Pathways, Outcomes, and Costs in Colon Cancer: Retrospective Evaluations in Two Distinct Databases

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Abstract

Purpose: The goal of this study was to use two separate databases to evaluate the clinical outcomes and the economic impact of adherence to Level I Pathways, an evidence-based oncology treatment program in the treatment of colon cancer.

Patients and Methods: The first study used clinical records from an electronic health record (EHR) database to evaluate survival according to pathway status in patients with colon cancer. Disease-free survival in patients receiving adjuvant treatment and overall survival in patients receiving first-line therapy for metastatic disease was calculated. The second study used claims data from a national administrative claims database to examine direct medical costs and use, including the cost of chemotherapy and of chemotherapy-related hospitalizations according to pathway status.

Results: Overall costs from the national claims database—including total cost per case and chemotherapy costs—were lower for patients treated according to Level I Pathways (on-Pathway) compared with patients not treated according to Level I Pathways. Use of pathways was also associated with a shorter duration of therapy and lower rate of chemotherapy-related hospital admissions. Survival for patients on-Pathway in the EHR database was comparable with those in the published literature.

Conclusion: Results from two distinct databases suggest that treatment of patients with colon cancer on-Pathway costs less; use of these pathways demonstrates clinical outcomes consistent with published evidence.

Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in the United States and the second leading cause of cancer-related deaths.¹ Survival has improved as a result of advancements in medical therapy and the availability of new treatments.² The introduction of new agents has resulted in increased variability in treatment options and increased costs.³

Cancer treatment guidelines,⁴⁻⁶ or clinical pathways, have been developed to standardize treatment and improve quality of care. Little information exists, however, regarding the impact of adherence to pathways on clinical outcomes, treatment complications, and cost of care. Data suggest that the use of clinical pathways in oncology can produce improvements in some areas—including length of hospital stay, complications, and financial outcomes⁷—and are cost-effective in treating non-small-cell lung cancer.⁸

Level I Pathways is a set of treatment guidelines established as the foundation of an evidence-based oncology treatment program developed and led by physicians in the US Oncology (The Woodlands, TX) network. It uses only high-level evidence to assess efficacy, toxicity, and cost when recommending therapies. Treatments are updated regularly by a multidisciplinary task force in collaboration with disease research committees and practicing community oncologists. Recommendations are based on lines of therapy and are integrated into the iKnowMed (iKM) electronic health records (EHR) system to provide point-of-care decision support.

The MedStat MarketScan database (Thomson Reuters, New York, NY) represents the inpatient and outpatient health

care service use of individuals nationwide covered by the benefit plans of large employers, health plans, and government and public organizations. The MarketScan database links paid claims and encounter data to detailed patient information across sites and types of providers over time. The annual medical database includes private sector health data from approximately 100 payers.

Our objective was to conduct two separate studies by using the two databases to evaluate the clinical outcomes and the economic impact of adherence to Level I Pathways in colon cancer treatment. The first study used clinical records from the iKM EHR database to evaluate survival. To address concern that pathways use may adversely impact quality of care in this study, we examined survival according to pathway status. In the second study, we applied a set of pathway rules to a separate cohort of patients with colon cancer from the MedStat national claims database to examine the cost of chemotherapy and chemotherapy-related adverse events.

Patients and Methods

Patient Identification and Characterization From the EHR Database

The first study was a retrospective cohort design identifying iKM EHR patients with a primary colon cancer diagnosis and initiating an adjuvant line of therapy or a first-line chemotherapy regimen for metastatic disease between July 1, 2006 and June 31, 2007 at US Oncology network practices. Patients who were in the middle of treatment, who were starting with second-

line therapy or beyond, or whose regimens were unassessable (as a result of missing or conflicting information) for pathway status were excluded. Using clinical data from the EHR and Pathways reporting center, chemotherapy regimens were electronically assigned a pathway status. Patients were classified as on-Pathway if all regimens during the study period were consistent with the Level I Pathways recommendations for colon cancer. Patients were classified as off-Pathway if treatments were not consistent with pathways or if treatments changed from on- to off-Pathway or vice versa.

