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Impact of monoclonal antibody therapy for head and neck cancer on end-of-life care utilization and costs

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Abstract

Background: The impact of monoclonal antibody therapy (mAB) for advanced head and neck cancer on end-of-life health care utilization and costs has yet to be adequately studied.

Methods: Retrospective cohort study of patients aged 65 and over with a diagnosis of head and neck cancer between 2007 and 2017 within the SEER-Medicare registry assessing the impact of mAB therapy (i.e., cetuximab, nivolumab, or pembrolizumab) on end-of-life health care utilization (ED visits, inpatient admissions, ICU admissions, and hospice claims) and costs.

Results: Of 12 544 patients with HNC, 270 (2.2%) utilized mAB therapy at the end-of-life period. On multivariable analyses adjusting for demographic and clinicopathologic characteristics, there was a significant association between mAB therapy and emergency department visits (OR: 1.38, 95% CI: 1.1–1.8, $p = 0.01$) and healthcare costs (β: \$9760, 95% CI: 5062–14 458, $p < 0.01$).

Conclusions: mAB use is associated with higher emergency department utilization and health care costs potentially due to infusion-related and drug toxicity expenses.

KEYWORDS
end-of-life care, head and neck cancer, health care costs, health care utilization

1 | INTRODUCTION

Advances in monoclonal antibody (mAB) therapy have altered practice patterns for recurrent or metastatic head

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and neck cancer (HNC) over the last 15 years.[1] Cetuximab, an epidermal-growth factor receptor blocker, received FDA approval for locoregionally recurrent or metastatic HNC in 2011 following clinical trial results.[2] More recently, a number of clinical trials have employed immune checkpoint inhibitors targeting programmed cell death 1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) for patients with locoregionally advanced or metastatic HNC. Integration of these therapies into care for patients with advanced disease has become increasingly heterogeneous in the era of individualized medicine.[3,4]

While the incorporation of mAB therapy into advanced oncologic care has been suggested to delay advanced care planning and use of palliative care services for patients and their families, there is no literature to date, to the best of our knowledge, on the effects of mAB therapy on end-of-life health care utilization and costs for patients with HNC.[5] Prior studies have demonstrated that HNC patients with late hospice enrollment have increased health care spending in the last 30 days of life.[5–7] Despite support for early advanced care planning, the expanding landscape of mAB therapy has further added to the complexity of decision-making regarding early integration of palliative care services and possible timing of mAB treatment withdrawal.

Here we seek to understand the effect of mAB therapy on end-of-life care utilization in patients with HNC. This retrospective cohort study uses the Surveillance, Epidemiology, and End Results (SEER)–Medicare-linked database to examine the association between use of mAB therapy and end-of-life care utilization such as emergency department (ED) visits, inpatient admissions, and intensive care unit (ICU) stays in patients with HNC. As a secondary objective, we seek to elucidate the associated total cost of care to inform delivery of high-value end-of-life care for patients with advanced HNC.

2 | MATERIALS AND METHODS

2.1 | Data source

The SEER-Medicare linked database includes cancer cases from 18 regional cancer registries which combine to approximately 26% of the US population.[6–8] The Centers for Medicare and Medicaid Services (CMS) and the National Cancer Institute (NCI) jointly sponsor the SEER-Medicare database, which links SEER to relevant clinical and economic data in the form of insurance claims, *International Classification of Disease* (ICD) Codes, and Healthcare Common Procedure Coding System (HCPCS) codes.[9] This study was determined to be exempt from the University of Michigan Institutional Review Board approval.

2.2 | Retrospective cohort identification

The SEER-Medicare database was queried for cases of HNC diagnosed between 2007 and 2017. Patients with primary tumors of the oral cavity, oropharynx, hypopharynx, and larynx were identified using *International Classification of Diseases for Oncology* site codes. Patients were included in the cohort if they were at least 65 years old, had a listed primary site, and had Medicare Part A and B coverage 1 month prior to their diagnosis. Patients were excluded for any lapses in Medicare Part A and B coverage from time of diagnosis to death, co-coverage with managed care, or if they did not have a month of death listed (Figure S1, Supporting Information).

