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Outcomes of Hepatic Metastasectomy for Colorectal Cancer Metastases in the Philippine General Hospital

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Rationale: The liver is the most common site of metastasis from colorectal cancer. Curative intent liver metastasectomy has shown improvement in overall survival. This manuscript will present the long-term oncologic outcomes of hepatic metastasectomy for colorectal cancer with resectable liver metastasis.

Methods: Data of patients with resectable liver metastases from colorectal cancer who underwent hepatic resection at the Philippine General Hospital over a 10-year period was reviewed. The primary outcome investigated was overall survival.

Results: Thirty patients were included in the study. The median overall survival was 20 months, with a 2-year and 5-year overall survival rate of 40% and 6.67% respectively. Eleven (36.67%) patients had disease recurrence, with a median disease-free survival of 16 months. A significant difference in survival was seen between patients with synchronous and metachronous liver metastasis (20.38 and 36.78 months respectively, p=0.0393) and in patients given adjuvant chemotherapy at any time in relation to the occurrence of the liver metastases versus patients who did not receive any adjuvant treatment (34.08 and 18.59 months respectively, p=0.0349). Trends towards improved overall survival were seen in patients 50 years old or less (36.86 versus 21.78 months, p=0.0837) and in patients with a clinical risk score of 2 or less (29.65 versus 19.62 months, p=0.1823), which may show significance in a higher powered study.

Conclusion: Improved overall survival was observed among patients with colorectal liver metastases undergoing hepatic metastasectomy compared to no liver resection.

Key words: colorectal cancer, liver metastasis, metastasectomy, Philippines

Colorectal cancer (CRC) is the third most common cancer in the Philippines and fourth in ranking in terms of mortality. There were an estimated 9625 new cases of CRC in the Philippines in both males and females, accounting for 8.81% of all newly diagnosed cancers in the year 2015.[1] There was an estimated 5523 mortalities from CRC in the Philippines from the same registry, accounting for 8.35% of all deaths due to cancer.[1]

Thirty to 50% of patients with CRC will develop liver metastasis (CRLM) over the course of their disease.[2,3] The liver is the most common site of metastatic disease due to the venous and lymphatic drainage from the splanchnic organs draining into the portal circulation. Ten to 25% of patients with CRLM are diagnosed at the time of their first consult or at surgery for the primary disease.[2,3] The presence of both resectable colorectal primary and hepatic metastases necessitates comprehensive strategies to treat the disease with curative intent, as CRC is one of the few primary malignancies in which resection of metastatic disease has been shown to confer a significant survival advantage.[2] Complete resection of the primary colorectal tumor and metastatic sites such as the liver, lung, and peritoneum, in conjunction with chemotherapeutic regimens have resulted in improved progression-free and overall survival rates for stage IV disease.[4,5] Technical advancements in liver surgery continue to expand the limits of resectable hepatic disease with acceptable morbidity and improved clinical and oncologic outcomes.

Multimodal treatment strategies for CRLM have been developed, but no one-size-fits-all strategy has been found to be most effective for its treatment. Treatment planning modified on a case-to-case basis has been advocated, under the direction of a multidisciplinary team composed of colorectal and hepatobiliary surgeons, medical oncologists, radiation oncologists, and other medical and paramedical personnel. There is currently

no published local data on the survival rates of patients with CRC who undergo hepatic metastasectomy.

This study aimed to describe the outcomes of patients with resectable hepatic metastases from colorectal cancer who have undergone liver metastasectomy under the Division of Hepatobiliary and Pancreatic Surgery of the University of the Philippines – Philippine General Hospital (UP-PGH) within a 10-year period.

Specifically, this study aimed to 1) compile demographic, clinical, and pathologic characteristics of patients who have undergone hepatic metastasectomy; 2) determine disease-free and overall survival rates of patients undergoing hepatic metastasectomy; 3) identify patient-specific and disease-specific factors which may impact on the survival of patients undergoing hepatic metastasectomy; and 4) compare local outcomes and survival rates with international data.

Methods

Study Design and Setting

The study included patients who have undergone hepatic metastasectomy for resectable liver metastases from a primary colorectal cancer from January 1, 2009 to December 31, 2018. This is a retrospective descriptive study involving a review of medical records. The Philippine General Hospital, a tertiary referral center, was the selected study site as the hospital has sufficient volume and variety of cases, and accessibility of medical records to be reviewed for data collection.

