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Colorectal cancer liver metastasis: Local treatment for a systemic disease?

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Introduction

Colorectal cancer is one of the leading causes of death in the Western world; its incidence is lower only than those of breast cancer in women and lung cancer in men. Radical surgery can cure only about 50% of patients [1]. Adjuvant chemotherapy is beneficial in 10% to 15% of high-risk patients with UICC stage III disease [2, 3].

It is estimated that more than 80% of the patients with metastatic disease have liver involvement either at the time of first diagnosis or at relapse after curative surgery [4]. The liver is the sole site of metastases in up to 30% of patients, of whom one-third may be resectable [5].

The probable therapy choices are no treatment ('wait-and-see'), locoregional treatment such as surgical resection, alcohol instillation, laser-induced hyperthermia, locoregional chemotherapy or systemic chemotherapy. Only a limited amount of information is available about the natural course of patients with liver metastasis only. Depending on the extent of the liver involvement (solitary vs. non-solitary lesions) a median survival of 11 or 17 months has been reported, which corresponds to a three-year survival rate of 10% to 13%, respectively [6]. However, no data from a randomized trial are available because most clinicians have been unwilling to expend unequal amounts of effort in the care of their patients, an attitude that is supported by the results of recent medical and surgical treatment. Data on laser-induced hyperthermia or percutaneous alcohol injection [7–9] are too preliminary and will not be discussed in this paper.

Favorable results (five-year survival rate of 38%) reported after the resection of hepatic metastases in a series of 456 consecutive patients associated with low mortality and morbidity rates (3% and 31%, respectively) led the authors to conclude that a randomized trial to investigate the efficacy of surgical resection – as opposed to no resection – can not ethically be performed [10].

This article will discuss the therapeutic alternatives in the care of patients with isolated liver metastases.

The value of surgical resection

Following the first report by Langenbuch in 1887 on liver resection [11] the procedure has become a safe one due to better supportive treatment and improvements in the operating technique. It is now a well accepted treatment for patients with colorectal liver metastases, which may be curative in approximately 30% of patients [10, 12–22]. These single-center retrospective analyses are supported by registry data including over 1500 patients [23, 24].

Although a radical (RO) resection may be possible in about 70% of patients, tumor relapse will occur in at least two out of three of them. Detailed information about the pattern of recurrences is available from the pooled data of an American, British and German registry database [23] (Figure 1). Interestingly, approximately 43% of resected patients will experience a recurrence in the liver either as the only site or in combination with other sites. About 27% of the patients will develop extrahepatic metastases with no effect on the liver. This data indicates that most of the patients will have intra- or extrahepatic occult disease already at the time of surgery which will constitute the source of relapse. It

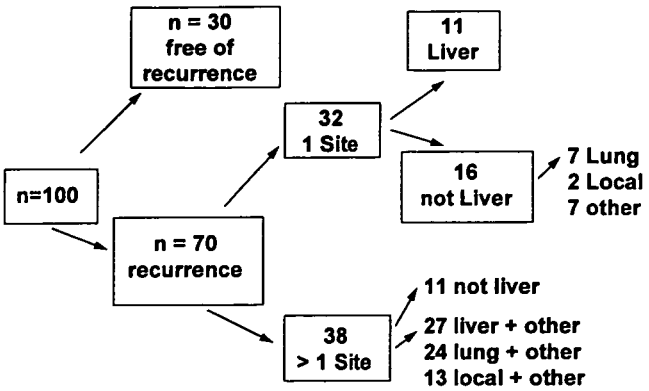

Figure 1. Pattern of recurrence within five years after resection of colorectal cancer hepatic metastases (according to [23]).

Table 1. Retrospective analysis of liver resection.

