				1				1			
Grade 2	1.263	1.093	1.459	0.0015	1.135	0.736	1.751	0.5667	1.281	1.097	1.494	0.0017
Unspecified (either grade 1 or 2)	1.558	1.262	1.923	<0.0001	2.532	1.503	4.268	0.0005	1.421	1.124	1.796	0.0033
Primary site												
Larynx, bronchus, lung, trachea, and other respiratory organs	1				1				1			
Cecum and appendix	1.120	0.913	1.375	0.2753	0.919	0.523	1.614	0.7685	1.118	0.892	1.401	0.3318
Colon	0.829	0.715	0.962	0.0135	0.855	0.512	1.428	0.5493	0.820	0.702	0.960	0.0132
Small intestine	1.349	1.205	1.511	<0.0001	0.967	0.649	1.440	0.8682	1.410	1.252	1.588	<0.0001
Pancreas	1.231	0.974	1.554	0.0814	0.687	0.372	1.270	0.2309	1.362	1.055	1.757	0.0176
Others	1.232	1.072	1.415	0.0033	1.189	0.752	1.880	0.4591	1.210	1.042	1.404	0.0122

(Continued on the following page)

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Table 4. Cox proportional hazard model for overall survival of local/regional stage patients (Cont'd)

	Whole group				Subgroup with carcinoid syndrome				Subgroup without carcinoid syndrome			
	HR	95% HR confidence limits		P	HR	95% HR confidence limits		P	HR	95% HR confidence limits		P
Resection of primary tumor												
No	1				1				1			
Yes	0.630	0.567	0.700	<0.0001	0.628	0.458	0.860	0.0037	0.641	0.573	0.718	<0.0001
Resection of liver metastases												
No	1				1				1			
Yes	1.161	0.548	2.458	0.6973	0.686	0.164	2.871	0.6055	1.388	0.569	3.387	0.4709
Chemotherapy												
No	1				1				1			
Yes	1.597	1.376	1.854	<0.0001	1.597	1.109	2.299	0.0118	1.560	1.320	1.844	<0.0001
Radiotherapy												
No	1				1				1			
Yes	1.845	1.551	2.195	<0.0001	2.011	1.235	3.273	0.0050	1.823	1.510	2.202	<0.0001
Year of diagnosis												
1999–2003	1				1				1			
2004–2007	0.971	0.890	1.059	0.5021	1.008	0.785	1.293	0.9531	0.971	0.884	1.066	0.5357

antiproliferative effect. The survival benefit of octreotide LAR among distant stage patients without carcinoid syndrome found in our analysis suggests that these physicians might have chosen octreotide LAR because there were no FDA-approved drugs for distant stage NET of nonpancreatic primary. Such off-label use among distant stage patients is common in oncology practice when there are limited treatment options available (16). It is also possible that the pattern of off-label use reflected physicians increasing awareness of the potential benefit of octreotide LAR for nonfunctional NETs. Specifically, our study included patients diagnosed between 1999 and 2009 and followed up until the end of 2011. Hence, it is possible that in the later years of our study period physicians became aware of two published studies in the literature, one clinical trial report in 2009 (6) and one observational study in 2008 (1), that signaled possible benefits of octreotide LAR. The PROMID trial reported that octreotide LAR prolonged time to progression among midgut NETs patients with advanced disease (6), whereas an observational study using SEER registry data showed that the survival of NET patients with distant metastatic disease improved significantly after the commercial introduction of octreotide LAR (1).

As a population-based study using the SEER-Medicare database, our study shared the limitations commonly found in observational studies. First, the presence of carcinoid syndrome might not be fully captured in Medicare claims and there may be other miscoding and inaccuracies in the claims. Second, there could be unobserved confounding in our analyses. For example, we were not able to distinguish whether the patients' disease was more progressive or stable. If oncologist were more likely to prescribe octreotide LAR to progressing patients with worse prognosis, then our results on the survival benefits of octreotide LAR would be potentially conservative. Nevertheless, our study is the first that reported a positive association between octreotide LAR and overall survival among NET patients without carcinoid syndrome, a finding worthy of verification and validation in future clinical trials.

Disclosure of Potential Conflicts of Interest

J.C. Yao reports receiving a commercial research grant from Novartis; and is a consultant/advisory board member for AAA, Ipsen, and Novartis. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The interpretation and reporting of these data are the sole responsibility of the authors. All authors had unrestricted access to the final study data on request, were responsible for data interpretation, manuscript preparation, and the decision to submit for publication, and attest to the completeness and accuracy of the data and statistical analysis.

Authors' Contributions

Conception and design: C. Shen, Y.-C.T. Shih, Y. Xu, J.C. Yao
Development of methodology: C. Shen, Y.-C.T. Shih, Y. Xu, J.C. Yao
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Shen, J.C. Yao
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Shen, Y.-C.T. Shih, Y. Xu, J.C. Yao
Writing, review, and/or revision of the manuscript: C. Shen, Y.-C.T. Shih, Y. Xu, J.C. Yao
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Shen, Y. Xu, J.C. Yao
Study supervision: Y.-C.T. Shih

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Octreotide Long-Acting Repeatable among Elderly Patients with Neuroendocrine Tumors: A Survival Analysis of SEER-Medicare Data

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