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Elective colon resection without curative intent in stage IV colon cancer

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ABSTRACT

Background: Evidence suggests that elective primary colon resection (ePCR) in patients with asymptomatic colon tumors and unresectable metastases is not required and may expose patients to unnecessary operative risk.
Methods: Stage IV colon cancer patients with liver metastases from 2000 to 2011 were identified with SEER-Medicare data. Liver-based therapy or urgent/emergent colectomies were excluded. Chemotherapy alone was compared to ePCR ± chemotherapy. Univariate and multivariate analyses were used to identify predictors of ePCR. Multivariate Cox regression compared survival.
Results: 5139 patients were identified. The ePCR rate decreased over time; 84% underwent ePCR in 2000, compared to 52% in 2011 ($p < 0.001$). In multivariate analysis, older patients were more likely to undergo ePCR, as were patients from rural areas (OR 1.65, $p < 0.001$). The odds of PCR in high poverty areas (> 10%) were almost 25% higher than those in low poverty areas (OR 1.23, $p = 0.03$). African-Americana were less likely to undergo PCR than Caucasians (OR 0.76, $p = 0.01$). In multivariate survival analysis, PCR was associated with a significant survival benefit (HR 0.59, $p < 0.001$).
Conclusions: Although ePCR is not recommended with unresectable metastases and the rate has decreased significantly, over 50% of patients with untreated hepatic metastases underwent ePCR in 2011. Disparities exist in use of ePCR that are likely multifactorial and deserve further study.

1. Introduction

Colorectal cancer remains third in incidence and mortality among cancers in the United States, and will be responsible for over 140,000 new diagnoses and nearly 50,000 deaths in 2018 [1]. Twenty-two percent of these patients present with metastatic disease, with a 5-year survival rate of 13.3% [2]. Recent advances in chemotherapeutic and surgical treatment of metastatic disease, however, have broadened treatment options and improved survival in these patients [3–9].

Although an increasing number of patients with Stage IV colon cancer have potentially resectable metastases, 75–90% present with unresectable disease [10]. In the past, many of these patients underwent resection of their colon tumor given concerns for perforation, bleeding or obstruction. Evidence, however, has shown a low complication rate and limited survival decrement associated with forgoing colectomy in these patients [11,12]. Studies have demonstrated that surgery without curative intent may expose patients to unnecessary risks and lead to a delay in chemotherapy without survival benefit [13,14]. Also, with modern chemotherapies, median survival rates have tripled to 24–36 months without resection of the primary tumor [15–17]. Based on this, the National Comprehensive Cancer Network and the American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines state that surgical resection of the primary tumor in patients with metastatic colon cancer should only be performed if cure is thought possible, or for imminent risk of tumor-related complications [18,19].

We explored the use ePCR[2] in stage IV colon cancer patients in the United States using the SEER-Medicare linked database. In addition to the overall rate of ePCR, we also used this comprehensive cancer and claims database to investigate the patient factors associated with ePCR to highlight any existing disparities.

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2. Methods

We obtained data from SEER-Medicare for patients diagnosed with Stage IV colon adenocarcinoma between 2000 and 2011. We obtained Medicare claims data for these patients starting in 1999, 12 months prior to the date the first patient's diagnosis. Because they lacked complete claims data, we excluded patients who were enrolled in HMOs or were not enrolled in Medicare Part A/B, within the prior 12 months or any time during follow-up. Patients older than 99 years or younger than 66 were also excluded. Additionally, patients were only included if colon cancer was their only primary cancer.

Identification of events, including diagnosis of hepatic metastases, receipt of colon resection, hepatic therapy, and receipt of chemotherapy was based on the presence of claims that occurred within 6 months prior to and 12 months after the date of colon cancer diagnosis. We identified patients who had evidence of hepatic metastases based on ICD-9 (International Classification of Diseases, 9th Revision) diagnosis codes (155.2 or 197.7) for secondary liver metastases. We identified patients who underwent PCR based on ICD-9 (International Classification of Diseases, 9th Revision) and CPT (Current Procedural Terminology, 2006) codes. Colon resection was classified as elective or urgent/emergent based on the admission type found in the Medicare claim file associated with the identified colon procedure. Additionally, receipt of liver resection/ablation was identified based on ICD-9 and CPT codes during the same time period. Procedures included laparoscopic liver resection (CPT 47370), wedge resection (CPT 47120, ICD-9 50.22), hepatic lobectomy (CPT 47125, 47130; ICD-9 50.3), hepatic trisegmentectomy (CPT 47122), laparoscopic/open radiofrequency ablation (CPT 47370, 47380), and laparoscopic/open cryoablation (CPT 47371, 47381). Chemotherapy was identified using claims data.

