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Socioeconomic determinants of the surgical treatment of colorectal liver metastases

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ABSTRACT

Objective: We hypothesized that differences in resection rates of colorectal liver metastases exist based on socioeconomic status (SES) inequalities.
Methods: The NCDB was utilized to study patients of different median household income diagnosed with colon adenocarcinoma from 2010 to 2015.
Results: A total of 21,258 patients met inclusion criteria, of whom 3,587 (16.9%) underwent metastasectomy. Patients of the highest income quartile were more likely to undergo metastasectomy compared to the lowest quartile (OR 1.20, CI 1.07–1.37, $p = 0.003$). Overall, patients in the highest income quartile had a median OS of 17.1 months compared with 13.0 months for the lowest quartile (HR 0.85, CI 0.81–0.90, $p < 0.001$). While metastasectomy was associated with improved OS across all groups, the disparity by income quartile widened (29.2 vs. 22.0 months, respectively; HR 0.51, CI 0.49–0.54, $p < 0.001$).
Conclusion: Higher income patients were more likely to undergo metastasectomy compared with lower income patients and were associated with longer OS.

Introduction

Colorectal cancer is the second leading cause of cancer death in the United States.[1] While survival has improved in recent years, the improvement has not been uniform across the population.[2,3] There are substantial socioeconomic disparities in colorectal cancer survival in the United States and Europe, with lower disease-specific survival and overall survival (OS) consistently demonstrated in patients with lower socioeconomic status (SES).[4,5] Although the underlying reasons for these findings are not fully understood, differences in colorectal cancer treatment by SES have also been demonstrated.[5] Poorer patients tend to have delayed treatment following diagnosis and have been shown to undergo less aggressive treatment, with lower rates of curative-intent surgery and adjuvant therapy.[5,6]

One fifth of patients newly diagnosed with colorectal cancer have synchronous metastases to the liver.[7,8] A metastasectomy in suitable patients is the only curative option for colorectal liver metastases (CRLM) with 5-year survival rates following metastasectomy reported to be as high as 70%.[9] The complexity of CRLM treatment poses potential barriers to access due to need for appropriate referrals and geographic concentration of specialist care. In a large population-based study in Sweden, neither income nor education were found to be associated with odds of undergoing liver resection for CRLM.[10] In contrast, in a national database study from the United Kingdom, socioeconomic deprivation was found to be associated with lower rates of liver resection and subsequent decreased 3-year survival.[11]

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There are relatively limited data regarding the effect of SES on rates of CRLM resection and subsequent survival in the United States. A previous study using the Nationwide Inpatient Sample database found that rates of metastectomy correlated with insurance status; patients who underwent resection were more likely to have private insurance.[12] However, long-term outcomes following metastasectomy were not evaluated. As CRLM resection is considered standard of care when feasible, it is important to understand what, if any, treatment disparities exist, in order to appropriately address treatment variability beyond surgical candidacy. The aim of this paper is to determine whether rates of liver metastasectomy differ by SES as measured by income quartile in the United States, and then evaluate the impact of SES and liver resection on OS.

Methods

Study design

The National Cancer Database (NCDB) was analyzed to retrospectively study patients diagnosed with colon adenocarcinoma from 2010 to 2015.[13] The NCDB is a prospectively collected database created by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It captures 70% of all new cancer diagnoses within the United States. The diagnosis of colon adenocarcinoma was confirmed using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), histology code 8140 was used.[14] Only patients with synchronous metastases to the liver were included. Patients were excluded if they did not have metastatic disease or if their clinical stage was unknown. Additional exclusion criteria included extrahepatic metastatic disease, history of prior malignancy, unknown survival data, and unknown income status. This study was exempt from Institutional Review Board review due to the de-identified nature of the database. The primary outcome measured was the rate of resection of liver metastases across income quartile. The principal secondary outcome was OS.

Variable definitions

Patient demographics and clinical characteristics available within NCDB include age, sex, race, insurance status, Charlson/Deyo Comorbidity Score (CDCC),[15] and carcinoembryonic antigen (CEA) level. Facility-level data captured within NCDB include facility type (academic, community hospital, integrated network) and hospital setting (metropolitan, urban, rural). Patient SES was quantified by income level. Income level data within NCDB are derived from the 2012 American Community Survey, which compiles data on median household income for each patient's zip code between 2008 and 2012. Income level is divided by quartile (quartile 1 less than $38,000, quartile 2 $38,000-$47,999, quartile 3 $48,000-$62,999, quartile 4 $63,000+). Education level is separated into quartiles and identifies the proportion of adults within the patient's zip code who did not graduate from high school (quartile 1 21% or more, quartile 2 13–20.9%, quartile 3 7–12.9%, quartile 4 less than 7%). These data were again obtained from the 2012 American Community Survey data between 2008 and 2012.

