Original Article

Is metastasectomy a worthy option?—the role of surgery in metastatic colon cancer to liver and lungs

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Background: The role of surgery and metastasectomy is controversial in the treatment of stage IV colon cancer (CC). The aim of this study was to investigate the relationship between primary tumor resection (PTR) with metastasectomy and survival in patients diagnosed with metastatic CC.

Methods: The National Cancer Data Base (NCDB) was retrospectively queried for patients diagnosed with colon adenocarcinoma from 2004 to 2013. Patient demographics, clinical characteristics, and short-term outcomes were collected. Groups were generated based on if surgery was performed and, if so, was metastasectomy involved. Associations between groups were evaluated using Kruskal-Wallis and Pearson Chi-square tests. Overall survival (OS) was summarized using standard Kaplan-Meier methods. The association between surgical group and OS was evaluated using the log-rank test.

Results: Of 31,172 patients, 13,214 (42.4%) had surgery while 17,958 (57.6%) did not. Among these, 81.3% of patients had liver metastases only, while 18.7% of patients had both liver and lung metastases. Median OS was 15.1 months (95% CI: 14.8 to 15.5 months) for the entire cohort. However, median OS was significantly better for those who had surgery (either PTR alone or PTR with metastasectomy) compared to those who did not (21.8 *vs.* 7.5 months, P<0.001). Patients who received PTR with metastasectomy had worse median OS (20.5 *vs.* 21.8 months, P=0.035) compared to those who only received PTR (P=0.211).

Conclusions: PTR in select patients diagnosed with metastatic CC provides a remarkable improvement to survival rate. The role of metastasectomy remains controversial as no difference in survival outcomes exists between patients who received it and who did not.

Keywords: Colon cancer (CC); metastasectomy; surgery; overall survival (OS); National Cancer Data Base (NCDB)

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Introduction

In 2014, 139,992 patients received a new diagnosis of colorectal cancer (CRC) in the United States and an additional 140,250 are expected in 2018; moreover, CRC is one of the most common causes of cancer death in both women and men (1). Thanks to the improvement of CRC screening programs, it has been possible for physicians to detect tumors at earlier stages (2,3). However, approximately 21% of new CRC cases are diagnosed at stage IV, for which

the 5-year overall survival (OS) is 13% (4).

In recent years, several studies have been conducted in order to assess and refine systemic regimens for advanced and metastatic colon cancer (CC) (5-7). There is consensus regarding the use of a multidisciplinary approach to treat stage II and III CC (8); however, the role of surgery and especially metastasectomy is still controversial for treating stage IV CC (with the exception of symptomatic/palliative treatment), and discrepancies exist between guidelines and surgical practice (9,10). Some authors have found that both primary tumor resection (PTR) and metastasectomy—in addition to systemic therapy—improve the 5-year OS for metastatic CC from 20% to 50% (11,12).

The aim of this study was to compare survival rate in patients diagnosed with CC metastatic to liver with or without lung metastases who received surgery versus those who did not; subsequently we aimed to evaluate whether performing metastasectomy in addition to PTR improves OS.

Methods

Patients

The National Cancer Data Base (NCDB) was retrospectively queried for patients diagnosed with colon adenocarcinoma between 2004 and 2013. Further inclusion criteria were pathological stage IV with liver metastasis and known status of lung metastasis. Lastly, only patients with known surgery status were included in the study. Patients with histology different from adenocarcinoma, carcinoma *in situ*, and more than 1 recorded malignancy were excluded from the analysis. Pathological stage I, II, III and IV with brain or bone metastasis were excluded as well. *Figure 1* summarizes the adopted inclusion and exclusion criteria. As this study utilized a nationwide, de-identified database, it was deemed exempt from the Institutional Review Board.

The following patient-specific characteristics were collected: age, gender, race, Hispanic ethnicity, education level, income, insurance status, area of residence and Charlson-Deyo score as a measure of comorbidity status. The tumor-related characteristics included primary site, preoperative carcinoembryonic antigen (CEA) levels, tumor grade, size, pathological T and N stage (7th edition AJCC staging), K-RAS status, presence of perineural and lymph-vascular invasion, and number of positive regional nodes. Treatment and outcome-related variables included margins status, number of regional nodes examined, administration of chemotherapy and radiotherapy, type of palliative care, facility type, length of stay, 30- and 90-day mortality, readmission, and vital status.

Statistical analysis

In our first analysis, patients were divided in 2 groups based on whether surgery was performed. Subsequently, patients who received surgery were divided in 2 groups based on whether metastasectomy was performed in addition to PTR. The associations of patient characteristics and short-term outcomes with groups were evaluated using the Kruskal-Wallis and Pearson Chi-square tests, as appropriate. OS was summarized by surgical group using standard Kaplan-Meier methods, where estimates of the median survival were obtained with 95% confidence intervals. The association between surgical group and OS was evaluated using the log-rank test. Statistically significant variables were subsequently included in a multivariate analysis and hazard ratio (HR) and its corresponding 95% CI were calculated for overall sample and stratified by group. All analyses were conducted in SAS v9.4 (Cary, NC, USA) at a significance level of 0.05.

Results

A total of 31,172 patients were included in the analysis after the application of the inclusion and exclusion criteria.