We initially identified 11,398 patients with stage IV colon cancer and evidence of hepatic only metastases. For analysis, we excluded patients who had identified liver therapy (n = 517). We then excluded patients who had a colectomy classified as urgent or emergent, recognizing that even in the setting of unresectable hepatic metastases, colonic resection is often indicated for symptoms (n = 3078). Finally, we excluded patients who had no evidence of surgical or chemotherapeutic treatment, as patients with Stage IV colon cancer who receive no treatment likely represent a group of patients with significantly advanced disease (n = 2273). Finally, we excluded patients with missing demographic information (n = 391). The remaining patients represented a cohort of patients with Stage IV colon cancer with synchronous liver metastases who had either chemotherapy alone or PCR without evidence of liver therapy.

Prior to analysis, we defined the categorical patient-associated variables we hypothesized would be associated with receipt of ePCR including patient age, race, gender, Klabunde-Charlson comorbidity score, socioeconomic status, urban/rural location, and year of diagnosis. Patient age was analyzed as a categorical variable (66–70, 71–75, 76–80, 81–85, and 86 and above). Because of the small number of nonwhite patients, we collapsed race into 3 categories, White, African-American and other. Patient comorbidity was assessed using the Klabunde modification of the Charlson comorbidity score represented by 3 categories: 0 (low), 1 (moderate), and 2 or greater (high) [20,21]. The percentage of people living below the poverty line in a patient's Census tract was used as a proxy for socioeconomic status. This was categorized as < 5%, 5 to < 10%, and ≥10% below the poverty line. The urban/rural location was based on the codes provided in the SEER PEDSF file and was categorized as follows: metropolitan area (population ≥ 1 million), metropolitan area (population < 1 million), and non-metropolitan. Finally, we also included tumor location, defined as proximal (proximal to the splenic flexure), distal (splenic flexure and distal) and unknown. This information is provided in the SEER PEDSF data.

2.1. Statistical analysis

Univariate associations between receipt of ePCR and the above-mentioned characteristics were assessed using Pearson's χ^2 tests for categorical variables. The adjusted association between the patient variables and ePCR were analyzed using a multivariable logistic regression including all variables previously identified as clinically important in the decisions regarding surgical therapy.

We also utilized join point regression to examine temporal trends in ePCR for Stage IV colon cancer patients [22,23]. This analysis allows for calculation and plotting of best-fit regression models for the function of a dependent variable (i.e. elective colon resection) as it relates to a continuous independent variable (i.e. time). Each interval change in the dependent variable over time is represented by the annual percentage change (APC). The overall change in the variable across the study period is the average annual percentage change (AAPC). When there are no join points defined across a regression curve, the APC is equal to the AAPC.

Multivariable Cox regression was performed, using the same variables described above, to assess the relationship between ePCR and disease-specific survival (DSS). Also included in this analysis were tumor grade (well/moderately differentiated versus poorly differentiated/undifferentiated versus unknown) and the receipt of chemotherapy, both of which are known to be associated with survival.

Two-tailed tests were used for all analyses and statistical significance was defined at $p < 0.05$. Statistical analysis was conducted using STATA 14.0 (STATA Inc., College Station, TX) and the Join point Regression Program (version 4.4.0.0 –June 2016; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD). The study was reviewed and exempted by the Institutional Review Board of the University of Pennsylvania.

3. Results

We identified 5139 patients with colon cancer and synchronous hepatic metastases who were treated with chemotherapy only or ePCR between 2000 and 2011 (Table 1). Over the course of the study, 3685 (71%) underwent ePCR. Cohort demographics are shown in Table 1.

The rates of ePCR decreased significantly; between 2000 and 2002, 83.3% (n = 1268) of patients underwent ePCR versus chemotherapy alone, whereas of 56.1% (n = 559) did between 2009 and 2011 ($p < 0.001$). This trend was significant on join point analysis (AAPC of −3.9% (95% CI -4.6%, −3.2%, $p < 0.001$) (Fig. 1).

