

Primary Tumor Resection and Multimodality Treatment for Patients with Metastatic Colon Cancer

Nader N. Massarweh, MD, MPH^{1,2}, Linda T. Li, MD², Shubhada Sansgiry, PhD^{1,4,5}, David H. Berger, MD, MHCM, FACS^{1,2}, and Daniel A. Anaya, MD, FACS³

¹VA HSR&D Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX; ²Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX; ³Department of Gastrointestinal Oncology, H Lee Moffitt Cancer Center & Research Institute, Tampa, FL; ⁴VA South Central Mental Illness Research and Education Clinical Center, Houston, TX; ⁵Department of Medicine, Baylor College of Medicine, Houston, TX

ABSTRACT

Background. Although controversial, recent data suggest a benefit associated with primary tumor resection (PTR) in metastatic colon cancer (mCC) patients. However, utilization of the various management strategies over time relative to surgery, in particular multimodality treatment (MMT), as well as the impact of age on treatment remains unclear.

Study Design. Historical cohort study of mCC patients in the National Cancer Data Base (1998–2009). Temporal trends in treatment utilization (chemotherapy, PTR alone, MMT) were evaluated. Using a landmark approach, the association between treatment, age, and risk of death was evaluated with multivariable Cox regression, including interaction.

Results. Among 103,100 mCC patients, PTR decreased 50.1 % during the study period, whereas MMT and chemotherapy increased 27.4 and 104.8 %, respectively (trend test, $p < 0.001$). Patients aged ≥ 75 years were the only group for whom PTR alone was the most common intervention over time and performed more commonly (33.8 %) than MMT (23.8 %) in the most recent study year. Relative to MMT, risk of death was higher for all other management strategies. The sequence of PTR and chemotherapy (reference—surgery first) did not affect risk of death (chemotherapy first—1.05 [0.95–1.15]), as long resection was a part of MMT (PTR alone—1.16 [1.08–1.23]). Patient age did not impact the relative benefit associated with competing management strategies.

Conclusions. Although the benefit associated with PTR in mCC patients is a function of MMT, PTR alone remains a common management strategy among older patients. Given the aging U.S. population, exploring provider biases and patient preferences may be necessary to optimize management of mCC patients.

Colorectal cancer is among the most common incident cancers and a leading cause of cancer-related mortality in the United States.¹ One in five colon cancer patients will present with metastatic disease at initial diagnosis.² Systemic therapy has been and remains a mainstay of treatment for metastatic colon cancer (mCC) patients. Recent improvements in systemic agents have significantly improved survival, which approaches a median of 2 years in contemporary cohorts.^{3–6} By comparison, the role for primary tumor resection (PTR) as a component of multimodality treatment (MMT) is a matter of ongoing debate.

Current guidelines recommend PTR in mCC patients who are symptomatic.⁷ In the United States in the 1990s, PTR was performed in the majority (64–72 %) of mCC patients.^{8,9} While two recently published analyses have described decreasing PTR utilization during the past decade, it is still performed more than 50 % of the time.^{10,11} However, an important drawback to these studies is the dichotomization of patients into surgery versus not. This neither provides relevant data regarding temporal changes in multimodal approaches to mCC management in relation to PTR nor improves our understanding of whether any benefit associated with PTR is related to surgery itself or is a function of MMT. Furthermore, a substantial decrease in the risk of death associated with PTR has been described.¹⁰ Despite multivariate and propensity adjustment, a comparison

of outcomes among patients who underwent PTR to those who did not is still likely subject to residual confounding due to survivor treatment bias.¹²

Given these limitations, several important questions regarding management of mCC patients remain. Utilization of systemic therapy and MMT over time relative to PTR, outcomes after the varying management strategies (in particular the value of PTR as a part of MMT), and the impact of patient age on treatment utilization as well as posttreatment outcome have not previously been well-characterized. Therefore, using data from the largest national cancer registry, capturing the majority of incident colon cancer cases in the United States and not restricted to elderly Medicare beneficiaries, our study goals were: to describe trends in the utilization of the competing management strategies for mCC during the past decade; to examine the impact of PTR in mCC patients alone and as a part of MMT; to examine the association between patient age, treatment utilization, and outcome.