2.3 | Determination of study variables and outcomes

Patient level variables including month of death, age, race, sex, marriage status, population density of home county, and percentage of home county that falls below the poverty line were abstracted from the Patient Entitlement and Diagnosis Summary File (PEDSF). Our primary exposure was persistent use of immunotherapy defined as claims for cetuximab, nivolumab, or pembrolizumab within the last 3 months of life. Immunotherapy claims were identified from the carrier claims file using HCPCS codes (Table S1, Supporting Information). Additionally, the Durable Medical Equipment (DME) file was queried with the same immunotherapy codes to assess for potential patients receiving therapy during clinical trials. This query of DME patients returned fewer than 11 patients that received immunotherapy and they were excluded from analysis. Of note, the number of patients with immunotherapy claims was relatively consistent from year to year throughout the study period. Since cetuximab is an approved radiation potentiator it has a role in definitive radiation therapy. Due to this, patients with codes for both radiation therapy and cetuximab within the first year following diagnosis were considered to have received cetuximab as a part of a definitive regimen and were therefore not counted as receiving mAB therapy in the end-of-life period.

The primary outcome in this study was inpatient health care utilization, defined as ED visits, inpatient admissions, ICU admissions, and hospice claims during

the last 3 months of life. ED visits were abstracted from the both the Outpatient File where they were defined with revenue center codes and the Medical Provider Analysis and Review File (MedPAR) where they were defined as an emergency department charge over $0 (Table S2).[10,11] Inpatient admissions and ICU admissions were abstracted from the MedPAR file. Hospice claims were abstracted from the hospice file and defined as a claim with a cost greater than $0.

Our secondary study outcome was total health care costs in the last 3 months of life. Total health care cost was calculated as line-item sum of payments to the provider, payments owed by the beneficiary, coinsurance amount, and deductible amount for all underlying data subsets (MedPAR, Outpatient, Carrier Claims, Durable Medical Equipment, Hospice Claims, and Medicare Part D). The NCI comorbidity index was calculated using SEER-Medicare provided SAS macro.[12,13] Clinicopathologic characteristics including SEER summary stage at diagnosis, histology, and grade were abstracted from the PEDSF.

2.4 | Statistical analysis

Demographic and clinicopathologic characteristics for patients with HNC subsites based on immunotherapy usage during the last 3 months of life were compared by using χ^2 testing. The NCI comorbidity index was categorized in a manner resulting in over 11 patients per category to maintain de-identification. Unadjusted regression assessing the association of mAB use and inpatient care utilization was completed with logistic regression for health care utilization variables and ordinary least squares (OLS) regression for costs. A subset analysis of patients who received both mAB therapy and radiation therapy compared to those receiving mAB therapy along in the last 3 months of life, who had been diagnosed over 1 year prior, was completed using χ^2 for utilization variables and Kruskall–Wallis testing for total costs.

Of 12 544 patients who met inclusion criteria, 6736 (53.7%) patients were missing information on one or more a priori defined covariates. Among these, marital status ($n = 3781$) and NCI index ($n = 2526$) had the

TABLE 1 Demographic and socioeconomic factors by immunotherapy status

Variable, *n* (%)	Immunotherapy *N* = 270	No immunotherapy *N* = 12 274	*p*-value
Age at diagnosis (quartiles)			0.05
≤70	58 (22.1)	2402 (21.3)	
71–76	85 (32.3)	2938 (26.1)	
77–83	76 (28.9)	3401 (30.2)	
>83	44 (16.7)	2530 (22.5)	
Sex			0.46
Female	87 (32.2)	3697 (30.1)	
Male	183 (67.8)	8577 (69.9)	
Race			0.04
White	247 (92.2)	10 816 (88.3)	
Non-white	21 (7.8)	1439 (11.7)	
Marriage status			0.11
Single	20 (9.5)	1026 (12.0)	
Married or domestic partnership	117 (55.7)	4146 (48.5)	
Separated, divorced or widowed	73 (34.8)	3381 (39.5)	
Percentage Below Poverty Line in census code			0.05
0%–5%	58 (22.1)	2402 (21.3)	
5%–10%	85 (32.3)	2938 (26.1)	
10%–20%	76 (28.9)	3401 (30.2)	
20%–100%	44 (16.7)	2530 (22.5)	
Metropolitan, urban, or rural county			0.16
Metropolitan county	232 (85.9)	10 143 (82.7)	
Urban or rural county	38 (14.1)	2128 (17.3)	

highest frequency of missing data. Due to this, multiple imputation with fully conditional specification (FCS) was used for multivariable modeling. FCS was chosen due to the presence of categorical predictors within the multivariable model. Twenty imputed datasets were created per model. All assessed auxiliary variables had a $r < 0.4$ so only a priori defined variables were included in final imputed models. Imputed variables within the multivariable model included marital status (30.1% missing), NCI comorbidity index (20.1% missing), stage (8.1% missing), poverty level (8.0% missing), and race (0.2% missing). Multivariable modeling adjusting for age, race, marital status, poverty level, site, stage, histology, and NCI index was completed with logistic regression for health care utilization variables alongside OLS regression for total health care costs. Analyses were compared across multiple methods of addressing missingness including multiple imputation, coding missingness into the model, and available case analysis (Table S3).