On univariate analysis, age, race, and location were associated with the use of ePCR (Table 1). The rates of ePCR were significantly different amongst age groups ($p = < 0.001$), with 80.5% (n = 350) of patients 86 + year old undergoing ePCR compared to 67.4% of 66–70-year-old patients ($p < 0.001$). ePCR was more common in white patients than in African American patients (72.6.3% and 66.2%, respectively, $p = 0.005$)., Additionally, ePCR was more common in patients from non-metro locations (79.3%) compared to large metro settings (69.4%) ($p < 0.001$). Finally, tumor location was associated with rates of ePCR; patients with distal colon tumors were less likely (72.9%) to undergo ePCR than patient with proximal colon tumors)76.9%, $p < 0.001$).

On multivariable analysis, the same relationships remained significant (Table 2). Patients diagnosed in 2009–2011 had > 75% lower odds of ePCR than patients diagnosed between 2000 and 2002 (HR 0.24, $p < 0.001$). Older patients had increased odds of ePCR. The odds of patients aged 76–80, 81–85 and 86 + were 1.36 ($p = 0.001$), 1.62 ($p < 0.001$) and 2.20 ($p < 0.001$) times higher, respectively, than those of a 66–70 year old. High poverty and non-metro location were also associated ePCR. The odds of a patient in a high poverty location undergoing ePCR were over 20% higher than those of a patient in a low poverty location (HR 1.21, $p = 0.03$). Similarly, patients in non-metro

Table 1
Cohort characteristics and univariate analysis by PCR status.

	N (%)	Univariate		
		No PCR n (%)	PCR N (%)	P value
Age				< 0.001
66-70	1272 (24.8)	415 (32.6)	857 (67.4)	
71-75	1342 (26.1)	417 (31.1)	925 (68.9)	
76-80	1228 (23.9)	330 (26.9)	898 (73.1)	
81-85	850 (16.5)	205 (24.1)	645 (75.9)	
86+	447 (8.7)	87 (19.5)	360 (80.5)	
Gender				0.14
Male	2446 (47.6)	716 (29.3)	1730 (70.3)	
Female	2693 (52.4)	738 (27.4)	1955 (72.6)	
Charlson				0.19
0	3296 (64.1)	906 (27.5)	2390 (72.5)	
1	1137 (22.1)	332 (29.2)	805 (70.8)	
2 =	706 (13.8)	216 (30.6)	490 (69.4)	
Location				< 0.001
Metro (> 1 million)	2721 (52.9)	832 (30.6)	1889 (69.4)	
Metro (< 1 milllion)	1525 (28.7)	437 (28.7)	1088 (71.3)	
Non-Metro	893 (17.4)	185 (20.7)	708 (79.3)	
Race				0.005
White	4292 (83.5)	1177 (27.4)	3115 (72.6)	
African-American	542 (10.6)	183 (33.8)	359 (66.2)	
Other	305 (5.9)	94 (30.8)	211 (69.2)	
Poverty				0.18
< 5%	1387 (27.0)	419 (30.2)	968 (69.8)	
5%- < 10%	1425 (27.7)	394 (27.6)	1031 (72.4)	
> =10%	2327 (45.3)	641 (27.5)	1686 (72.5)	
Year				< 0.001
2000-02	1522 (29.6)	254 (16.7)	1268 (83.3)	
2003-05	1410 (27.4)	347 (24.6)	1063 (75.4)	
2006-08	1211 (23.6)	416 (34.4)	795 (65.6)	
2009-11	996 (19.4)	437 (43.9)	559 (56.1)	
Tumor Location				< 0.001
Proximal	2683 (52.2)	619 (23.1)	2064 (76.9)	
Distal	2212 (41.3)	574 (27.1)	1547 (72.9)	
Unknown	335 (6.5)	261 (77.9%)	74 (22.1)	

Table 2
Multivariable analysis of patient characteristics and odds of PCR.

	OR	95% CI	P value
Age			
66-70	Reference		
71-75	1.07	0.91, 1.27	0.41
76-80	1.36	1.13, 1.61	0.001
81-85	1.62	1.32, 1.99	< 0.001
86+	2.20	1.68, 2.89	< 0.001
Gender			
Male	Reference		
Female	1.04	0.92, 1.20	0.51
Charlson			
0	Reference		
1	0.99	0.84, 1.16	0.89
2 =	0.93	0.77, 1.13	0.47
Location			
Metro (> 1 million)	Reference		
Metro (< 1 milllion)	1.11	0.95, 1.28	0.19
Non-Metro	1.70	1.39, 2.1	< 0.001
Race			
White	Reference		
African-American	0.80	0.64, 0.98	0.03
Other	0.97	0.74, 1.27	0.82
Poverty			
< 5%	Reference		
5%- < 10%	1.14	0.96, 1.36	0.14
> =10%	1.21	1.03, 1.43	0.03
Year			
2000-02	Reference		
2003-05	0.60	0.50, 0.73	< 0.001
2006-08	0.35	0.29, 0.43	< 0.001
2009-11	0.24	0.20, 0.30	< 0.001
Tumor Location			
Proximal	Reference		
Distal	0.80	0.70, 0.92	0.02
Unknown	0.08	0.06, 0.11	< 0.001

