Natural History of Patients with Subcentimeter Pulmonary Nodules Undergoing Hepatic Resection for Metastatic Colorectal Cancer

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BACKGROUND: CT imaging frequently detects subcentimeter pulmonary nodules (SPN) in patients undergoing resection of colorectal cancer liver metastases. Their clinical significance is unknown.

STUDY DESIGN: Patients were identified who underwent hepatic resection for colorectal cancer liver metastases between October 2004 and March 2006. The presence and imaging features of preoperative SPN were analyzed for their association with progression-free survival (PFS), disease-specific survival (DSS), and SPN progression.

RESULTS: One hundred sixty patients underwent liver resection and 68 (43%) had SPN identified preoperatively. Median number of nodules was 1 (75^{th} percentile: ≤2 nodules) and median size of the largest was 3 mm (25^{th} to 75^{th} percentile: 2 to 5 mm). SPN were unilateral in 77%, calcified in 19%, solid in 92%, and smooth in contour in 95% of patients. At median follow-up of 31 months for survivors, SPN were proven to be metastatic disease in 35% of patients (24 of 68), either by radiographic increase in size or number (n = 12) or histologic confirmation after resection (n = 12). Median PFS for the 160 patients was 16 months and 3-year DSS was 78%. There was a trend toward shorter median PFS in patients with preoperative SPN compared with patients with no SPN (12 versus 20 months; p = 0.242). There was no difference in 3-year DSS (70% versus 83%; p = 0.46). SPN progression after hepatic resection did not substantially affect 3-year DSS. Calcified nodules were less likely to progress compared with noncalcified nodules (8% versus 42%; p = 0.03).

CONCLUSION: SPN are common among patients undergoing resection of colorectal cancer liver metastases and approximately one-third of these will prove to be metastatic disease. Presence of limited preoperative SPN might be associated with shorter PFS after hepatectomy, but does not substantially impact 3-year DSS, and should not necessarily preclude resection of hepatic metastases. (J Am Coll Surg 2010;210:31–38. © 2010 by the American College of Surgeons)

Resection of hepatic colorectal cancer metastases, when feasible technically and in the appropriate clinical setting, is the standard of care. With improvements in perioperative outcomes and systemic chemotherapy, 5-year survival of patients with metastatic disease is reported to be 25% to 58%.[1,2] Modern preoperative evaluation typically includes a CT scan of the chest, abdomen, and pelvis to determine the extent of disease before initiating an aggressive treatment regimen, which might include a partial hepatectomy. Use of routine chest CT scan in patients with a normal chest x-ray before performing hepatic resection for colorectal metastases has been questioned previously.[3] However, the enhanced resolution of modern-day multidetector CT imaging has considerably improved the ability to identify not only hepatic metastases, but also sites of extrahepatic disease in regional lymph nodes, peritoneum, and lungs. The presence of extrahepatic disease introduces pause before proceeding with resectional therapy because its presence has been associated with worse outcomes.[4]

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Abbreviations and Acronyms
DSS = disease-specific survival
PFS = progression-free survival
SPN = subcentimeter pulmonary nodules

The enhanced resolution of thin-slice (5 mm) multidetector CT imaging, although beneficial in many circumstances, has introduced a new clinical dilemma. Radiologists frequently report the presence of subcentimeter pulmonary nodules (SPN), which is not surprising because of the incidence of this finding in a healthy, general population can approach 25%.[5] It can be difficult to interpret these findings, and the clinical significance of these SPN is particularly problematic in patients with known stage IV colorectal cancer. Whether these lesions represent metastatic disease, an evolving primary lung cancer, or a benign inflammatory process, can ultimately affect outcomes and influence the decision to resect the liver metastases. Current management guidelines for performing additional diagnostic tests on SPN, such as biopsy or excision, are directed at detecting early lung cancers.[6,7] In addition, the diagnostic tests themselves can be problematic because SPN can fall below the threshold of detection for PET scans, fine-needle aspiration might not be feasible, they can be difficult to localize thoracoscopically, and morbidity of a diagnostic thoracotomy seems unwarranted.

The aim of this study was to define the natural history and clinical significance of SPN in the context of patients with resectable hepatic colorectal cancer metastases. We also sought to describe the radiologic and clinical characteristics that best predict SPN progression after hepatic resection, confirming a diagnosis of metastatic pulmonary disease.

METHODS

A prospectively maintained hepatobiliary surgery database at Memorial Sloan-Kettering Cancer Center was reviewed for all patients with a diagnosis of colorectal cancer who underwent partial hepatectomy for metastatic disease between October 2004 and March 2006. Permission from Memorial Sloan-Kettering Cancer Center's Institutional Review Board was obtained before data review, and Health Insurance Portability and Accountability Act compliance was ensured. This time period was chosen to include only patients who underwent thin-slice (5 mm) multidetector CT imaging and to allow for adequate follow-up time postoperatively. Per standard protocol, patients underwent thin-slice CT imaging of their chest, abdomen, and pelvis every 3 months after undergoing hepatic resection, regardless of the presence of preoperative SPN. Preoperative and subsequent follow-up CT scans that documented pulmonary nodules were re-examined by a single chest radiologist (MSG); the presence and imaging features of SPN on preoperative scans and changes over time were analyzed for their association with progression-free (PFS) and disease-specific survival (DSS). SPN progression was defined as a documented radiographic increase in size or number of lesions or a histologic diagnosis of cancer, both of which satisfied diagnostic criteria of metastatic pulmonary disease. CT scans of patients with no previous documentation of SPN were not reviewed. Patients with preoperative pulmonary nodules >10 mm in size were excluded from analysis.

Radiologic characteristics of SPN were assessed with respect to number, size, and laterality. The largest nodule was categorized based on the presence of calcification, a solid versus ground-glass appearance, and the contour of the lesion (spiculated, smooth, or lobular). When calcified and noncalcified nodules were present simultaneously, radiologic characterization was recorded for the noncalcified nodules.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences 15.0 for Windows (SPSS, Inc). A combination of chi-square and Kaplan-Meier log-rank survival analysis was used to assess the association of the presence and progression of SPN with individual smoking history, site of primary disease (ie, colon versus rectum), clinical risk score,[8] and survival. Logistic regression analysis was conducted to determine which clinical parameters and radiographic characteristics predicted SPN progression.

RESULTS

During the designated time period of October 2004 to March 2006, 164 patients underwent a partial hepatectomy for metastatic colorectal cancer. Four patients were excluded because of the presence of pulmonary nodules >10 mm in size, leaving 160 patients for analysis. Median age was 56 years (range 27 to 85 years) and 60% (n = 95) were male. Median follow-up time was 31 months for survivors, at which time 73 patients (46%) had no evidence of disease, 59 (37%) were alive with disease, 27 (17%) had died from disease progression, and 1 patient died from an unrelated cause. CT scan images of patients with SPN, based on initial reports, were chosen for review; all scans were obtained within 4 weeks of operation. In 11 of these patients, the re-review showed that SPN were in fact absent, and the patients were reclassified appropriately.