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ScienceDirect
EJSO 37 (2011) 336–343
EJSO the Journal of Cancer Surgery
www.ejso.com

R1 resection for aggressive or advanced colorectal liver metastases is justified in combination with effective prehepatectomy chemotherapy

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Accepted 6 January 2011
Available online 31 January 2011

Abstract

Aims: Here we reassess anticipated inability to obtain a microscopically clear surgical margin as an absolute contraindication to surgery for colorectal liver metastases in view of improvements in treatment modalities adjunctive to surgery.
Methods: We retrospectively analysed 310 patients treated at our institution to estimate the survival benefit from R1 hepatectomy performed to remove liver metastases from colorectal cancer.
Results: Considering all 310 patients evaluated, the R1 resection group (positive margin; $n = 55$) showed a lower disease-free rate ($P < 0.01$) and worse overall survival ($P < 0.01$) than the R0 resection group (negative margin; $n = 255$). When patients were divided according to initial resectability, similar differences in disease-free rate and overall survival ($P = 0.03$) between R1 ($n = 19$) and R0 ($n = 182$) were observed in patients whose metastases were resectable. However, superior impact of R0 resection ($n = 73$) compared to R1 resection ($n = 36$) on disease-free rate ($P = 0.44$) and overall survival ($P = 0.50$) was not confirmed in patients with initially unresectable or marginally resectable metastases, especially those with a favourable response to prehepatectomy chemotherapy.
Conclusions: A predicted positive surgical margin after resection no longer should be an absolute contraindication to surgery for aggressive or advanced liver metastases.

Keywords: Colorectal cancer; Liver metastasis; Hepatectomy; R1 resection; Survival

Introduction

Numerous retrospective and prospective series involving large numbers of patients have demonstrated a long-term survival benefit of liver resection for patients with hepatic metastases from colorectal cancer, while also examining various factors affecting long-term survival including surgical margin status. Ekberg et al.[1] first suggested crucial importance of achieving a 1.0-cm tumour-free margin during potentially curative liver resection for colorectal liver metastases to optimise long-term survival. Other investigators similarly noted shorter overall[2,3] and disease-free survival[2,4] when the surgical margin was less than 1.0 cm. Anticipation of a 1.0-cm surgical margin thus became a selection criterion for liver resection. However, such a margin was obtained at hepatic resection in only 34–47% of patients, even where most patients had few metastases.[2,5,6]

Some recent investigators have concluded that width of a negative surgical margin had no effect on survival. Altendorf-Hofmann and Scheele[7] noted that while patients with a microscopically positive margin (R1) had a worse prognosis than patients with a microscopically negative margin (R0), survival was not affected by the extent of the negative surgical margin. Furthermore, no influence of width of a negative surgical margin on recurrence risk or site of recurrence was reported.[5] More recently, Adam et al.[8] reported a 5-year survival rate of 57% in 202 patients who underwent R1 resection, a designation denoting histopathologically evident cancer cells at the line of resection after resection believed curative by the surgeon.

Recent advances in chemotherapy and surgical technique allow us to extend indications for surgery in the

Abbreviations: CA, Carbohydrate antigen; CDDP, Cisplatin; CEA, Carcinoembryonic antigen; CT, Computed tomography; DFR, Disease-free rate; FA, Folinic acid; 5-FU, 5-Fluorouracil; PD, Progressive disease; PR, Partial response; SD, Stable disease.

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doi:10.1016/j.ejso.2011.01.007

presence of multiple, massive, unfavourably located colorectal cancer metastases including those invading major vascular structures: The importance of surgical margin status therefore should be reassessed. Less arbitrary consideration of the margin ultimately might benefit patients.

We retrospectively analysed patients treated at our institution to estimate the survival benefit from R1 hepatectomy performed to remove colorectal cancer metastases from the liver.

Patients and methods

Patients

Between 1992 and 2009, members of our Department of Gastroenterological Surgery at the Yokohama City University Graduate School of Medicine treated 351 patients in whom colorectal liver metastases were diagnosed at liver resection with curative intent. Among these patients, 20 were excluded from study: curative hepatectomy could not be undertaken in four patients, while concomitant extrahepatic metastases precluded R0 resection in 16 others who had a curative liver resection. Twenty-three patients who underwent concomitant local treatment (microwave ablation) in addition to liver resection (including three of the patients whose extrahepatic disease precluded R0 resection) also were excluded. One patient with solitary metastasis who died within 60 days of surgery from postoperative bleeding, sepsis, and multiple organ failure was excluded from analysis. Data from 310 patients remained (Fig. 1).

