

Treatment Patterns for Patients With Advanced/Metastatic Cancers by Site of Care

Suvapun Bunniran, PhD; Yihua Xu, PhD; Cliff Molife, PhD; Radhika Nair, PhD; Yajun Emily Zhu, MS; Gebra Cuyun Carter, PhD; Sheetal Sheth, PharmD, BCOP; and Lisa M. Hess, PhD

Currently, more than 80% of all cancer care is delivered in outpatient oncology practice settings.¹ Patients may have a choice in the selection of where to receive treatment after a diagnosis of cancer, whether it is the hospital outpatient or physician office setting. Over time, cancer care has increasingly occurred in the hospital outpatient practice setting rather than in physician offices. Hospital outpatient–based cancer care has grown from only 4% to more than 45% of all cancer care in the United States over a 10-year period.² This trend has been influenced in part by health care reimbursement policies and the acquisition of smaller practices by larger health care systems. A number of studies and reports have identified increased health care costs among patients with cancer treated in hospital-based outpatient settings, even when limited to patients enrolled in Medicare, who would be assumed to have limited impact of reimbursement factors on health care costs.³⁻¹¹

Although the trend toward hospital outpatient–based cancer care may influence cost, less is known about the impact on the therapy received, utilization of health services, and patient outcomes. Some studies^{3,4,6-8} have suggested different cancer treatment patterns between the hospital outpatient and physician office practice settings, whereas other studies^{5,9} have found no difference. When evaluating specific differences in therapies by site of care, one study has reported that use of low-value therapy trended higher for Medicare beneficiaries receiving cancer care in physician offices compared with those in hospital outpatient practices.⁸ In that study, low-value therapy was defined as drugs characterized by a lack of benefit, potential harm, or availability of an equally efficacious but less expensive alternative. Other studies have reported more frequent use and longer duration of chemotherapy for patients receiving cancer care in physician office practices and enrolled in Medicare or commercial health plans.^{3,4,6-8} In contrast, a study of commercially insured patients found no meaningful differences in patient characteristics, treatment patterns, or resource use among patients with cancer receiving chemotherapy in the physician office vs hospital outpatient settings, although trends in increased use of some drugs and shorter duration of first-line (1L) therapy were noted in physician office practices.⁵

ABSTRACT

OBJECTIVES: To compare treatments, overall survival (OS), and total costs among patients receiving anticancer therapy in hospital outpatient vs physician office settings.

STUDY DESIGN: This retrospective observational study utilized claims data from a large national health plan to identify patients with advanced/metastatic non–small cell lung cancer (aNSCLC), metastatic colorectal cancer (mCRC), or metastatic breast cancer (mBC) treated in hospital outpatient or physician office settings.

METHODS: Patients enrolled in Medicare Advantage Prescription Drug or commercial plans for at least 180 days prior to and at least 30 days after start of first-line (1L) therapy were included. Treatments by lines of therapy, OS, and total costs were evaluated by site of care.

RESULTS: Eligible patients included 4618 with aNSCLC, 2304 with mCRC, and 1411 with mBC. There were no major differences in 1L, second-line, or third-line therapy by site of care. Patients with aNSCLC in physician office had longer 1L duration (hospital outpatient, 96 days vs physician office, 102 days; $P < .01$), but there were no differences in duration of therapy by site of care for mBC or mCRC. Costs were higher in the hospital outpatient setting for mCRC and mBC, but there were no differences in OS for any of the cancers.

CONCLUSIONS: Although patients received similar care in hospital outpatient and physician office settings, the differences in duration of treatment and costs warrant further evaluation.

Am J Manag Care. 2021;27(4):e105-e113. doi:10.37765/ajmc.2021.88619

TAKEAWAY POINTS

Treatment patterns, overall survival, and costs were compared for patients receiving anticancer therapy in the hospital outpatient vs physician office setting.

- ▶ Whereas prior research focused on first-line treatment only, this research focused beyond the first line.
- ▶ There were no major differences in treatment, line of therapy, or survival by site of care. There were some differences in duration of therapy and time between lines of therapy.
- ▶ Total costs were higher for patients treated in hospital outpatient settings for metastatic breast and colorectal cancer. This is a similar finding to prior research and should be evaluated further.

It is possible that the cost difference by site of care could be related to site variation in hospitalizations or care for adverse events. Robinson and Beyer found that although patients treated in the hospital outpatient setting had fewer courses of chemotherapy, they had longer infusion times and more treatment-related adverse events.¹² A number of studies have shown that commercially insured patients receiving cancer care in hospital outpatient practices had higher rates of hospitalizations, emergency department (ED) visits, and provider visits.^{3,5,7} However, some have reported higher rates of ED visits⁷ and supportive care medication use⁸ in the physician office care setting compared with the hospital outpatient setting.

As noted above, the previous site-of-care analyses have reported mixed results and mainly focused on patients receiving chemotherapy for varying cancer types in the IL setting. The current study was designed to contribute to the body of knowledge by evaluating and comparing overall treatment patterns (ie, not limited to a specific treatment or regimen) across multiple lines of therapy, overall survival (OS), and total costs by site of care (hospital outpatient vs physician office). We selected the 3 most common causes of cancer death in the United States, namely advanced or metastatic non-small cell lung cancer (aNSCLC), metastatic colorectal cancer (mCRC), and metastatic breast cancer (mBC). These data may help clarify for health care policy and decision makers how the trend to hospital-based cancer care may affect cancer care.

METHODS

This was a retrospective observational study using claims data from a large national health plan for patients in the United States enrolled in Humana Inc's Medicare Advantage Prescription Drug (MAPD) plan (composed mostly of senior adults) or commercial plans with aNSCLC, mCRC, or mBC. Patients were required to have at least 2 claims for the specific cancers (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]: 174.xx, 162.2-162.9, 153.xx-154.xx; *ICD, Tenth Revision, Clinical Modification* [ICD-10-CM]: C50.xx, C34.xx, C18.xx-C21.xx) on different dates between July 1, 2012, and December 31, 2016, along with a code for metastatic disease (ICD-9-CM: 196.xx-199.xx except 197.0 for NSCLC, 198.81 and 196.3 for BC, and 197.5 for CRC; ICD-10-CM: C77.x-C79.x except C78.0 for NSCLC, C78.5 for CRC, and C79.81 and C77.3 for BC)

within 60 days of the first diagnosis of the cancer. For NSCLC, the use of metastatic codes identifies patients with advanced (stage IIIB) or metastatic (stage IV) disease. In the absence of patient charts, we are unable to distinguish between stage III and IV, hence the labeling of advanced/metastatic NSCLC.

Patients were required to have at least 1 claim for an anticancer treatment (eAppendix Tables [eAppendix available at ajmc.com]) within 6 months of metastatic diagnosis. The date of first anticancer medication after metastatic

diagnosis was defined as the index date for this study. Eligible patients were between 18 and 89 years of age and enrolled in a MAPD or commercial plan for at least 6 months (180 days) prior to and at least 30 days after the index date. Among eligible patients, those with at least 6 months postindex enrollment were included in the cost analyses. Among eligible patients, for the OS analyses, patients were followed through end of plan enrollment, end of study period, or death, whichever came first.