METHODS

A historical cohort study of mCC patients (diagnosed 1998–2009) in the National Cancer Data Base (NCDB) was conducted. NCDB is a prospectively collected, hospital-based registry that is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society. Previous work has detailed the nature, quality, and utility of the dataset.^{13–15} This study was approved by the Baylor College of Medicine Institutional Review Board and the Michael E. DeBakey VA Medical Center Research & Development Committee.

All patients with a diagnosis of mCC at presentation were included ($n = 158,630$). Exclusions were made for the following: patients not treated at the reporting institution ($n = 4587$); histology inconsistent with adenocarcinoma ($n = 10,503$); topography code other than colon ($n = 3967$); colon cancer not the first and only cancer diagnosis ($n = 26,049$); death at diagnosis ($n = 866$); unknown receipt of chemotherapy or surgery ($n = 4740$); receipt of chemotherapy and surgery on the same day ($n = 4818$). The final cohort included 103,100 patients. Patients not treated at the reporting institution were excluded to increase the accuracy of treatment ascertainment.

Data on the administration and sequence of cancer treatment were used to categorize patients as having had no treatment, chemotherapy only, PTR only, or MMT (both chemotherapy and PTR). Categorical and continuous variable distributions were assessed using standard descriptive statistics. A Cochran–Armitage test of trend was applied to evaluate changes in utilization of the various therapies across study years. The primary outcome was overall survival. We restricted survival analyses to the

subgroup diagnosed from 2003 through 2005 because data on the burden of comorbid conditions was added to NCDB starting in 2003 and complete long-term follow-up data was only available for patients diagnosed through 2005. In addition, a landmark approach (of survival to at least 6 months after diagnosis) was utilized to address underlying survivor treatment bias ($n = 17,436$).¹⁶

Multivariable Cox regression was used to evaluate the association between risk of death and treatment. The model was constructed using a non-parsimonious approach. Covariates included treatment, age, sex, race, insurance, income, education, rurality, patient comorbidity, and hospital type. An interaction term between age and treatment was then added to the model. To delineate the robustness of our findings, we performed additional sensitivity analyses. Surgical treatment was dichotomized into “No PTR” (untreated patients and those treated only with chemotherapy) and “PTR” (surgery only and MMT patients) to allow a comparison to recently published SEER data.¹⁰ To better understand the impact of MMT treatment sequence, surgical patients were categorized as surgery alone, surgery before chemotherapy, or surgery after chemotherapy. For this analysis, we restricted to those with no 30-day postoperative readmission and a length of stay (LOS) ≤ 7 days ($n = 6720$) to account for potential variability in the postoperative course that could have affected a patient’s ability to receive chemotherapy. As previously defined, these exclusions were used to create a subgroup in whom a major complication or other surgically related contraindication to chemotherapy would have been unlikely.¹⁷

Within the cohort, 10.8 % of study subjects were missing at least one covariate data point. Rates of 5-year overall survival of patients stratified by missing and nonmissing data were evaluated and although there was a statistically significant difference (13.4 % nonmissing vs. 15.1 % missing, $p < 0.02$), it was deemed not clinically meaningful (absolute difference 1.7 %). As such, analyses were conducted using a case-complete approach and using multiple imputation in chained equations to handle missing values.¹⁸ There were no notable differences in either analytic approach and therefore imputed values for multivariate models are presented. For the interaction model, point estimates and confidence intervals were similar across imputed datasets. All analyses were performed using SAS 9.3 (SAS Institute). Statistical comparisons were two-sided and considered significant at the $p < 0.05$ level.

RESULTS

The cohort included 103,100 mCC patients, of whom 71.9 % underwent PTR (28.9 % PTR alone and 42.9 % as part of MMT) and 13.6 % received chemotherapy alone.