Analysis of the main cohort

The overall patient characteristics and short-term outcomes are summarized in *Table 1*. *Figure 2* shows the Kaplan-Meier curve for OS of both surgery and non-surgery groups. The median survival for all patients was 15.1 months, patients who underwent surgery survived longer compared to those who did not (P<0.001).

The results of the multivariate model used to calculate the HR for each variable are shown in *Table 2*. Patient characteristics significantly associated with better survival rate were Hispanic ethnicity, higher education and income, being covered by a private insurance, and residing in a metropolitan area. Conversely older patients who had a comorbidity score of 1 or more were associated with poorer outcomes. Undergoing surgery and/or receiving chemotherapy were associated with better survival outcomes, while radiation therapy was found not significant. When looking at tumor characteristics, better survival outcomes were observed in patients who had their

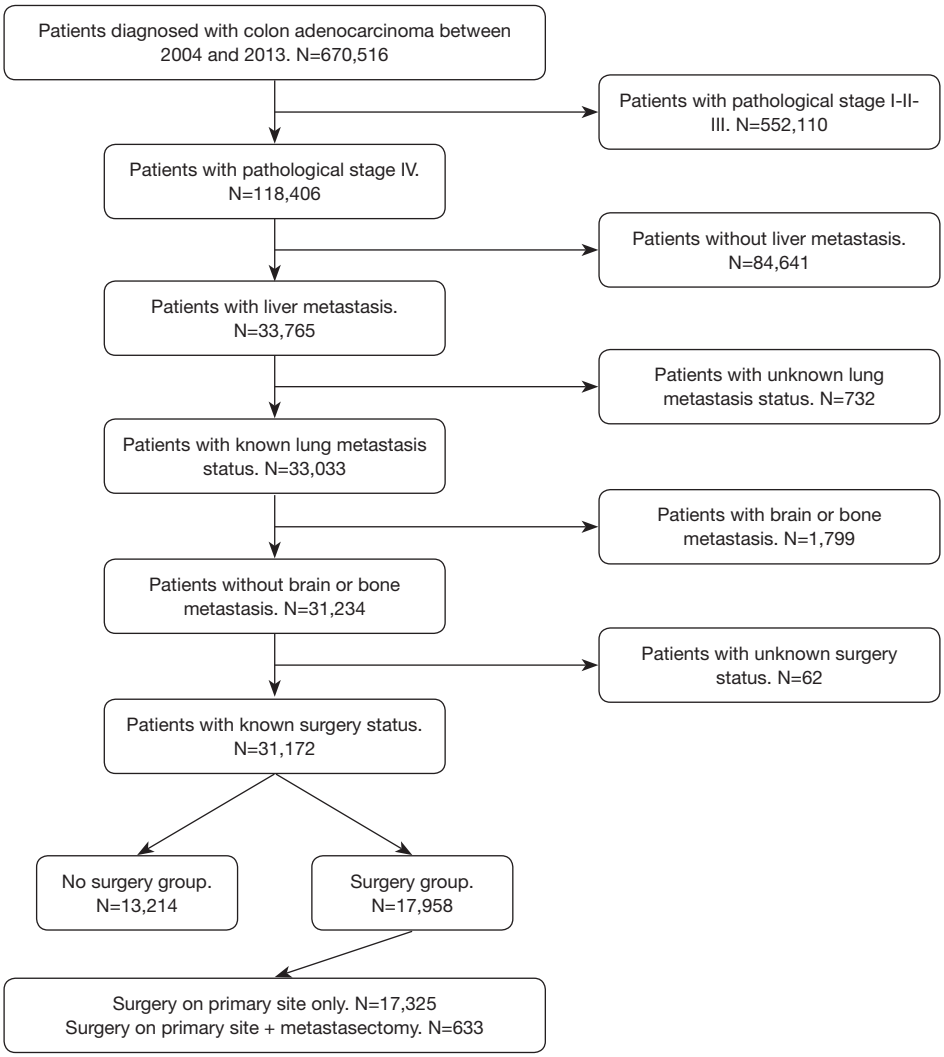


Figure 1 Flow chart showing the inclusion and exclusion criteria used to select patients.

primary tumor located in either the descending colon or the appendix, and who had more than 15 lymph nodes examined; on the contrary, patients with positive lymph nodes and lung metastasis had worse outcomes.

Analysis on surgical sub-cohort

Specific characteristics and short-term outcomes for surgical patients are summarized in *Table 3*. *Figure 3* shows the Kaplan-Meier curve for OS of both metastasectomy and non-metastasectomy groups. Patients who received PTR alone survived longer compared to those who underwent PTR and metastasectomy (P=0.035).

