Characterizing Medical Care by Disease Phase in Metastatic Colorectal Cancer

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Objective: To characterize patterns of medical care by disease phase in patients with newly diagnosed metastatic colorectal cancer (mCRC).

Methods: Patients with mCRC newly diagnosed between 2004 and 2008 were selected from a large US national commercially insured claims database and were observed from initial mCRC diagnosis to death, disenrollment, or end of study period (July 31, 2009), whichever occurred first. The observation period was divided into 3 distinct phases of disease: diagnostic, treatment, and death. Within each phase, patterns of medical care were examined by the mutually exclusive service categories of inpatient, emergency department (ED), outpatient office and facility, outpatient pharmacy, chemotherapy, and biologic therapy, as measured by estimation of aggregate and category costs per patient per month.

Results: A total of 6675 patients with newly diagnosed mCRC were analyzed. Mean age was 64.1 years; 55.5% were males. Mean costs per patient per month for diagnostic, treatment, and death phases were $16,895, $8891, and $27,554, respectively. Inpatient care was the primary driver of medical care for both the diagnostic (41.7% of costs) and death (71.4% of costs) phases. The largest category of medical care for the treatment phase was outpatient care (45.0% of costs). Chemotherapy and biologic therapy accounted for 15.6% and 17.6% of costs in the treatment phase, respectively.

Conclusion: Substantial differences in patterns of medical care were found between mCRC disease phases. Inpatient care was the key driver of medical care in the diagnostic and death phases compared with outpatient care in the treatment phase.

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An estimated 51,370 Americans will die from colorectal cancer (CRC) in 2010,[1] making CRC the second leading cause of death resulting from cancer in the United States.[2] Approximately 20% of patients with CRC already have metastases at time of diagnosis, and up to 50% of all patients will develop metastases over the course of the disease.[3]

Advances in systemic therapies have improved overall survival (OS) for patients with metastatic CRC (mCRC). Survival increased from 5 months with best supportive care[4] to 10.5 months when fluorouracil (FU) was the sole therapeutic option,[5] to 12 to 14 months with FU plus leucovorin (LV),[6] to 14 to 15 months with bolus FU/LV plus irinotecan,[7] and up to 20 months with FU/LV plus oxaliplatin (FOLFOX) and FU/LV plus irinotecan (FOLFIRI).[8] Currently, FOLFOX and FOLFIRI are the most commonly used chemotherapy regimens for first- and second-line treatment of mCRC, producing similar OS results regardless of which regimen is used first.[8] Another improvement in survival occurred with the introduction of monoclonal antibodies in combination with chemotherapy. Although the benefit accrued seems to vary with the monoclonal antibody, chemotherapy backbone, and patients included in the clinical trial, improvement in median OS close to 2 years has been observed with cetuximab in combination with FOLFIRI and panitumumab in combination with FOLFOX in first-line patients with wild-type *KRAS* mCRC.[9,10]

Given the current evidence, treatment for mCRC will continue to combine multiple approaches and therapies, including surgery, chemotherapy, and biologic therapy. It is likely that patterns of treatment and resulting medical care use and costs will differ depending on the phase of mCRC disease. Using data from 1998 to 2004, Paramore et al[11] examined mCRC-related monthly costs by disease phase in patients with newly diagnosed mCRC and found lower costs in the treatment phase relative to diagnostic and death phases. However, the time period for that study was before the availability of biologic agents in mCRC treatment. Lang et al[12] examined lifetime and treatment-phase costs in patients with CRC using SEER-Medicare data from 1996 to 2005 and found that patients with CRC incurred excess costs of $33,500 in the initial phase, $4500 per year in the continuing phase, and $14,500 in the terminal phase. Their study population was patients with CRC, not mCRC, and they examined total

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cost instead of cost drivers (eg, inpatient costs, outpatient costs, pharmacy costs, and so on). To our knowledge, there are no current studies examining patterns of care by phase of disease in the treatment of mCRC after the introduction of biologics, which are now part of standard care in the treatment of mCRC. Our study was intended to fill this gap by providing updated cost estimates and comparing differences in patterns of care during different phases of mCRC. With a standard of care that now often includes biologic agents in combination with chemotherapy,[13,14] data on patterns of treatment and medical care in the various phases of disease are lacking. The objective of the current study was to characterize the patterns and costs of medical care and identify cost drivers by phase of disease in patients with mCRC diagnosed from 2004 to 2008 and observed up to July 2009.