Statistical analysis

All statistical analyses were performed using Stata software®, version SE 15.0 (StataCorp, College Station, TX, USA). Continuous variables were compared with the student 2-sample *t*-test. Categorical variables were analyzed with the Pearson's chi-squared test. Median values are presented with interquartile range (IQR). All tests were 2-sided and statistical significance was accepted at the $p < 0.05$ level. Multivariable logistic regression was utilized to determine the odds ratio (OR) of undergoing liver resection. An adjusted cox regression analysis was used to analyze OS, which was modeled by use of a Kaplan Meier graph. Results of the logistic regression and cox analysis were reported as odds ratios (OR) and hazard ratios (HR), respectively, with corresponding 95% confidence intervals (CI) and p-values. Given that many determinants of SES (income, education, insurance) are inter-related, a test of multicollinearity was diagnosed by means of variance inflation factor (VIF). Any factor too identical to income was excluded from the logistic regression so as to not destabilize the study of interactions.[16] CEA level was excluded from all adjusted analyses due to one-third of values being unknown or unreported.

Results

Patient demographics

A total of 47,892 patients were diagnosed with new primary colon adenocarcinoma and synchronous liver metastases within the study period. Of those patients, 21,258 patients met inclusion criteria. The median age was 64 and 53% were male. The cohort was divided into 4 income quartiles. The 1st quartile was designated the lowest income group while the 4th quartile designated the highest. No significant difference in sex was identified between income groups. However, there were significant differences in the remaining demographics, including race, CDCC comorbidities, and CEA level (Table 1).

The highest income quartile was predominantly composed of white race patients at 81%, while white race only accounted for 52.5% of the lowest income quartile. The lowest quartile was 38.1% black race with only 9% black race in the highest income quartile ($p < 0.001$). Hispanic race comprised 7.4% of the lowest income quartile, and gradually decreased to 4.6% in the highest income quartile ($p < 0.001$). Patients in the highest income group had fewer comorbidities, with 76.9% CDCC 0 patients compared with 71.1% in the lowest income quartile. The lowest quartile had higher proportions of CDCC 1, 2, and 3+, compared to the other quartiles ($p < 0.001$). The highest income patients were more likely to have an elevated CEA level ($p < 0.001$).

Socioeconomic demographics

Additional socioeconomic variables were found to significantly vary across income quartile (Table 2). Patients in the highest and lowest quartile were most likely to receive care at an academic hospital while the middle two quartiles were more likely to be treated at a community hospital ($p < 0.001$). Patients in the highest income quartile received care in metropolitan hospitals 97.7% of the time compared to 70.7% of patients in the lowest income quartile. Lower income patients had a higher incidence of receiving care in either an urban (24.5% vs. 2.1% in highest group) or rural (4.8% vs. 0.2% in highest group) care setting ($p < 0.001$).

Almost half of the patients in the highest income quartile were privately insured (45.8%) compared to less than a third of patients in the lowest quartile (29.7%). The lowest quartile had higher rates of Medicaid (13.8% v. 5.5% in highest quartile) or did not have insurance (9.5% v. 3.8%; $p < 0.001$). Education levels also differed between income quartiles. The highest income quartile had the most number of patients in the highest education level quartile (56.3% vs. 1.0% in lowest quartile), while the lowest income quartile had the greatest number in the lowest education level quartile (57.1% vs. 1.2% in highest quartile; $p < 0.001$).

Table 1
Patient demographics.