The results of the multivariate model used to calculate the HR for each variable are shown in *Table 4*. Patient characteristics associated with better survival rate were Hispanic ethnicity, higher income and being covered by a private insurance. Conversely, older patients who had a comorbidity score of 1 or more were associated with poorer outcomes. Tumor and treatment specific outcomes associated with better survival were the amount of regional nodes examined higher than 14, receiving chemotherapy, being treated at an academic center and not being readmitted unless planned. On the contrary, patients with regional nodes positive and lung metastasis were associated with poorer outcome. Furthermore, patients who had their primary tumor located in the descending colon were more likely to survive compared to those who had it in

Table 1 Baseline patient characteristics and short-term outcomes for overall patients

Variable	Subgroup	No surgery (n=13,214)	Surgery (n=17,958)	P value
Age	Mean/Std/N	66.7/13.8/13,214	63.9/13.5/17,958	<0.001
Gender	Female	6,326 (47.9%)	8,466 (47.1%)	0.202
	Male	6,888 (52.1%)	9,492 (52.9%)	
	Missing	–	–	
Race	Asian	410 (3.1%)	560 (3.1%)	<0.001
	Black	2,534 (19.2%)	2,858 (15.9%)	
	Other	100 (0.8%)	106 (0.6%)	
	White	10,043 (76.0%)	14,307 (79.7%)	
	Missing	127 (1.0%)	127 (0.7%)	
Ethnicity	Hispanic	779 (5.9%)	978 (5.4%)	0.080
	Not Hispanic	11,882 (89.9%)	16,267 (90.6%)	
	Missing	553 (4.2%)	713 (4.0%)	
Distance	Mean/Std/N	23.6/95.7/13,070	29.2/114.1/17,803	<0.001
Education	<14%	4,091 (31.0%)	5,794 (32.3%)	0.056
	14–20%	2,969 (22.5%)	4,026 (22.4%)	
	20–29%	3,205 (24.3%)	4,212 (23.5%)	
	>29%	2,525 (19.1%)	3,325 (18.5%)	
	Missing	424 (3.2%)	601 (3.3%)	
Income	<30	2,019 (15.3%)	2,711 (15.1%)	0.334
	30–35	2,427 (18.4%)	3,287 (18.3%)	
	35–46	3,636 (27.5%)	4,804 (26.8%)	
	>46	4,710 (35.6%)	6,557 (36.5%)	
	Missing	422 (3.2%)	599 (3.3%)	
Insurance	Medicaid	1,198 (9.1%)	1,477 (8.2%)	<0.001
	Medicare	6,894 (52.2%)	8,213 (45.7%)	
	None	878 (6.6%)	933 (5.2%)	
	Other	96 (0.7%)	183 (1.0%)	
	Private	3,920 (29.7%)	6,890 (38.4%)	
	Missing	228 (1.7%)	262 (1.5%)	
Area of residence	Metro	10,759 (81.4%)	14,192 (79.0%)	<0.001
	Urban	1,837 (13.9%)	2,851 (15.9%)	
	Rural	242 (1.8%)	404 (2.2%)	
	Missing	376 (2.8%)	511 (2.8%)	
Charlson-Deyo[a]	0	9,621 (72.8%)	13,257 (73.8%)	<0.001
	1	2,492 (18.9%)	3,585 (20.0%)	
	2	1,101 (8.3%)	1,116 (6.2%)	
	Missing	–	–	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Subgroup	No surgery (n=13,214)	Surgery (n=17,958)	P value
Primary site	Appendix	74 (0.6%)	236 (1.3%)	<0.001
	Left	4,651 (35.2%)	7,177 (40.0%)	
	Overlapping/NOS	2,739 (20.7%)	820 (4.6%)	
	Right	4,904 (37.1%)	8,193 (45.6%)	
	Transverse	846 (6.4%)	1,532 (8.5%)	
	Missing	–	–	
CEA[b]	Elevated	9,041 (68.4%)	10,404 (57.9%)	<0.001
	Normal	774 (5.9%)	2,224 (12.4%)	
	Missing	3,399 (25.7%)	5,330 (29.7%)	
Tumor size	Mean/Std/N	686.6/445.3/13,214	123.8/247.9/17,958	<0.001
Tumor grade	Well	471 (3.6%)	1,036 (5.8%)	<0.001
	Moderate	4,584 (34.7%)	11,222 (62.5%)	
	Poor	1,548 (11.7%)	4,017 (22.4%)	
	Undifferentiated	91 (0.7%)	690 (3.8%)	
	Missing	6,520 (49.3%)	993 (5.5%)	
Pathological T stage	pT0	–	57 (0.3%)	
	pT1	–	118 (0.7%)	
	pT2	–	610 (3.4%)	
	pT3	–	9,625 (53.6%)	
	pT4	–	6,623 (36.9%)	
	Missing	–	925 (5.2%)	
Pathological N stage	pN0	–	2,826 (15.7%)	
	pN1	–	6,049 (33.7%)	
	pN2	–	8,114 (45.2%)	
	Missing	–	969 (5.4%)	
KRAS	Mutated	1,615 (12.2%)	3,087 (17.2%)	0.297
	Normal	2,002 (15.2%)	3,665 (20.4%)	
	Missing	9,597 (72.6%)	11,206 (62.4%)	
Tumor deposits	Mean/Std/N	0.4/4.5/1,147	0.9/3.7/12,259	<0.001
Perineural invasion	No	2,108 (16.0%)	10,407 (58.0%)	<0.001
	Yes	82 (0.6%)	4,817 (26.8%)	
	Missing	11,024 (83.4%)	2,734 (15.2%)	
Lymph-vascular invasion	No	1,190 (9.0%)	5,970 (33.2%)	<0.001
	Yes	192 (1.5%)	9,625 (53.6%)	
	Missing	11,832 (89.5%)	2,363 (13.2%)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Subgroup	No surgery (n=13,214)	Surgery (n=17,958)	P value
Lung metastasis	No	9,577 (72.5%)	15,767 (87.8%)	<0.001
	Yes	3,637 (27.5%)	2,191 (12.2%)	
	Missing	–	–	
Regional nodes examined	Mean/Std/N	4.4/20.1/13,214	20.0/14.9/17,958	<0.001
Regional nodes positive	Mean/Std/N	96.4/12.5/13,214	8.9/19.6/17,958	<0.001
Length of stay	Mean/Std/N	5.7/15.5/169	7.9/8.4/15,820	<0.001
Margins	Negative	–	13,696 (76.3%)	<0.001
	Positive	–	3,579 (19.9%)	
	Missing	–	683 (3.8%)	
Surgical procedure	Local	–	894 (4.98%)	
	Partial	–	13,995 (77.93%)	
	Total	–	750 (4.18%)	
	Missing	–	2,319 (12.91%)	
Chemotherapy	No	4,849 (36.7%)	4,499 (52.1%)	<0.001
	Yes	7,949 (60.2%)	12,791 (71.2%)	
	Missing	416 (3.1%)	668 (3.7%)	
Radiation	No	12,827 (97.1%)	17,375 (96.8%)	0.041
	Yes	248 (1.9%)	397 (2.2%)	
	Missing	139 (1.1%)	186 (1.0%)	
Palliative care	Chemotherapy	1,032 (7.8%)	823 (4.6%)	<0.001
	Combination	352 (2.7%)	250 (1.4%)	
	None	11,204 (84.8%)	16,503 (91.9%)	
	Pain management	265 (2.0%)	58 (0.3%)	
	Radiation	58 (0.4%)	40 (0.2%)	
	Surgery	300 (2.3%)	281 (1.6%)	
	Missing	3 (0.0%)	3 (0.0%)	
Facility type	Academic	4,490 (34.0%)	5,153 (28.7%)	<0.001
	Community	1,698 (12.9%)	2,587 (14.4%)	
	Comprehensive	5,754 (43.5%)	8,335 (46.4%)	
	Integrated	865 (6.5%)	1,208 (6.7%)	
	Missing	407 (3.1%)	675 (3.8%)	
Readmission[c]	Not-unplanned	12,984 (98.3%)	16,386 (91.2%)	<0.001
	Unplanned	159 (1.2%)	1,177 (6.6%)	
	Missing	71 (0.5%)	395 (2.2%)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Subgroup	No surgery (n=13,214)	Surgery (n=17,958)	P value
30-day mortality	No	124 (0.9%)	12,430 (69.2%)	0.352
	Yes	12 (0.1%)	907 (5.1%)	
	Missing	13,078 (99.0%)	4,621 (25.7%)	
90-day mortality	No	107 (0.8%)	11,332 (63.1%)	0.023
	Yes	29 (0.25)	1,910 (10.6%)	
	Missing	13,078 (99.0%)	4,716 (26.3%)	
Vital status	Dead	7,642 (57.8%)	8,573 (47.7%)	<0.001
	Alive	1,839 (13.9%)	5,051 (28.1%)	
	Missing	3,733 (28.3%)	4,334 (24.1%)	