locations were over 50% more likely to undergo ePCR than those patients in major metropolitan centers (OR 1.70, $p < 0.001$). Also, African Americans were less likely to undergo ePCR than Caucasian patients (OR 0.80, $p = 0.03$). Finally, the odds of a patient with a distal tumor undergoing eCPR were 20% lower that the odds for a patient with a proximally located tumor (OR 0.80, $p = 0.02$).

Multivariable Cox regression analysis was performed to evaluate the independent association between ePCR and DSS (Table 3, Fig. 2). EPCR was associated with significantly improved survival (HR 0.56, $p < 0.001$). Despite this statistically significant result, the clinical difference was small. Median survival for patients who did not get ePCR was 9 months compared to 11 months for patient who did get ePCR.

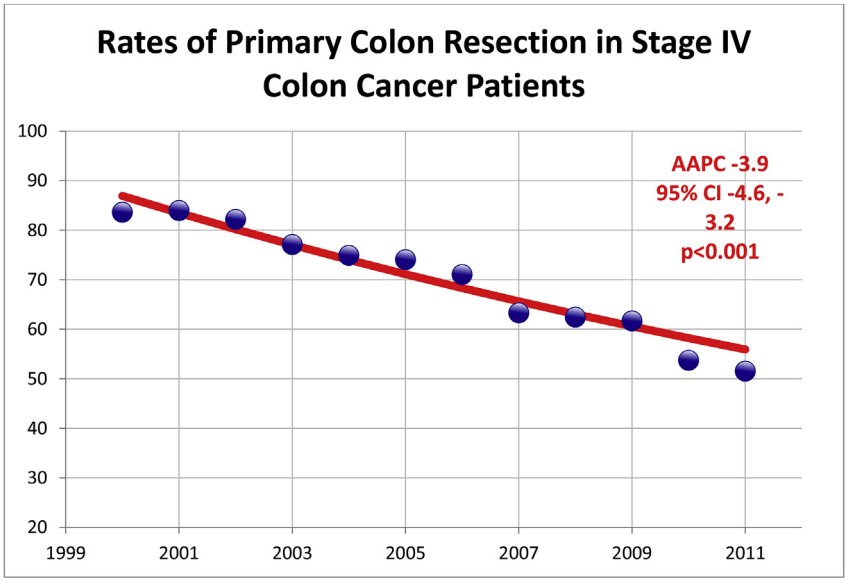

Fig. 1. Rates of ePCR over time – Trend of ePCR rates over time using join point analysis.

Table 3
Multivariable Cox Survival analysis – Disease specific survival.

	HR	95% CI	P value
Colon resection			
No	Reference		
Yes	0.56	0.51, 0.61	< 0.001
Tumor Grade			
Well/Moderate			
Poor/Undifferentiated	1.48	1.38, 1.59	< 0.001
Unknown	1.18	1.08, 1.31	0.001
Chemotherapy			
No			
Yes	0.47	0.43, 0.50	< 0.001
Age			
66-70	Reference		
71-75	1.04	0.96, 1.13	0.33
76-80	1.15	1.05, 1.25	0.001
81-85	1.23	1.12, 1.35	< 0.001
86+	1.29	1.13, 1.45	< 0.001
Gender			
Male	Reference		
Female	1.06	0.99, 1.12	0.08
Charlson			
0	Reference		
1	0.95	0.88, 1.02	0.16
2+	1.06	0.97, 1.16	0.21
Location			
Metro (> 1 million)	Reference		
Metro (< 1 milllion)	1.03	0.96, 1.09	0.51
Non-Metro	1.12	1.03, 1.22	0.01
Race			
White	Reference		
African-American	1.14	1.03, 1.25	0.01
Other	0.87	0.77, 0.98	0.03
Poverty			
< 5%	Reference		
5%- < 10%			
> = 10%			
Year			
2000-02	Reference		
2003-05	0.90	0.83, 0.97	0.006
2006-08	0.84	0.77, 0.91	< 0.001
2009-11	0.83	0.76, 0.91	< 0.001
Tumor Location			
Proximal	Reference		
Distal	0.82	0.77, 0.88	< 0.001
Unknown	1.05	0.92, 1.19	0.46

4. Discussion

Our study uses a large, comprehensive cancer registry linked to complete Medicare claims data to examine trends and disparities in the use of ePCR among elderly patients with untreated hepatic metastases. Our data confirm that, in accordance with published data and recommendations [19–21,23], the use of ePCR decreased significantly between 2000 and 2011. We identified disparities in the use of ePCR based on age, race, economic status and location.