Take-Away Points

This study provides an assessment of patterns and costs of medical care by phase of mCRC disease, employing a study period (2004 to 2009) that captures the impact of biologic agents bevacizumab, cetuximab, and panitumumab.

- Substantial differences in patterns of medical care were found among mCRC disease phases. Mean costs per patient per month for diagnostic, treatment, and death phases were $16,895, $8891, and $27,554, respectively.
- Inpatient care was the key driver of medical care in the diagnostic and death phases compared with outpatient care in the treatment phase.

METHODS

Data Source

Data were derived from the Thomson Reuters MarketScan Commercial Claims and Encounter Database (commercial database) and the Medicare Supplemental and Coordination of Benefits Database (Medicare database) from January 1, 2004, to July 31, 2009. The databases are constructed from claims and enrollment data provided by medium-sized to large employer-sponsored health plans from across the United States and are Health Insurance Portability and Accountability Act compliant. Combined, these 2 databases include patient-level medical and pharmacy claim histories, and in 2008, they contained the health care experience of 37 million covered lives.

Enrollees are covered under a variety of plan types, including both capitated (eg, health management organizations) and noncapitated (eg, fee for service) product lines. The databases capture the full continuum of care for reimbursable services delivered across all settings, including physician office visits, emergency department (ED) visits, hospital stays, and outpatient pharmacy claims. Detailed cost data are available, and within the Medicare database, both the Medicare-covered portion of payment (represented as the coordination of benefits amount) and employer-paid portion are included. Age and sex distributions of patients in MarketScan are similar to those in the Medical Expenditure Panel Survey and Medicare Beneficiary Survey.

Patient Selection

CRC was determined by the presence of at least 1 inpatient or at least 2 outpatient claims containing *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes 153.0 to 153.4, 153.6 to 153.9, 154.0, 154.1, and 154.8 from January 1, 2004, to December 31, 2008. Metastasis was defined as the occurrence of at least 1 inpatient or at least 2 outpatient claims containing *ICD-9-CM* diagnosis codes 196.0, 196.1, 196.3, 196.5, 197.0 to 197.4, 197.6 to 197.8, 198.x, or 199.0 at most 30 days before or any time after first CRC diagnosis from 2004 to 2008. The date of the first claim for metastatic disease was assigned as the index date. Patients were required to have 6 months of continuous enrollment before the index date. Patients with diagnoses of 153.5 (appendix), 154.2 (anal canal, anal sphincter), or 154.3 (anus, unspecified) before first CRC diagnosis and patients with other primary cancer diagnoses or metastases during the 6-month preperiod were excluded. Patients included in the study were required to be 18 years or older on the index date, and there was no restriction on maximum age. The site of the index diagnosis was considered the initial site of metastasis.[11,13] In cases when more than 1 metastatic diagnosis occurred on the same date, the earliest diagnosis was chosen over subsequent diagnoses.

Phases of mCRC Disease

Length of follow-up for each patient was variable, starting from the index diagnosis of metastatic disease and ending at death, the end of continuous enrollment, or the end of the study period (July 31, 2009), whichever came first. Because claims data are limited in terms of reporting mortality, we applied a previously published algorithm for identifying deaths.[11,15] Indicators for death included the following: hospital discharge status of death; hospital or ED event within 30 days of the last date of enrollment; and use of cardiac-stimulating medications such as epinephrine or lidocaine, diagnosis codes for cardiac arrest or failure, or procedure codes for resuscitation or defibrillation within 30 days of the last date of enrollment. Patients who were still enrolled at the end of the study period and who did not have any of the preceding indicators were considered to have survived.

Each patient's observation (follow-up) period after the date of mCRC diagnosis was divided into 3 phases of disease according to a previously published algorithm: diagnostic phase, treatment phase, and death phase.[11,16] For patients

who survived, the diagnostic phase included the index date through the first 3 months of observation. For survivors with more than 3 months of observation, the remaining months were assigned to the treatment phase. For patients identified as having died, the death phase was determined first and consisted of the last 3 months of observed claims. For those with more than 3 months but less than or equal to 6 months of observed claims, the remaining claims were assigned to the diagnostic phase. For patients who died after more than 6 months of observation, after assignment of the diagnostic and death phases, the remaining claims were assigned to the treatment phase.