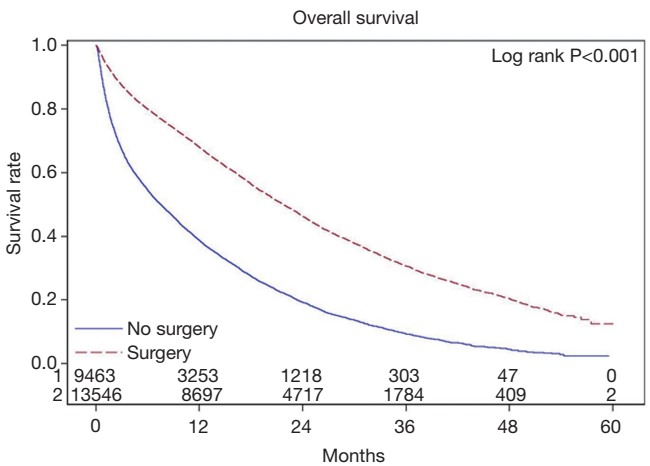
[a], Charlson-Deyo comorbidity score is an estimate of comorbid conditions based on ICD-9 diagnosis codes. A score of 0 indicates no comorbidities. Point values are assigned to comorbid conditions based on severity. The NCDB truncates possible scores to 0, 1 and 2 due to the small proportion of cases exceeding a score of 2; [b], carcinoembryonic antigen; [c], not-unplanned = planned readmission (n=653; 3.5%) + no readmission (n=28,717; 96.5%).

the ascending colon; the other sections of the colon were instead not significantly different in terms of survival. Ultimately receiving metastasectomy in addition to PTR was not associated with either lower or higher risk of death.

Discussion

In this retrospective analysis of the NCDB we report that PTR can be performed safely and is associated with improved survival—compared to systemic treatment only—for select patients with metastatic CC. The role of metastasectomy, however, is still not clear as no difference was found in our results.