Inclusion Criteria

All patients who have undergone wedge resection or formal segmental resection for resectable hepatic metastasis from colorectal adenocarcinoma as proven by histopathologic examination under the Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, UP-PGH.

Exclusion Criteria

Patients who have metastatic disease to the liver from primary sites other than the colon and rectum, and patients who underwent hepatic resection for presumed metastatic disease from colorectal cancer but whose final histopathologic diagnosis revealed benign or non-metastatic hepatic lesions.

Data Collection

Patients qualifying for inclusion in the study were identified using the Integrated Surgical Information System (ISIS) operation query function using the keywords ‘hepatectomy’ and ‘metastasectomy’ for the period of January 1, 2009 to December 31, 2018. These were further screened by limiting the final clinical and histopathologic diagnoses to adenocarcinoma from the colon or rectum. The records of the identified patients were retrieved from both the UP-PGH Medical Records Division and the OpenMRS electronic medical records system. Charts from in-patient admissions and out-patient consultations, laboratory and histopathologic examination results, operative reports, and other available hospital data were collected by the principal investigator.

Demographic data, stage, characteristics of the primary disease and the hepatic metastases, treatment regimens, histopathologic features, and other patient-specific and disease-specific factors were compiled and recorded using a standard data collection form. Metachronous metastatic disease was defined as metastasis diagnosed >6 months from the diagnosis of the primary tumor, while synchronous disease was defined as metastases diagnosed before or within 6 months after the diagnosis of the primary tumor. The clinical risk score (CRS) defined by Fong, et al. was computed by assigning a point for each of the factors identified to influence long-term survival after hepatic resection for metastatic CRC, as listed in Table 1.[6] Disease-free survival (DFS) was determined as the length of time from the surgical procedure until documentation of disease recurrence at any organ site, while overall survival (OS) was determined as the length of time from hepatic metastasectomy until the date of death, date of last consult, or last diagnostic examination performed. Disease free survival and overall survival were the primary outcomes, while morbidity and recurrence rates were the secondary outcomes.

Table 1. Clinical risk scoring (CRS) system by Fong, et al. for predicting outcomes in patients undergoing hepatic resection for metastatic colorectal cancer*.

Factor	Point
Node-positive primary tumor Disease-free interval from primary to metastasis <12 months Number of hepatic tumors >1 Largest hepatic tumor >5 cm Carcinoembryonic antigen level >200 ng/mL	1 point for each factor present

*Predictor of recurrence and estimates survival for patients undergoing hepatic resection for colorectal cancer metastases CRS=0, 60% 5-year overall survival; CRS=1, 44% 5-year overall survival; CRS= 2, 40% 5-year overall survival; CRS=3, 20% 5-year overall survival; CRS=4, 25% 5-year overall survival; CRS=5, 14% 5-year overall survival

Data Management

Patient and disease characteristics were expressed as median values or percentages. Disease free survival and OS were expressed in months, while time-specific survival rates such as 2-year and 5-year survival rates were expressed as percentages (patients surviving by the specified duration over the total number of patients). Patients that were lost to follow-up and in whom additional information cannot be obtained were presumed to have experienced the worst outcome (disease recurrence or death) after the last follow-up. Data analysis was done using statistical software (Epi Info version 7.2.4.0). The mean overall survival between patient groups (e.g., OS of patients 50 years old and below versus OS of patients above 50 years of age) were compared using the independent T-test. A p value of ≤ 0.05 was considered statistically significant.

Results

A total of 52 patients who underwent hepatic metastasectomy for colorectal adenocarcinoma under the Department of Surgery from the period of January 2009 to December 2018 were identified. Twenty-two cases were excluded due to difficulty in retrieving the records or lack of data regarding long-term outcomes. Thirty patients were included in the final data collection and analysis. Thirteen patients had documented mortality dates, while seventeen patients had the date of their consult or contact with any component of the PGH system used as a substitute for overall survival. Tables 2 and 3 summarize the surgical and histopathologic characteristics of the study population.