TABLE 1 Patient and facility characteristics stratified by type of treatment (*N* = 103,100)

	Type of treatment			
	None (<i>n</i> = 15,033)	Chemotherapy (<i>n</i> = 13,979)	PTR only (<i>n</i> = 29,841)	MMT (<i>n</i> = 44,247)
Mean age ± SD, years	72.4 ± 12.8	62.5 ± 13.1	71.1 ± 13.0	61.2 ± 12.8
Age, years (%)				
≤50	6.1	16.7	7.0	18.8
50–64	19.6	37.5	21.6	39.0
65–74	23.4	25.5	24.8	25.8
≥75	50.9	20.4	46.6	16.4
Male sex (%)	47.1	53.3	45.4	50.3
Race (%)				
White	76.7	78.5	81.7	82.1
Black	19.1	17.3	14.6	13.9
Other	3.2	3.0	2.9	3.2
Missing	1.1	1.2	0.9	0.8
Insurance status (%)				
Insured	92.0	91.0	93.3	93.3
Uninsured	4.9	5.3	3.6	4.4
Missing	3.1	3.7	3.1	2.4
Income (%) ^a				
≥\$46,000	32.1	35.4	32.5	35.4
Missing	4.9	5.6	5.2	5.7
Education (%) ^a				
≥86 %	28.1	30.7	29.8	31.9
Missing	4.9	5.6	5.2	5.7
Rurality (%)				
Metropolitan	81.2	79.1	78.6	76.9
Urban	12.2	13.3	13.9	15.2
Rural	1.5	1.9	2.0	1.9
Missing	5.1	5.7	5.5	6.0
Comorbidity index (%) ^b				
0	65.7	79.0	67.8	77.8
1	22.7	15.9	23.0	17.9
≥2	11.6	5.1	9.3	4.3
Hospital type				
Academic/research	29.7	37.3	25.3	29.8
Comprehensive Cancer Center	48.5	46.1	52.1	51.3
Community Cancer Center	19.5	15.0	20.3	17.3
Other	2.3	1.5	2.3	1.6
Region				
West	19.4	18.7	20.6	17.3
East	24.8	24.2	20.9	20.2
North	28.8	30.2	29.7	32.0
South	27.0	26.9	28.8	30.5

Column percentages may not add up to 100 % due to rounding

PTR primary tumor resection, *MMT* multimodality therapy (*PTR* + chemotherapy)

^a Based on 2000 census data. For income, the percentage of patients whose area of residence (based on year 2000 Census data) had a median household income ≥\$46,000 is presented. For education, the percentage of patients whose area of residence (based on year 2000 Census data) had 86 % or more adults who attained a high school education is presented

^b Comorbidity data are only available for patients diagnosed 2003 and beyond. Percentages shown are for the cohort diagnosed 2003–2009

Table 1 summarizes patient demographic and clinical characteristics as well as hospital characteristics stratified by treatment. Overall, there were similarities in the distribution of patient sociodemographic and clinical factors between those who received no treatment and PTR alone and between those who were treated with chemotherapy

alone and MMT. Among untreated and PTR-only treated patients, there was a higher proportion of patients older than age 75 years and more patients had a higher burden of comorbid illness.

Figure 1a–e present utilization rates of the competing management strategies in the overall cohort and stratified