Total (n = 21,258)	1st Quartile - Lowest (n = 4,284)	2nd Quartile (n = 5,149)	3rd Quartile (n = 5,535)	4th Quartile - Highest (n = 6,290)	*P* value
Male, n (%)	2,252 (52.6%)	2,774 (53.9%)	2,949 (53.3%)	3,262 (51.9%)	0.16
Age, yr, median (IQR)	63 (54–73)	64 (55–74)	64 (54–75)	64 (53–75)	**0.04**
Race, n (%)					
White	2,232 (52.5%)	3,900 (76.6%)	4,283 (78.4%)	5,014 (81.0%)	**<0.001**
Black	1,621 (38.1%)	779 (15.3%)	674 (12.3%)	559 (9.0%)	
Hispanic	316 (7.4%)	307 (6.0%)	320 (5.9%)	283 (4.6%)	
Asian	53 (1.3%)	94 (1.8%)	170 (3.1%)	326 (5.2%)	
American Indian	29 (0.7%)	15 (0.3%)	13 (0.3%)	11 (0.2%)	
Comorbidity, n (%)					
CDCC 0	3,047 (71.1%)	3,765 (73.1%)	4,156 (75.1%)	4,839 (76.9%)	**<0.001**
CDCC 1	873 (20.4%)	1,027 (20.0%)	1,006 (18.2%)	1,079 (17.2%)	
CDCC 2	247 (5.8%)	253 (4.9%)	248 (4.5%)	247 (3.9%)	
CDCC 3+	117 (2.7%)	104 (2.0%)	125 (2.3%)	125 (2.0%)	
CEA Level, n (%)					
Normal	2,723 (63.6%)	3,244 (63.0%)	3,415 (61.7%)	3,769 (59.9%)	**0.001**
Elevated	379 (8.8%)	528 (10.3%)	553 (10.0%)	674 (10.7%)	
Unknown	1,182 (27.6%)	1,377 (26.7%)	1,567 (28.3%)	1,847 (29.4%)	

yr, year; IQR, interquartile range; CDCC, Charlson-Deyo combined comorbidity score; CEA, carcinoembryonic antigen.

Resection rates

Of 21,258 patients, a total of 3,587 (16.9%) underwent resection of their liver metastases. Patients of the highest income quartile were more likely to undergo metastasectomy compared to the lowest quartile (18.4% vs. 15.0% of lowest quartile; p < 0.001; Table 3). When adjusted for patient demographics, patients in the highest income quartile were still more likely to undergo liver resection compared to patients in the lowest income quartile (adjusted OR 1.20, CI 1.07–1.37, p < 0.01; Table 4). Increased likelihood of metastasectomy was also associated with receiving care at a hospital in an urban setting (OR 1.20, CI 1.07–1.34, p < 0.01). Factors associated with a decreased likelihood of metastasectomy include age over 65, black or Hispanic race, elevated CDCC score, and care at either a community hospital or integrated network (Table 4).

Analysis of overall survival

Patients in the highest income quartile had a median OS of 17.1 months compared with 13.0 months for the lowest quartile (Table 3, p < 0.001). This remained significant after adjusting for patient and socioeconomic factors (adjusted HR 0.85, CI 0.81–0.90; p < 0.001; Table 5, Fig. 1). While metastasectomy was associated with improved OS across all groups, the disparity in OS by income quartile widened in patients who underwent surgical resection, with the highest income patients surviving a median of 29.2 months and the lowest income patients surviving 22.0 months (p < 0.001, Table 3). On multivariable regression analysis of patients who underwent metastasectomy, high income remained a significant predictor of survival (adjusted HR 0.66, CI 0.57–0.76, p < 0.001; Fig. 2). Metastasectomy, independent of income, was significantly associated with improved survival (HR 0.51, CI 0.49–0.54, p < 0.001, Table 5).

Multiple demographic factors were associated with survival on multivariable logistic regression. Age over 65 (HR 1.71, CI 1.66–1.77, p < 0.001) and female sex (HR 1.06, CI 1.03–1.10, p < 0.001) were associated with worse survival. Black race (HR 1.07, CI 1.02–1.12, p < 0.01) was associated with worse survival while Hispanic race was protective (HR 0.79, CI 0.73–0.85, p < 0.001). The associated

Table 2
Patient socioeconomic characteristics.

