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Clinical Science

Tumor growth pattern as predictor of colorectal liver metastasis recurrence

Rafael S. Pinheiro, M.D.[a,*], Paulo Herman, M.D.[a], Renato M. Lupinacci, M.D.[a], Quirino Lai, M.D.[b], Evandro S. Mello, M.D.[c], Fabricio F. Coelho, M.D.[a], Marcos V. Perini, M.D.[a], Vincenzo Pugliese, M.D.[a], Wellington Andraus, M.D.[a], Ivan Cecconello, M.D.[a], Luiz Carneiro D'Albuquerque, M.D.[a]

[a]Department of Gastroenterology, University of São Paulo Medical School, Hospital das Clínicas, Rua Dr Enéas de Carvalho Aguiar, 255, 9° Andar-sala 9113/9114, CEP 05403-900, São Paulo, Brazil; [b]Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Umberto I Policlinic of Rome, Rome, Italy; [c]Department of Pathology, University of São Paulo Medical School, São Paulo, Brazil

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Abstract

BACKGROUND: Surgical resection is the gold standard therapy for the treatment of colorectal liver metastases (CRM). The aim of this study was to investigate the impact of tumor growth patterns on disease recurrence.

METHODS: We enrolled 91 patients who underwent CRM resection. Pathological specimens were prospectively evaluated, with particular attention given to tumor growth patterns (infiltrative vs pushing).

RESULTS: Tumor recurrence was observed in 65 patients (71.4%). According to multivariate analysis, 3 or more lesions ($P = .05$) and the infiltrative tumor margin type ($P = .05$) were unique independent risk factors for recurrence. Patients with infiltrative margins had a 5-year disease-free survival rate significantly inferior to patients with pushing margins (20.2% vs 40.5%, $P = .05$).

CONCLUSIONS: CRM patients with pushing margins presented superior disease-free survival rates compared with patients with infiltrative margins. Thus, the adoption of the margin pattern can represent a tool for improved selection of patients for adjuvant treatment.

Colorectal cancer (CRC) is the fourth leading cause of cancer-related death among men and the fifth among women.[1,2] About 60% of patients with CRC treated with curative intent will present with metastatic disease[3]; in most cases, it is confined to the liver.[4] Several studies have shown that the resection of colorectal liver metastases (CRM) can lead to 5-year survival rates of 25% to 58%.[5,6]

Many reports have shown a strong correlation between surgical margins greater than 1 cm and disease-free long-term survival. Among them, surgical margin evaluation has become a controversial issue. Many reports have shown a strong correlation with surgical margins larger than 1 cm and disease-free long-term survival. However, in recent years, the aggressive surgical approach in patients with multiple and bilobar nodules has made the 1-cm target margin hard to

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* Corresponding author. Tel.: +55-11-2661-3323; fax: +55-11-2661-6250.

E-mail address: rsnpinheiro@gmail.com

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achieve because of insufficient remnant liver parenchyma or the proximity of the tumor from vascular structures.[7–9] In recent years, studies addressing surgical margins showed that patients submitted to CRM resection with subcentimetric margins or R1 resections had excellent outcomes.[10]

In patients with CRC, the tumor growth pattern has been studied as an indirect tumor behavior factor predicting tumor recurrence.[11] Disease recurrence was strongly associated with infiltrative margins when compared with patients with pushing margins.[12–14] The adoption of this classification had been used mainly for primary CRC, and there are only a few studies evaluating metastatic liver disease growth pattern showing similar results.[15,16] The aim of the present study was to evaluate the impact of the tumor growth pattern on local recurrence and survival in patients with metastatic CRC submitted to liver resection.

Patients and Methods

From January 2000 to December 2009, 117 patients underwent hepatic resection for CRM. Patients with incomplete macroscopic resection (R2, n = 2), preoperatively detected metastatic extrahepatic disease (n = 7), early postoperative death (within 90 days, n = 2), and those with unavailable specimens for histological assessment (n = 15) were excluded.