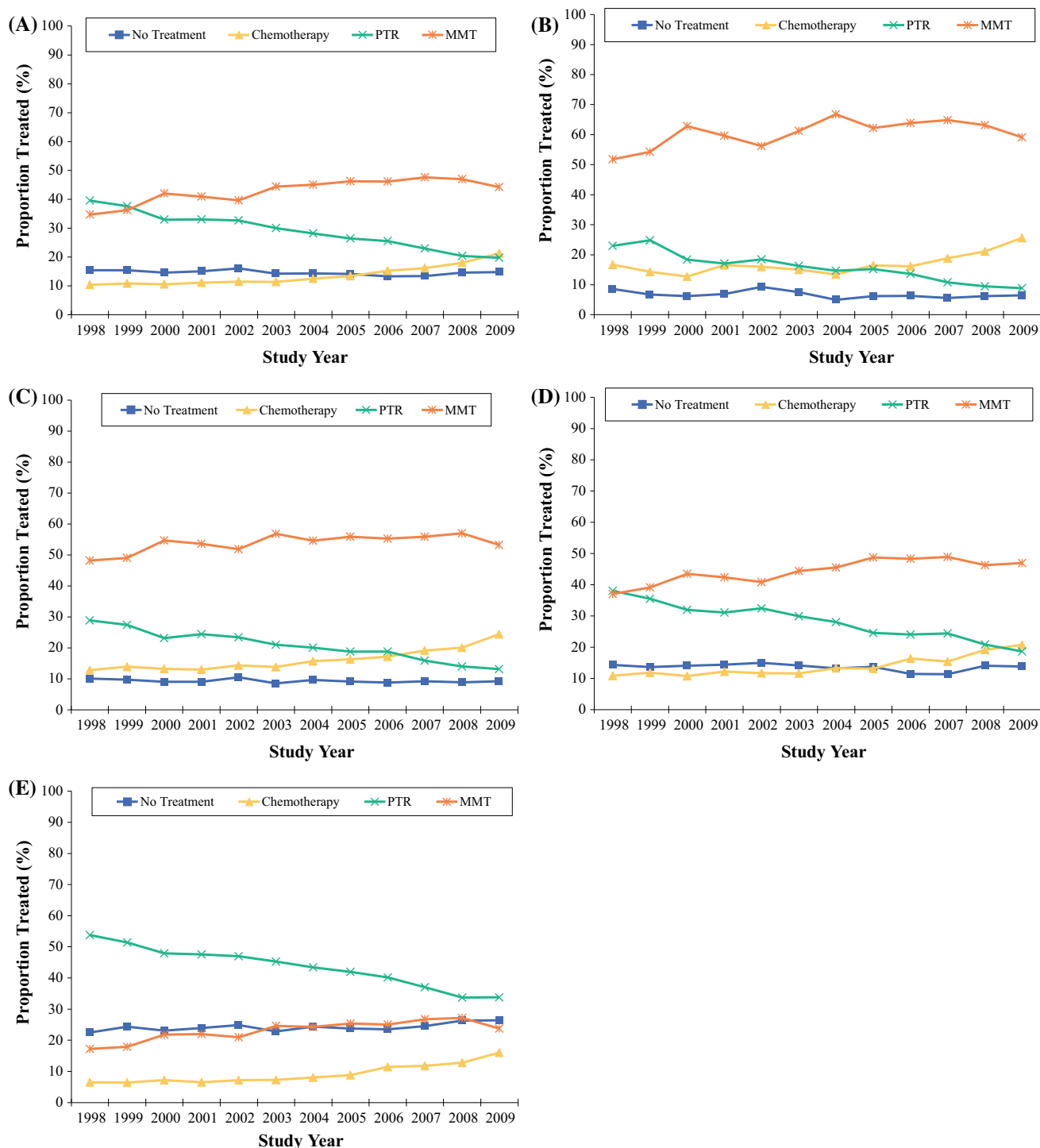


FIG. 1 Secular trends in metastatic colon cancer treatment type for **a** the overall cohort, **b** age <50 years, **c** age 50–64 years, **d** age 65–74 years, and **e** age ≥75 years. *PTR* primary tumor resection, *MMT* multimodality therapy (PTR + chemotherapy)

by age category. The proportion of patients managed with systemic therapy alone doubled during the 12 study years (10.4 % 1998 vs. 21.3 % 2009; trend test, $p < 0.001$). Utilization of PTR overall (alone and MMT) significantly decreased over the study period (74.2 % 1998 vs. 63.9 % 2009; trend test, $p < 0.001$). This was primarily explained by a decrease in PTR alone (39.5 % 1998 vs. 19.7 % 2009;