Analyses

Patient demographics were measured at index date and included age, sex, geographic region, urban versus rural location, insurance plan type, and commercial versus Medicare status. Race and ethnicity were not reported for the study population because of the lack of such information in the claims data. Mean length of follow-up was calculated. The Deyo-Charlson comorbidity index (CCI) was used to assess overall patient levels of comorbid conditions and was measured during the 6-month preperiod.[17] The Deyo CCI takes on values between 0 and 12, with higher scores representing higher risk of impending mortality based on presence of various chronic diseases. The first CRC diagnosis was reviewed, and percentage of patients with colon (vs rectal) cancer as the initial diagnosis was determined. Percentage of patients with metastases at specific sites was also reported.

Within each phase, patterns of medical care were examined by mutually exclusive service categories of inpatient, ER, outpatient office and facility, outpatient pharmacy, chemotherapy, and biologic therapy, as measured by estimation of aggregate and category costs. Surgeries that occurred during inpatient admissions were counted as part of inpatient costs, and surgeries that occurred in the outpatient setting were counted as part of outpatient costs. Costs were all-cause total direct healthcare costs and were based on paid amounts of adjudicated claims, including insurer and health plan payments, copayments, and deductibles. Direct cost components included inpatient costs, outpatient costs, ED costs, costs of chemotherapy, costs of biologics, and other pharmacy costs. No indirect costs, such as costs associated with absence from work or lost productivity, were included in the cost calculation. Costs were determined across all patients with mCRC for the entire variable-length follow-up and standardized as per patient per month costs. Costs were also reported per patient per month for each disease phase, using only those patients with mCRC who contributed months to a specific phase and using only the months for that phase. Costs for claims processed under a fee-for-service arrangement were the allowed charges (ie, actual amounts paid by primary and secondary insurers plus patient cost share amounts [copayments and deductibles]). Costs for claims processed under a capitated arrangement were estimated using the average cost of non-capitated claims, by procedure, geographic region, and year. All costs were adjusted to 2009 US dollars using the medical service component of the Consumer Price Index.

Means and standard deviations (SDs) were calculated for continuous variables. Counts and percentages were calculated for categorical variables. Nonparametric bootstrapping was used to create 95% confidence intervals [CIs] for mean cost in each disease phase using 1000 iterations. Generalized linear models with log link and gamma distribution were estimated on monthly costs for each phase, controlling for age, sex, region, urban residence, health plan type, capitation indicator, Medicare, CCI, site of cancer (colon vs rectal), site of metastasis, and length (days) of each phase. Length of each phase was included in the model to account for censoring because of different length of follow-up.

RESULTS

Demographics and Clinical Characteristics

A total of 6675 patients with newly diagnosed mCRC met all study criteria, with a mean age of 64.1 years (SD, 13.1 years; Table 1) and 55 to 75 in the quartile distribution. Males comprised 55.5% of the study sample. The largest percentage of patients resided in the South (40.6%), followed by the North Central (29.3%) and West (20.2%) regions, in predominantly urban areas (81.5%). Approximately 43% of patients were covered under Medicare. Mean length of follow-up was 492 days. Nearly 75% of patients had a CCI score of 2. Colon (vs rectal) cancer was the initial diagnosis in 69.7% of patients. The most common identified sites of metastases were the liver (46.8%), lung (15.1%), retroperitoneum and peritoneum (11.6%), other respiratory/digestive system (5.1%), and lymph nodes (2.7%). The follow-up period ended because of death for 27.2% of patients, end of continuous enrollment for 63.3%, and end of the study period (July 31, 2009) for the remaining 9.5%. The proportion of patients receiving biologics increased from 30.0% for patients diagnosed in 2004 to 39.9% for patients diagnosed in 2008. The corresponding proportion of patients receiving chemotherapy was 59.0% and 58.1% in the same time period, respectively.

Duration of Disease Phases

Among patients with mCRC, 91%, 80%, and 27% had diagnostic, treatment, and death phases, respectively. The treatment phase had the longest duration, with a mean of 16.4

months, and durations for the diagnostic and death phases were similar at means of 2.8 months and 2.4 months, respectively (Table 2).