Patients with claims for anticancer drugs used for the treatment of small cell lung cancer (SCLC), diagnosed with 2 or more cancers (NSCLC, CRC, and BC), or participating in a clinical trial (identified using ICD-9-CM code V70.7 or ICD-10-CM code Z00.6) were excluded. Patients with ICD-9-CM or ICD-10-CM codes for NSCLC, CRC, or BC during the 6 months prior to the eligible cancer diagnosis were excluded to ensure incident cancer cohorts. Patients were classified into either the hospital outpatient or physician office setting based on site of service for infusions during the postindex period. Only patients receiving all of the anticancer infusions in a single site of care were included in comparative analyses. Patients with multiple sites of care or unknown site of care (no anticancer infusion to assign a site of care) during the treatment period were not included in the analysis. The study focused on patients receiving anticancer therapy in the hospital outpatient or physician-based practice setting groups to assign site of care.

Baseline demographic and clinical characteristics were evaluated and compared between patients treated in the hospital outpatient vs physician office setting by cancer cohort (aNSCLC, mCRC, or mBC) using bivariate analyses (χ^2 tests for categorical variables and *t* tests for continuous variables). Geographic region as defined by the US Census Bureau included the following categories: Northeast, Midwest, South, and West.¹³ Population density was divided into 3 categories (rural, urban, and suburban) and assigned by matching patient zip codes (at index date) to Rural-Urban Commuting Area codes.^{14,15} Income was a categorical variable, with the following income levels: \$49,999 or less (reference), \$50,000 to \$99,999, \$100,000 or more, and unknown.

Comorbidities were assessed using the Deyo-Charlson Comorbidity Index (DCI) and the RxRisk-V scores. The DCI is based on 17 categories of comorbidities (including cancer and metastatic cancers) to calculate a score that reflects the cumulative increased likelihood

of 1-year mortality.^{16,17} The evolution of the Deyo-Charlson methodology has permitted researchers to use the score as an assessment of overall patient health risk. The RxRisk-V score is based on the identification of 45 distinct medical condition categories via their associated medication treatments.¹⁸ This score is determined by summing the number of unique condition categories such that a higher score indicates a greater comorbidity burden.¹⁸⁻²⁵

Treatment patterns and duration of therapy were assessed within each cancer cohort and compared between patients treated in hospital outpatient clinics vs physician offices by line of therapy. Medications used to determine treatment regimens included all systemic anticancer therapies (oral and infused). Treatment duration was defined as the number of days from the start of the treatment regimen to the end of the treatment regimen within each respective line of therapy.

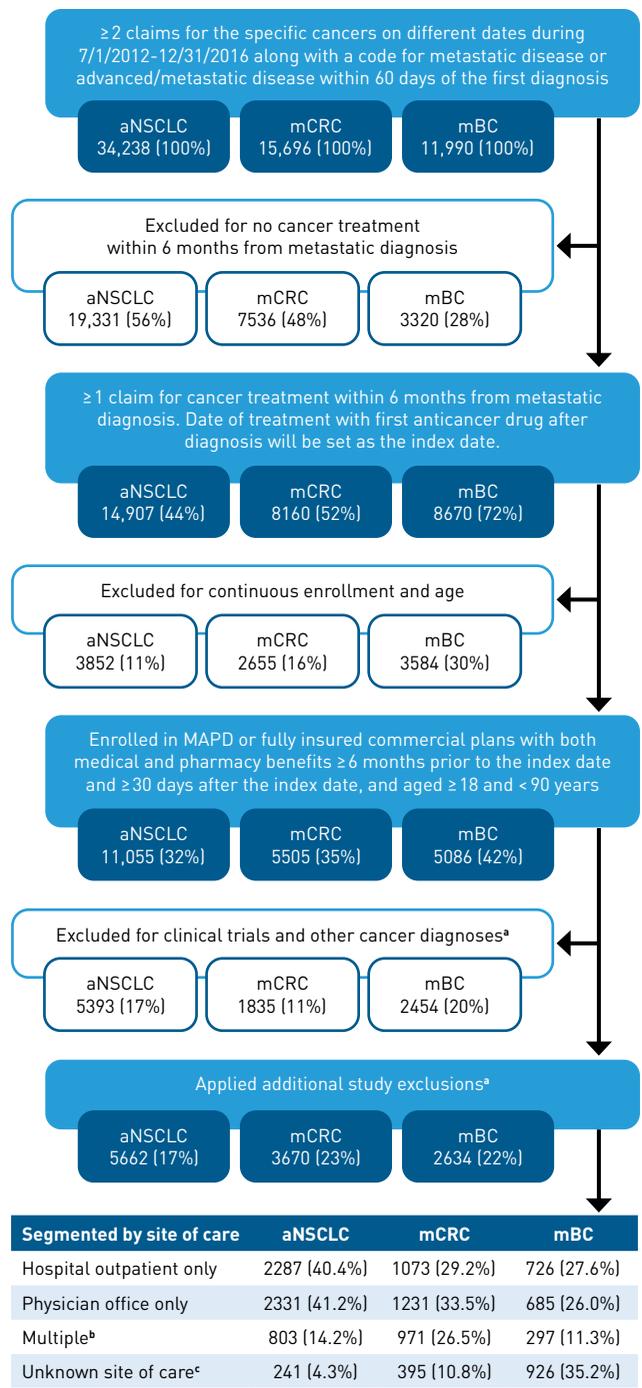
Postindex 6-month total health care costs were compared by site of care (patients treated in hospital outpatient clinics vs physician offices) using Wilcoxon rank-sum tests, and further evaluated using generalized linear models (GLMs) with log link and gamma distribution for each cancer cohort. Due to the risk of differential follow-up, only patients with at least 6 months postindex enrollment coverage were included in the cost analysis. In the GLMs, the dependent variable was total health care costs (adjusted to 2016 US\$ utilizing the Medical Consumer Price Index), and site of care (hospital outpatient vs physician offices) was the independent variable, controlling for patient demographic, socioeconomic, and clinical characteristics.

OS was calculated as time from index date to death only for patients enrolled in a MAPD plan. In this data source, mortality information including death dates are regularly updated from CMS and are not imputed or estimated. Death was coded as 1 if the patient died after the index date up to the end of follow-up or disenrollment. Patients were censored at end of follow-up or disenrollment (death was coded as 0). Nonparametric Kaplan-Meier (KM) analysis was conducted to compare the survival curves for site of care and estimate the median survival time. In addition, differences in OS by site of care among the patients enrolled in a MAPD plan were assessed using Cox proportional hazard regression models with site of care as the primary independent variable, while controlling for patient baseline demographic, socioeconomic, and clinical characteristics. Proportional hazard assumption was assessed by fitting a Cox regression model with site of care and its interaction term with log of time to death.

RESULTS

The site-of-care assignment was based on the site of administration for postindex anticancer infusions. A total of 5662 patients with aNSCLC met eligibility criteria. Of those, 2287 (40.4%) and 2331 (41.2%) patients were classified as receiving all anticancer therapy in the hospital outpatient setting and physician office setting, respectively (Figure). A small percentage of patients (n=803; 14.2%) received care in multiple sites, and 4.3% (n=241) were categorized

FIGURE. Attrition



aNSCLC, advanced/metastatic non-small cell lung cancer; mBC, metastatic breast cancer; mCRC, metastatic colorectal cancer.