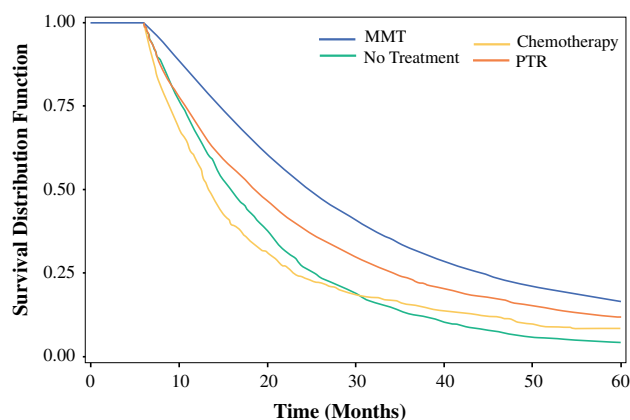


FIG. 2 Unadjusted survival stratified by treatment type for the overall study cohort. *PTR* primary tumor resection, *MMT* multimodality therapy (PTR + chemotherapy)

trend test, $p < 0.001$)—a consistent trend across all categories of patient age (<50 years: 23.0 % 1998 vs. 8.9 % 2009; 50–64 years: 28.9 % 1998 vs. 13.1 % 2009; 65–74 years: 38.0 % 1998 vs. 18.6 % 2009; ≥ 75 years: 53.8 % 1998 vs. 33.8 % 2009; trend test, $p < 0.001$ for all). By comparison, PTR as part of MMT increased overall (34.7 % 1998 vs. 44.2 % 2009; trend test, $p < 0.001$) and across all age categories (<50 years: 51.8 % 1998 vs. 59.1 % 2009; 50–64 years: 48.2 % 1998 vs. 53.2 % 2009; 65–74 years: 37.0 % 1998 vs. 46.9 % 2009; ≥ 75 years: 17.2 % 1998 vs. 23.8 % 2009; trend test, $p < 0.001$ for all). Similar trends were noted across hospital types and geographic regions.

Using a landmark approach, there were significant differences in overall survival with varying treatment. Median overall survival (Fig. 2a) was significantly different (log-rank, $p < 0.001$) among the various treatment strategies. Survival estimates decreased with increasing patient age (Fig. 2b–e), but the pattern of survival across treatment strategies was similar. After adjusting for relevant covariates (Fig. 3), risk of death was significantly higher for all treatment strategies compared with MMT (no treatment: hazard ratio [HR] 1.74 [1.60–1.88]; chemotherapy: HR 1.86 [1.77–1.95]; PTR alone: HR 1.21 [1.16–1.26]). Results from the interaction model are presented in