Current clinical practice guidelines recommend that surgical resection of both primary tumor and metastases should be based on a multidisciplinary approach, but it is feasible and appropriate when tumor regression is obtained through systemic therapy. However, in the setting of unresectable stage IV disease, surgical approach is not indicated unless symptoms or complications related to the primary tumor occur (13). Multiple studies analyzed this aspect and reported that in select patients, PTR is associated with improved OS in association with systemic therapy (14,15), potentially even when performed as the first treatment step (16). However there is no consensus on the role of PTR as routine treatment for unresectable stage IV CC; several other studies reported increased morbidity and mortality and no improvement in OS for surgical patients (17,18). Furthermore there is a high risk that the improvement in OS reported by some studies was affected by selection bias and/or confounders because patients who are candidates for surgery are usually associated with less comorbidities, better performance status, less metastatic burden and, therefore, better chances to receive palliative systemic therapy (18).



	Median Survival (months)
Surgery	21.8 (21.2, 22.3)
No Surgery	7.5 (7.1, 7.9)
Overall	15.1 (14.8, 15.5)

Figure 2 Kaplan-Meier curve showing 5-year overall survival for surgery and no surgery groups.

Table 2 Multivariate analysis with hazard ratio and the corresponding 95% CI for overall sample

Variable	Subgroup	Hazard ratio and 95% CI	P value
Primary tumor resection	No	–	<0.001
	Yes	0.53 (0.47, 0.59)	
Age (1-year increase)		1.02 (1.02, 1.02)	<0.001
Gender	Male	–	0.080
	Female	0.97 (0.94, 1.00)	
Race	White	–	0.046
	Asian	0.90 (0.81, 1.00)	
	Black	1.03 (0.98, 1.08)	
	Other	0.84 (0.65, 1.09)	
Ethnicity	Non-Hispanic	–	<0.001
	Hispanic	0.78 (0.71, 0.85)	
Distance (1-mile increase)		1.00 (1.00, 1.00)	0.109
Education	<14%	–	0.002
	14–20%	1.03 (0.98, 1.08)	
	20–29%	0.96 (0.91, 1.02)	
	>29%	0.91 (0.85, 0.98)	
Income	<30	–	<0.001
	30–35	0.93 (0.88, 0.99)	
	35–46	0.94 (0.88, 1.00)	
	>46	0.85 (0.79, 0.91)	
Insurance	Uninsured	–	<0.001
	Medicaid	1.06 (0.97, 1.17)	
	Medicare	0.93 (0.86, 1.02)	
	Other	1.05 (0.85, 1.29)	
	Private	0.90 (0.83, 0.98)	
Area of residence	Rural	–	0.008
	Metro	0.85 (0.75, 0.95)	
	Urban	0.89 (0.79, 1.00)	
Charlson-Deyo[a]	0	–	<0.001
	1	1.09 (1.04, 1.14)	
	2	1.34 (1.26, 1.42)	
Primary site	Transverse	–	<0.001
	Appendix	0.75 (0.60, 0.93)	
	Left	0.78 (0.73, 0.84)	
	Overlapping/NOS	1.00 (0.93, 1.09)	
	Right	1.05 (0.98, 1.12)	

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Subgroup	Hazard ratio and 95% CI	P value
Lung metastasis	No	–	<0.001
	Yes	1.29 (1.24, 1.35)	
Regional nodes examined	0	–	<0.001
	1–14	1.02 (0.92, 1.13)	
	15+	0.84 (0.77, 0.93)	
Regional nodes positive	0	–	<0.001
	>0 positive nodes	1.63 (1.53, 1.74)	
Chemotherapy	No	–	<0.001
	Yes	0.33 (0.32, 0.34)	
Radiation	No	–	0.105
	Yes	0.91 (0.80, 1.02)	
Facility type	Integrated	–	<0.001
	Academic	0.84 (0.78, 0.90)	
	Community	0.99 (0.91, 1.07)	
	Comprehensive	1.02 (0.96, 1.10)	
Readmission	Unplanned	–	<0.001
	Not-unplanned	0.76 (0.70, 0.82)	

[a], Charlson-Deyo comorbidity score is an estimate of comorbid conditions based on ICD-9 diagnosis codes. A score of 0 indicates no comorbidities. Point values are assigned to comorbid conditions based on severity. The NCDB truncates possible scores to 0, 1 and 2 due to the small proportion of cases exceeding a score of 2.

Lung and/or liver metastasectomy has been reported beneficial for eligible patients who undergo a multidisciplinary evaluation aiming to define an individualized treatment strategy (19,20). In select patients, it is in fact associated with improved survival rate (21) and repeated metastasectomy has been demonstrated a valid option as well (22,23).

Our results show that PTR improves survival outcomes for patients with stage IV CC. Patients who underwent surgery had in fact 47% lower risk of death; their median survival was also considerably higher compared to patients who did not receive surgery.

When looking at patients who underwent surgery (either PTR alone or PTR with metastasectomy), no difference was found between the 2 groups regarding mortality. Conversely, median survival was statistically significant in favor of patients who did not receive metastasectomy. However, this finding might not have a relevant clinical significance; it would be expected, in fact, that patients undergoing PTR with metastasectomy have a higher mortality rate due to the more extensive treatment they receive and the related complications and side effects. It is possible that surgeons selected patients who were healthy enough to tolerate surgery with minimal distant metastatic disease. Unfortunately, NCDB does not capture this information which makes this aspect difficult to evaluate. Additionally, there may also be statistical limitations given the small sample in the metastasectomy group. Thus, the role of metastasectomy still remains unclear and hardly generalizable. The decision on whether a patient with stage IV CC receives extensive surgery should be based on the clinical characteristics of the individual and a multidisciplinary approach (13).