Table 2. Demographics and histopathologic characteristics of the primary colorectal tumor in study population, n=30

Characteristic	Median	Range (SD)
Age (years)	57	33-75 (9.58)
Carcinoembryonic antigen (ng/mL)	23.43	1.18-408.75 (79.47)
Characteristic Number (%)		
Gender		
Male	22	73.33
Female	8	26.67
Primary site		
Colon	12	40
Rectum	18	60
Tumor differentiation		
Well-differentiated	14	46.67
Moderately-differentiated	9	30
Poorly-differentiated	3	10
Not otherwise specified	4	13.33
Nodal metastases		
Absent	9	30
Present	19	63.33
Not otherwise specified	2	6.67
Lymphovascular invasion		
Absent	7	23.33
Present	13	43.33
Not otherwise specified	10	33.33
Margin status of primary tumor		
Negative	22	73.33
Positive	1	3.33
Not otherwise specified	7	23.33
Neoadjuvant treatment for primary		
No treatment	19	63.33
With treatment	11	36.67
Systemic treatment		
No treatment	17	56.67
With treatment	13	43.33

Table 3. Histopathologic characteristics of liver metastases in the study population, n=30

Characteristic	Median	Range (SD)
Number of hepatic metastases	2	1-9 (2.16)
Largest size of hepatic metastases (cm)	3	0.4-10.2 (2.16)
Characteristic	**Number**	**(%)**
Timing of diagnosis of metastases		
Synchronous	21	70
Metachronous	9	30
Type of Hepatic resection		
Wedge resection	16	53.33
Formal hepatectomy	14	46.67
Timing of hepatic surgery		
Simultaneous resection with primary	13	43.33
Staged resection	17	56.67
Fong clinical risk score		
0	1	3.33
1	5	16.67
2	11	36.67
3	12	40
4	1	3.33
5	0	0

Four patients developed post-operative morbidities. Two patients had anastomotic leaks from the simultaneous resection of their primary tumors, and both required operative intervention (one transanal drainage of abscess and one open repair of anastomotic leak). The third patient developed post-operative ileus which was managed medically. The last patient had transient hepatic insufficiency after a formal right hepatectomy, which was only identified through monitoring of biochemical parameters and did not affect the usual course of the patient's recovery. No other liver-specific post-operative complications such as post-operative bleeding or bile leak were observed. There was no 30-day mortality reported among all the patients included in the study. The morbidity and mortality rates are tabulated in Table 4.

The DFS ranged from 0 to 77 months, with a median value of 16 months. Six patients had recurrence in the liver, one patient each had recurrence in the lungs, bone, and at the colonic primary site, and two patients had recurrences at multiple sites (liver/lung and lung/bone). The median OS for all 30 patients was 20 months, with a range from 4 to 79 months. Twelve patients reached 2 years of follow-up while two patients survived beyond 5 years, with resulting 2-year and 5-year OS rates of 40% and 6.67%, respectively. Eighteen patients did not survive beyond 2 years. The survival outcome parameters are summarized in Table 5.

Patient-, disease-, and surgery-specific factors were analyzed to check for correlations to overall survival. The means of OS compared between patient groups are summarized in Table 6. The average OS for patients diagnosed with metachronous hepatic metastases was 36.78 months, compared to patients with synchronous hepatic metastases at 20.38 months, p=0.0393. A significant survival advantage was also noted for patients who received adjuvant therapy regardless of timing relative to the resection of the hepatic metastases, with a mean OS of 34.08 months for those who received adjuvant chemotherapy compared to 18.59 months for those who did not, p=0.0349.

Patients 50 years old or less have a tendency towards improved OS as compared to those older than 50 years, but this did not reach statistical significance

Table 4. Morbidity and mortality of hepatic metastasectomy, n=30

Outcome	Number	(%).
Post-operative morbidity after metastasectomy		
None	26	86.67
With morbidity[A]	4	13.33
Liver-specific morbidity after metastasectomy		
None	29	96.67
With morbidity[B]	1	3.33
30-day mortality after metastasectomy		
None	30	100
With mortality	0	0

[A]Two patients had anastomotic leaks, one patient had post-operative ileus, and one patient had transient hepatic insufficiency

[B]Only the patient with transient hepatic insufficiency was considered as a liver-specific morbidity

Table 5. Oncologic outcomes after hepatic metastasectomy

Outcome	Number n=30	(%)
2-year overall survival	12	40
5-year overall survival	2	6.67
Outcome	Median	Range (SD)
Disease-free survival (months)	16	0-77 (25.28)
Overall survival (months)	20	4-79 (20.20)

(36.86 versus 21.78 months, p=0.0837). Subset analysis to determine the relationship of other patient factors in relation to age and overall survival was not performed. Patients with a CRS of 2 or less had a higher mean OS as compared to those with a CRS of 3 or higher, 29.65 versus 19.62 months, p=0.1823.