*Patients were excluded if they were identified with more than 1 of the selected cancers in the study period (mBC, aNSCLC, and mCRC), had a diagnosis for the specific cancer under consideration during the 6 months prior to eligible cancer diagnosis, or were participating in a clinical trial.

^bThese patients had anticancer therapy procedures from more than 1 type of place (hospital outpatient, physician office, and/or other places such as home).

^cNo anticancer therapy procedures were identified for these patients.

TABLE 1. Baseline Demographic and Clinical Characteristics

	Advanced/metastatic NSCLC			Metastatic colorectal cancer			Metastatic breast cancer		
	Hospital outpatient	Physician office	P	Hospital outpatient	Physician office	P	Hospital outpatient	Physician office	P
n	2287	2331		1073	1231		726	685	
Age in years									
Mean (SD)	70.0 (7.7)	70.9 (7.5)	<.01	67.0 (10.7)	69.1 (9.4)	<.01	65.7 (11.8)	67.0 (10.8)	.03
Median	71.0	71.0		69.0	70.0		67.0	69.0	
Sex, female, n (%)	907 (39.7%)	923 (39.6%)	.97	448 (41.8%)	565 (45.9%)	.05	713 (98.2%)	663 (96.8%)	.09
Race/ethnicity (Medicare only), n (%)									
White	1760 (85.2%)	1857 (85.7%)		659 (78.8%)	852 (81.2%)		396 (76.7%)	433 (80.6%)	<.001
Black	267 (12.9%)	240 (11.1%)	.01	143 (17.1%)	147 (14.0%)	.15	106 (20.5%)	76 (14.2%)	
Other	39 (1.9%)	69 (3.2%)		34 (4.1%)	50 (4.8%)		14 (2.7%)	28 (5.2%)	
Insurance plan type, n (%)									
MAPD	2068 (90.4%)	2169 (93.1%)		841 (78.4%)	1052 (85.5%)		518 (71.3%)	538 (78.5%)	<.001
Commercial	219 (9.6%)	162 (6.9%)	.001	232 (21.6%)	179 (14.5%)	<.001	208 (28.7%)	147 (21.5%)	<.001
RxRisk-V score									
Mean (SD)	6.3 (3.2)	6.5 (3.1)	.08	5.0 (3.0)	5.4 (2.9)	<.01	5.2 (3.0)	5.4 (3.0)	.22
Median	7.0	7.0		5.0	5.0		5.0	5.0	
DCI score*									
Mean (SD)	6.9 (3.9)	6.9 (3.9)	.49	7.7 (3.5)	7.9 (3.6)	.12	5.2 (3.8)	5.4 (4.1)	.27
Median	8.0	8.0		8.0	9.0		4.0	5.0	
DCI comorbidities, n (%)									
Peripheral vascular disease	309 (13.5%)	348 (14.9%)	.17	83 (7.7%)	113 (9.2%)	.22	23 (3.2%)	42 (6.1%)	.01
Diabetes with complications	115 (5.0%)	171 (7.3%)	<.01	73 (6.8%)	116 (9.4%)	.02	20 (2.8%)	56 (8.2%)	<.01
Renal disease	202 (8.8%)	272 (11.7%)	<.01	105 (9.8%)	154 (12.5%)	.04	35 (4.8%)	77 (11.2%)	<.01
Moderate or severe liver disease	12 (0.5%)	<10 ^b	.04	12 (1.1%)	10 (0.8%)	.45	<10 ^b	0 (0.0%)	.17

DCI, Deyo-Charlson Comorbidity Index; MAPD, Medicare Advantage Prescription Drug; NSCLC, non-small cell lung cancer.

*Only statistically significant components of DCI reported.

^bCell counts less than 10 suppressed due to the Health Insurance Portability and Accountability Act.

as patients with unknown site of care. This unknown site-of-care category represented patients who did not have any anticancer therapy in the hospital outpatient clinic or physician office during the postindex period.

Of the 3670 patients with mCRC who met eligibility criteria, 1073 (29.2%) patients received all postindex anticancer therapy in hospital outpatient clinics and 1231 (33.5%) patients in physician offices (Figure). Approximately a quarter (n=971; 26.5%) of the patients received therapy at multiple sites, and 10.8% (n=395) were marked as having unknown site of care. Among the 2634 eligible patients with mBC, 726 (27.6%) received all postindex anticancer therapy in hospital outpatient clinics, and 685 patients (26.0%) received all postindex anticancer therapy in physician offices (Figure). Eleven percent (n=297) of patients received care in multiple sites, and 35% (n=926) of patients were classified as having unknown site of care; however, most (97%) of the patients categorized as unknown were dispensed oral anticancer medications at an outpatient pharmacy and therefore did not fall into either the hospital or physician office settings.

The majority of the patients (> 70%) in all cohorts were enrolled in a MAPD plan. On average, for all 3 cancers, patients treated in the physician office setting were slightly older than patients receiving therapy in the hospital outpatient setting (Table 1). The average RxRisk-V scores at baseline were slightly higher for patients treated in the physician office compared with patients treated in the hospital outpatient clinic setting for the mCRC cohort, but there were no differences in the DCI scores. There were no significant differences in baseline RxRisk-V scores for the aNSCLC or the mBC cohort treated in the hospital outpatient vs physician office setting.

Table 2 and Table 3 depict the top 3 regimens for the first 3 lines of therapy and duration of each line of therapy, respectively. This includes all infusion and oral anticancer therapy. In general, the top 3 regimens for the first 3 lines of therapy did not differ by site of care for any of the cancer cohorts. In the aNSCLC cohort, 29.1% received second-line (2L) treatment in the hospital outpatient setting and 29.6% (P=.67) in the physician office setting, and 6.6% and 7.9% (P=.11) received third-line (3L) treatment in the hospital outpatient setting and physician office setting, respectively. In the mCRC cohort,

26.9% of patients received 2L treatment in the hospital outpatient setting and 24.8% ($P = .24$) in the physician office setting; 8.2% and 6.2% ($P = .06$) received 3L treatment in the hospital outpatient setting and physician office setting, respectively. In the mBC cohort, 64.0% of the patients received 2L treatment in the hospital outpatient setting and 65.1% in the physician office setting ($P = .68$); 27.0% and 25.8% ($P = .62$) received 3L treatment in the hospital outpatient setting and the physician office setting, respectively.

Patients receiving therapy for aNSCLC in the physician office setting had longer median (interquartile range) duration of 1L therapy (Table 3) compared with patients in the hospital outpatient setting (78 [48-127] days vs 71 [43-119] days; $P \leq .01$). In the mCRC and mBC cohorts, there were no statistically significant differences in duration of therapy (1L, 2L, or 3L) in the physician office setting compared with the hospital outpatient setting.

In the aNSCLC cohort, a greater proportion of patients in the hospital outpatient setting received radiation (results not shown) prior to starting 1L therapy than in the physician office setting (50.2% vs 44.9%; $P < .01$) and received radiation after discontinuation of 1L therapy (18.0% vs 13.2%; $P < .01$). A greater proportion of patients in the mCRC cohort treated in the hospital outpatient setting had radiation during 2L therapy (12.5% vs 7.2%; $P = .03$). In the mBC cohort, a greater proportion of patients treated in the hospital outpatient setting had radiation during 1L therapy (20.8% vs 14.6%; $P < .01$) than patients treated in the physician office setting.