Patient Identification and Characterization From a National Claims Database

The second study used MedStat 2005, 2006, and 2007. A retrospective cohort design was used to query this large, commercial insurance database containing data for approximately 4.9 million insured lives with patient characteristics of 24 months of comprehensive fee-for-service coverage (medical and prescription coverage but no capitation) in 2005 and 2006 and at least one day of coverage in 2007, younger than age 70, and an active employee or spouse of an active employee. All patients with colon cancer who initiated cytotoxic chemotherapy during the first 6 months of 2006 and had not received chemotherapy in the 12 months before their initial chemotherapy date were identified. Colon cancer was identified by the presence of ICD-9 (International Classification of Diseases, 9th Revision) code 153.xx in 2006 with two or more examination and management physician claims or one or more inpatient facility or emergency room facility claim. Treatment was classified as adjuvant if patients had colon resection followed by chemotherapy that began within 60 days after resection; all other patients were considered metastatic. For each patient, the data were organized to produce a timeline of care, including details by dates of surgery, radiation therapy, and chemotherapy. Chemotherapy was categorized into regimens and lines of therapy. The care was compared manually with the 2006 Level I Pathways for colon cancer. Pathway status was calculated on the basis of cycle 1 of each line of therapy using drug combination rules. For example, if a Pathways regimen consisted of three drugs (eg, A + B + C), all had to be present for the patient to be considered on-Pathway. If a drug was omitted (eg, A + C only), added (eg, A + B + C + D), or substituted (eg, A + B + X), the regimen was considered off-Pathway. A nurse and team of pharmacists experienced in clinical oncology and pathways reviewed the timelines. Patients who received any care off-Pathway were classified as being off-Pathway.

Survival Analysis

Disease-free survival (DFS) and overall survival (OS) were compared between patients treated on-Pathway and off-Pathway by using the Kaplan-Meier method and an intention-to-treat analysis. DFS was calculated in patients starting an adjuvant line of therapy from chemotherapy initiation date to recurrence date, death, or censored for last date of contact. Because of the limited number of patients with stage II disease and pathway treatment changes occurring during the study period, these patients

were excluded from the DFS analysis given that the groups could not be reliably separated according to treatment regimen. For patients starting first-line therapy for metastatic disease, OS was calculated from the chemotherapy initiation date to the date of death or last contact. Date of initiation of chemotherapy was defined as the date the chemotherapy regimen was ordered. Because of difficulty in obtaining radiology reports, the date of initiation of subsequent chemotherapy after adjuvant therapy was used to indicate relapse. Date of death, if available, was obtained from the EHR. If no relapse or death was noted, the last date of contact with documented patient vital signs was used.

Cost and Use Analysis

Allowed amounts (before cost sharing) from MedStat were tabulated during the chemotherapy period, which was from the date of the first chemotherapy to the last chemotherapy plus 30 days or until December 31, 2007, whichever came first, with a maximum of 18 months of total observation. Total patient care costs and chemotherapy costs, including oral and infused products, were tabulated. In addition, chemotherapy-related hospital admissions during the chemotherapy period were tabulated. These were defined by the presence on the claim of a likely chemotherapy-related adverse effect as the primary diagnosis or the primary designation of a cancer diagnosis with one of the secondary diagnoses as a chemotherapy-related adverse effect. Statistical significance was calculated by using the Wilcoxon rank sum test.

Results

Clinical Results From an EHR Database

The study included 910 patients from 11 states with a diagnosis of colon cancer who met the EHR eligibility criteria. During the study period, 433 patients (48%) initiated adjuvant therapy, and 477 (52%) initiated first-line therapy for metastatic disease. Of the total study population, 756 patients (83%) were treated on-Pathway, and 154 (17%) were treated off-Pathway. All patients had at least 35 months of observation with data through May 31, 2010. Patient characteristics of the adjuvant and metastatic populations according to pathway status are listed in Tables 1 and 2, respectively.

Take-Away Points

This report assesses the impact of adherence to evidence-based treatment pathways on clinical outcomes, treatment complications, and cost of care in colon cancer. This information can be used in practice and policy decisions when evaluating programs to address quality and value in cancer care, including the different data sources and the strengths and limitations of clinical and claims information.

