Articles

Liver resections for colorectal cancer metastases

Bilić Zdenko, Glavčić Goran

Department of Surgery, University Hospital "Sestre milosrdnice" Zagreb, Croatia

Biomedicine and Surgery

ABSTRACT

AIM: Colorectal cancer is the second most common cancer in the Western world. Surgery is currently the only curative method of treatment.

METHODS: Age, gender, the number and size of the largest metastases, distribution according to Gennari, as well as the type of liver resection according to the timing of metastasis detection were assessed for 51 patients who underwent liver resections. Overall 3-year survivals were compared.

RESULTS: Gender (p=0.223), age (p=0.243), number (p=0.120) and distribution (p=0.516) of metastases did not significantly influence survival. Patients with the largest metastasis 5 cm or less than in diameter had significantly greater 3-year survival rate compared to those with metastases larger than 5 cm (65.7% vs. 30%, p=0.034). Simultaneous resections of colorectal cancer and liver metastases were associated with significantly longer survival compared to delayed resections (69.7% vs. 44.7%, p=0.018).

CONCLUSION: Liver resection for colorectal cancer metastases is justifiable and safe even in older patients. Metastases over 5 cm and delayed resections were associated with shorter survival. In the multivariate survival model, among these factors, simultaneous resection of synchronous metastases was found to be the only significant factor influencing 3-year survival.

KEY WORDS: colorectal neoplasms; neoplasm metastasis; liver; hepatectomy; human

Correspondence to: Bilić Zdenko, Department of Surgery, University Hospital "Sestre milosrdnice", Vinogradska cesta 29, HR-10000 Zagreb, Croatia, e-mail: bilic84@gmail.com

Data received: December 10th 2016
Date accepted: February 18th 2017

INTRODUCTION

Colorectal cancer is the second most common cancer in the Western world. Approximately 15 to 25% of patients already have liver metastases at the time of initial presentation, and in another 20 to 25% of patients liver metastases develop within the next two years (1). Patients with untreated liver metastases have an average survival of approximately 9 months (2), and only 1% is expected to survive 5 years (3).

Surgery is the only potentially curative method of treating patients with liver metastases secondary to colorectal cancer, with 5-years survival rates up to 50% (4). Morbidity after liver resection for colorectal metastases is generally reported to be 20-40% and mortality is below 5% (5). Although chemotherapy may prolong survival to a certain extend, the survival is generally poor, with 2-year survival 25-30% (6), and other therapeutic modalities, such as cryosurgery, are purely palliative (7).

Since liver resection clearly represents the treatment of choice for selected patients with metastases from colorectal cancer, it should be attempted whenever possible (8). Accordingly, factors determining the benefit of surgical treatment of liver metastases must be clearly identified.

The purpose of this paper is to analyze the influence of patient and disease related factors on survival, and to assess the importance of surgical strategies in the treatment of hepatic metastases of primary colorectal cancer.

METHODS

Total of 51 liver resections for metastatic colorectal cancer entered the study. Twenty-two patients underwent simultaneous resection of colorectal cancer and hepatic metastases. Twenty-nine patients had delayed resection of liver metastases some time after the resection of primary colorectal cancer (median 24 months, range 1-48 months) and liver resection alone was performed in these patients. The mean age on admission was 62.3 years (range 30 – 78 years).

Data regarding liver resection were collected from admission records, surgeon's reports and histological examination of the removed specimens (resected liver).

Age, gender staging of liver metastases according to Gennari's classification (9), lobar distribution of liver metastases, the number of metastatic lesions and the size of the largest metastasis were recorded.

All resections were performed using intraoperative ultrasound for determination of the location of metastases and the line of resection and involved at least 1 cm tumor-free margin (R0 resection).

Postoperative complications diagnosed during postoperative hospital stay were noted. Total of 13 (25.5%) patients developed complications in the postoperative course and one patient (2%) died on the sixth postoperative day from liver failure due to too small volume of functional liver remnant.

Patients were followed up for median of 13.9 months (range 1-61 months). Only patients surviving at least 30 days were included in survival analysis. Survival was determined using Kaplan-Meier product-limit method and Cox's F-test statistics for group comparisons. Proportional hazard (Cox) regression model was used to determine the influence of different factors on survival.