Total (n = 21,258)	1st Quartile - Lowest (n = 4,284)	2nd Quartile (n = 5,149)	3rd Quartile (n = 5,535)	4th Quartile - Highest (n = 6,290)	*P* value
Type of Hospital, n (%)					
Academic Center	1,417 (34.4%)	1,361 (27.4%)	1,603 (30.1%)	2,171 (36.0%)	**<0.001**
Community Hospital	2,277 (55.3%)	3,097 (62.3%)	3,111 (58.4%)	3,237 (53.6%)	
Integrated Network	421 (10.2%)	517 (10.4%)	609 (11.4%)	628 (10.4%)	
Hospital Setting, n (%)					
Metropolitan	3,000 (70.7%)	3,692 (73.2%)	4,761 (88.0%)	5,967 (97.7%)	**<0.001**
Urban	1,038 (24.5%)	1,216 (24.1%)	582 (10.8%)	129 (2.1%)	
Rural	205 (4.8%)	139 (2.8%)	66 (1.2%)	11 (0.2%)	
Insurance Coverage, n (%)					
None	398 (9.5%)	325 (6.4%)	326 (6.0%)	239 (3.8%)	**<0.001**
Private	1,251 (29.7%)	1,801 (35.6%)	2,115 (38.8%)	2,845 (45.8%)	
Medicaid	580 (13.8%)	501 (9.9%)	462 (8.5%)	342 (5.5%)	
Medicare	1.942 (46.1%)	2,371 (46.8%)	2,491 (45.7%)	2,748 (44.2%)	
Other	42 (1.0%)	64 (1.3%)	56 (1.0%)	42 (0.7%)	
Education Level, n (%)					
Quartile 1 - Lowest	2,448 (57.1%)	1,056 (20.5%)	526 (9.5%)	78 (1.2%)	**<0.001**
Quartile 2	1,526 (35.6%)	2,338 (45.4%)	1,654 (29.9%)	457 (7.3%)	
Quartile 3	269 (6.3%)	1,558 (30.3%)	32,601 (47.0%)	2,212 (35.2%)	
Quartile 4 - Highest	41 (1.0%)	197 (3.8%)	754 (13.6%)	3,543 (56.3%)	

Table 3
Rates of resection & overall survival.

Total (n = 21,258)	1st Quartile - Lowest (n = 4,284)	2nd Quartile (n = 5,149)	3rd Quartile (n = 5,535)	4th Quartile - Highest (n = 6,290)	*P* value
Resection of Liver Metastases, n (%)	644 (15.0%)	845 (16.4%)	940 (17.0%)	1,158 (18.4%)	**<0.001**
Overall Survival, m, median (IQR)	13 (3.5–26.1)	14.7 (3.8–27.9)	15 (4–29.3)	17.1 (5.3–31)	**<0.001**
Overall Survival of Patients with Liver Resection, m, median (IQR)	22 (10.1–36.5)	24.6 (11.6–38.9)	26 (13.8–39.6)	29.2 (16.9–44.6)	**<0.001**

m, months; IQR, interquartile range.

Table 4
Odds ratio of undergoing liver resection.

Variable	Odds Ratio	95% Confidence Limits	*P* value
Income Level			
Quartile 1 – Lowest	Reference		
Quartile 2	1.09	0.97–1.23	0.16
Quartile 3	1.13	1.01–1.27	**0.04**
Quartile 4 – Highest	1.20	1.07–1.37	**<0.01**
Age			
<65	Reference		
≥65	0.66	0.61–0.71	**<0.001**
Sex			
Male	Reference		
Female	1.07	0.99–1.16	0.08
Race			
White	Reference		
Black	0.74	0.66–0.83	**<0.001**
Hispanic	0.76	0.64–0.91	**<0.01**
Asian	0.89	0.72–1.11	0.32
American Indian	0.91	0.46–1.80	0.78
Comorbidity			
CDCC 0	Reference		
CDCC 1	1.03	0.94–1.14	0.50
CDCC 2	0.76	0.62–0.92	**<0.01**
CDCC 3+	0.49	0.34–0.69	**<0.001**
Facility Type			
Academic Center	Reference		
Community Hospital	0.55	0.51–0.60	**<0.001**
Integrated Network	0.70	0.61–0.79	**<0.001**
Hospital Setting			
Metropolitan	Reference		
Urban	1.20	1.07–1.34	**<0.01**
Rural	1.27	0.98–1.66	0.08

CDCC, Charlson-Deyo combined comorbidity score.

Table 5
Multivariable adjusted cox regression.