Table 1. EHR Patient Characteristics for the Adjuvant Population

Characteristic	Adjuvant Total (n = 433)		Pathway Status			
			On (n = 344)		Off (n = 89)	
	No.	%	No.	%	No.	%
Age, years						
Median*	65		65		60	
Range	27-94		27-94		31-81	
< 50	69	16	48	14	21	24
50-59	82	19	62	18	20	22
60-69	121	28	91	26	30	34
70-79	111	26	98	28	13	15
≥ 80	41	9	39	11	2	2
Unknown	9	2	6	2	3	3
Sex						
Male	208	48	170	49	38	43
Female	216	50	168	49	48	54
Unknown	9	2	6	2	3	3
Stage at diagnosis						
I	0	0	0	0	0	0
IIA	72	17	27	8	45	51
IIB	23	5	4	1	19	21
IIIA	58	13	55	16	3	3
IIIB	166	38	158	46	8	9
IIIC	114	26	100	29	14	16
IV	0	0	0	0	0	0
Unknown/missing	0	0	0	0	0	0
Karnofsky performance status						
< 50	1	0	1	0	0	0
50-60	3	1	2	1	1	1
70-80	43	10	38	11	5	6
90-100	195	45	161	47	34	38
Unknown/missing	191	44	142	41	49	55
No. of involved clinics	36		34		24	
Distribution of patients according to state						
Arizona	24	6	22	6	2	2
Colorado	58	13	45	13	13	15
Florida	5	1	5	1	0	0
Illinois	18	4	12	3	6	7
Indiana	20	5	14	4	6	7
Missouri	20	5	17	5	3	3
New York	47	11	41	12	6	7
Oregon	41	9	33	10	8	9
Texas	83	19	62	18	21	24
Virginia	108	25	87	25	21	24
Washington	9	2	6	2	3	3

Abbreviation: EHR, electronic health record.

* Median based on total records age known.

DFS: Adjuvant Chemotherapy

DFS was calculated for the 338 patients with stage III disease initiating adjuvant therapy during the study period. Eighty-five events (recurrence or death) occurred. Approximately

23% of on-Pathway patients (71 of 313) and 56% of off-Pathway patients (14 of 25) experienced an event. Median DFS was 26.9 months for off-Pathway patients and has not yet been reached for on-Pathway patients (Fig 1; $P < .05$;

Table 2. EHR Patient Characteristics for the Metastatic First-Line Population

Characteristic	Metastatic Total (n = 477)		Pathway Status			
			On (n = 412)		Off (n = 65)	
	No.	%	No.	%	No.	%
Age, years						
Median*	66		66		66	
Range	26-96		26-96		29-93	
< 50	59	12	46	11	13	20
50-59	90	19	82	20	8	12
60-69	129	27	111	27	18	28
70-79	113	24	101	25	12	18
≥ 80	69	14	58	14	11	17
Unknown	17	4	14	3	3	5
Sex						
Male	267	56	239	58	28	43
Female	193	40	159	39	34	52
Unknown	17	4	14	3	3	5
Karnofsky performance status						
< 50	4	1	3	1	1	2
50-60	10	2	7	2	3	5
70-80	103	22	94	23	9	14
90-100	165	35	142	34	23	35
Unknown/missing	195	41	166	40	29	45
No. involved clinics	36		36		22	
Distribution of patients according to state						
Arizona	29	6	24	6	5	8
Colorado	52	11	48	12	4	6
Florida	8	2	7	2	1	2
Illinois	20	4	15	4	5	8
Indiana	21	4	20	5	1	2
Missouri	22	5	18	4	4	6
New York	61	13	49	12	12	18
Oregon	51	11	46	11	5	8
Texas	79	17	69	17	10	15
Virginia	117	25	102	25	15	23
Washington	17	4	14	3	3	5

Abbreviation: EHR, electronic health record.

* Median based on total records age known.

hazard ratio, 4.98; 95% CI, 2.11 to 11.74). The estimated 1-year, 2-year, and 3-year DFS for on-Pathway and off-Pathway patients were 91% versus 72%, 80% versus 51%, and 73% versus 41%, respectively.

OS: Metastatic Disease

OS was calculated for the 477 patients initiating first-line therapy for metastatic disease. A total of 229 deaths occurred. Approximately 47% of on-Pathway patients (194 of 412) and 54% of off-Pathway patients (35 of 65) died. Median OS for on-Pathway was 26.9 versus 20.1 months for off-Pathway (Fig 2; $P = .03$; hazard ratio, 1.57; 95% CI, 1.04 to 2.39). The

1-year estimated survival for on-Pathway was 80%; it was 74% for off-Pathway.

Economic Analysis: Cost and Use

From the MedStat national claims database, 220 patients with colon cancer treated with chemotherapy were identified who met study criteria. Table 3 lists patient demographics. Classification of patients as receiving adjuvant therapy or as having metastatic disease and as receiving treatment that adhered to Level I Pathways for colon cancer were determined by examining details of therapy as represented in the claims. This examination showed that 41% of patients were treated on-Pathway

Figure 1. Disease-free survival according to pathway status for patients with stage III disease who were initiating an adjuvant line of therapy.

and 59% were treated off-Pathway. Cost and use results are listed in Table 4. For adjuvant treatment, total costs, chemotherapy costs, and the chemotherapy period were significantly lower for patients on-Pathway ($P < .05$). Costs per case and per patient per month were lower for patients on-Pathway, which was statistically significant for patients on adjuvant therapy. The chemotherapy-related admissions were lower in both adjuvant and metastatic on-Pathway patients, but this did not achieve statistical significance.