Patterns of Medical Care by Disease Phase

Compared with mean cost per patient per month in the diagnostic phase ($16,895; 95% CI, $16,390 to $17,400), costs were significantly higher in the death phase ($27,554; 95% CI, $23,636 to $31,474) but significantly lower in the treatment phase ($8891; 95% CI, $8618 to $9165). The high costs in the diagnostic phase included initial treatment costs. Multivariate regression adjusted monthly costs were $16,938 (SD, $6642) in the diagnostic phase, $8976 (SD, $4497) in the treatment phase, and $26,689 (SD, $19,561) in the death phase.

For patients with capitated insurance, mean costs per patient per month were $16,042 in the diagnostic phase, $8606 in the treatment phase, and $22,140 in the death phase; for patients with noncapitated services, the corresponding costs were $17,066, $8947, and $28,752, respectively. Multivariate regressions suggested that capitation did not have a significant impact on costs in the diagnostic and treatment phases, but it significantly decreased costs in the death phase, compared with patients with noncapitated plans.

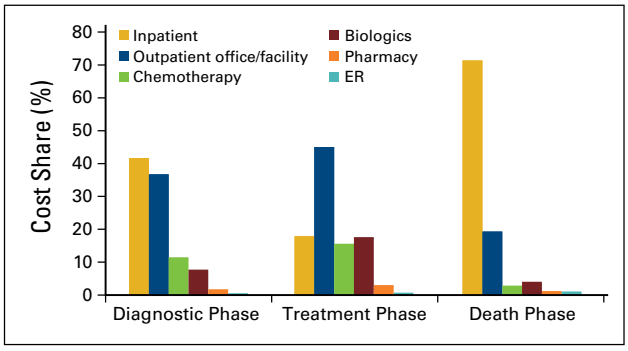
Patterns of medical care as measured by cost for categories of inpatient, ED, outpatient office and facility, outpatient pharmacy, chemotherapy, and biologic therapy varied depending on phase of disease (Figure). Although inpatient care was the highest component of medical care in the diagnostic (41.7% of costs) and death (71.4% of costs) phases, it accounted for

Table 1. Demographics and Clinical Characteristics of Patients With mCRC

	Patients (N = 6675)	
Characteristic	**No.**	**%**
Age, years		
Mean	64.1	
SD	13.1	
Male	3704	55.5
Geographic region		
North Central	1958	29.3
Northeast	657	9.8
South	2711	40.6
West	1349	20.2
Urban	5439	81.5
Insurance plan type		
Comprehensive	1837	27.5
PPO	2893	43.3
HMO	1215	18.2
Other	730	10.9
Medicare beneficiary	2856	42.8
Length of follow-up, days		
Mean	492	
SD	426	
Charlson comorbidity index		
2	4892	73.3
3	1278	19.1
4	297	4.4
5	138	2.1
≥6	70	1.0
Colon (vs rectal) cancer initial diagnosis	4651	69.7
Site of metastases		
Lymph nodes	179	2.7
Lung	1009	15.1
Liver	3124	46.8
Retroperitoneum and peritoneum	772	11.6
Other respiratory/digestive	343	5.1
Other site	1248	18.7
Reason for end of follow-up		
Death	1818	27.2
End of continuous enrollment	4222	63.3
End of study period (July 31, 2009)	635	9.5
Treatment[a]		
Biologics		
2004		30.0
2008		39.9
Chemotherapy		
2004		59.0
2008		58.0

HMO indicates health maintenance organization; mCRC, metastatic colorectal cancer; PPO, preferred provider organization; SD, standard deviation.
[a]Based on year of mCRC diagnosis. The proportion of patients treated with biologics and chemotherapy was measured during the follow-up period, which included 2009 for patients diagnosed in 2008.

Figure. Patterns of Medical Care by Phase of Disease; Categories of Service as Percentage of Total Costs



ER indicates emergency room.

only 17.9% of costs in the treatment phase. Outpatient care was the leading driver for medical care in the treatment phase (45.0% of costs). The proportion of costs resulting from biologics and chemotherapy also differed by phase of disease. Biologics contributed 7.7%, 17.6%, and 4.1% of costs, whereas chemotherapy accounted for 11.5%, 15.6%, and 2.9% of costs in the diagnostic, treatment, and death phases, respectively (Figure).

DISCUSSION

This study provides an assessment of medical care patterns during phases of mCRC disease, employing a study period that captures the impact of biologic agents bevacizumab, cetuximab, and panitumumab. Mean time in the treatment phase was the longest at 16.4 months, followed by 2.8 months in the diagnostic phase and 2.4 months in the death phase. Inpatient care drove medical care in both the diagnostic and death phases, accounting for 41.7% and 71.4% of costs, respectively, whereas outpatient care was the primary driver in the treatment phase (45.0% of costs).