Discussion

Median survival after hepatic metastasectomy has been shown to range from 23 to 46 months, with 5-year survival rates reported from 16% to 70%.[2,7-9] In comparison, the study showed a median OS of 20 months, with a 2-year and 5-year OS rates of 40% and 6.67%, respectively. The lower survival rates seen in the study may be partially explained by the use of surrogate markers of survival, such as date of last consult or last diagnostic test done.

A population-based study in France showed significantly lower rates of 1-, 3-, and 5-year OS after a diagnosis of synchronous metastases compared to metachronous metastases (46.5%, 16.1%, and 7.2% versus 68.7%, 33.0%, and 17.6%, p<0.001).[10] The presence of synchronous metastases is associated with a poorer prognosis, as these tumors present with more aggressive biology and has greater metastatic potential. Patients with synchronous metastatic tumors also have more unfavorable characteristics present, such as higher T stage, elevated LDH, colonic primary tumor, worse performance status, and predominantly hepatic site of metastases.[11] Despite synchronous metastatic tumors having unfavorable features at initial presentation, effective surgical and chemotherapeutic treatments

Table 6. Comparison of overall survival between groups based on clinical variables

Characteristic	OS (months)	p-value
Age		
≤50 years	36.86	0.0837
>50 years	21.78	
Gender		
Male	24.73	0.8019
Female	26.86	
Carcinoembryonic antigen		
≤5 ng/mL	21.60	0.6549
>5 ng/mL	24.88	
Primary site		
Colon	25.33	0.9943
Rectum	25.23	
Tumor differentiation		
Well-differentiated	25.79	
Moderately-differentiated	24.33	0.9828
Poorly-differentiated	25.67	
Nodal metastases		
Absent	21.33	0.9613
Present	21.63	
Lymphovascular invasion		
Absent	25.57	0.8163
Present	23.77	
Margin status of primary tumor		
Negative	24.27	0.9399
Positive	21.00	
Timing of diagnosis of metastases		
Synchronous	20.38	0.0393
Metachronous	36.78	
Hepatic resection type		
Wedge resection	24.00	0.7134
Formal hepatectomy	26.79	
Timing of hepatic surgery		
Simultaneous resection with primary	26.62	0.7612
Staged resection	24.29	
Number of hepatic metastases		
1	22.25	0.6510
>1	25.71	
Largest size of hepatic metastases (cm)		
<5 cm	23.92	0.3502
≥5 cm	34.25	
Neoadjuvant treatment for primary		
No treatment	27.94	0.3546
With treatment	20.72	
Systemic treatment		
No treatment	18.59	0.0349
With treatment	34.08	
Fong clinical risk score		
≤2	29.65	0.1823
>2	19.62	

may compensate for this disadvantage. Some reports have stated that synchronous metastases have higher response rates to initial chemotherapeutic regimens, potentially due to metachronous disease having some partial resistance from adjuvant treatments previously given.[11] An R0 resection also appears to decrease the negative impact of synchronous metastases compared to metachronous metastases, with similar 5-year survival for both groups (47.3% and 61.5%, p=0.120).[10] When patients with unresected primary tumors were included in the synchronous groups, a clear benefit is seen for metachronous tumors.

Various studies investigating the effects of age and comorbidities on survival from CRC have shown negative associations between increasing age and increased number of comorbidities, when the Charlson comorbidity index was used.[12,13] The same trend regarding increasing age and decreasing overall survival was also observed. Further investigation with greater sample size and with inclusion of other variables such as comorbid conditions and functional status may strengthen the said associations within the patient groups.

The correlation between survival and the clinical risk score of patients in the current study is consistent with the findings of the original article by Fong, et al. A higher CRS was associated with poorer survival for patients undergoing hepatic metastasectomy for primary colorectal cancer.[6] Those with a CRS of 2 or lower had expected favorable outcomes and outright surgical resection of metastatic disease was a valid option, while those with a score of 3 or more have more guarded prognoses and may benefit from prolonged observation, intensive imaging studies to identify other foci of metastases, or neoadjuvant chemotherapy to document tumor responsiveness.[6]