Shapiro et al. also used the SEER database to examine the use of colectomy in untreated metastatic disease and found a similar downward trend of the rate of PCR [4]. Our study used the SEER data linked to Medicare claims. This linkage provides significantly improved specificity to more accurately identify the presence of hepatic metastases, the treatment of the metastatic disease, and the operative urgency of the colectomy, all of which are impossible to identify with SEER alone, but add to the clinical context regarding the true incidence of ePCR.

Although ePCR decreased over the study period, over 50% of patients with untreated hepatic metastases still underwent ePCR in 2011. Using retrospective data, unfortunately, it is not possible to determine why a patient received ePCR. It is possible that a metastatic workup was not performed prior to ePCR and therefore the clinical oversight was in lack of preoperative staging rather than selection of appropriate treatment. ePCR may also be performed in patients in whom obstruction appears to be imminent, but not urgent–a decision which is unable to be determined from retrospective claims data. Informed patient choice to avoid palliative chemotherapy may also factor into the process; a patient may undergo an ePCR to avoid future obstruction/hemorrhage while he lives out his remaining life.

In reality, the rate of truly elective resection the setting of unresectable metastatic disease is likely lower than that shown here, for the reasons above. Despite this, however, disparities still exist that are worth exploring. Interestingly, older patients were more likely to undergoing ePCR. The exact reason for this is unclear. Perhaps with increasing minimally invasive techniques, providers feel the perceived risks and benefits of surgery versus palliative chemotherapy are changing. As such, providers may feel many elderly patients are not good chemotherapy candidates: only 36% of these stage IV patients over 85 received chemotherapy. It is possible ePCR is offered to elderly patients deemed unfit for systemic chemotherapy to avoid possible complications of primary tumor growth. Indeed, if our analysis is limited to only

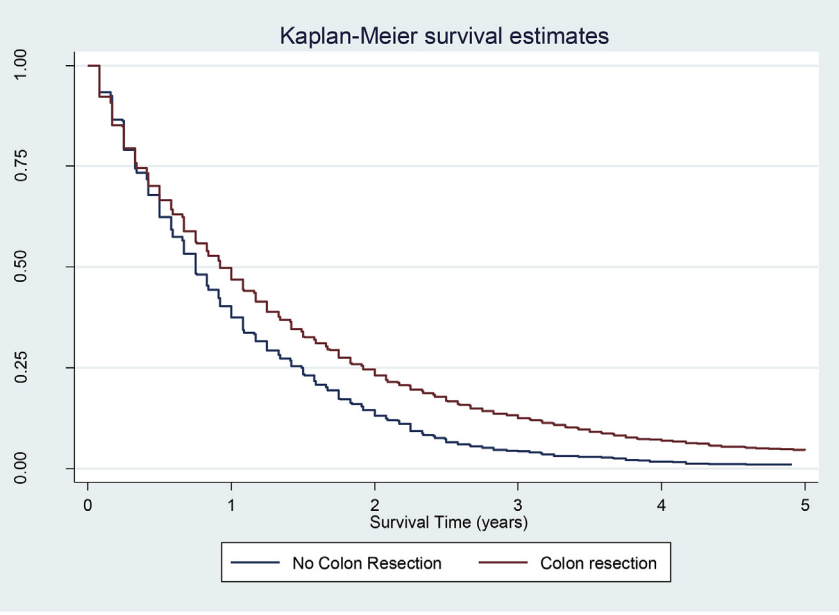

Fig. 2. Kaplan Meier 5-year survival – Survival of patients undergoing ePCR compared to no resection of the primary tumor over 5 years.

ePCR patients who also had chemotherapy, the odds of ePCR is noted to actually decrease with increasing age.

We also demonstrate that patients with tumors proximal to the splenic flexure are more likely to undergo ePCR that patients with more distal tumors. In general, more proximal tumors can be treated with a right colectomy, or possibly extended right colectomy. These are often viewed as more straightforward operations with lower-risk anastomoses (ileo-colonic as compared to colo-rectal) than the left or sigmoid colectomies required by more distal tumors. Providers, believing they are preventing longer-term tumor complications, may be more willing to perform a lower risk operation, even in the setting of untreatable hepatic metastatic disease.