Patients receiving anticancer treatment in the hospital outpatient setting had higher median unadjusted total costs (results not shown) in the 6 months postindex period than patients treated in the physician office setting for all 3 cancers (aNSCLC: \$46,118 vs \$43,739; $P < .01$; mCRC: \$43,274 vs \$38,187; $P < .01$; mBC: \$45,654 vs \$38,722; $P < .01$). After controlling for baseline patient characteristics (demographics and DCI), there was no longer a significant difference in total costs by site of care for patients with aNSCLC (Table 4). The differences, however, remained for patients in the mCRC and mBC cohorts. Patients treated in the hospital outpatient settings had 12% and 22% higher costs for the mCRC (cost ratio estimate [95% CI], 1.12 [1.05-1.19]) and mBC (1.22 [1.12-1.33]) cohorts, respectively (results not shown).

The percentage of MAPD patients who died in each of the cancer cohorts did not differ between the hospital outpatient vs physician office settings (aNSCLC: 68.2% [1410 of 2068] vs 67.3% [1459 of 2169]; $P = .52$; mCRC: 41.4% [348 of 841] vs 41.3% [434 of 1052]; $P = .96$; mBC: 31.5% [163 of 518] vs 26.0% [140 of 538]; $P = .05$). The KM analysis did not find differences in the survival curves between hospital outpatient setting vs physician office in any of the cancer types (log-rank test P value $> .2$ for all 3 cancer cohorts; results not shown). The median survival time was 294 (95% confidence limit [CL], 270-317) vs 297 (95% CL, 275-323) days in aNSCLC and 759 (95% CL, 690-934) vs 894 (95% CL, 768-1070) days in mCRC for hospital outpatient vs physician office setting, respectively. The median survival time was 1496 (95% CL, 1254-1654) days in mBC for the hospital outpatient setting but was undefined for the physician office setting. After adjusting for baseline differences in patient

TABLE 2. Top 3 Regimens: Comparison by Lines of Therapy and Cancer Type

Advanced/metastatic non-small cell lung cancer			
Top 3 regimens	Hospital outpatient	Physician office	P^a
First line, n (%)			
Patients received first line	2287 (100%)	2331 (100%)	
Carboplatin, paclitaxel	488 (21.3%)	575 (24.7%)	.01
Carboplatin ^b	557 (24.4%)	573 (24.6%)	.86
Carboplatin, pemetrexed	454 (19.9%)	439 (18.8%)	.38
Second line, n (%)			
Patients received second line	665 (29.1%)	691 (29.6%)	.67
Nivolumab	210 (31.6%)	197 (28.5%)	.22
Pemetrexed	80 (12.0%)	83 (12.0%)	.99
Gemcitabine	60 (9.0%)	56 (8.1%)	.55
Third line, n (%)			
Patients received third line	152 (6.6%)	183 (7.9%)	.11
Nivolumab	47 (30.9%)	47 (25.7%)	.29
Gemcitabine	26 (17.1%)	23 (12.6%)	.24
Pemetrexed	<10 ^c	18 (9.8%)	.12
Metastatic colorectal cancer			
Top 3 regimens	Hospital outpatient	Physician office	P^a
First line, n (%)			
Patients received first line	1073 (100%)	1231 (100%)	
Fluorouracil, oxaliplatin	466 (43.4%)	528 (42.9%)	.79
Bevacizumab, fluorouracil, oxaliplatin	253 (23.6%)	300 (24.4%)	.66
Fluorouracil	130 (12.1%)	160 (13.0%)	.52
Second line, n (%)			
Patients received second line	289 (26.9%)	305 (24.8%)	.24
Bevacizumab, fluorouracil, irinotecan	79 (27.3%)	97 (31.8%)	.23
Fluorouracil, irinotecan	25 (8.7%)	40 (13.1%)	.08
Bevacizumab, fluorouracil, oxaliplatin	18 (6.2%)	28 (9.2%)	.18
Third line, n (%)			
Patients received third line	88 (8.2%)	76 (6.2%)	.06
Bevacizumab, fluorouracil, irinotecan	15 (17.0%)	<10 ^c	.35
Regorafenib	<10 ^c	<10 ^c	.79
Bevacizumab, fluorouracil, oxaliplatin	<10 ^c	<10 ^c	.78

(continued)

characteristics, there were no statistically significant differences in OS by site of care for any of the cancer cohorts (Table 4 Cox model results). The 95% CIs of the HR (hospital outpatient vs physician office) estimates include 1 in all 3 cancer cohorts: HR, 0.99 (95% CI, 0.92-1.07) in aNSCLC; HR, 1.03 (95% CI, 0.90-1.19) in mCRC, and HR, 1.21 (95% CI, 0.96-1.53) in mBC.

CLINICAL

TABLE 2. (Continued) Top 3 Regimens: Comparison by Lines of Therapy and Cancer Type

Metastatic breast cancer ^d			
Top 3 regimens	Hospital outpatient	Physician office	P ^a
First line, n (%)			
Patients received first line	726 (100%)	685 (100%)	
Anastrozole	67 (9.2%)	49 (7.2%)	.16
Cyclophosphamide, doxorubicin	191 (26.3%)	188 (27.4%)	.63
Letrozole	52 (7.2%)	33 (4.8%)	.06
Second line, n (%)			
Patients received second line	465 (64.0%)	446 (65.1%)	.68
Anastrozole	92 (19.8%)	102 (22.9%)	.26
Tamoxifen	44 (9.5%)	29 (6.5%)	.10
Letrozole	46 (9.9%)	44 (9.9%)	.99
Third line, n (%)			
Patients received third line	196 (27.0%)	177 (25.8%)	.62
Anastrozole	14 (7.1%)	25 (14.1%)	.03
Tamoxifen	12 (6.1%)	13 (7.3%)	.64
Letrozole	<10 ^c	13 (7.3%)	.26

^aP value was based on χ^2 test.

^bCarboplatin single-agent was used with radiation therapy during first line in 64.3% in hospital outpatient vs 61.4% in physician office ($P = .32$).

^cCell counts less than 10 suppressed due to the Health Insurance Portability and Accountability Act.

^dFor metastatic breast cancer, one-third of patients filled prescriptions for oral therapy at outpatient pharmacies throughout the study period, hence these patients were not assigned a site of care (unknown), as site-of-care assignment was based on an anticancer procedure code. Results for metastatic breast cancer should be interpreted with caution.

TABLE 3. Duration of Lines of Therapy by Site of Care for Each Cancer

Advanced/metastatic non-small cell lung cancer				
		Hospital outpatient	Physician office	P ^a
		Mean (SD); median (IQR)	Mean (SD); median (IQR)	
Duration of each line of therapy, days	First line	96 (91); 71 (43-119)	102 (83); 78 (48-127)	<.01
	Second line	104 (109); 70 (36-127)	117 (140); 75 (41-133)	.30
	Third line	113 (117); 82 (37-147)	112 (122); 76 (40-141)	.87
Metastatic colorectal cancer				
		Hospital outpatient	Physician office	P ^a
		Mean (SD); median (IQR)	Mean (SD); median (IQR)	
Duration of each line of therapy, days	First line	175 (130); 162 (81-229)	179 (129); 161 (85-228)	.60
	Second line	167 (179); 115 (61-217)	154 (156); 120 (53-196)	.48
	Third line	112 (105); 75 (41-148)	106 (94); 95 (33-154)	.70
Metastatic breast cancer				
		Hospital outpatient	Physician office	P ^a
		Mean (SD); median (IQR)	Mean (SD); median (IQR)	
Duration of each line of therapy, days	First line	190 (262); 85 (47-216)	156 (196); 75 (50-166)	.34
	Second line	275 (305); 150 (64-377)	293 (330); 164 (64-393)	.69
	Third line	218 (250); 113 (56-286)	227 (264); 145 (64-295)	.49

IQR, interquartile range.