Variable	Hazard Ratio	95% Confidence Limits	*P* value
Income Level			
Quartile 1 – Lowest	Reference		
Quartile 2	0.97	0.92–1.02	0.20
Quartile 3	0.93	0.89–0.98	**<0.01**
Quartile 4 – Highest	0.85	0.81–0.90	**<0.001**
Age			
<65	Reference		
≥65	1.71	1.66–1.77	**<0.001**
Sex			
Male	Reference		
Female	1.06	1.03–1.10	**<0.001**
Race			
White	Reference		
Black	1.07	1.02–1.12	**<0.01**
Hispanic	0.79	0.73–0.85	**<0.001**
Asian	0.96	0.87–1.06	0.47
American Indian	0.99	0.74–1.33	0.94
Comorbidity			
CDCC 0	Reference		
CDCC 1	1.13	1.08–1.18	**<0.001**
CDCC 2	1.42	1.32–1.53	**<0.001**
CDCC 3+	1.87	1.69–2.08	**<0.001**
Facility Type			
Academic Center	Reference		
Community Hospital	1.15	1.11–1.20	**<0.001**
Integrated Network	1.14	1.08–1.21	**<0.001**
Hospital Setting			
Metropolitan	Reference		
Urban	1.00	0.96–1.05	0.89
Rural	1.06	0.94–1.18	0.34
Surgical Resection			
No resection	Reference		
Resection	0.51	0.49–0.54	**<0.001**

CDCC, Charlson-Deyo combined comorbidity score.

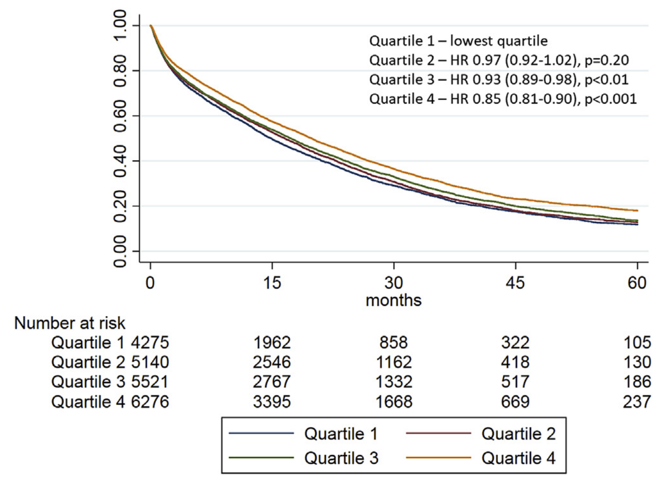

Fig. 1. Overall survival of patients with liver metastases.

worsening in survival increased with increasing CDCC score. Community hospitals (HR 1.15, CI 1.11–1.20, p < 0.001) and integrated networks (HR 1.14, 1.08–1.21, p < 0.001) were both associated with worse OS when compared to academic centers. No effect was seen with urban vs. rural hospital setting.

Discussion

The overarching aim of this paper was to determine whether rates of liver metastasectomy differed by SES as measured by income quartile in the United States. This study determined that higher income was associated with a greater likelihood of undergoing a metastasectomy for patients with colorectal adenocarcinoma with synchronous liver metastases. In addition, patients with a higher income had improved OS compared to low income patients (17.1 months vs. 13 months, respectively). Interestingly, when analyzing only patients who had undergone metastasectomy, the discrepancy in OS between income groups widened (29.2 months vs. 22 months), further highlighting the disparity between SES groups as defined by income, in addition to the potential anticipated benefit of metastasectomy.

Disparities in cancer treatment are well described. Low SES, lack of insurance, and black race have each been associated with decreased survival in patients with colorectal cancer.[17,18] However, the specific effect of disparities on rates of metastasectomy for patients with CRLM and the associated implications on OS have not been thoroughly explored in the modern era. The prognosis for patients with untreated CRLM is poor, where fewer than 30% of patients survive one year and less than 5% survive 5 years.[7] Munene and colleagues reported disparities in access to CRLM in the United States utilizing the Nationwide Inpatient Sample database.[12] Among their cohort of patients examined between 1993 and 2007, only 2.6% underwent metastasectomy. Concerning disparities in resection rates were found in blacks, Hispanics, and patients with Medicaid insurance compared to private insurance. Our work corroborates these findings by providing more recent data using an alternative source. While there has been a substantial increase in the overall rate of metastasectomy at 16.9%, there appears to be continuation of the concerning trends elucidated by their study. Resection rates of hepatic metastases in non-white minorities continue to be lower than resection rates among white patients (OR 0.74, {CI 0.66–0.83} in blacks and OR 0.76 {CI 0.64–0.91} in Hispanic patients). Income was also important, and was linearly correlated with the likelihood of resection as income levels rose.