Discussion

Little is known regarding the extent of adoption or the impact of cancer treatment guideline adherence on survival, toxicities,

Figure 2. Overall survival according to pathway status for patients with metastatic disease who were initiating first-line therapy.

and costs. We studied the impact of adherence to Level I Pathways for colon cancer on survival by using an EHR database (iKM) with almost 3 years of follow-up for all patients. Pathways are designed for common types of cancer rather than rare or complex cases. Our analyses revealed that Level I Pathways provide efficacious treatment options with benefits in terms of costs. Narrowing treatment options did not compromise care or negatively impact survival for on-Pathway patients. Additionally, outcome results were comparable with the published literature, which support our findings.^{2,9,10}

We also assessed the direct medical costs associated with adherence to Level I Pathways for colon cancer by using national claims data from multiple payers. The retrospective claims analysis shows that costs are lower for patients on-Pathway. Use of pathways is also associated with a shorter duration of therapy and lower rate of chemotherapy-related admissions. The lack of statistical significance for costs in the metastatic cancer results was not surprising given the small number of on-Pathway patients. Notably, adherence to pathways was 41% from the national claims database compared with 83% from the EHR database. This may be an effect of integration of the evidence-based treatment recommendations directly into the EHR. Additionally, exclusion of unassessable regimens can increase the adherence rate if many of those excluded were off-Pathway. In the absence of direct methodology validation, each retrospective analysis is an important supplement to the other and is consistent with an earlier publication of clinical data related to Level I Pathways that reported lower chemotherapy costs for on-Pathway versus off-Pathway treatment in non-small-cell lung cancer.⁸ This study provides additional support for the concept that Level I Pathways can lower costs and adhere to high-level evidence.

Since 1996, six new therapeutic agents have been approved for colon cancer, which has resulted in increased treatment options, variability, and costs.¹¹ Three new agents are monoclonal antibodies and contribute upwards of a 340-fold increase in the cost of chemotherapy compared with previous treatments.^{11,12} This information has quality and financial implications for patients and the health care system.¹³ Of note, the Level I Pathways include these newer chemotherapy agents when the evidence supports their use.

Different approaches can be used to assess adherence to cancer treatment guidelines. EHR and claims analysis each have strengths and limitations. Payer databases can capture diagnoses, medical service procedures, drug therapy use, and costs, including inpatient, outpatient, and prescription drug costs. This makes it possible to capture all patient treatments and medical costs. Large payer databases may provide significant sample sizes even after applying stringent conditions and may provide findings that are not specific to certain practice sites or regions. However, there are inherent restrictions in the analyses of claims data, regardless of whether an analysis is prospective or retrospective. Claims analysis suffers from the absence of important clinical information including cancer stage and line of therapy, which makes assessment of adherence challenging. Claims data may also contain coding errors, inconsistencies, or

Table 3. Claims Database Patient Characteristics

Stage and Pathway Status	Patients		Age (years)			Male (%)
	No.	%	Average	Minimum	Maximum	
Adjuvant						
On	80	53	54.2	37	64	52.5
Off	70	47	53.5	28	64	52.9
Total	150		53.9	28	64	52.7
Metastatic						
On	10	14	52.7	45	62	20.0
Off	60	86	54.7	37	65	61.7
Total	70		54.4	37	65	55.7
Adjuvant plus metastatic						
On	90	41	54.0	37	64	48.9
Off	130	59	54.1	28	65	56.9
Total	220		54.1	28	65	53.6

NOTE. All non-Medicare patients.

omissions. Patient outcomes, including mortality, are difficult to determine. Commercial insurance data make it possible to identify when an individual loses coverage, but it is generally not possible to determine whether that loss results from death, switches in insurance coverage, or another cause. Conversely, patient charts and EHRs can capture clinical information that claims cannot such as staging, line of therapy, histologic subtypes, and tumor marker information. In an era of personalized

medicine, these data are important when assessing adherence to guidelines. Importantly, clinical outcomes and mortality information may also be obtained. However, EHRs may not provide information regarding inpatient admissions, services obtained outside the practice, or outpatient pharmacy use.