^aP value was based on Wilcoxon rank-sum test.

DISCUSSION

This study adds to the body of knowledge regarding differences in treatment patterns and patient outcomes by site of care. Overall, there were no notable differences by site of care in patient characteristics or systemic treatments received across lines of therapy for aNSCLC, mCRC, or mBC. However, radiation therapy was more common in the hospital outpatient setting for the 3 cancers, and duration of 1L therapy was longer for patients with aNSCLC receiving care in the physician office setting. For patients enrolled in a MAPD plan (>70% of the overall cohort), there was no significant difference in median survival by site of care. Despite similar systemic treatment patterns and survival across both sites of care, adjusted total costs were 12% and 22% higher for patients with mCRC and mBC, respectively, in the hospital outpatient setting than the physician office setting. These findings corroborate

previous evidence and may have important implications for patients, providers, health plans, and policy makers, as more patients are receiving care in the hospital outpatient rather than the physician office setting.

Consistent with findings of a previous study using the Humana research database, the most common 1L regimens for aNSCLC, mCRC, and mBC were similar between the hospital outpatient and physician office settings.⁹ Studies in the literature have focused mainly on the first line of treatment^{3,5,7,9} and some have reported treatment patterns only for matched populations,^{26,27} thus limiting the interpretation and generalizability of their findings. The current study provides a broader view by showing no differences by site of care in treatments received, duration of therapy, or proportion of unmatched patients receiving additional therapy beyond the 1L setting. These data may provide some reassurance that patients with cancer may be managed or treated similarly, irrespective of site of care.²⁸

TABLE 4. Postindex Cost and Overall Survival

		Regression model total cost (6 months post index) ^a				
		β coefficient (95% CI)	Exp β (95% CI)			
Advanced/metastatic NSCLC (n = 2789)	Hospital outpatient vs physician office (ref)	0.03 [-0.02 to 0.08]	1.03 (0.98-1.08)			
Metastatic colorectal cancer (n = 1804)	Hospital outpatient vs physician office (ref)	0.11 (0.05-0.18)	1.12 (1.05-1.19)			
Metastatic breast cancer (n = 1214)	Hospital outpatient vs physician office (ref)	0.20 (0.11-0.28)	1.22 (1.12-1.33)			
Cox models for overall survival in MAPD patients						
Parameter		Parameter estimate	Standard error	χ^2	Pr > χ^2	HR (95% CI)
Advanced/metastatic NSCLC (n = 4237)	Hospital outpatient vs physician office (ref)	-0.01	0.04	0.04	0.85	0.99 (0.92-1.07)
Metastatic colorectal cancer (n = 1893)	Hospital outpatient vs physician office (ref)	0.03	0.07	0.21	0.65	1.03 (0.90-1.19)
Metastatic breast cancer (n = 1056)	Hospital outpatient vs physician office (ref)	0.19	0.12	2.60	0.11	1.21 (0.96-1.53)

MAPD, Medicare Advantage Prescription Drug; NSCLC, non-small cell lung cancer; ref, reference.

^aGeneralized linear model with log link and gamma distribution was used for cost analysis. Total costs include medical and pharmacy costs. Covariates controlled for in the regression models include the following: age, sex, race, geographic region, urban/rural designation, income, and Deyo-Charlson Comorbidity Index score. Insurance type and baseline costs were also included in the generalized linear models for cost analysis.

aNSCLC and mCRC treatment patterns observed in this study were largely consistent with recommendations from the National Comprehensive Cancer Network²⁹ and the American Society of Clinical Oncology³⁰ clinical guidelines and observational studies^{31,32} during the time frame of this study. Although common usage of endocrine therapy for mBC was expected, the frequent use of 1L cyclophosphamide plus doxorubicin (AC regimen) in both the hospital outpatient and physician office settings was likely overestimated in this cohort. This is most likely due to the exclusion of patients receiving oral therapies (ie, resulting in their site of care being the pharmacy and not hospital outpatient or physician office), as well as potential misclassification of metastatic disease due to secondary neoplasm coding in claims. Therefore, the findings from the mBC cohort related to the high utilization of AC should be interpreted with care.

In line with prior evidence, there were no meaningful differences in patient demographic characteristics or comorbidity burden by site of care.^{3,5,7} However, it is possible that disease severity, comorbidities, functional status, disease progression, and symptoms of study cohorts were underestimated because clinical information and rationale for treatment decisions are not available in claims data. In contrast to current findings, prior descriptive analyses^{33,34} have suggested that patients treated in hospital outpatient practices were more likely to be Black, Hispanic, female, or younger, or to have metastatic disease, higher comorbidity burden, lower income, less education, Medicaid or no insurance, or higher prior utilization of hospitals and EDs. Despite the lack of observed differences in unmatched patient characteristics and treatment patterns by site of care in the current study, outcomes analyses were adjusted for potential confounders in order to minimize selection bias.

In the results of several previous studies, the site of cancer care has been shown to be associated with differences in cost of care.^{3-11,20} The current study confirms these previous findings for the mCRC and mBC cohorts, and the 6-month costs in this study are within range of those reported in the literature.¹¹ However, the cost differential by site of care was smaller than previously reported. In the claims analysis of 283,502 patients with cancer receiving chemotherapy,¹¹ the cost of cancer care was 48% lower in the physician office than the hospital outpatient setting (\$43,700 [95% CI, \$42,885-\$44,517] vs \$84,660 [95% CI, \$82,969-\$86,352]; $P = .001$). Similarly, a claims analysis of patients enrolled in commercial plans treated with chemotherapy suggested that total costs of care were 46% higher in the hospital outpatient setting than the physician office setting. A matched cohort analysis of patients with NSCLC, breast cancer, and colorectal cancer reported that the cost of care was 59.9% higher in the hospital outpatient setting.²⁶ However, these analyses utilized databases with no or limited Medicare representation and evaluated only patients receiving chemotherapy in the 1L setting. In the current study, most patients were enrolled in a MAPD plan, and to reflect the rapidly evolving oncology treatment landscape, 1L treatment was not restricted to any specific drug.

