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Predictors of surgical non-referral for colorectal liver metastases

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ABSTRACT

Background: Surgical resection is the only curative option for patients with colorectal liver metastases (CRLM). The objective of our study was to identify factors associated with failure to refer patients with CRLM to a surgeon with oncologic and hepatobiliary expertise.
Materials and methods: Data were retrospectively reviewed on 75 patients with CRLM treated at our institution. Patients were divided into referred and nonreferred groups for comparison. Quantitative assessment of association was tabulated using the odds ratio (OR). Statistical comparison was performed using the chi-square test and multiple regression models. Overall survival (OS) was calculated using the Kaplan–Meier method. Multivariate analysis was done using Cox regression.
Results: Factors independently associated with lower surgical referral rates included age $\geq$ 65 y (OR 0.29, 95% confidence interval [CI] 0.09-0.89, $P = 0.032$), bilobar CRLM (OR 0.35, 95% CI 0.09-0.97, $P = 0.048$), and presence of >3 CRLM (OR 0.33, 95% CI 0.11-0.94, $P = 0.044$). The 5-y OS for referred patients was 33% compared with only 8% in patients who were not referred ($P < 0.001$). Factors independently associated with worse OS included age $\geq$ 65 y (hazard ratio [HR] 2.01, 95% CI 1.12-3.59, $P = 0.019$), bilobar hepatic metastases (HR 3.04, 95% CI 1.62-5.70, $P < 0.001$), and the presence of extrahepatic metastases (HR 2.11, 95% CI 1.02-4.16, $P = 0.011$). Referral to a surgeon was associated with improved OS (HR 0.42, 95% CI 0.24-0.74, $P = 0.003$).
Conclusions: Failure to refer CRLM patients for surgical evaluation is associated with aggressive biologic features that do not necessarily preclude resection. Determination of resectability should be made with input from appropriately trained surgical experts.

Introduction

Colorectal cancer remains the third leading cause of cancer-related death in the United States.[1] Approximately 25% of patients with colorectal adenocarcinoma present with metastatic disease at initial diagnosis, and nearly another 50% will develop metastases during their lifetime.[2] The most common site of metastatic involvement in colorectal cancer patients is the liver, and advancements in multimodality treatment have significantly improved clinical outcomes.[3,4] Liver-directed therapies including surgical resection are critical components of curative

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approaches for eligible colorectal liver metastases (CRLM) patients.[3-5]

Despite the abundance of evidence surrounding the role of surgery for CRLM, it remains an underutilized resource.[6,7] A substantial proportion of patients with CRLM who may benefit from resection are never referred for surgical evaluation.[7] Delay in surgical treatment of CRLM is associated with worse survival,[8] suggesting that surgical input is an important contributor to optimal oncologic outcomes. The effective utilization of multimodality care in such patients remains particularly challenging in community settings.[9]

The decision to perform a liver resection involves a complex synthesis of disease biology, hepatobiliary anatomic details, and liver functional assessments. After resection of both CRLM and lung metastases, 5-y survival rates of up to 31% have been reported, suggesting that extrahepatic disease should not categorically preclude CRLM resection.[10] Similarly, curative liver resection is possible in 16% of patients who present initially with unresectable disease.[11] Expert surgical input is required to determine resectability even in the setting of advanced disease.[12] A decision to not refer a CRLM patient due to extensive intrahepatic disease or the presence of extrahepatic metastases may not be appropriate.

To examine the variables influencing surgical referral practices for patients with CRLM, we analyzed data from our community cancer center tumor registry. The objective of our study was to identify factors associated with surgical referral of CRLM patients and the association of referral practices on outcomes. We hypothesized that clinical features associated with advanced disease may inappropriately exclude patients from surgical evaluation.

Methods

With approval of the institutional review board and in accordance with Health Insurance Portability and Accountability Act regulations, a prospectively maintained Roger Williams Cancer Center hepatobiliary database was used. Between 2004 and 2011, 79 patients with CRLM met inclusion criteria who were treated by our expert surgical oncology team at our Commission on Cancer–accredited Academic Comprehensive Cancer Program. Four patients were subsequently excluded secondary to lack of treatment data. Retrospective chart review was then performed, and we analyzed data in regard to gender, age, carcinoembryonic antigen level, tumor size, burden of hepatic metastases, presence of extrahepatic metastases, insurance status, surgical referral, surgical intervention, and survival. Referred patients were defined as patients who underwent evaluation by a surgeon with hepatobiliary or oncologic expertise.

Quantitative assessment of association was tabulated using the odds ratio (OR). Univariate statistical comparison was performed using the Pearson chi-square test. All the associated variables were tested for correlation using the Pearson product–moment correlation test, and a correlation matrix was derived. Multivariate association using multiple regression model was calculated among the variables found significant on univariate statistics. Survival was estimated by the Kaplan–Meier model. Statistical comparison of Kaplan–Meier curves was performed using the log-rank test. Multivariate survival analysis using Cox proportional hazards model was performed using variables significant on univariate assessment. All statistical analyses report 95% confidence intervals (CIs) and were performed using SPSS for windows (SPSS Inc, Chicago, IL). Significance of difference was assumed at $P < 0.05$.

Results

Demographics and clinicopathologic features

Of the 75 patients in our study, 49 patients (65%) were referred to a surgical oncologist. Resection of CRLM was performed on 33 patients, which represented 67% of those referred for surgical evaluation. Table 1 outlines the demographic characteristics of all patients. Forty-five patients (60%) were aged older than 65 y. The male-to-female ratio was approximately 1:1. Sixty-nine percent of patients had tumors of colonic origin, whereas the remainder of cases were rectal adenocarcinomas. The median carcinoembryonic antigen level was 17.5 ng/mL (0.5-3008 ng/mL), and that cutoff was used for stratified analysis.

We examined several variables to determine the extent of disease in the patients (Table 1). Most patients had more than three CRLM. Bilobar hepatic involvement was seen in 63% of our patients. Twenty-seven percent of patients had a CRLM greater than 5 cm in size. Extrahepatic metastases were present in 37% of patients at the time of initial diagnosis, with lung being the most common site. Medicare and/or Medicaid patients accounted for 60% of all patients, with the remainder having either private or no insurance. Of those who were not referred for surgical assessment, 50% had no evidence of extrahepatic disease, 19% had involvement of only one side of the liver, and 24% had three or fewer liver tumors (Fig. 1).

Referral analysis

Several factors were correlated with likelihood of surgical referral at our institution (Fig. 2). We found that age $\geq$ 65 y was associated with a lower rate of surgical referral (OR 0.42, 95% CI 0.18-0.92, $P = 0.041$) whereas gender, primary tumor site, and insurance status did not correlate with referral practices. Among CRLM tumor characteristics, factors associated with lower referral rate included bilobar hepatic disease (OR 0.27, 95% CI 0.08-0.83, $P = 0.021$) and presence of more than three CRLM (OR 0.3, 95% CI 0.10-0.88, $P = 0.029$). A trend was seen toward lower referral rate in patients who had extrahepatic metastases, but it was not found to be statistically significant (OR 0.40, $P = 0.069$). On multivariate analysis, factors independently associated with lower surgical referral rates included age $\geq$ 65 y, bilobar disease, and presence of greater than three liver metastases (Fig. 2). Presence of extrahepatic metastases was negatively correlated with surgical referral (−0.154); however, it was not statistically significant (Table 2). Age $\geq$ 65 y, presence of greater than three liver metastases, bilobar disease, and the presence of extrahepatic metastases were positively correlated among each other (Table 2).