Differences in the percentages of complications were analyzed using Fisher's exact probability test (FEP). Data were presented either as median values with range given in parentheses, or mean values and standard deviations (SD). Values of $p<0.05$ were considered to represent statistical significance.

RESULTS

There were 28 (54.9%) female and 23 (45.1%) male patients. There was no statistically significant difference in age between female and male patients (mean 62.4 [SD 11.5] vs. 62.1 [SD 8.0] respectively, p=0.904). Median survival of female patients was 46 months and the median survival of male patients was 12 months. Overall 3-year survival was 64.9% for women and 43.5% for men. Although female patients had longer survival, this difference was not statistically significant (p=0.223).

Twelve (23.5%) patients were 70 years of age or older, whereas 39 (76.5%) patients were under 70. Median survival of patients under 70 years of age was 45.1 months. Patients who were 70 years of age or older had median survival 19.7 months. Overall 3-year survival was 62.9% for patients under 70 years of age and 0% for patients who were 70 or older. This difference was not statistically significant (p=0.243). The rate of complications in patients 70 years and older was 33.3% and in patients younger than 70 years of age was 23.1% (FEP, p=0.358).

The majority of metastases were located in the right hepatic lobe, 27 (52.9%), followed by bilateral distribution of metastases in 13 (25.5%) patients, whereas 11 (21.6%) of patients had metastases confined to the left hepatic lobe. Patients with unilobar metastases (confined to either left or right hepatic lobe) had median survival of 39 months and those with bilobar metastases 21.6 months. Overall 3-year survival was 60.3% for patient with unilobar distribution of liver metastases, compared to 49.7% for patients with bilobar metastases. No significant difference in survival was observed between patients with unilobar and bilobar distribution of hepatic metastases (p=0.516).

Median survival of patients with solitary metastasis (n=21) was 23.2 months, while patients with multiple metastases (n=30) it was 40.9 months. Patients with solitary metastases had 3-year survival 54.4% while 61.9% of patients with multiple metastases survived 3 years. This difference was not statistically significant (p=0.120).

Patients with Gennari stage 3 had median survival 16.1 months and of those patients with Gennari stages 1 and 2 was 43 months. Overall 3-years survival was 39.3% for patients with stage 3 and 65.1% for patients with Gennari stages 1 or 2. No significant difference in overall 3-year survival was observed between patients with Gennari 3 stage liver metastases and those with Gennari stages 1 and 2 (p=0.134).

The median diameter of the largest metastasis was 3.0 cm (range 0.3-17 cm). Patients with largest metastasis measuring 5 cm or less had median survival 42.4 months and overall 3-year survival rate 63.1%. On the other hand, patients with largest metastasis greater than 5 cm in diameter had median survival of 15.9 and only 35.7% overall 3-year survival (p=0.034).

Patients with simultaneous resection of primary colorectal cancer and hepatic metastases had significantly longer survival compared to those in whom the delayed resection was performed (due to metachronous occurrence of metastases). As much as 69% of patients survived 3 years after simultaneous colorectal and liver surgery, compared to 45.7% of patients after delayed resection (p=0.018) (figure 1). Complications developed in 22.7% patients who underwent simultaneous resections and 27.6% for patients in whom delayed resection of metachronous metastases was performed (FEP, p=0.693).

Among the diameter of the largest metastasis, the number of metastases, Gennari's classification of liver metastases, unilobar versus bilobar distribution of metastases and the type of hepatic resection (simultaneous or delayed), only the type of hepatic resection significantly influenced the survival (table 1).