Median OS for patients with mCRC has increased with use of newer therapies, from 12 to 14 months with FU/LV to approximately 20 months with the addition of oxaliplatin or irinotecan.[8] Use of biologic agents with chemotherapy has increased OS even further, with recent studies demonstrating a median OS of almost 2 years.[9,10] Other factors such as better surgical approach and better follow-up may also help increase OS. An increase in duration of survival is an important consideration as we examine care patterns in each disease phase. At 16.4 months, the treatment phase in the current study was the longest mCRC phase, yet this phase had the lowest per patient per month costs. A study by Paramore et al[11] that measured mCRC disease phases before the availability of biologic agents found similar mean length compared with the current study in the diagnostic and death phases but a much shorter mean length in the treatment phase (10.1 months).

Costs in the current study were higher compared with those in that by Paramore et al,[11] which found per patient per month costs of $12,205, $4722, and $12,328 for the diagnostic, treatment, and death phases, respectively. A number of factors likely contributed to the cost differences between the 2 studies. The study by Paramore et al used the amount reimbursed by payers for costs, whereas the current study also included patient cost share amounts. Costs in the study by Paramore et al were reported in 2005 US dollars. If adjusted to 2009 dollars, those costs would be $14,215, $5500, and $14,358, respectively. It is worth noting that in addition to use of newer data (2004 to 2009), which allowed capture of the impact of new treatment options (eg, biologic agents) on medical care utilization, our study also focused on examining differences in patterns of medical care between phases of mCRC disease. The Paramore et al and current studies used the same algorithm to define phases of mCRC. Patterns of mCRC care using different definitions of phases may be an interesting topic in future studies. A recent report by Lang et al[12] estimated lifetime and treatment-phase costs in patients with CRC. Because of the difference in study populations between the Lang et al study and our study (CRC vs mCRC), it is difficult to compare cost estimates from these 2 studies.

In addition to the commonly recognized constraints of administrative claims data,[18] several limitations specific to this study should be noted when interpreting the results. First, given the lack of a specific *ICD-9-CM* code that identifies mCRC, we followed the approach used by Paramore et al,[11] initially identifying patients with CRC and then select-

Table 2. Duration and Costs According to Phase of Disease

	Diagnostic Phase (n = 6063)		Treatment Phase (n = 5313)		Death Phase (n = 1818)	
Measure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Months in phase	2.8	0.5	16.4	13.8	2.4	1.0
Cost per patient per month, $	16,895	19,594	8891	10,387	27,554	86,150
95% CI	16,390 to 17,400	8618 to 9165	23,636 to 31,474			

CI indicates confidence interval; SD, standard deviation.

ing a subset with indicators of metastatic disease consistent with CRC. This is also consistent with stages C and D in the Dukes staging system for colorectal cancer.[19] To the extent that cancer at other sites did not result from metastases from CRC, patients may have been incorrectly identified as patients with mCRC. However, patients with diagnoses of other primary cancers were excluded from the analysis; thus, we would expect the misclassification, if any, to be minimal. Second, because death indicators were not consistently available from the data used for the analysis, we used a proxy measure for death that was used in previous publications.[11,15] To the extent that this measure incorrectly identified a survivor as having died, that patient's follow-up period would have been inaccurately categorized by phase. However, follow-up for patients who died was first assigned to the death phase. Because death phase costs were typically the highest, including nondeath phase costs would have biased results toward lower costs; however, this phenomenon was not observed in the current study. Third, costs for patients with capitated services (25.5% of patients) were imputed based on mean cost of noncapitated claims and thus may not be reflective of the actual costs incurred. Fourth, indirect costs were not included in the analysis, and thus costs presented in the current study underestimate the economic impact of mCRC. Finally, the study population was composed of commercially insured and Medicare-insured patients, and patterns of medical care during phases of disease may not be representative of all patients with mCRC, especially the uninsured or those covered by Medicaid.

Substantial differences existed between the mCRC disease phases with regard to patterns of medical care, both in magnitude and key drivers of use. Inpatient care was the leading driver for medical care in the diagnostic and death phases, whereas medical care in the treatment phase was primarily driven by outpatient care.

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