As most studies have focused on patients treated with chemotherapy, the magnitude of difference in cost by site of care may not be as high as previously reported or may depend on other factors such as the population characteristics (eg, Medicare vs commercial, chemotherapy vs immunotherapy treatment) and the cancer type evaluated. Although this study focused only on aNSCLC, mCRC, and mBC, previous studies in the literature included either all cancer types or varied numbers, stages, and types of cancer.^{10,11,28}

For example, Hayes et al⁶ evaluated 9 cancer types; Fisher et al⁵ examined early breast cancer or mBC, metastatic lung cancer, mCRC, non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL); Lipitz-Snyderman et al⁸ assessed mBC, NSCLC, and colon, esophagus, pancreatic, and stomach cancers; Parthan et al⁷ focused on early breast cancer; Byfield et al³ included only CLL and NHL; Kalidindi et al¹⁰ evaluated early- or late-stage prostate, colon, and lung cancers and leukemia and lymphoma; and Gordan et al²⁶ assessed head and neck cancer, bladder cancer, renal cell carcinoma, and melanoma regardless of cancer severity or stage. Indeed, the study by Hayes et al found that the cost of care ranged from 20% to 39% lower in the hospital outpatient setting than the physician office setting, depending on cancer type.⁶

The factors associated with differences in costs were not explored in the current study; however, these findings raise potential hypotheses that may be examined in future research. The lack of a statistically significant difference in total costs between the physician office and hospital outpatient settings for patients with aNSCLC may be partly due to longer duration of 1L treatment in the physician office setting. Of note, the duration of treatment did not differ between sites of care for mCRC and mBC, as was observed in other studies.^{26,27} Previous reports have suggested that the underlying drivers of cost differences may include differing billing practices,⁵ reimbursement rates,⁶ differences in the type and level of resource use,^{3,5,7} level of access to or participation in clinical trials, or a combination of these factors.

Although the focus on costs by previous studies is appropriate given the increased focus on cost-effectiveness and efficiency in cancer care, there has been little focus on evaluating how the shift to hospital outpatient-based care affects survival outcomes. Prior studies by Pfister et al³⁵ and Shulman et al³⁶ have evaluated survival differences by hospital type using the Surveillance, Epidemiology, and End Results–Medicare databases and National Cancer Data Base, respectively, among patients with lung, prostate, breast, and colorectal cancer. In these studies, risk-adjusted survival was different for patients at different hospital types, with National Cancer Institute–designated Comprehensive Cancer Centers having the highest survival rates, followed by academic medical centers, and then community hospitals. Further, patients treated at larger community hospitals had better survival than those treated at smaller community hospitals. In the present study, no differences in OS were identified for MAPD-enrolled patients by site of care, both before and after risk adjustment. However, it should be noted that potential confounders such as socioeconomic data, disease severity, and functional status were not available for adjustment. As survival is a potential quality metric for sites of care,³⁷ more research is needed to further investigate the cost differential by site of care.

Limitations

The results of this study should be evaluated while taking important limitations into consideration. Claims data are collected for administrative and billing purposes and not for research. These data

may be incomplete or inaccurate and may contain billing coding errors. Although analyses were adjusted for baseline differences and limited to patients with advanced or metastatic cancer, residual confounding may still remain due to the potential imbalance of unknown and known unmeasured confounders (eg, disease severity) between sites of care. Therefore, cause-and-effect relationships cannot be established from this study.

There is no specific diagnosis code to specify NSCLC vs SCLC. Thus, claims for anticancer drugs used for treatment of SCLC were used to identify patients with SCLC for exclusion, as a proxy to identify patients who likely had NSCLC. Although this proxy is standard practice for studies using claims data, it may have overestimated the NSCLC cohort because some patients with SCLC may receive the same therapies recommended for NSCLC. Nearly half (46%) of the patients with mBC were excluded from the study cohort because they either received care at multiple sites (11.3%) or filled prescriptions for oral therapy at outpatient pharmacies throughout the study period (35.2%) and could therefore not be assigned to a site of care. By design, patients who filled prescriptions for therapy only at outpatient pharmacies, with no record of anticancer infusions in either the hospital outpatient or physician office setting, were excluded. Therefore, observed treatment patterns and outcomes for mBC may not be generalizable across all patients with mBC.

Health care costs were assessed only for the 6-month follow-up period, which may not reflect the seasonality of health care use over the year and hence may under- or overestimate total costs. Furthermore, although this study population was drawn from the membership of a national health plan, most of the membership reside in the Southern and Midwestern regions of the United States, limiting the generalizability of the results. Despite these limitations, this study advances the discussion regarding quality of care and costs by site of cancer care.

CONCLUSIONS

This study contributes to the growing body of work related to site of care. In demonstrating that patients receive similar care and experience outcomes that do not differ by site of care, assurance is provided to some degree that treatments in the physician office setting are comparable with treatments in the hospital outpatient setting, even beyond the 1L treatment. Although there were no major differences in treatment received by site of care, the higher cost of care for patients receiving therapy in the hospital outpatient setting warrants deeper evaluation. ■

Author Affiliations: Humana Healthcare Research Inc (SB, YX, RN), Louisville, KY; Eli Lilly and Company (CM, YEZ, GCC, LMH), Indianapolis, IN; Humana Pharmacy Solutions (SS), Louisville, KY.

Source of Funding: Eli Lilly and Humana.

Author Disclosures: Drs Bunniran, Xu, and Nair are employed by Humana Healthcare Research, which received funding from Eli Lilly to conduct this study. Dr Molife, Ms Zhu, and Dr Carter are employed by and hold stock in Eli Lilly, a manufacturer of anticancer therapy. Dr Hess is employed by Eli Lilly. Dr Sheth reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (YX, RN, YEZ, GCC, SS, LMH); acquisition of data (YX); analysis and interpretation of data (SB, YX, CM, RN, YEZ, GCC, SS, LMH); drafting of the manuscript (SB, CM, RN, LMH); critical revision of the manuscript for important intellectual content (SB, YX, CM, RN, YEZ, GCC, SS, LMH); statistical analysis (YX, YEZ); provision of patients or study materials (SB); obtaining funding (SB); administrative, technical, or logistic support (SB, CM); and supervision (SB).

Address Correspondence to: Supapun Bunniran, PhD, Humana Healthcare Research Inc, 515 W Market St, Louisville, KY 40202. Email: sbunniran@humana.com.