Noticeable findings were found with regards of multiple demographic characteristics. Patient with higher level of education who resided in a metropolitan area had better survival outcomes in the overall cohort, while higher income, being covered by a private insurance and receiving care in an academic center were associated with lesser risk of death in both overall and surgical cohorts. This highlights the potential presence of healthcare disparities for patients

Table 3 Baseline patient characteristics and short-term outcomes for surgical groups

Variable	Subgroup	Primary tumor resection (n=17,325)	Primary tumor resection + metastasectomy (n=633)	P value
Age	Mean/Std/N	63.94/13.56/17,325	64.31/13.03/633	0.416
Gender	Female	8,160 (47.1%)	306 (48.3%)	0.539
	Male	9,165 (52.9%)	327 (51.7%)	
	Missing	–	–	
Race	Asian	540 (3.1%)	20 (3.2%)	0.806
	Black	2,764 (16.0%)	94 (14.8%)	
	Other	101 (0.6%)	5 (0.8%)	
	White	13,797 (79.6%)	510 (80.6%)	
	Missing	123 (0.7%)	4 (0.6%)	
Ethnicity	Hispanic	938 (5.4%)	40 (6.3%)	0.357
	Not Hispanic	15,693 (90.6%)	574 (90.7%)	
	Missing	694 (4.0%)	19 (3.0%)	
Distance	Mean/Std/N	29.21/114.39/17,173	27.66/104.72/630	0.129
Education	14–20%	3,892 (22.5%)	134 (21.2%)	0.251
	20–29%	4,050 (23.4%)	162 (25.6%)	
	<14%	5,607 (32.4%)	187 (29.5%)	
	>29%	3,198 (18.5%)	127 (20.1%)	
	Missing	578 (3.3%)	23 (3.6%)	
Income	30–35	3,164 (18.3%)	123 (19.4%)	0.795
	35–46	4,633 (26.7%)	171 (27.0%)	
	<30	2,615 (15.1%)	96 (15.2%)	
	>46	6,337 (36.6%)	220 (34.8%)	
	Missing	576 (3.3%)	23 (3.6%)	
Insurance	Medicaid	1,420 (8.2%)	57 (9.0%)	0.040
	Medicare	7,906 (45.6%)	307 (48.5%)	
	None	911 (5.3%)	22 (3.5%)	
	Other	172 (1.0%)	11 (1.7%)	
	Private	6,665 (38.5%)	225 (35.5%)	
	Missing	251 (1.4%)	11 (1.7%)	
Area of residence	Metro	13,696 (79.1%)	496 (78.4%)	0.308
	Rural	393 (2.3%)	11 (1.7%)	
	Urban	2,738 (15.8%)	113 (17.9%)	
	Missing	498 (2.9%)	13 (2.1%)	
Charlson-Deyo[a]	0	12,786 (73.8%)	471 (74.4%)	0.196
	1	3,471 (20.0%)	114 (18.0%)	

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Subgroup	Primary tumor resection (n=17,325)	Primary tumor resection + metastasectomy (n=633)	P value
	2	1,068 (6.2%)	48 (7.6%)	
	Missing	–	–	
Primary site	Appendix	226 (1.3%)	10 (1.6%)	0.123
	Left	6,917 (39.9%)	260 (41.1%)	
	Overlapping/NOS	797 (4.6%)	23 (3.6%)	
	Right	7,922 (45.7%)	271 (42.8%)	
	Transverse	1,463 (8.4%)	69 (10.9%)	
	Missing	–	–	
CEA[b]	Elevated	10,069 (58.1.4%)	335 (52.9%)	0.880
	Normal	2,151 (12.4%)	73 (11.5%)	
	Missing	5,105 (29.5%)	225 (35.5%)	
Tumor size	Mean/Std/N	123.30/247.25/17,325	137.29/265.82/633	0.105
Tumor grade	Moderate	10,831 (62.5 %)	391 (61.8%)	0.607
	Poor	3,867 (22.3%)	150 (23.7%)	
	Undifferentiated	667 (3.8%)	23 (3.6%)	
	Well	1,006 (5.8%)	30 (4.7%)	
	Missing	954 (5.5%)	39 (6.2%)	
Pathological T stage	pT0	57 (0.3%)	–	0.411
	pT1	112 (0.6%)	6 (0.9%)	
	pT2	587 (3.4%)	23 (3.6%)	
	pT3	9,281 (54.6%)	344 (54.3%)	
	pT4	6,404 (37.0%)	219 (34.6%)	
	Missing	884 (5.1%)	41 (6.5%)	
Pathological N stage	pN0	2,707 (15.6%)	119 (18.8%)	0.013
	pN1	5,867 (33.9%)	182 (28.8%)	
	pN2	7,826 (45.2%)	288 (45.5%)	
	Missing	925 (5.3%)	44 (7.0%)	
KRAS	Mutated	2,986 (17.2%)	101 (16.0%)	0.329
	Normal	3,529 (20.4%)	136 (21.5%)	
	Missing	10,810 (62.4%)	396 (62.6%)	
Tumor deposits	Mean/Std/N	0.92/3.63/11,820	1.02/4.57/439	0.683
Perineural invasion	No	10,054 (58.0%)	353 (55.8%)	0.376
	Yes	4,640 (26.8%)	177 (28.0%)	
	Missing	2631 (15.2%)	103 (16.3%)	