Figure 1. Overall survival according to the type of hepatic resection

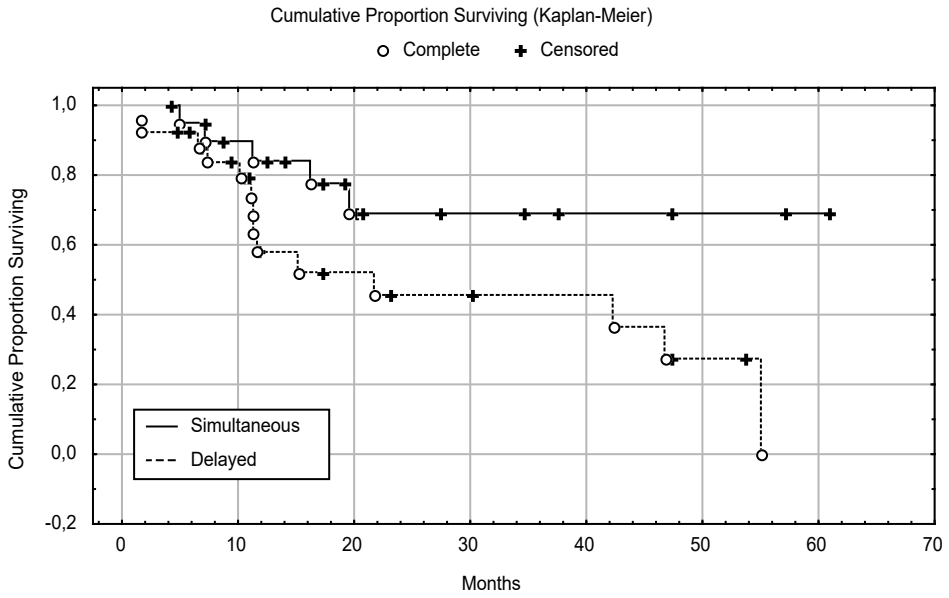

Table 1. Influence of the number, size and distribution of hepatic metastases and the type of hepatic resection on survival of patients with hepatic metastases from colorectal cancer. Proportional hazard (Cox) regression model

	Beta	SE	t-value	P
Gennari's stage	-0.293000	0.534487	-0.548204	0.584
Number of metastases	0.007338	0.114743	0.063953	0.949
Size of the largest metastasis	0.105479	0.108620	0.971086	0.332
Distribution *	0.661700	0.722398	0.915977	0.360
Type of resection **	1.259842	0.610060	2.065113	0.039

Beta = regression factor, SE = standard error, t-value = regression factor / SE. Levels of p<0.05 were considered statistically significant

* distribution of hepatic metastases was coded 0 for unilobar and 1 for bilobar distribution of metastases;

** type of resection was coded 0 for simultaneous and 1 for delayed resection

DISCUSSION

The prognosis for patients with liver metastases from colorectal cancer is still poor. Thus, patient selection for hepatic resection is essential to improve the poor results of the procedure (10).

In the last decades, mortality sex ratios for colorectal cancer in Europe have shown more favorable trends for females, which may be attributable, in part, to the introduction of exogenous hormones (11). Furthermore, hormonal replacement therapy in older women may, again, reduce the risk of genetically unstable tumors (12). Gender-associated immunological differences in the response to surgery were also hypothesized (13). Significant gender differences have been reported in both disease-free and overall survival after curative resection for rectal cancer. Disease-free survival was significantly longer in women than in men (51.6 months versus 46.0 months, $p<0.05$). Also, the overall survival was significantly longer in women than in men (57.8 months versus 52.0 months, $p < 0.05$); however, such a gender related difference in survival was not observed for colon cancer (13). Our results also indicate the difference in overall survival after hepatic resection for colorectal metastases between male and female patients, but this difference was not statistically significant. This is in accordance with the findings of most studies, demonstrating no significant gender related difference in survival after hepatic resection of colorectal metastases to the liver (1, 5).

In several clinical trials age was found to influence survival. The recurrence rates was found to be similar for patients younger than 70 years of age and those older than 70 (56% vs. 66%), but mean survival was longer for younger patients (22.9 vs. 33.5 months) (14). Another study reported 1-, 3-, and 5-year survival rates of 69%, 38% and 25% for patient over 70 years of age operated for liver metastases. In comparison with patients younger than 70 years, no significant differences were found in early and late postoperative results, with 28% morbidity and 6% mortality rate (14). Our results demonstrated shorter 3-year survival for patients over 70 years of age. However, no significant difference in overall survival between patients over 70 years of age and those younger than 70 years was observed in this study. Also, older patients did not have significantly more complications compared to younger patients. As a result of these findings, older patients should be regarded as equal candidates for curative resection of colorectal liver metastases. It should be pointed out, however, that survival analysis in this trial was based on overall survival only, and not disease-free survival. Therefore, although no significant difference was found in overall survival according to age (with cut-off point at 70 years) and no significant difference was observed in the rate of postoperative complications, patients in advanced age should be individually evaluated (15).