Total health care cost was categorized into terciles for analysis. Total health care cost in the last 3 months of life was right skewed and contained outliers. Health care spending outliers convey important information regarding cost drivers in the health care system so they were

TABLE 2 Clinicopathologic features, patient comorbidities, health care utilization, and health care costs by immunotherapy status

Variable	Immunotherapy $N = 270$	No immunotherapy $N = 12\,274$	p-value[a]
Site, *n* (%)			<0.01
Oral cavity	109 (40.4)	4421 (36.0)	
Oropharynx	28 (10.4)	882 (7.2)	
Hypopharynx	25 (9.2)	8227 (6.7)	
Larynx	108 (40.0)	6144 (50.1)	
Stage at diagnosis, *n* (%)			<0.01
Localized	74 (28.9)	5745 (51.0)	
Regional by direct extension or nodes	116 (45.3)	3257 (28.9)	
Distant sites/nodes involved	66 (25.8)	2266 (20.1)	
Histology, *n* (%)			<0.01
Squamous cell carcinoma	263 (97.4)	11 252 (91.7)	
Grade, *n* (%)			0.40
I or II	158 (75.6)	6660 (73.0)	
III or IV	51 (24.4)	2464 (27.0)	
NCI comorbidity index			<0.01
0	136 (61.5)	4765 (48.6)	
>0 and ≤1	58 (26.2)	3644 (37.2)	
>1	27 (12.2)	1388 (14.2)	
Any Emergency department visits, *n* (%)	134 (49.6)	5045 (41.1)	<0.01
Any inpatient admissions, *n* (%)	182 (67.4)	7849 (64.0)	0.24
Any ICU admissions, *n* (%)	79 (29.3)	4014 (32.7)	0.24
Any hospice claims, *n* (%)	130 (48.9)	5654 (46.1)	0.36
Cost (terciles)			<0.01
≤$7024	69 (25.6)	6427 (52.7)	
>$7024–≤$25767	109 (40.4)	2877 (23.4)	
>$25767	92 (34.1)	2925 (23.8)	
Monoclonal antibody agent, *n* (%)			
Cetuximab	242 (89.6)		
Nivolumab	16 (6.0)		
Pembrolizumab	12 (4.4)		

[a]*p*-values calculated using chi-square.

Multivariable logistic regression			
Variable	**Odds ratio**	**95% confidence interval**	***p*-value**
Any hospice claim	1.1	(0.8, 1.3)	0.41
Any ED visit	1.4	(1.1, 1.8)	<0.01
Any hospitalization	1.2	(0.9, 1.6)	0.15
Any ICU admission	0.9	(0.7, 1.1)	0.37
Multivariable ordinary least squares regression			
Variable	Beta-coefficient	95% confidence interval	*p*-value
Health care cost	$9592	($4800, $14384)	<0.01

TABLE 3 Multivariable models assessing the impact of immunotherapy within the last 3 months of life on health care utilization and total cost adjusting for age, race, marriage, SES, stage, site, histology, and NCI comorbidity index using multiple imputation with fully conditional specification ($n = 12\,444$)

not removed from analyses. OLS regression was utilized given that our models are descriptive in nature, and identification of factors associated with increased cost using claims data relying on descriptive OLS models have previously been reported in the literature.[14–16] All statistical testing was two-sided and conducted at a significance level of $\alpha = 0.05$. Effect sizes with 95% confidence intervals were reported whenever possible to estimate precision.[17] Data extraction and analysis was completed with SAS v9.4 (Cary, NC).

3 | RESULTS

Our initial SEER-Medicare query returned 172 088 patients with carcinoma diagnosed between 2007 and 2017; 12 544 met inclusion and exclusion criteria and were included in the study (Figure S1). Primary sites of malignancy in this cohort included 4530 (36.1%) oral cavity cancer cases, 910 (7.3%) oropharyngeal cancer cases, 852 (7.8%) hypopharyngeal cancer cases, and 6252 (49.8%) laryngeal cancer cases. Of these, 270 (2.2%) received immunotherapy in the last 3 months of life. Of those receiving mAB therapy, 242 (89.6%) received cetuximab, 16 (6.0%) received nivolumab, and 12 (4.0%) received pembrolizumab. Among those receiving mAB therapy, the median cost per claim was $2584 for cetuximab, $5201 for nivolumab, and $9150 for pembrolizumab.

