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Hepatectomy for Breast Cancer Metastasis and Sarcoma are more likely to have Adverse Outcomes than Hepatectomy for Primary Hepatocellular Cancer or for Colorectal Metastasis

Hassan Aziz[1], **Kamil Hanna**[2], **Muhammad Wasif Saif**[3], **Muhammad Ameen Rauf**[4], **Yuri Genyk**[1], **Mohd Raashid Sheikh**[1]

[1]Department of Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

[2]Westchester Medical Center, Valhalla, NY, USA

[3]Northwell Health Cancer Institute, Zucker School of Medicine and Feinstein Institutes of Research, Manhasset, NY, USA

[4]Vanderbilt University Medical Center, Nashville, Tennessee, USA

Abstract

INTRODUCTION—Outcomes for hepatectomy for breast cancer metastasis and sarcomatous disease processes are not well defined in literature. We sought to use a national database to identify outcomes in these patients compared to subset of patients more well studied in literature – primary Hepatocellular cancer patients and patients with colorectal metastasis.

METHODS—We identified patients undergoing major hepatectomy (≥ 3 segments) for primary hepatocellular cancer (HCC), sarcoma metastasis, breast cancer metastasis, and colorectal metastasis using NSQIP database. The Primary outcome measure was 30-day mortality. Secondary outcome measures were 30-day readmission and complication rates.

RESULTS—A total of 5580 patients underwent major hepatectomy during the study period. Patients who underwent hepatectomy for breast cancer metastasis had higher incidence of in-hospital complications (37%) compared to sarcoma (29%), colon (26%), and HCC patients (24%) and 30-days readmission rate (37% *vs.* 29% - sarcoma *vs*. 26% - colon *vs*. 25% HCC). There was no difference in 30-days mortality among the groups.

CONCLUSION—Patients undergoing major hepatectomies for breast cancer metastasis and sarcoma are more likely to have adverse outcomes than compared to their counterparts. This difference highlights the lack of experience in managing breast cancer and sarcoma with metastatic disease to the liver. This also highlights the difference in tumor biology among all the lesions we studied. An extensive discussion should take place when dealing with breast and sarcoma lesions in the liver because of these outcomes.

Correspondence should be addressed to Mohd Raashid Sheikh, MohdRaashid.Sheikh@med.usc.edu.

Keywords

Hepatectomy; Breast cancer; Metastasis; Sarcoma; Primary hepatocellular cancer; Colorectal cancer

INTRODUCTION

Several established indications exist for hepatic resections for metastatic cancers [1]. In US the most common surgical resection performed in terms of metastatic disease is from colorectal origin [2]. As survival and outcomes with other oncologic disease processes like breast cancer, and sarcoma have improved; we are seeing more patients undergoing liver resection for these metastatic cancers [3].

Distant metastases are expected in almost half of patients diagnosed with breast cancer, this fact being responsible for the high number of breast cancer-related deaths in women diagnosed with this malignancy worldwide [4]. The presence of distant metastases is usually a sign of systemic, with an extremely poor prognosis, the reported survival of untreated patients ranging between 3 months and 6 months [5]. In all these cases the traditional therapeutic approach consists of systemic therapy including intravenous chemotherapy, anti-hormonal therapy or monoclonal antibodies; however the reported survival after the apparition of liver metastases remains very poor, ranging from 3 months to 15 months [4,6]. Once the benefits of liver resection were widely demonstrated in cases with hepatic metastases from colorectal primaries [7–9], attention has been focused on a possible benefit of hepatic resection for breast cancer liver metastases [4,10–13]. The reported results after breast cancer liver metastases remain heterogeneous with 5-years overall survival rates ranging between 21% and 61% [4,10,14–16]. Few prognostic factors such as tumor dimensions, number of lesions and disease-free survival between breast cancer surgery and apparition of liver lesions have been incriminated as predictors of long-term survival after liver resection; however, the results vary widely between different studies. Approximately 10% of breast cancer patients will present with solid organ metastases, while up to 30% will develop metastatic disease during their treatment course. Liver metastases are usually treated with systemic chemotherapy [17]. Although, colorectal liver metastases are routinely resected, this is not yet the standard of care for breast cancer-related liver metastases. An increasing number of studies examining the role of therapeutic hepatic metastatectomy show encouraging survival results. The median overall survival was 40 (range, 15–74) months and median 5-years survival rate was 40% (range, 21% - 80%) [18].