Patient data were obtained from a prospectively collected database. Variables analyzed were sex, age, synchronous (up to 1 year) or metachronous disease, TNM staging, pre- and postoperative serum carcinoembryonic antigen, neoadjuvant chemotherapy, number of nodules, size of the largest nodule, presence of uni- or bilateral liver disease, type of liver resection, tumor differentiation grade, surgical margin status, tumor margin growth pattern (pushing or infiltrative), presence and time of recurrence, and site of recurrence.

All specimens were re-evaluated by a senior pathologist. Margins were considered microscopically affected (R1) when the tumor was in contact with the surgical margin; a margin of 1 mm or less was considered coincidental but cancer free (R0). The standard growth pattern classification for colorectal cancer as proposed by Jass et al[11] was adopted to categorize hepatic metastases. It stratified metastatic growth pattern in "infiltrative", when the tumor spread freely through the surrounding tissue, dissecting between normal hepatocytes in an effortless fashion, usually unopposed by any form of inflammatory host response. Or "pushing", when the tumor's edges expanded, pushing the adjacent liver tissue reasonably well circumscribed or involved by a thin capsule (Fig. 1). Uncommonly, it is possible to observe dubious areas to precisely define the growth pattern as infiltrative or pushing. In these cases, the overall findings were used as major criteria to easily stratify it.

Statistical analysis

Univariate logistic regression analysis was performed to evaluate the risk factors for recurrence. Variables with potential biological or clinical relevance were analyzed. Multivariate logistic regression was performed with variables that had a *P* value less than .20 according to univariate analysis. The goodness of fit in each model was analyzed with the Hosmer-Lemeshow test. Risk prediction was reported in terms of *P* values, odds ratios (ORs), and 95% confidence intervals (CIs). A *P* value less than or equal to .05 indicated statistical significance. The Kaplan-Meier method was adopted to evaluate recurrence rates, and the log-rank test was used for comparison between groups.

Results

Fifty men and 41 women with a mean age of 59 years (range 28 to 81 years) were evaluated. The study population characteristics are reported in Table 1. In 43 cases (47.2%), metastases were synchronous; the remaining patients with metachronic metastases had a median time of 17 months between primary tumor resection and the diagnosis of liver

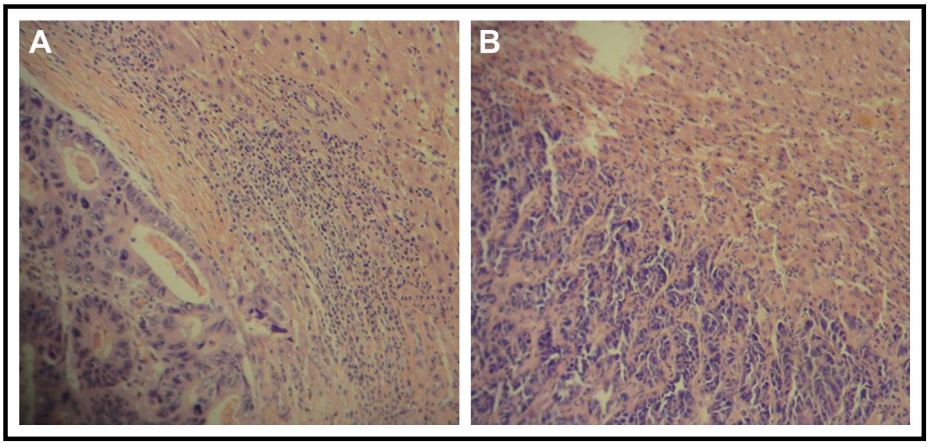

Figure 1 A microscopic view of CRM with typical growth pattern representations. (A) Pushing type: tumoral edges expand, pushing the surrounding hepatic tissue. (B) Infiltrative type: the tumor freely expands into the normal hepatic tissue.