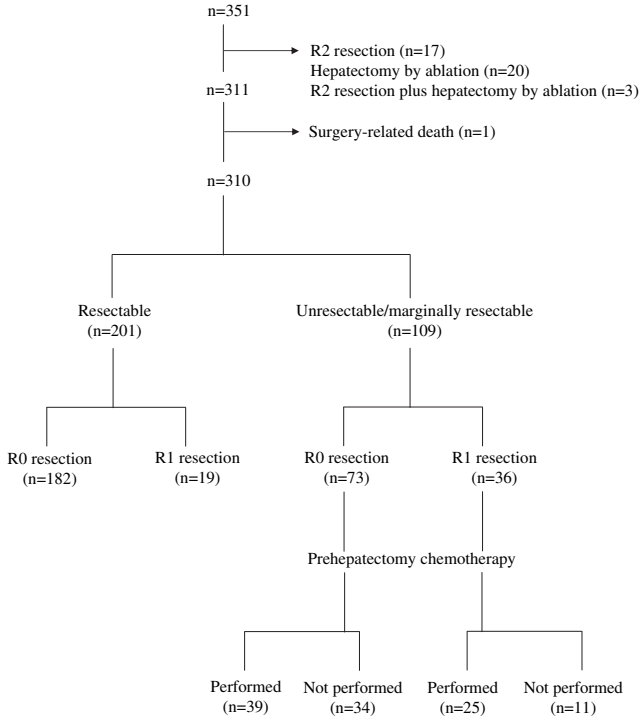

Figure 1. Patient disposition.

These patients consisted of 199 men and 111 women. Their median age was 65 years (range, 30 to 85). Numbers of metastases were one in 140 patients, two in 55, three in 25, and four or more in 90; the median number of metastases at diagnosis was two (range, one to 21). The median maximum size of metastases was 30 mm (range, 5 to 185). Concomitant extrahepatic disease treated with curative resection achieving a clear margin was present in 45 patients. Median follow-up duration for the 310 patients was 34 months (range, 2 to 221). Among these patients, 55 had a microscopically determined minimal tumour-free margin of 0 mm, although macroscopically complete removal of tumour tissue had been performed. These patients represented the R1 resection group, meaning that tumour was identified microscopically at the line of resection even though macroscopically visible tumour at the margin was not evident to the surgeon. The other 255 patients, who had no microscopically evident tumour cells at the resection margin, were defined as the R0 resection group (Fig. 1).

Preoperative evaluation

Preoperative staging included physical examination, measurement of serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9, colonoscopy, barium enema, abdominal imaging by ultrasonography and computed tomography (CT), and chest imaging by routine radiography or CT. Since 2002, positron-emission tomography has been used for preoperative staging.

Disease resectability was determined through multidisciplinary assessment by a team including surgeons and medical oncologists, with unresectability usually based on insufficient remnant liver (less than 25–30%) or excessive risk of surgery considering location and anticipated resected volume. Patients with marginally resectable metastases were those with four or more metastases including lesions in both major lobes; massive tumour 80 mm or more in diameter; or unfavourable tumour location with invasion of major vascular structures.

Prehepatectomy chemotherapy

As a rule, patients whose liver metastases initially were deemed unresectable or marginally resectable had prehepatectomy chemotherapy. However, treatment strategy depended on several factors in addition to initial assessment of resectability, so patients were categorised on a case-by-case basis.

Preoperative chemotherapy was given to 64 patients, including 39 in the R0 group and 25 in R1 (Fig. 1). Thirty patients received final prehepatectomy chemotherapy via the hepatic artery with a combination of 5-fluorouracil (5-FU), L-folinic acid (FA), and cisplatin (CDDP). Twenty-one patients received both hepatic arterial infusion chemotherapy as outlined above and systemic chemotherapy. The other 13 patients received only systemic chemotherapy.