Similar to breast cancer metastasis, patients with metastatic sarcoma to the liver presents a unique set of patients whose outcomes are not well defined [19]. The value of hepatic resection for liver metastases from sarcoma is unknown; the few published reports are mostly anecdotal [20]. MSKCCC experience shows that the postoperative 1 year, 3 years, and 5-years actuarial survival rates were 88%, 50%, and 30%, respectively, with a median of 39 months. In contrast, the 5-years survival rate of patients who did not undergo complete resection was only 4% [20]. Because of lack of national studies in this area the aim of the study was to evaluate outcomes after liver resection in breast and sarcoma patients relative to HCC patients.

METHODS

We identified patients undergoing major hepatectomy (≥3 segments) for primary hepatocellular cancer (HCC), sarcoma metastasis, breast cancer metastasis, and colorectal metastasis using NSQIP database. Primary outcome measure was difference in 30-days mortality.

We utilized ACS National Surgical Quality Improvement Program (NSQIP) for years 2014–2017 as the source of our data. The ACS NSQIP is a quality improvement database that collects preoperative and postoperative data through 30 days after the procedure for a variety of surgical procedures [16]. All data collected are compliant with the privacy requirements of the Health Insurance Portability and Accountability Act (HIPAA). Institutional review board approval was not required for this study because the collected information was de-identified, no protected health information was reviewed, and the analysis was retrospective.

Data points

The following data points were analyzed for each patient: demographics (age, gender, and race); preoperative laboratory parameters (Serum albumin, Hematocrit, International normalized ratio, Liver function tests); comorbidities (Coronary artery disease, Chronic kidney disease, Diabetes mellitus, Hypertension, and Congestive heart failure); American Society of Anesthesiologists Classification score; hospital and intensive care unit length of stay; discharge disposition; and mortality.

Outcomes

The following 30-days outcomes were included: surgical site infection (SSI), cardiac arrest, renal failure, stroke, transfusion occurrence, readmission, and return to operating room. Secondary outcome measures were 30-days readmission and morbidity.

Data presentation & statistical analysis

We performed multiple imputations using a missing value analysis technique to account for the missing values. To impute the datasets, the original dataset was analyzed for random missing data points using little’s missing completely at random (MCAR) test. We used the Markov Chain Monte Carlo method for multiple imputations. This method refers to a collection of methods for simulating random draws from non-standard distributions.

We have reported the data as a mean with standard deviation for continuous parametric data and as median with interquartile range for non-parametric data. We have reported proportions for categorical variables. We utilized the student’s t-test and the Mann-Whitney U test to explore the differences between parametric and non-parametric data in our two groups, respectively. The chi-square test was utilized for evaluating differences in categorical variables. A p-value <0.05 is considered statistically significant in our study.

We performed multivariate regression analysis to control for confounders. To assess the association between each potential dependent variable and the binary outcomes, we first performed a univariate analysis. Variables with a *p-value* less than 0.2 on the univariate analysis were then used in a multivariate logistic regression model. On the multivariate logistic regression analysis, variables were considered significant at a *p-value* less than 0.05. All statistical analyses in our study were performed using the Statistical Package for Social Sciences (SPSS, Version 24; SPSS, Inc., Chicago, IL).

RESULTS

We identified 5580 patients who underwent hepatectomy for primary hepatocellular cancer or metastatic liver disease. Overall, the mean age was 60 ± 12 years, 62% were male and 64% were white. The most common indication for resection was metastatic disease (61%) followed by primary HCC (31%). Patients with primary HCC were more likely to be diabetic ($p<0.01$) and smokers ($p<0.01$) relative to the other groups. Patients with colon cancer were more likely to have received neoadjuvant chemotherapy when compared to patients with HCC ($p<0.01$). There was no difference in preoperative labs across the study groups (Table 1) highlights patient characteristics.

Most of the patients underwent an open procedure. However, patients with liver lesions from metastatic breast cancer were likely to have a laparoscopic approach (13%) compared to the other groups. Sarcoma resection had the lowest mean operative time 137 minutes compared to the other subsets of patients. Table 2 highlights operative characteristics. The NSQIP predictor for morbidity and mortality was higher in the HCC and the CRM groups than the breast and sarcoma patients. In terms of complication rates; patients with breast cancer metastasis (3.1%) and sarcoma (3.1%) had a higher rate of re-operation when compared to patients with HCC (1.3%) and colorectal (1.1%) cancer. They also had higher rates of intraoperative blood transfusions (1.8% - Breast, and 1.7% - sarcoma) and Pulmonary embolisms in post-operative periods (Table 3).

Breast patients and sarcoma patients were more likely to have biliary complications than the other groups. The incidence of bile leak was highest in breast patients - 3.9% whereas the incidence of post-operative liver failure was highest among sarcoma patients - 3.1%.