Those receiving mAB therapy were more likely to be younger ($p = 0.04$), white ($p = 0.04$), and live in counties with a lower percentage of the population below the poverty line ($p < 0.01$; Table 1). Additionally, the mAB cohort was more likely to have locoregionally advanced or distant disease at diagnosis ($p < 0.01$), squamous cell carcinoma histology ($p < 0.01$), lower comorbidity scores ($p < 0.01$), and a lower proportion of patients with laryngeal cancer ($p < 0.01$; Table 2).

Comparison of inpatient care utilization based on mAB status was notable for significantly higher ED visits in the mAB group ($p < 0.01$) and no differences in the likelihood of inpatient admissions, ICU admissions, or hospice claims. Patients who received mAB therapy were more likely to be in a higher tercile of cost, with 47.2% falling in the second and third terciles ($p < 0.01$; Table 2).

Comparison of care utilization in the last 3 months of life among patient receiving cetuximab who were diagnosed over 1 year prior was notable for a decreased likelihood of having a hospice claim in patients who received cetuximab and radiation therapy compared to those who only cetuximab (35.9% vs. 55.9%, $p < 0.01$). There were no significant differences in other utilization variables and EOL costs (Table S4).

Unadjusted logistic regression of health care utilization variables was notable for increased odds of ED visits in the mAB group compared to the non-mAB group (OR: 1.4, 95% CI: 1.1, 1.8, $p = 0.01$). Multivariable logistic regression utilizing multiple imputation with FCS controlling for age, race, marriage status, poverty level, site, stage, histology, and NCI index also demonstrated increased odds of ED visits among mAB patients (OR: 1.38, 95% CI 1.1, 1.8, $p < 0.01$) alongside no significant difference in hospice claims, hospital admissions, or ICU admissions (Tables 3 and S6). Unadjusted OLS estimation illustrated significantly higher end-of-life costs with a $9274 increase in end-of-life cost among those who received mAB therapy compared to those who did not (β: $9274, 95% CI: 4438–14110; $p < 0.01$) (Table S5). OLS regression in fully adjusted multivariable models utilizing multiple imputation with FCS demonstrated a significant positive association between mAB use and end-of-life costs with an additional $9592 increase in costs among those receiving mAB therapy (β: 9592, 95% CI: 4801–14 384; $p < 0.01$) (Tables 3 and S7).

4 | DISCUSSION

This is the first study to our knowledge elucidating the effects of mAB therapy on end-of-life care utilization for patients with HNC. Patients who received mAB therapy in the last 3 months of life were more likely to be white, have a higher socioeconomic status, and lower

comorbidity scores than those who did not receive mAB therapy. Most patients with HNC receiving mAB therapy had locoregionally advanced or distant disease. In the multivariable model, patients on mAB therapy were 1.4 times more likely to have an ED visit compared to the non-mAB therapy cohort; however, there was no significant difference among other markers of inpatient care utilization. Further, among patients diagnosed over 1 year prior treated with cetuximab in the last 3 months of life, patients receiving radiation therapy and cetuximab were less likely to have hospice claims than those receiving cetuximab alone.

While use of mAB did not demonstrate a statistically significant impact on end-of-life inpatient care utilization, the subset of mAB patients receiving both cetuximab and radiation therapy in the EOL period were less likely to have a hospice claim than those receiving cetuximab alone. This suggests that patients receiving both cetuximab and radiation therapy may be less likely to utilize hospice care in the EOL period and should be further investigated. Additionally, while inpatient utilization did not differ between those who did and did not receive mAB therapy, it is notable that over 40% of patients with HNC presented to the emergency room during the last 3 months of life, over 60% had an inpatient admission, and approximately 30% had an ICU admission during this period. This significant inpatient care utilization may be attributable in part to challenging symptoms associated with end stage HNC such as airway obstruction, bleeding, disfiguring appearance, and complex wound care needs that can be difficult to manage at home. Previous studies have also identified frequent inpatient care utilization in this patient population at the end-of-life. A study using the private insurance Optum database found that 38.5% of patients with HNC were admitted in the final 30 days of life.[18] Heinonen et al. found that 66% of patients with HNC receiving palliative care in Finland had emergency department visits. Of note, study authors did identify improved rates of home hospice care and death at home for patients with use of specialized palliative home care services.[14]