REFERENCES

- Buchsel BC, Yarbro CH. *Oncology Nursing in the Ambulatory Setting*. 2nd ed. Jones and Bartlett; 2005.
- Hess LM, Cinfio FN, Wetmore S, et al. Enhancing the budget impact model for institutional use: a tool with practical applications for the hospital oncology pharmacy. *Hosp Pharm*. 2016;51(6):452-460. doi:10.1310/hpj5106-452
- Byfield SD, Small A, Becker LK, Reyes CM. Differences in treatment patterns and health care costs among non-Hodgkin's lymphoma and chronic lymphocytic leukemia patients receiving rituximab in the hospital outpatient setting versus the office/clinic setting. *J Cancer Ther*. 2014;5(2):208-216. doi:10.4236/jct.2014.52026
- Engel-Nitz NM, Yu EB, Becker LK, Small A. Service setting impact on costs for bevacizumab-treated oncology patients. *Am J Manag Care*. 2014;20(11):e515-e522.
- Fisher MD, Punekar R, Yim YM, et al. Differences in health care use and costs among patients with cancer receiving intravenous chemotherapy in physician offices versus in hospital outpatient settings. *J Oncol Pract*. 2017;13(1):e37-e46. doi:10.1200/JOP.2016.012930
- Hayes J, Hoverman RJ, Brow ME, et al. Cost differential by site of service for cancer patients receiving chemotherapy. *Am J Manag Care*. 2015;21(3):e189-e196.
- Parthan A, Santos E, Becker L, et al. Health care utilization and costs by site of service for nonmetastatic breast cancer patients treated with trastuzumab. *J Manag Care Spec Pharm*. 2014;20(5):485-493. doi:10.18553/jmcp.2014.20.5.485
- Lipitz-Snyderman A, Atona CL, Schleicher SM, Bach PB, Panageas KS. Practice patterns for older adult patients with advanced cancer: physician office versus hospital outpatient setting. *J Oncol Pract*. 2019;15(1):e30-e38. doi:10.1200/JOP.18.00315
- Hopson S, Casebeer A, Stemkowski S, et al. Does site-of-care for oncology infusion therapy influence treatment patterns, cost, and quality in the United States? *J Med Econ*. 2018;21(2):152-162. doi:10.1080/13696998.2017.1384736
- Kalidindi Y, Jung J, Feldman R. Differences in spending on provider-administered chemotherapy by site of care in Medicare. *Am J Manag Care*. 2018;24(7):328-333.
- Winn AN, Keating NL, Trogdon JG, Basch EM, Dusetzina SB. Spending by commercial insurers on chemotherapy based on site of care, 2004-2014. *JAMA Oncol*. 2018;4(4):580-581. doi:10.1001/jamaoncol.2017.5544
- Robinson WR, Beyer J. Impact of shifting from office- to hospital-based treatment facilities on the administration of intraperitoneal chemotherapy for ovarian cancer. *J Oncol Pract*. 2010;6(5):232-235. doi:10.1200/JOP.000058
- Census regions and divisions of the United States. US Census Bureau. Accessed January 1, 2019. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf
- Rural-urban commuting area codes. US Department of Agriculture Economic Research Service. Accessed January 1, 2019. <https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.aspx>
- West AN, Weeks WB, Wallace AE. Rural veterans and access to high-quality care for high-risk surgeries. *Health Serv Res*. 2008;43(5, pt 1):1737-1751. doi:10.1111/j.1475-6773.2008.00876.x
- Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. doi:10.1016/0895-4356(92)90133-8
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83
- Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care*. 2003;41(6):761-774. doi:10.1097/01.MLR.0000064641.84967.B7
- Sales AE, Liu CF, Sloan KL, et al. Predicting costs of care using a pharmacy-based measure risk adjustment in a veteran population. *Med Care*. 2003;41(6):753-760. doi:10.1097/01.MLR.00000649502.75914.DD
- Fishman PA, Goodman MJ, Hornbrook MC, Meenan RT, Bachman DH, O'Keeffe Rosetti MC. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. *Med Care*. 2003;41(1):84-99. doi:10.1097/00005650-200301000-00011
- Farley JF, Harley CR, Devine JW. A comparison of comorbidity measurements to predict healthcare expenditures. *Am J Manag Care*. 2006;12(2):110-119.
- Johnson ML, El-Serag HB, Tran TT, Hartman C, Richardson P, Abraham NS. Adapting the Rx-Risk-V for mortality prediction in outpatient populations. *Med Care*. 2006;44(8):793-797. doi:10.1097/01.mlr.0000218804.41758.ef
- Fan VS, Maciejewski ML, Liu CF, McDonnell MB, Finn SD. Comparison of risk adjustment measures based on self-report, administrative data, and pharmacy records to predict clinical outcomes. *Health Serv Outcomes Res Methodol*. 2006;6:21-36. doi:10.1007/s10742-006-0004-1
- Vitry A, Wong SA, Roughhead EE, Ramsay E, Barratt J. Validity of medication-based co-morbidity indices in the Australian elderly population. *Aust N Z J Public Health*. 2009;33(2):126-130. doi:10.1111/j.1753-6405.2009.00357.x
- Lu CY, Barratt J, Vitry A, Roughhead E. Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting. *J Clin Epidemiol*. 2001;64(2):223-228. doi:10.1016/j.jclinepi.2010.02.015
- Gordan L, Blazer M, Saundankar V, Kazza D, Weidner S, Eaddy M. Cost differences associated with oncology care delivered in a community setting versus a hospital setting: a matched-claims analysis of patients with breast, colorectal, and lung cancers. *J Oncol Pract*. 2018;14(12):e729-e738. doi:10.1200/JOP.17.00040
- Gordan L, Blazer M, Saundankar V, Kazza D, Weidner S, Eaddy M. Cost differential of immuno-oncology therapy delivered at community versus hospital clinics. *Am J Manag Care*. 2019;25(3):e66-e70.
- Richardson LC, Tangka FK. Ambulatory care for cancer in the United States: results from two national surveys comparing visits to physicians' offices and hospital outpatient departments. *J Natl Med Assoc*. 2007;99(12):1350-1358.
- NCCN guidelines & clinical resources: NCCN guidelines for treatment of cancer by site. National Comprehensive Cancer Network. Accessed January 1, 2019. https://www.nccn.org/professionals/physician_gls/default.aspx#site
- Guidelines, tools, & resources. American Society of Clinical Oncology. Accessed January 1, 2019. <https://www.asco.org/research-guidelines/quality-guidelines/guidelines>
- Hess LM, Cui ZL, Mytelka DS, Han Y, Goodloe R, Schelman W. Treatment patterns and survival outcomes for patients receiving second-line treatment for metastatic colorectal cancer in the USA. *Int J Colorectal Dis*. 2019;34(4):581-588. doi:10.1007/s00384-018-03227-5
- Molife C, Hess LM, Cui ZL, et al. Sequential therapy with ramucicromab and/or checkpoint inhibitors for non-small-cell lung cancer in routine practice. *Future Oncol*. 2019;15(25):2915-2931. doi:10.2217/fo-2018-0876
- Demiralp B, Belausteguigoitia D, Zhang Q, Koenig L. Comparison of cancer patients treated in hospital outpatient departments and physician offices: final report. American Hospital Association. November 13, 2014. Accessed January 1, 2019. <https://www.aha.org/system/files/2018-03/comparison-hospd-physician-offices.pdf>
- Gordan L. The value of community oncology: site of care cost analysis. Community Oncology Alliance. September 25, 2017. Accessed January 1, 2019. <https://communityoncology.org/the-value-of-community-oncology-site-of-care-cost-analysis/>
- Pfister DG, Rubin DM, Elkin EB, et al. Risk adjusting survival outcomes in hospitals that treat patients with cancer without information on cancer stage. *JAMA Oncol*. 2015;1(9):1303-1310. doi:10.1001/jamaoncol.2015.3151
- Shulman LN, Patis BE, McCabe R, et al. Survival as a quality metric of cancer care: use of the National Cancer Data Base to assess hospital performance. *J Oncol Pract*. 2018;14(1):e59-e72. doi:10.1200/JOP.2016.020446
- Porter ME. What is value in health care? *N Engl J Med*. 2010;363(26):2477-2481. doi:10.1056/NEJMp1011024

Visit ajmc.com/link/88619 to download PDF

Supplement NSCLC Line End Rules

- The first line therapy treatment regimens were first identified prior to determining the end date of first line, which include all medications received within the first 28 days beginning at the anti-cancer drug initiation date.
- Second line regimens (2L) include the set of agents received within the initial 28-day period beginning at the *change of a line of therapy*.