On univariate analysis, breast cancer patients to have higher 30-days complications and readmission rates (Table 4). We didn't find any different in mortality among the groups. Analysis of multivariable logistic regression is summarized in Table 5.

DISCUSSION

We performed an outcomes study using a national database to assess outcomes in patients undergoing major hepatectomy for different malignant etiologies. We found a higher 30-days complication rate and readmission in patients undergoing hepatectomy for breast cancer metastasis followed by sarcoma of the liver. We found no difference in mortality among the groups.

We don't know why the difference in outcomes in patients with sarcoma and breast metastasis have higher complication rates. We do believe that the aggressive nature of the disease, along with limited data in terms of managing these rare forms of liver lesions has a role to play [20]. Different tumor biology of the underlying cancers, differing medical histories and time intervals between the primary cancer and liver metastasis including variation in preceding endocrine treatment as well as chemotherapy, and different surgical approaches lead to an inevitable inhomogeneity [21]. Significant literature is present in managing HCC and colorectal metastasis whereas there is a dearth of good data in managing liver sarcomas and metastatic breast disease to the liver. We believe our study has evoked an important question - how well we understand these patients with sarcoma and breast metastasis that are undergoing liver resections?

Liver surgery has improved, and new techniques of resection and a wider understanding of the perioperative treatment are constantly reducing the perioperative morbidity and mortality [22]. Today, wherever feasible, a malignant tumor of the liver should be resected.

During the past decades, liver surgery has become safe, thereby liberalizing its indications. However, it is pivotal to meticulously select patients who are candidates for potentially curative resection. Discussion in multidisciplinary tumor boards has demonstrated to be essential in selecting patients who might benefit from surgery.

The strength of our study is the relatively large sample size from a population-based data set. Furthermore, this study provides detailed information on intra and postoperative complications, which are rare in population-based data sets. However, certain limitations do apply to our current analysis. Retrospective studies do present with an inherit selection bias. The only way to really test whether the reported outcomes are related to the therapeutic impact of resection or selection bias would be a prospective trial randomizing patient with resectable disease to systemic therapy or surgery. This has not happened and will not likely ever happen because of the rarity of the situation and limited willingness of practitioners. An alternative study is a retrospective case series comparing similar patients who, for whatever reason, were picked for either surgery or systemic therapy alone.

CONCLUSION

Patients undergoing major hepatectomies for breast cancer metastasis are more likely to have adverse outcomes than compared to their counterparts. This difference highlights the lack of experience in managing breast cancer with metastatic disease to the liver.

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Table 1:

Baseline characteristics of the study sample.

Variable	Primary (N = 1729)	Colon (N = 2451)	Breast (N = 99)	Sarcoma (N = 341)	P-Value
Age, mean ± SD	64 ± 11	59 ± 12	52 ± 12	57 ± 15	<0.01
Male, n (%)	1262 (73)	1397 (57)	0 (0)	109 (32)	<0.01
White, n (%)	916 (53)	1691 (69)	76 (77)	249 (73)	<0.01
Hispanic, n (%)	104 (6)	93 (4)	7 (7)	34 (10)	0.02
BML, Kg/m^2,mean ± SD	27 ± 6	28 ± 6	27 ± 6	27 ± 6	0.1
Comorbidities, n (%)					
Diabetes	484 (28)	363 (15)	6 (6)	51 (15)	<0.01
Smoker	467 (27)	294 (12)	10 (10)	1 (2)	<0.01
Dyspnea	121 (7)	93 (4)	3 (3)	24 (7)	0.19
COPD	121 (7)	74 (3)	3 (3)	0 (0)	<0.01
CHF	5 (0.3)	10 (0.4)	0 (0)	0 (0)	0.96
HTN	1055 (61)	1078 (44)	19 (19)	133 (39)	<0.01
CKD	121 (7)	147 (6)	4 (4)	17 (5)	0.45
CVA	121 (7)	93 (4)	2 (2)	14 (4)	<0.01
MI	104 (6)	74 (3)	3 (3)	14 (4)	<0.01
Preop Interventions, n (%)					
Neoadjuvant Therapy	190 (11)	1520 (62)	45 (45)	143 (42)	<0.01
Transfusion ≤72h	17 (1)	7 (0.3)	0 (0)	0 (0)	0.22
Preop Parameters, mean ± SD					
BUN (mg/dL)	16 ± 7	15 ± 8	13 ± 4	15 ± 6	0.2
Creatinine (mg/dL)	0.94 ± 0.32	0.88 ± 0.33	0.71 ± 0.19	0.91 ± 0.33	0.1
Albumin (g/dL)	3.8 ± 0.5	3.9 ± 0.4	4 ± 0.7	3.9 ± 0.6	0.2
Bilirubin (mg/dL)	0.63 ± 0.53	0.56 ± 0.33	0.52 ± 0.32	0.55 ± 0.31	0.2
SGOT (IU/L)	54 ± 53	31 ± 31	27 ± 10	23 ± 9	<0.01
ALK-Phosphatase	108 ± 6S	104 ± 54	99 ± 72	119 ± 82	0.21
WBC (1000 $cells/mm^3$)	7.3 ± 2.1	6.4 ± 2.3	5.7 ± 3.1	8 ± 3.1	<0.01