Table 3 (*continued*)

Table 3 (*continued*)

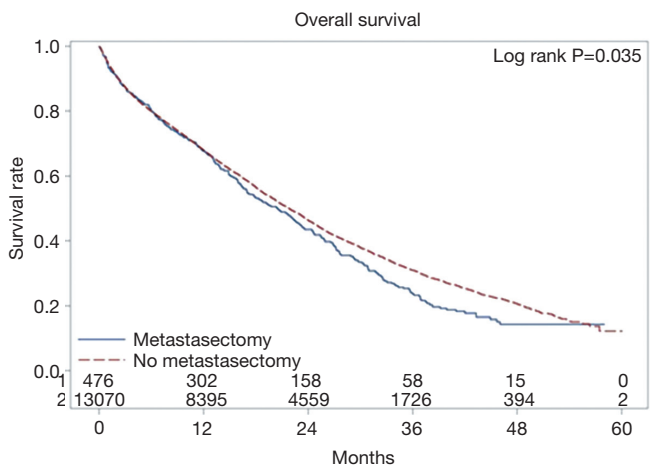
Variable	Subgroup	Primary tumor resection (n=17,325)	Primary tumor resection + metastasectomy (n=633)	P value
Lymph-vascular invasion	No	5,760 (33.2%)	210 (33.2%)	0.961
	Yes	9,285 (53.6%)	340 (53.7%)	
	Missing	2,280 (13.2%)	83 (13.1%)	
Lung metastasis	No	15,206 (87.8%)	561 (88.6%)	0.518
	Yes	2,119 (12.2%)	72 (11.4%)	
	Missing	–	–	
Regional nodes examined	0	432 (2.5%)	15 (2.4%)	0.160
	1–14	5,900 (34.1%)	239 (37.8%)	
	15+	9,912 (57.2%)	341 (53.9%)	
	Missing	1,081 (6.2%)	38 (6.0%)	
Regional nodes positive	0	3,108 (17.9%)	132 (20.9%)	0.061
	>0 positive nodes	14,217 (82.1%)	501 (79.1%)	
	Missing	–	–	
Length of stay	Mean/Std/N	7.94/8.45/15,256	7.78/6.86/564	0.785
Margins	Negative	13,225 (76.3%)	471 (74.4%)	0.149
	Positive	3,438 (19.8%)	141 (22.3%)	
	Missing	662 (3.8%)	21 (3.3%)	
Surgical procedure	Local	889 (5.1%)	5 (0.8%)	<0.001
	Partial	13,464 (77.7%)	531 (83.9%)	
	Total	712 (4.1%)	38 (6.0%)	
	Unknown	2,260 (13.0%)	59 (9.3%)	
	Missing	–	–	
Chemotherapy	No	4,330 (25.0%)	169 (26.7%)	0.298
	Yes	12,353 (71.3%)	438 (69.2%)	
	Missing	642 (3.7%)	26 (4.1%)	
Radiation	No	16,762 (96.8%)	613 (96.8%)	0.789
	Yes	382 (2.2%)	15 (2.4%)	
	Missing	181 (1.0%)	5 (0.8%)	
Palliative care	Chemotherapy	799 (4.6%)	24 (3.8%)	0.648
	Combination	240 (1.4%)	10 (1.6%)	
	None	15,914 (91.9%)	589 (93.0%)	
	Pain management	55 (0.3%)	3 (0.5%)	
	Radiation	39 (0.2%)	1 (0.2%)	
	Surgery	275 (1.6%)	6 (0.9%)	
	Missing	3 (0.0%)	–	

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Subgroup	Primary tumor resection (n=17,325)	Primary tumor resection + metastasectomy (n=633)	P value
Facility type	Academic	4,974 (28.7%)	179 (28.3%)	0.984
	Community	2,493 (14.4%)	94 (14.8%)	
	Comprehensive	8,037 (46.4%)	298 (47.1%)	
	Integrated	1,165 (6.7%)	43 (6.8%)	
	Missing	656 (3.8%)	19 (3.0%)	
Readmission	Not-unplanned	15,806 (91.2%)	580 (91.6%)	0.722
	Unplanned	1,133 (6.5%)	44 (7.0%)	
	Missing	386 (2.2%)	9 (1.4%)	
30-day mortality	No	12,000 69.3%)	430 (67.9%)	0.527
	Yes	872 (5.0%)	35 (5.5%)	
	Missing	4,453 (25.7%)	168 (26.5%)	
90-day mortality	No	10,936 (63.1%)	396 (62.6%)	0.885
	Yes	1,842 (10.6%)	68 (10.7%)	
	Missing	4,547 (25.7%)	169 (26.7%)	

[a], Charlson-Deyo comorbidity score is an estimate of comorbid conditions based on ICD-9 diagnosis codes. A score of 0 indicates no comorbidities. Point values are assigned to comorbid conditions based on severity. The NCDB truncates possible scores to 0, 1 and 2 due to the small proportion of cases exceeding a score of 2; [b], carcinoembryonic antigen.