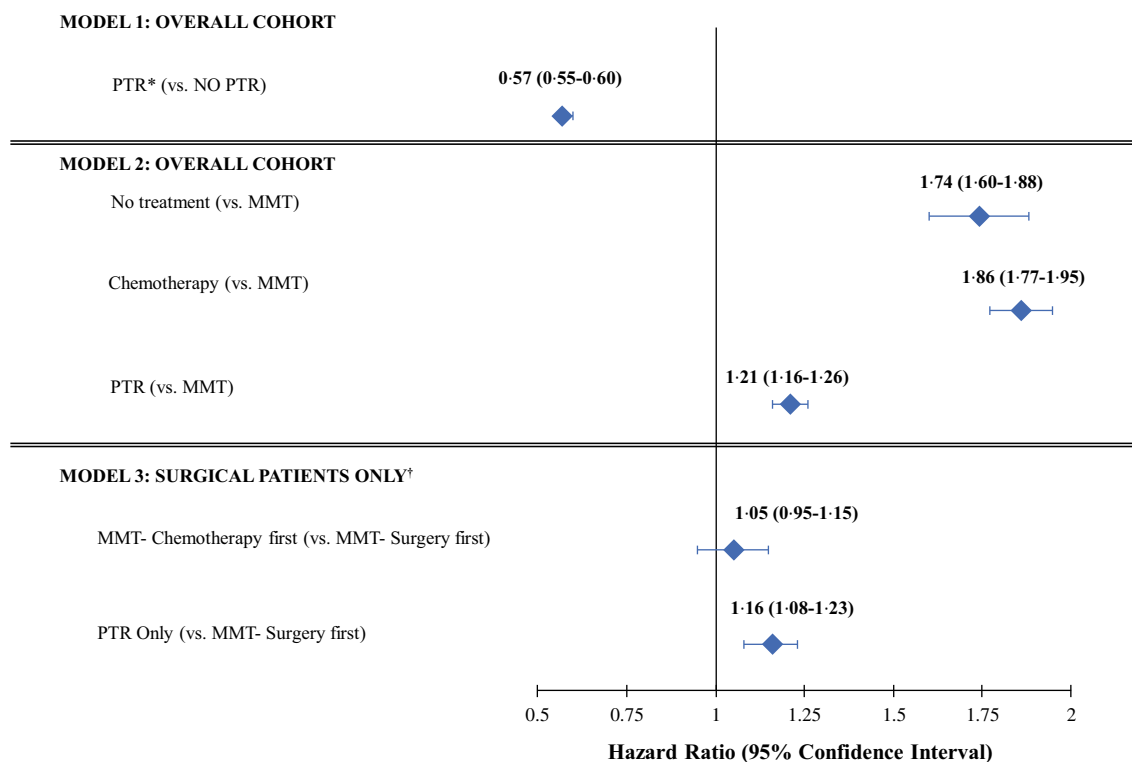


FIG. 3 Association between treatment and overall risk of death. *PTR* primary tumor resection; *MMT* multimodality therapy (PTR + chemotherapy). All survival analyses restricted to patients

diagnosed 2003–2005. *Includes surgery alone and MMT. †Surgically resected patients with no 30-day postoperative readmission and a postoperative length of stay ≤ 7 days

TABLE 2 Multivariate model of risk of death with interaction between age and treatment type

Stratified on age	Hazard ratio (95 % CI)	Stratified on treatment	Hazard ratio (95 % CI)
<50 years		No treatment	
Chemotherapy vs. no treatment	1.14 (0.88–1.49)	Age 50–64 vs. <50	0.99 (0.74–1.31)
MMT vs. no treatment	0.59 (0.46–0.76)	Age 65–74 vs. <50	1.12 (0.83–1.49)
No treatment vs. PTR	1.56 (1.19–2.04)	Age ≥75 vs. <50	1.68 (1.28–2.21)
MMT vs. PTR	0.92 (0.81–1.05)	Age 50–64 vs. 65–74	0.88 (0.71–1.10)
Chemotherapy vs. PTR	1.78 (1.53–2.1)	Age 50–64 vs. ≥75	0.59 (0.48–0.71)
MMT vs. chemotherapy	0.52 (0.46–0.58)	Age 65–74 vs. ≥75	0.66 (0.54–0.81)
50–64 years		Chemotherapy	
Chemotherapy vs. no treatment	1.14 (0.97–1.35)	Age 50–64 vs. <50	0.98 (0.87–1.11)
MMT vs. no treatment	0.61 (0.52–0.71)	Age 65–74 vs. <50	1.12 (0.98–1.28)
No treatment vs. PTR	1.53 (1.29–1.81)	Age ≥75 vs. <50	1.33 (1.15–1.55)
MMT vs. PTR	0.93 (0.86–1.00)	Age 50–64 vs. 65–74	0.88 (0.79–0.98)
Chemotherapy vs. PTR	1.74 (1.58–1.92)	Age 50–64 vs. ≥75	0.74 (0.65–0.94)
MMT vs. chemotherapy	0.53 (0.49–0.58)	Age 65–74 vs. ≥75	0.84 (0.73–0.97)
65–74 years		PTR	
Chemotherapy vs. no treatment	1.15 (0.95–1.38)	Age 50–64 vs. <50	1.01 (0.88–1.15)
MMT vs. no treatment	0.62 (0.53–0.73)	Age 65–74 vs. <50	1.42 (1.24–1.63)
No treatment vs. PTR	1.22 (1.03–1.46)	Age ≥75 vs. <50	1.76 (1.55–2.01)
MMT vs. PTR	0.76 (0.70–0.83)	Age 50–64 vs. 65–74	0.71 (0.64–0.78)
Chemotherapy vs. PTR	1.40 (1.25–1.57)	Age 50–64 vs. ≥75	0.57 (0.52–0.62)
MMT vs. chemotherapy	0.54 (0.49–0.60)	Age 65–74 vs. ≥75	0.81 (0.74–0.88)
≥75 years		MMT	
Chemotherapy vs. no treatment	0.91 (0.77–1.07)	Age 50–64 vs. <50	1.01 (0.96–1.07)
MMT vs. no treatment	0.51 (0.45–0.58)	Age 65–74 vs. <50	1.17 (1.10–1.25)
No treatment vs. PTR	1.49 (1.30–1.70)	Age ≥75 vs. <50	1.46 (1.36–1.56)
MMT vs. PTR	0.76 (0.71–0.82)	Age 50–64 vs. 65–74	0.86 (0.82–0.91)
Chemotherapy vs. PTR	1.35 (1.19–1.52)	Age 50–64 vs. ≥75	0.70 (0.65–0.74)
MMT vs. chemotherapy	0.57 (0.50–0.64)	Age 65–74 vs. ≥75	0.81 (0.75–0.86)