Limitations of these results should be noted. This report comprised two independent studies with distinct patient populations; therefore, direct comparisons of results between the

Table 4. Claims Analyzed Cost and Use Results

Cost and Use	Adjuvant			Metastatic		
	Values		P	Values		P
	On-Pathway (n = 80)	Off-Pathway (n = 70)		On-Pathway (n = 10)	Off-Pathway (n = 60)	
Member months*						
Mean	17.5	17.1		16.7	17.0	
SD	1.6	2.0		2.6	2.3	
Total cost per case, \$						
Mean	103,379	156,020	< .001	131,059	191,222	.067
SD	113,272	104,014		107,461	133,649	
Per patient per month, \$						
Mean	5,907	9,121	≤ .001	7,862	11,244	.102
SD	6,544	6,346		6,554	8,253	
Chemotherapy cost, \$						
Mean	22,564	60,787	< .001	41,894	65,358	.305
SD	23,145	53,496		24,754	63,488	
Chemotherapy period (months)						
Mean	5.7	8.7	< .001	7.5	10.8	.053
SD	3.3	5.2		2.8	6.3	
No. of chemotherapy-related admissions per patient						
Mean	0.23	0.30	.236	0.20	0.43	.181
SD	0.57	0.62		0.42	0.70	

Abbreviation: SD, standard deviation.

* Member months were calculated by adding the chemotherapy period and additional observation period together.

studies cannot be made. The reasons for treating off-Pathway are not known. Given that risk factors in these patients are not completely understood and numbers are limited until databases are expanded, survival may not be the best outcome measurement for off-Pathway patients on the basis of EHR databases. This is an area for future exploration. The EHR population included Medicare patients, and the claims population did not. Rules were applied to claims to determine pathway status. Surgery, in a 60-day window, is an arbitrary indicator of adjuvant therapy and may include patients with metastatic disease. Pathway status was assigned electronically in the EHR compared with manually in the claims analysis. In addition, on the basis of EHR confines, this was an intention-to-treat analysis using treatment initiation dates that were based on when regimens were ordered for patients. Although Level I Pathways includes chemotherapy choices to address comorbidities, a selection bias for the off-Pathway cohort in either study cannot be excluded. A randomized trial of on- versus off-Pathway treatment is unlikely, so we are left with retrospective evaluations. The strength of these separate analyses is in the ability to query comprehensive EHR and national claims data to separately evaluate the impact of adherence to Level I Pathways on clinical outcomes, medical costs, and medical use. Additional research in these areas will aid in future comparative effectiveness studies.

Keys to successful guidelines as discussed by Smith et al⁷ include inclusion of clinicians in the development with the opportunity for critique during the development process, dissemination through targeted communication and educational efforts, implementation through patient-specific reminders, and accountability for process and outcomes.⁷ These components all exist in the Level I Pathways program.

In conclusion, two independent implications can be drawn from these analyses: treatment on-Pathway costs less, and no decrease in patient survival was observed. This study represents the exploration of comparative effectiveness by using novel methods of mining retrospective databases to make assessments about care delivery and value. Innovative collaborations between providers and payers to share clinical and economic information will help address quality and cost issues in the treatment of cancer.

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References

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. *CA Cancer J Clin* 60:277-300, 2010
2. Kopetz S, Chang GJ, Overman MJ, et al: Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 27:3677-3683, 2009
3. Meropol NJ, Schulman KA: Cost of cancer care: Issues and implications. *J Clin Oncol* 25:180-186, 2007
4. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: colon cancer. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

5. Labianca R, Nordlinger B, Beretta GD, et al: Primary colon cancer: ESMO clinical practice guidelines for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* 21:v70-v77, 2010 (suppl 5)
6. Desch CE, Benson AB 3rd, Somerfield MR, et al: Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 23:8512-8519, 2005
7. Smith TJ, Hillner BE: Ensuring quality cancer care by the use of clinical practice guidelines and critical pathways. *J Clin Oncol* 19:2886-2897, 2001
8. Neubauer MA, Hoverman JR, Kolodziej M, et al: Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *J Oncol Pract* 6:12-18, 2010

9. André T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350:2343-2351, 2004
10. Sargent DJ, Wieand HS, Haller DG, et al: Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: Individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 23:8664-8670, 2005

11. Ferro SA, Myer BS, Wolff DA, et al: Variation in the cost of medications for the treatment of colorectal cancer. *Am J Manag Care* 14:717-725, 2008
12. Schrag D: The price tag on progress: Chemotherapy for colorectal cancer. *N Engl J Med* 351:317-319, 2004
13. Howard DH, Kauh J, Lipscomb J: The value of new chemotherapeutic agents for metastatic colorectal cancer. *Arch Intern Med* 170:537-542, 2010