The prognostic significance of the distribution of liver metastases (unilobar versus bilobar) is controversial. Some investigators have shown that the distribution of liver metastases influences survival (16, 17). In a study by Yamaguchi et al., bilobar distribution of liver metastases was associated with worse prognosis and lower rates of 3, 5 and 7-year survival (18). In the presented series, bilobar distribution of liver metastases was found in 25% of patients, which corresponds to the findings of other authors (18). Overall 3-year survival in the presented series was not significantly different, and was less than 4% greater in patients with unilobar distribution of metastases. Since all resections in this study were R0 resections with at least 1 cm tumor-free margin, as assessed by intraoperative ultrasound, such outcome is not surprising.

The similar controversy exists for the prognostic value of the number of liver metastases. General opinion is that four or more metastases inversely affect the outcome (8). However, the significance of the number of metastases for the survival is still the matter of debate. Some authors found that two or more metastases are related to poorer outcome, and no significant difference in survival was observed between patients with fewer than four and those with four and more metastases (8). Others reported significant differences in survival for patients with four and more metastases versus those with fewer than four lesions, but no significant difference in survival between patients with solitary and multiple metastases (19). Finally, some studies reported no significant influence of the number of metastases on survival (20, 21). These differences in observed impact of the number of metastases on survival may largely be attributed to the fact that multiple metastases often require extensive resections when tumor-free margins are less frequent; also, the chance of missed lesions is greater in cases with multiple metastases (8). Intraoperative ultrasound, which is today accepted as a standard aid in resections for liver metastases, may reveal up to 58% of lesions otherwise undetectable at the time of surgery (22). In the presented study, even greater percentage of patients with multiple metastases survived three years compared to patients with solitary

metastases, confirming no significant influence of the number of metastases on overall survival. It is our opinion that this is a direct consequence of accurate identification of the number and location of liver metastases as assessed with intraoperative ultrasound, enabling R0 resections.

The maximum size of the largest metastasis has been investigated as a prognostic indicator for patients with liver metastases from colorectal cancer (5), as well as the percentage of liver replacement by the tumor (23). The size of the largest metastasis was found to be significantly associated with survival in this study, but not the stage of liver metastases according to Gennari.

Some reports have shown that the prognosis for patients with synchronous liver metastases is worse than that for those with metachronous liver metastases (10, 15). Therefore, the timing of liver resection is of special importance. However, the timing of liver resection is still the point of continuing controversy. Some investigators recommend delayed liver resection with a period of time ranging from several weeks to months, while others favor the resection of the metastases immediately after their detection (24). We have previously demonstrated that simultaneous resections can be safely performed and are not associated with significantly greater percentage of postoperative complications (25). Lyass et al. also found that simultaneous resections were safe, with morbidity 27% as compared to 35% morbidity for patients who underwent staged resections for metachronous metastases (26). Our results clearly demonstrate that the survival of patients with synchronous metastases, which were treated simultaneously with primary colorectal cancer, is significantly better than that of patients with metachronous resections. In a multiple regression model, among the diameter of the largest metastasis, the number of metastases, Gennari's classification of liver metastases, unilobar versus bilobar distribution of metastases and the type of hepatic resection (simultaneous or delayed), only the type of hepatic resection significantly influenced the survival. Also, the rate of postoperative complications did not differ between simultaneous and delayed resection groups.

The results of this study evidently show that liver resection for colorectal cancer metastases is justifiable and can be safely performed even in older patients. Gender, bilobar distribution, the number of metastases and percentage of hepatic replacement by tumor did not significantly influence survival. Metastases larger than 5 cm were associated with shorter survival. Simultaneous resections of synchronous metastases were found to have the greatest impact on survival.