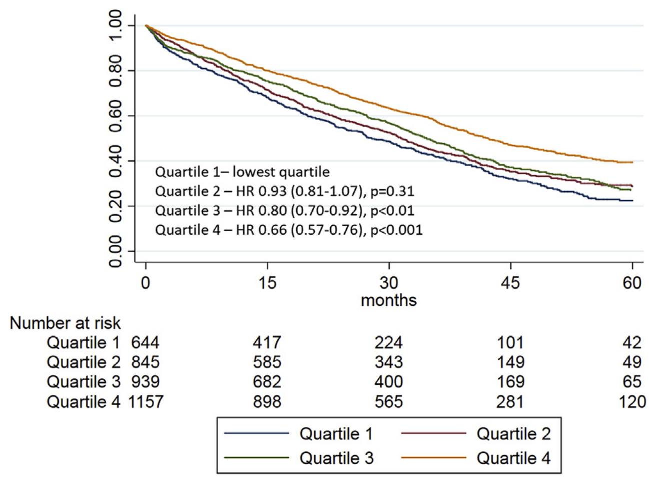

Fig. 2. Overall Survival of Patients who Underwent Metastasectomy.

Although Munene and colleagues reported an overall in-hospital mortality of 3.1% and identified Medicare insurance as an independent predictor of increased mortality,[12] our work extended beyond in-hospital mortality to evaluate oncologic outcomes in patients with CRLM. As patient SES, defined by rising income levels, improved, so did OS. Patients in the highest income quartile lived an average of 4 months longer than those in the lowest quartile. Among resected patients, this disparity widened to over 7 months. Interestingly, these survival disparities occurred despite higher income patients having a significantly higher CEA level at presentation.

Social inequalities in care are not limited to the United States. Vallance and colleagues reported similar findings in the British National Health System (NHS).[11] Interestingly, the authors reported a comparable hepatic resection rate of 16.2%. Their cohort was divided into quintiles based upon an SES "Index of Multiple Deprivation". The authors showed that patients in the 'least deprived' quintile were more likely to undergo metastasectomy (OR 1.42 CI 1.18–1.70) compared to the 'most deprived' patients, in keeping with our findings. Several theories were proposed to justify the presence of the disparity within the NHS, and predominantly included access to care and specialists that was driven by SES inequality.[19] Lejeune and colleagues also separately reported that low SES was associated with delayed treatment in the NHS.[6] The authors demonstrated that low SES patients with colorectal cancer were less likely to receive treatment within 6 months of diagnosis when compared to patients of higher SES. Interestingly, the authors showed that there was no difference in OS among patients of varying SES levels who underwent treatment within 1 month of diagnosis, supporting, once again, general early access as an important determinant of prognosis.

Given the OS difference noted among the entire cohort (not just resected patients), the difference in OS cannot be attributed solely to metastasectomy. This finding suggests that SES level itself may be an important determinant for survival. This supports prior work that suggests that lower SES is an important variable contributing to inferior survival rates of black patients compared to white patients.[18] In that report by White and colleagues, the authors confirmed the presence of persistent racial disparities in survival even after controlling for numerous tumor and treatment specific variables, including tumor stage, tumor grade, hospital type, and hospital teaching status. Therefore, while the goal for equivalence in rates of metastasectomy between races is ideal, it may not be sufficient. While, the reason for these disparities appears to be multifactorial, SES, determined by education, insurance and income level, is a prominent determinant in patient survival.

There are limitations to this study. The principal limitation is the lack of additional variables within the NCDB database. Most notably this includes the inability to further characterize the extent of liver metastases. Variables such as number of metastases, size of metastases, and unilobar versus bilobar spread would certainly aid in the interpretation of the results as these variables are utilized in the determination of which patients can undergo a metastasectomy. Additionally, the type of liver resection (i.e. segmentectomy, lobectomy) is unknown. Finally, this database currently records only OS and does not include disease-free survival or disease-specific survival.

Conclusion

For patients diagnosed with colon adenocarcinoma and synchronous metastases to the liver, higher income patients were more likely to undergo metastasectomy compared with lower income patients and were associated with improved OS. Furthermore, among resected patients, the discrepancy in survival widened across income groups. These findings, which may be secondary to inconsistencies in referral and management patterns of patients of variable SES, warrant urgent examination.

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