Model also adjusted for sex, race, income, insurance, facility type, and comorbidity

PTR primary tumor resection, *MMT* multimodality therapy (PTR + chemotherapy)

Table 2. For most treatment and age combinations, the direction, magnitude, and 95 % confidence intervals were similar. The most notable difference was with respect to MMT and PTR. Among those aged 65–74 years (HR 0.76 [0.70–0.83]) and ≥75 years (HR 0.76 [0.71–0.82]) MMT was associated with a significantly lower risk of death compared to PTR alone. By comparison, this was not significant among those aged <50 and 50–64 years. When treatment was dichotomized into “PTR” versus “no PTR,” surgery was associated with a lower risk of death (HR 0.57 [0.55–0.60]). Among surgical patients treated with MMT, the sequence of chemotherapy and surgery did not affect risk of death (surgery first—reference group; chemotherapy first (HR 1.05 [0.95–1.15])). However, PTR alone was associated with a significantly higher risk of death (HR 1.16 [1.08–1.23]).

DISCUSSION

During the past decade, available chemotherapeutic options for mCC patients have increased and survival associated with these treatments has improved. During this same time period, oncologic practitioners have continued to debate the value of and role for PTR among patients presenting with mCC. The findings from this national cohort of mCC patients support several important conclusions. First, one in five mCC patients undergo resection without receiving chemotherapy. Second, patient age does not appear to impact the relative utilization and associated survival of any of the available treatment strategies—including MMT. Despite this, one third of mCC patients aged ≥75 years continue to be treated with PTR alone (this was the most common intervention in this age group over

time) and represent the only age group for whom PTR is currently performed more commonly (33.8 %) than MMT (23.8 %). Finally, because the sequence of PTR and chemotherapy does not impact risk of death (as long as the patient receives MMT), we believe the previously described survival benefit associated with PTR is predominantly a function of MMT.

The role for PTR in the management of mCC patients remains unclear. Short-term, primary tumor-associated symptoms are reported to occur infrequently during systemic therapy.^{19,20} While often cited as a reason to defer or not perform PTR, in these studies nearly one third of patients initially managed without PTR eventually underwent resection or a nonoperative (endoscopic or radiation) intervention during follow-up. Although not previously a consideration, against the backdrop of contemporary chemotherapy which has substantially increased survival, the natural history of an unresected colonic primary may now need to be factored in when discussing management options with mCC patients. For example, mCC patients who undergo PTR are more likely to receive systemic therapy than those who do not.⁸ In addition, those requiring emergent surgical intervention less frequently resume or initiate chemotherapy.²¹ Therefore, among patients with (potentially) resectable metastatic disease, PTR may have a role as an important component of a well-conceived, multimodal treatment plan. For patients presenting asymptotically who have synchronous and *unresectable* metastatic disease, the role for PTR is less clear. However, these patients can develop symptoms during systemic therapy requiring surgical or nonsurgical (but invasive) treatment.²² As such, in certain patients PTR may be a means of avoiding tumor-related complications, minimizing the risk of chemotherapy interruptions, and thus providing a meaningful survival benefit.