REFERRENCES

1. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. The British journal of surgery. 1990;77(11):1241-1246.
2. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet (London, England). 1994;343(8910): 1405-1410.
3. Bengmark S, Hafstrom L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer. 1969;23(1):198-202.
4. Nakamura S, Suzuki S, Baba S. Resection of liver metastases of colorectal carcinoma. World journal of surgery. 1997;21(7):741-747.
5. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF. Liver resection for colorectal metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1997;15(3):938-946.
6. Kemeny N, Fata F. Hepatic-arterial chemotherapy. The Lancet Oncology. 2001;2(7):418-428.
7. Onik G, Rubinsky B, Zemel R, Weaver L, Diamond D, Cobb C, Porterfield B. Ultrasound-guided hepatic cryosurgery in the treatment of metastatic colon carcinoma. Preliminary results. Cancer. 1991;67(4):901-907.
8. Imamura H, Kawasaki S. Treatment strategy for multiple hepatic metastases of colorectal carcinoma. Journal of hepato-biliary-pancreatic surgery. 1999;6(1):23-29.
9. Gennari L, Doci R, Bignami P, Bozzetti F. Surgical treatment of hepatic metastases from colorectal cancer. Annals of surgery. 1986;203(1):49-54.
10. Fujita S, Akasu T, Moriya Y. Resection of synchronous liver metastases from colorectal cancer. Japanese journal of clinical oncology. 2000;30(1):7-11.
11. Fernandez E, Bosetti C, La Vecchia C, Levi F, Fioretti F, Negri E. Sex differences in colorectal cancer mortality in Europe, 1955-1996. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2000;9(2):99-104.
12. Slattery ML, Potter JD, Curtin K, Edwards S, Ma KN, Anderson K, Schaffer D, Samowitz WS. Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. Cancer research. 2001;61(1):126-130.
13. Wichmann MW, Muller C, Hornung HM, Lau-Werner U, Schildberg FW, Colorectal Cancer Study G. Gender differences in long-term survival of patients with colorectal cancer. The British journal of surgery. 2001;88(8):1092-1098.
14. Zieren HU, Muller JM, Zieren J. Resection of colorectal liver metastases in old patients. Hepato-gastroenterology. 1994;41(1):34-37.
15. Scheele J, Altendorf-Hofmann A. Resection of colorectal liver metastases. Langenbeck's archives of surgery. 1999;384(4):313-327.

16. Bakalakos EA, Kim JA, Young DC, Martin EW, Jr. Determinants of survival following hepatic resection for metastatic colorectal cancer. World journal of surgery. 1998;22(4):399-404; discussion 404-395.
17. Nakamura S, Suzuki S, Konno H. Resection of hepatic metastases of colorectal carcinoma: 20 years' experience. Journal of hepato-biliary-pancreatic surgery. 1999;6(1):16-22.
18. Yamaguchi J, Yamamoto M, Komuta K, Fujioka H, Furui JI, Kanematsu T. Hepatic resections for bilobar liver metastases from colorectal cancer. Journal of hepato-biliary-pancreatic surgery. 2000;7(4):404-409.
19. Iwatsuki S, Esquivel CO, Gordon RD, Starzl TE. Liver resection for metastatic colorectal cancer. Surgery. 1986;100(4):804-810.
20. Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. The British journal of surgery. 1991;78(7):797-801.
21. Rosen CB, Nagorney DM, Taswell HF, Helgeson SL, Ilstrup DM, van Heerden JA, Adson MA. Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. Annals of surgery. 1992;216(4):493-504; discussion 504-495.
22. Machi J, Isomoto H, Kurohiji T, Yamashita Y, Shirouzu K, Kakegawa T, Sigel B, Zaren HA, Sariego J. Accuracy of intraoperative ultrasonography in diagnosing liver metastasis from colorectal cancer: evaluation with postoperative follow-up results. World journal of surgery. 1991;15(4):551-556; discussion 557.
23. Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hagerstrand I, Ranstam J, Bengmark S. Determinants of survival in liver resection for colorectal secondaries. The British journal of surgery. 1986;73(9):727-731.
24. Yedibela S, Reck T, Hohenberger W. [Resection of liver metastases--goal, timing and results]. Therapeutische Umschau Revue therapeutique. 2001;58(12):713-717.
25. Doko M, Zovak M, Ledinsky M, Mijic A, Peric M, Kopljar M, Culinovic R, Rode B, Doko B. Safety of simultaneous resections of colorectal cancer and liver metastases. Collegium antropologicum. 2000;24(2):381-390.
26. Lyass S, Zamir G, Matot I, Goitein D, Eid A, Jurim O. Combined colon and hepatic resection for synchronous colorectal liver metastases. Journal of surgical oncology. 2001;78(1):17-21.