	Median Survival (months)
Primary tumor resection	21.8 (21.3, 22.3)
Primary tumor resection + metastasectomy	20.5 (17.2, 23.0)
Overall	21.8 (21.2, 22.3)

Figure 3 Kaplan-Meier curve showing 5-year overall survival for metastasectomy and no metastasectomy groups.

being treated for stage IV CC and finds confirm in the current literature (24,25). Patients with those characteristics may in fact have an easier access to healthcare, specialized surgeons and/or more technically advanced centers (26). The healthcare disparities phenomenon has been extensively studied in recent years for multiple settings and conditions (27-29). However, it still represents a major concern as certain patients may receive suboptimal treatments, develop more complications, and be at risk of worse survival outcomes.

Limitations of this study include its retrospective design, with the biases therein. A main limitation is the lack of granularity, with special regards to the number of metastases and the type of performed procedures. The NCDB does not record information about the number of metastases and their location within the same organ, as well as it does not include what type of surgical procedure was used for the metastasis resection. This represents barrier for classifying patients affected by either resectable or unresectable disease, and therefore for their selection. Ultimately, some risk factors were not included in the multivariate analyses because they were not statistically significant in the

Table 4 Multivariate analysis with hazard ratio and the corresponding 95% CI for surgical patients

Variable	Subgroup	Hazard ratio and 95% CI	P value
Metastasectomy	No	–	0.211
	Yes	1.08 (0.95, 1.23)	
Age (1-year increase)		1.02 (1.02, 1.02)	<0.001
Gender	Male	–	0.328
	Female	0.98 (0.93, 1.02)	
Race	White	–	0.150
	Asian	0.89 (0.76, 1.03)	
	Black	0.98 (0.91, 1.05)	
	Other	0.71 (0.47, 1.06)	
Ethnicity	Non-Hispanic	–	<0.001
	Hispanic	0.76 (0.67, 0.86)	
Distance (1-mile increase)		1.00 (1.00, 1.00)	0.077
Education	<14%	–	0.299
	14–20%	1.06 (0.99, 1.14)	
	20–29%	1.04 (0.96, 1.13)	
	>29%	1.00 (0.91, 1.10)	
Income	<30	–	0.024
	30–35	0.96 (0.88, 1.05)	
	35–46	0.96 (0.88, 1.05)	
	>46	0.87 (0.79, 0.96)	
Insurance	None	–	0.001
	Medicaid	1.03 (0.89, 1.19)	
	Medicare	0.89 (0.78, 1.01)	
	Other	0.89 (0.66, 1.20)	
	Private	0.85 (0.75, 0.96)	
Area of residence	Rural	–	0.055
	Metro	0.82 (0.70, 0.97)	
	Urban	0.85 (0.73, 1.01)	
Charlson-Deyo[a]	0	–	<0.001
	1	1.08 (1.02, 1.15)	
	2	1.26 (1.15, 1.39)	
Primary site	Transverse	–	<0.001
	Appendix	0.80 (0.62, 1.05)	
	Left	0.81 (0.74, 0.89)	
	Overlapping/NOS	1.01 (0.87, 1.16)	
	Right	1.14 (1.04, 1.25)	

Table 4 (*continued*)

Table 4 (*continued*)

Variable	Subgroup	Hazard ratio and 95% CI	P value
Lung metastasis	No	–	<0.001
	Yes	1.47 (1.37, 1.57)	
Regional nodes examined	0	–	<0.001
	1–14	1.03 (0.87, 1.21)	
	15+	0.83 (0.70, 0.97)	
Regional nodes positive	0	–	<0.001
	>0 positive nodes	1.69 (1.58, 1.82)	
Chemotherapy	No	–	<0.001
	Yes	0.33 (0.31, 0.35)	
Radiation	No	–	0.263
	Yes	0.91 (0.77, 1.08)	
Facility type	Integrated	–	<0.001
	Academic	0.84 (0.76, 0.94)	
	Community	1.10 (0.98, 1.23)	
	Comprehensive	1.10 (1.00, 1.21)	
Readmission	Unplanned	–	<0.001
	Not-unplanned	0.74 (0.68, 0.82)	

[a], Charlson-Deyo comorbidity score is an estimate of comorbid conditions based on ICD-9 diagnosis codes. A score of 0 indicates no comorbidities. Point values are assigned to comorbid conditions based on severity. The NCDB truncates possible scores to 0, 1 and 2 due to the small proportion of cases exceeding a score of 2.

univariate model. Nonetheless, to our knowledge this study included the analysis of surgical outcomes on the largest cohort of patients diagnosed with stage IV CC.

In conclusion, the results of this study support PTR in select patients diagnosed with metastatic CC, as it provides a remarkable improvement to survival rate. The role of metastasectomy remains however controversial and no difference in survival outcomes exists between patients who received it and who did not. Ultimately, we report the presence of potential healthcare disparities as patients with higher income, education and better insurance status are more likely to survive. More research and especially prospective studies are needed to better understand these critical aspects, in order to provide systematized strategies for stage IV CC patients undergoing surgery.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. As this study utilized a nationwide, de-identified database, it was deemed exempt from the Institutional Review Board.

Disclaimer: The American College of Surgeons Committee on Cancer provided the Participant User File from the National Cancer Data Base, but has not reviewed or

validated the results or conclusions of our study.

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