Postoperative complications occur commonly after colorectal surgery and may result in delayed or omitted systemic therapy administration.^{21,23–26} As such, a treatment plan that minimizes systemic therapy delays and/or interruptions is crucial. In our study, among surgical patients less likely to have had a postoperative complication (which might have precluded initiation or delayed resumption of chemotherapy), PTR alone was associated with a higher risk of death compared with MMT. However, when patients are treated with MMT, the sequence of surgery and chemotherapy did not affect survival. Compared with recently published work suggesting an outright benefit associated with PTR, our findings support a more nuanced view of surgery in mCC patients.¹⁰ Although our data suggest that those receiving MMT can be treated with upfront PTR, a given patient's risk for postoperative complications, their clinical and performance status, and the likelihood of initiating chemotherapy postoperatively

must all be carefully considered. Given these factors, when planning MMT, unless there is a compelling clinical reason to perform upfront resection, starting treatment with systemic therapy first seems a conservative and reasonable approach.

Providers often anticipate poor outcomes when managing older colon cancer patients.²⁷ However, elderly patients do appear to benefit from MMT and the relative benefit of these treatment modalities is actually independent of chronologic age.^{28–31} In our analysis, older patients who underwent surgical resection benefited from MMT (compared with PTR alone), whereas the difference between these two management approaches in younger patients was not statistically significant. Despite this finding, PTR alone was consistently the most common intervention for older patients throughout the study and, in the most recent study year, approximately one in three underwent resection alone. It is unclear whether this suggests older patients experience primary tumor-related complications requiring surgery at a higher rate, they are more frequently treated with surgical resection up front and subsequently do not receive systemic therapy due to patient and/or provider preferences, or are simply unable to tolerate postoperative systemic therapy. Given that the elderly segment of the US population is expected to increase dramatically in the coming years and they represent the overall majority of new cancer diagnoses, future work evaluating multimodal management of elderly mCC patients and better data to help define optimal approaches to management of these patients will be valuable.³²

There are several notable limitations to consider when interpreting these results. Because NCDB does not report patient symptoms, we were unable to ascertain the intent or reason for surgery. We lacked information on extent, location, and possible resectability of patients' metastatic disease. Similarly, we did not have information on subsequent operations potentially performed with curative intent (i.e., hepatectomy for a liver metastasis). We attempted to at least partially account for any survival differences based on these and other unmeasured patient (e.g., functional/performance status, burden/severity of comorbid conditions, etc.) and/or disease-related (e.g., tumor biology, burden of metastatic disease, etc.) factors by using a 6-month landmark to deal with survivor treatment bias—an approach not previously utilized in other studies. Despite this approach, residual confounding by indication is unlikely to have been completely addressed. As such, some of our results may be attributable to more frequent use of multimodality treatment among fitter patients with less advanced metastatic disease. However, we believe this to be a relatively conservative bias (i.e., favoring a more selective approach to PTR) compared with other studies, suggesting an outright benefit associated with PTR,

regardless of systemic therapy administration. The dataset only provides information on the receipt and initiation of a given treatment. Therefore, among MMT patients treated with chemotherapy first, we were neither able to delineate whether chemotherapy was reinitiated after PTR nor the amount of chemotherapy a patient received. Similarly, data on the specific chemotherapeutic regimen received is not provided. Finally, information on patients' treatment preferences may have been useful in understanding the underlying reasons treatment approaches changed over time, especially among the elderly.

Optimal management of mCC patients remains unclear. Future work examining specific patients for whom PTR alone may be beneficial for palliative purposes as well as providers' views and patients' preferences of surgery in the metastatic setting would be useful. Eventual data from ongoing randomized trials may provide data to help inform the discussion about when and whether resection should be offered and the expected benefit.^{33,34} In the meantime, our work suggests that PTR may provide a meaningful survival benefit when incorporated as a part of MMT, regardless of age. However, the role for PTR as a means to optimize delivery of systemic therapy and prevent chemotherapy interruptions related to primary tumor-related complications requires further evaluation.

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