Variable	Primary (N = 1729)	Colon (N = 2451)	Breast (N = 99)	Sarcoma (N = 341)	P-Value
HCT (%)	41 ± 5	39 ± 4	37 ± 4	37 ± 6	<0.01
Platelet count (100,000 per mm^3)	212 ± 93	212 ± 69	213 ± 52	218 ± 87	0.2
INR	1.05 ± 0.13	1.01 ± 0.15	0.99 ± 0.05	1.16 ± 0.51	0.96
PTT	31 ± 6	30 ± 5	31 ± 9	30 ± 8	0.06

Table 2:

Perioperative characteristics of the study sample.

Variable	Primary (N = 1729)	Colon (N = 2451)	Breast CN = 99)	Sarcoma (N = 341)	P-Value
Emergency case, n (%)	1.3	0.2	0	0	<0.01
Wound classification, n (%)					
Clean	17	13	3	15	<0.01
Clean/contaminated	80	83	90	85	0.18
Contaminated	3	4	7	0	0.35
Dirty/infected	0.3	0.7	0	0	0.47
ASA Classification, n (%)					
1-Healthy person	0.5	0.3	0	0	0.48
2-Mild systemic disease	18	21	19	20	0.09
3-Severe systemic disease	71	71	77	78	0.13
4-Life threatening	11	7	3.2	2.4	<0.01
NSQIP Probability, mean ± SD					
Morbidity	19 ± 2	18 ± 3	15 ± 1	18 ± 4	<0.01
Mortality	15 ± 2	21 ± 5	13 ± 3	27 ± 5	<0.01
Surgical approach, n (%)					
Laparoscopic	18	10	23	5	<0.01
Laparaoscopic with, open assist	5	6	7	0	0.07
Laparascopic with, unplanned conversion to open	4	4	7	2	0.06
Open	72	79	65	93	<0.01
Total operation time mins, Mean ± SD	224 ± 5	251 ± 3	210 ± 15	137 ± 21	<0.01

Table 3:

Complications.

	Primary (N = 1729)	**Colon (N = 2451)**	**Breast (N = 99)**	**Sarcoma (N = 341)**	***P***
Complications, %					
Superficial SSI	0.9%	1.2%	0.9%	1%	0.2
Organ specific SSI	1.3%	1.6%	2.1%	2.2%	0.03
Pneumonia	0.6%	1.6%	2.9%	3.1%	0.01
Unplanned intubation	1.3%	0.7%	0.7%	0.9%	0.4
DVT	2.6%	2.7%	2.8%	2.8%	0.13
PE	1.2%	1.4%	1.9%	2.1%	0.02
Transfusions	1.0%	1.1%	1.8%	1.7%	0.01
Return to OR	1.3%	1.1%	3.1%	3.1%	0.01

Table 4:

Univariate analysis of outcomes.

Variable	Primary (N = 1729)	Colo (N = 2451)	Breast (N = 99)	Sarcoma (N = 341)	P-Value
30-Day Complications, n (%)	415 (24)	637 (26)	37 (37)	99 (29)	0.01
30-Day Readmission, n (%)	138 (8)	270 (11)	19 (19)	51 (15)	0.01
30-Day Mortality, n (%)	21 (1.2)	32 (1.3)	1 (1)	0 (0)	0.25

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Table 5:

Multivariable logistic regression.

	OR	95% CI	*P* value
In Hospital Complications			
HCC	Ref	-	-
Colon	1.12	0.94 – 2.97	0.15
Breast	2.19	1.24 – 3.49	0.02
Sarcoma	1.74	1.15 – 2.46	0.04
30-Days Readmission			
HCC	Ref	-	-
Colon	1.04	0.87 – 2.11	0.26
Breast	1.24	1.07 – 3.64	0.04
Sarcoma	1.16	1.09 – 2.85	0.04