The study added to the survival advantage provided by adjuvant chemotherapy. However, there are no clear recommendations regarding the sequencing of treatment, between surgery or giving perioperative chemotherapy first for CRLM. A systematic review by Baltatzis, et al. looking at the variations in surgical sequencing (synchronous versus liver-first versus bowel-first surgery) for synchronous hepatic metastases showed no significant difference between 5-year survival rates for all three options.[14] The data analysis, however, did not consider the effect of the different schedules for perioperative chemotherapy given to the subjects. The European Organization for Research and Treatment of Cancer (EORTC) trial demonstrated an improvement in progression-free survival of 8.1% for the FOLFOX chemotherapy plus surgical resection compared to surgical resection alone (36.2% and 28.1%, p=0.041).[4,15] Long-term follow-up showed no significant difference in terms of both median overall survival (61.3 months and 54.3 months) or 5-year overall survival (51.2% and 47.8%, p=0.34).[4,15] The study did not investigate the relationship between the timing of administration of chemotherapy, as the surgery-only group did not receive any form of adjuvant chemotherapy. A study which investigated the impact of adjuvant chemotherapy after resection of CRLM showed an advantage in both disease-free and overall survival for treatment with either an oral fluorouracil (uracil-tegafur) or an oxaliplatin-based regimen in patients with CRLM detected either at the time of diagnosis of the primary tumor or up to 1 year after (5-year OS 77.9% versus 44.5%, p=0.021 in CRLM diagnosed at the same time as primary, 81.5% versus 39.5%, p=0.015 in CRLM diagnosed up to 1 year from primary).[5] There was no significant benefit for giving adjuvant chemotherapy after hepatic metastasectomy in patients with metachronous liver metastasis diagnosed more than 1 year from the time of detection of the primary colorectal cancer (5-year OS 76.1% versus 65.4%, p=0.411).[5] Some patients in all groups received adjuvant treatment for the primary tumors, as well as neoadjuvant chemotherapy for the CRLM, but the impact of these regimens were not included in the analysis. Further investigations into the optimal schedules and regimens for adjuvant chemotherapy in the context of metastatic CRC can further improve outcomes.

Current survival data of CRC with unresectable hepatic metastases have shown a median survival of 5 to 21 months, and a 5-year survival rate of less than 2%.[2,3] These figures are similar for patients with apparently resectable metastases who forego resection, suggesting that the survival benefit is derived from removal of the metastatic foci rather than the actual disease burden. The results of the current study show a survival benefit with hepatic metastasectomy and reinforce complete resection as the preferred management for resectable Stage IV CRC. The discrepancy with international

survival estimates reiterates the need to improve data collection methods, encourage patient follow-up and adherence to the recommended treatment regimens. The establishment and maintenance of a formal tumor registry, with dedicated staff for data collection and patient monitoring can improve the quality of information obtained from these data sets.

Providing acceptable standards of care for indigent patients with colorectal cancer remains a challenge for most government health care institutions in the Philippines. The economic burden of treatment has been partly mitigated with the implementation of the colorectal cancer Z benefit package of the Philippine Health Insurance Corporation (PHIC), the national socialized universal health coverage provider. At present, the colorectal Z package only covers patients with Stage I to III colon and rectal cancer and excludes patients with resectable metastatic disease.[16] This places patients with potentially curable Stage IV colorectal cancer at a disadvantage, as improved survival for Stage IV disease can be achieved if managed according to current standards of care. The Colorectal Cancer Study Group of the Philippine General Hospital has demonstrated better treatment outcomes and high rates of completion of treatment regimens when patients were enrolled in the colorectal Z package, with 90%, 77%, and 96% compliance rates to surgery, chemotherapy, and radiotherapy treatment plans respectively. The study population, comprised mostly of rectal cancer patients with Stage III disease, was able to achieve a 3-year survival rate of 70%, which is comparable to international data.[17] The high compliance rates could be attributed to the financial support obtained from the Z benefits package and the dedicated personnel for patient coordination and treatment follow-up. Modification of the inclusion criteria of the Z benefits package to allow enrollment of potentially curable Stage IV colorectal cancer patients, would result in the equitable distribution of limited resources to improve local survival outcomes.

Conclusion

The outcomes of patients undergoing hepatic metastasectomy for liver metastasis from colorectal cancer primary at the Philippine General Hospital has shown improved survival. The survival rates are still inferior as compared to international data. Potential correlations identified between overall survival and the timing of development of metastases, use of adjuvant chemotherapy, patient age, and clinical risk score may guide patient selection in patients who would benefit from hepatic metastasectomy.

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