Third line regimens (3L) include the set of agents received within the initial 28-day period beginning at the *change of second-line therapy*. All drugs listed must be received within that period for the regimen assignment.

Rules of First Line End rules:

Patients remain on first-line therapy until a treatment change or discontinuation. At the time of the treatment change or discontinuation, a second line of therapy begins. Change to the first line of therapy rules are as follows:

1. New agent added after the initial 28 days
 - a. New agent was defined as any medication that was not part of the first line treatment regimens described above with the following exceptions:
 - Cisplatin, carboplatin, and oxaliplatin were considered interchangeable and did not change the line if one replaced another
 - Augmentation with bevacizumab (maintenance therapy) alone did not change the line of therapy
2. Discontinuation.
 - a. Patients stop receiving all medication in first line regimen
 - b. The last agent infused/administered was defined as the last date of the line of therapy.
 - c. In case of interchangeable medications or augmentation with single agent bevacizumab after the initial 28 days, first line did not end as long as patients were still on the interchangeable medication or bevacizumab
3. Gap of >90 days.
 - a. If there is a gap of >90 days without evidence of any medication in first line regimens, or interchangeable medications/bevacizumab if applicable, the line of therapy would change. The end of the current line of therapy was the last recorded date of infusion/administration of an agent prior to the gap, or end of the day supply in case of oral medications with day supply indicated in claims data.
4. End of follow up.
 - a. The end of follow up could be due to death, end of the database, or disenrollment.

The rules for progression from 2L to 3L and so on were the same as above, other than maintenance therapy, which was only considered at first line treatment.

CRC Line End Rules

First line regimens (1L) include the set of agents received within the initial 28-day period beginning at the anti-cancer initiation date. Second line regimens (2L) include the set of agents received within the initial 28-day period beginning at the start of *the second line of therapy*. Third line regimens (3L) include the set of agents received within the initial 28-day period beginning at the start of *the third line of therapy*. End and change of line rules are presented below:

1. Discontinuation of all treatment
2. A gap of more than 6 months in treatment,
3. Patient dis-enrolled from the health plan (including death), or study period ended,
4. New agents not on the initial treatment regimens start after the initial 28 days with the following exceptions:
 - a. Fluorouracil and capecitabine are considered interchangeable, thus not considered a new agent if one replaced the other
 - b. If a biologic is *added* after the initial 28 days but within 6 months, the line does not change
 - i. The added biologic would be used to augment the initial regimen identified using the first 28 days
 - ii. Please note, if a new biologic *replaced* an existing one, the line would change
 - c. For patients who initiate therapy with single-agent fluorouracil or single-agent capecitabine then add either irinotecan or oxaliplatin within 6 months of initiation, lines of therapy does not change.
 - i. The initial regimens are augmented with the added medication

BC Line End Rules

First line regimens (1L) will be the set of agents received within the initial 28-day period beginning at the treatment initiation date. Second line regimens (2L) will be the set of agents received within the initial 28-day period beginning at the *change of a line of therapy*. Third line regimens (3L) will be the set of agents received within the initial 28-day period beginning at the *change of second-line therapy*. All drugs listed must be received within that period for the regimen assignment.

End and change of line of therapy rules are presented below:

1. Discontinuation of all treatment
2. A gap of more than 90 days in treatment,
3. Patient dis-enrolled from the health plan (including death), or study period ended,
4. New agents not on the initial treatment regimens started after the initial 28 days end the current line and start a new line, with the following exceptions:
 - Sequential treatments that are known to be standard regimens, such as the combination of doxorubicin plus cyclophosphamide followed after four cycles by weekly or biweekly paclitaxel ("ACTH"), will be considered continuation of the same line of therapy.
 - Other exceptions:

Condition/Exception	Rule
Change from anastrozole to letrozole (or vice versa)	Not a change in LOT
Change from doxorubicin to pegylated doxorubicin (or vice versa)	Not a change in LOT
Change from paclitaxel to nab-paclitaxel (or vice versa)	Not a change in LOT
Change from cisplatin to carboplatin (or vice versa)	Not a change in LOT

Appendix A

Appendix A-1: Anti-cancer treatment medications for NSCLC

Drug name
AFATINIB
ALECTINIB
ATEZOLIZUMAB
Bevacizumab
BRIGATINIB
CABOZANTINIB
Carboplatin
CERITINIB
Cetuximab
Cisplatin
CRIZOTINIB
DABRAFENIB MESYLATE
Docetaxel
ERLOTINIB
Etoposide
Gefitinib
Gemcitabine
Irinotecan
NECITUMUMAB
Nivolumab
OSIMERTINIB MESYLATE
Paclitaxel
Pembrolizumab
Pemetrexed
RAMUCIRUAB
TRAMETINIB DIMETHYL SULFOXIDE
Trastuzumab
VEMURAFENIB TAB 240 MG
Vinblastine
Vinorelbine Tartrate

Appendix A-2: Anti-cancer treatment medications for CRC

Drug name
Bevacizumab
Capecitabine
Carboplatin
CETUXIMAB
Cisplatin
Cyclophosphamide
Docetaxel
Doxorubicin
ETOPOSIDE
Fluorouracil
Folinic acid
Gemcitabine

Irinotecan
Methotrexate
Nivolumab
Oxaliplatin
Paclitaxel
Panitumumab
Pembrolizumab
RAMUCIRUAB
Regorafenib
Trifluridine-Tipiracil
ziv-aflibercept

Appendix A-3: Anti-cancer treatment medications for BC

Drug name
Ado-trastuzumab emtansine
Anastrozole
BEVACIZUMAB
Capecitabine
Carboplatin
Cisplatin
Cyclophosphamide
Docetaxel
Doxorubicin
Epirubicin
Eribulin
ETHINYL ESTRADIOL
ETOPOSIDE
Everolimus
Exemestane
Fluorouracil
Fluoxymesterone
Fulvestrant
Fulvestrant
Gemcitabine
Goserelin acetate
Ixabepilone
Lapatinib ditosylate
Letrozole
Leuprolide acetate
Megestrol acetate
Methotrexate
Paclitaxel
Palbociclib
Pertuzumab
RAMUCIRUAB
Tamoxifen
Toremifene
Trastuzumab
Vinorelbine Tartrate

Appendix B: Chemotherapy procedure codes used to identify POC

Description	Code
Chemotherapy administration	Q0085,Q0084,Q0083,96445,96440,96446,96450,96423,96425,96422,96420,96415,96417,96416,96413, G0359,C8955,96414,96412,C8954,96410,C8953,96408,G0355,96400,96402,96401,96406,96405,96411, 96409
Administration(s) of experimental drug(s) only in a medicare qualifying	G0292
Chemotherapy assessment	G9029,G9030,G9031,G9032,G9021,G9022,G9023,G9024,G9025,G9026,G9027,G9028
Chemotherapy documentation	G8371,G8372,G8373,G8374,G8377
Encounter for antineoplastic chemotherapy	V5811
Encounter for antineoplastic immunotherapy	V5812
Home infusion/specialty drug administration	S9329,S9330,S9331,99601,99602,S9559
initiation of prolonged chemotherapy infusion (more than eight hours),	G0361
Provision of chemotherapy agent	96545
Refilling and maintenance of portable/implantable pump	96,530,965,229,652,100,000
Unlisted chemotherapy procedure	96549