Though there was no difference in inpatient care utilization based on persistent use of mAB, there was notably a significant difference in total cost of care between the two groups. HNC patients with end-of-life mAB therapy use had increased cost of care in the last 3 months of life. This is likely attributable to infusion-related costs, evidenced by a median cost per claim of $2584, $5201, and $9150 for cetuximab, nivolumab, and pembrolizumab, respectively. Further drivers of cost in the mAB therapy group may be related to the management of side effects of mAB therapy. However, since there is no ICD-9 diagnosis code for mAB-related toxicities and the ICD-10 diagnosis codes are non-specific, we are unable to adequately measure this in our cohort.[15] Within our cohort, greater than 75% of patients with HNC on mAB therapy had over $15916 in Medicare claims in the last 3 months of life compared to only 49% of patients not on mAB therapy. mAB was associated with an additional $10000 of end-of-life care costs, which can be attributed to per cycle infusion-related costs ranging from $2500 to $10000. Prior studies have demonstrated that median monthly cost of head and neck cancer treatment rose $1000 after the introduction of mAB therapy, and when factoring in the cost of drug-associated adverse events, 24 months of mAB therapy, specifically cetuximab and pembrolizumab, ranged from $13000 to $150000.[19,20]

The inherent limitations of this study include its retrospective nature and use of a national database with missing data. We have addressed the missing data through multiple imputation. Further, our timeframe limits our ability to assess the impact of checkpoint inhibitors on utilization and cost outcomes, so our sample is predominately cetuximab. Further study aimed at identifying the impact of the recent expansion of checkpoint inhibitors is required moving forward. Additionally, an important limitation of SEER-Medicare registry is its unreliability in identifying cancer recurrence or disease progression. Due to this, we used time since diagnosis to identify which patients were receiving definitive therapy versus palliative therapy. We considered claims for cetuximab and radiation therapy within 1 year of diagnosis to be definitive treatment, which is supported by previous analysis from the National Cancer Database which indicated that fewer than 10% of HNC patients had a time to treatment from diagnosis of greater than 90 days and the median time to treatment was 26 days.[16] However, it is plausible that patients receiving definitive therapy may have experienced delayed treatment past 1 year. Due to this, further study is required to better investigate our finding of fewer hospice claims in patients diagnosed over 1 year prior who received both cetuximab and radiation therapy in the EOL period. Further, month of death rather than an exact date of death is available for analyses. Additionally, managed care beneficiaries were excluded from analyses as managed care plans have not traditionally been required to submit claims or service-related data from their Medicare beneficiaries; therefore, the included Medicare fee-for-service data offers a more reliable understanding of the patient population and cost estimates. In terms of generalizability, this national data set of linked SEER-Medicare data offers longitudinal, comprehensive estimates of the burden of cancer care in those age greater than 65. The linkage of SEER and Medicare claims represents approximately 26% of the US population.[6] Ultimately, the cost of care only accounts for

Medicare claims during the study period without accounting for unreimbursed aspects of care and associated financial toxicity for patients and their families.

Given the expanding landscape of oncologic therapeutics, thoughtful, early integration of palliative care services can inform advanced care planning and facilitate regular goals of care conversations for patients with advanced HNC. Early involvement of palliative care services has previously been shown to lead to improved symptom management and family satisfaction at time of death for patients who have died from HNC.[21] Palliative care services have also been associated with improvements in quality of life and decreased use of aggressive interventions at the end-of-life for patients with other solid malignancies.[22] Use of novel immunotherapies for advanced HNC not amenable to traditional therapy modalities present the challenge of identifying when discontinuation of these immune checkpoint inhibitors may be appropriate and in keeping with individual goals of care. The Quality Oncology Practice Initiative of the American Society of Clinical Oncology reports outcome metrics for oncology practices such as goals of care discussions and end-of-life hospital and chemotherapy utilization, which are important considerations when incorporating mAB therapy into advanced HNC care.[23]

This study explores inpatient care utilization and highlights the high cost of care at the end-of-life for patients with end stage HNC on mAB therapy. Future studies investigating medically vulnerable populations, such as those undergoing palliative radiation and mAB therapy, alongside quality of life outcomes of patients with advanced HNC treated with mAB therapy at the end-of-life can further inform these goals of care conversations and treatment decisions.[1]

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

This study used the linked SEER-Medicare database. Additionally information on accessing SEER-Medicare linked data can be found through: https://healthcaredelivery.cancer.gov/seermedicare/obtain/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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