A more noteworthy disparity is that patients in poorer and more rural locations were more likely to under ePCR. There is a large body of literature suggesting that low socioeconomic status and rural locations are associated with decreased access to cancer treatments, including chemotherapy, and increased cancer mortality [24,25]. For example, these patients, who may not have access to chemotherapy as readily as urban, less poor, patients, may be referred for colectomy, as discussed above with the elderly, to avoid complications of their primary tumor in the setting of no treatment. Even if we look only at patients who had ePCR and chemotherapy, however, a significant disparity in use of ePCR still exists. This indicates that while the above explanation may contribute to some of the disparity, it does not explain it entirely. There may be a limited dispersion of current evidenced-based recommendations to practitioners in these vulnerable areas. A lack of recognition of its limited benefit, may result in inappropriate recommendation of ePCR despite unresectable metastatic disease.

We also note that African American patients are less likely to undergo ePCR. This is consistne with most evidence demonstrating lower incidence of aggressive treatment in this population in general. It has been shown that race influences provider recommendations for invasive procedures [26]. Also, African Americans may be less likely to seek out surgical evaluation on their own if it is not offered by their treating physicians. Finally, African American patients hold more fatalistic views about their disease and are more likely to refuse recommended treatment [20,27]. Our finding that African Americans undergo ePCR less frequently than white patients likely reflects the above considerations more than the fact that they are actually being treated more appropriately.

Finally, in our survival analysis, as with other retrospective studies, ePCR appears to be associated with a significant DSS benefit [28–31]. We believe that this result should be viewed cautiously. First, while the result is statistically significant, the clinical difference was small. Second, many clinical factors go into surgical decision making, many of which cannot be captured using retrospective claims data. It is likely that patients in whom ePCR is performed are more fit for surgery and have less burden of metastatic disease than those who do not, subtle clinical factors that we cannot capture and that will skew survival analysis in favor of ePCR. We feel that it is difficult, if not impossible, to draw definitive conclusion regarding survival benefits of ePCR using retrospective data such as this.

Several limitations of this study are worth mentioning. First, the analysis is limited to patients aged > 65 years. More than half of CRC patients, however, are diagnosed after age 65. Most importantly, we cannot know the true indication for elective colectomy. It is possible that some patients did have symptoms prompting need for surgical intervention that did not rise to the level of urgent or emergent. In these patients, colectomy would be an appropriate therapy. This misidentification, however, should be similar across all patient groups. So, although the rate of ePCR may be lower than noted here, the fact that we see differences in the use of ePCR across groups indicates that disparities likely exist.

Additionally, although we know the patients here presented with Stage IV disease as coded by the SEER abstractor, we cannot verify that they had liver metastases. In fact, SEER-Medicare reviewers have substantive concerns about using these data to identify sites of metastases. We recognize that the SEER-Medicare reviewers feel findings from this analysis may be inaccurate or misleading. We believe, however, that we addressed this by only including patients if an ICD-9 code for secondary liver malignancy was present in the peri-diagnosis time period. By only including patients who had an identifiable code, feel that these patients represent a clean cohort of Stage IV colon cancer patients with hepatic metastases at the time of diagnosis. Additionally, as mentioned above, any under-diagnosis, or misdiagnosis, of metastatic disease site should be equal across groups and would not affect the identified disparities.

5. Conclusions

In spite of consensus guidelines to the contrary, ePCR was performed in over half of elderly patients with synchronous colon cancer and untreated hepatic metastases in 2011. Significant disparities exist in the use of ePCR. While older patients appear more likely to undergo ePCR, this may be related to lower use of chemotherapy. Those elderly patients who do not get chemotherapy get ePCR more often. Older patients should be carefully considered for systemic chemotherapy and/or palliative care as opposed to surgical resection in order to avoid the morbidity of aggressive surgical resection when no cure is possible.

Patients from poor and rural areas were more likely to undergo ePCR. This may reflect lack of access to specialists and chemotherapy, and may also indicate a lack of dispersion of current recommendations. Increased access to specialist care and increased dispersion of evidence-based recommendations are needed to address this alarming disparity. It is recognized, however, that retrospective data cannot fully identify all the of the nuanced clinical decision-making that goes into the decision for ePCR. Further study is needed to determine why these differences continue to exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.11.010.

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