Number of patients	Recruitment period	Synchroneous	Solitary	Extra hepatic disease	Operative mortality	Five-year overall survival	Reference
141	1948–1982	~25%	~75%	8%	4%	25%	[12]
75	1971–1982	~29%	n.a.	15%	7%	35%	[13]
62	1950–1981	55%	68%	0%	10%	34%	[14]
60	1975–1985	22%	63%	0%	0%	45%	[15]
80	1970–1985	54%	53%	0%	5%	25%	[16]
122	1981–1989	39%	52%	n.a.	4%	30%	[17]
100	1980–1989	n.a.	n.a.	n.a.	5%	30%	[18]
207	1960–1988	47%	54%	13%	6%	31%	[19]
280	1960–1987	38%	62%	3%	4%	25%	[20]
110	1984–1992	23%	62%	7%	5%	30%	[21]
204	1981–1991	73%	45%	n.a.	0%	32%	[22]
456	1985–1991	n.a.	53%	10%	3%	38%	[10]

Registry data

Number of patients	Recruitment period	Number of sites	Five-year overall survival	Reference
607	1948–1985	38	33%	[23]
1568	1968–1990	16	28%	[24]

has been speculated that the liver resection itself may stimulate hepatic mitotic activity through growth factors for liver regenerative functions and that these factors might promote tumor growth after partial hepatectomy, as has been demonstrated in experimental studies [25].

To identify patients at high risk for intra- or extrahepatic failure is, therefore, of major importance. A French group has collected information on 1, 568 patients undergoing hepatic surgery for colorectal cancer metastases [24]. Derived from a multivariate analysis the following variables associated with an unfavorable prognosis have been identified: age above 60 years, extension into serosa or lymphatic spread of the primary cancer, time interval from primary tumor to metastases of less than two years, size of the largest metastases greater than 5 cm, more than three hepatic metastases and surgical clearance of less than one centimeter. A CEA level of greater than 5 mg/l or greater than 30 mg/l may be used as a substitute variable for age. Patients with up to two of these factors had a low risk of recurrence and a two-year survival rate of 79% which decreased to 56% in instances of three or four risk factors and to 34% in instances of five or more risk factors. In the latter cohort survival of longer than five years was rare and the value of surgery may be debatable.

The role of adjuvant postoperative chemotherapy

The success of adjuvant systemic chemotherapy after curative resection of the primary tumor [2, 3] has rekindled interest in its use after resection of hepatic metastases. Various attempts have been made using intraarterial, portal vein, peritoneal, systemic chemo- or immunotherapy to improve the cure rate of patients by the use of adjuvant chemotherapy [13, 26–37]. In some of these pilot studies a positive effect on survival was claimed, so at least four randomized multicenter trials were initiated comparing i.v. or HAI 5-FU/FA or FUDR *versus* a control group or systemic 5-FU treatment [21]. A randomized trial conducted by the Arbeitsgemeinschaft für Lebermetastasen (ALM) in Germany investigated the role of hepatic arterial infusion (HAI) after liver resection [38]. A total of 226 patients have been randomized to receive 5-FU (1000 mg/m^2/day/five days) plus folinic acid (200 mg/m^2/day/five days) or no further chemotherapy. At 18 months' median observation time the recurrence rate in the liver was 33% with and 37% without adjuvant treatment (P = 0.715). This first interim analysis demonstrated a median survival of 35 months *versus* 41 months without postoperative HAI (P = 0.15) The study was closed because the relative risk of death was at best reduced by 15% and at worst doubled by the application of adjuvant treatment.

Because of low patient accrual, the European Organization for Research and Treatment of Cancer (EORTC), in collaboration with the NCI Canada, have unfortunately discontinued the randomization of patients after hepatic surgery to receive either 5-FU plus folinic acid (Mayo-Clinic regimen) or no treatment until development of metastases.

The value of locoregional or systemic chemotherapy in patients with liver metastases

Patients for whom surgery is not suitable are frequently offered locoregional or systemic chemotherapy. It is

generally accepted that such a cohort of patients comprises a more favorable subgroup than patients with more widespread disease, but comprises a more unfavorable cohort than those with resectable lesions. Comparison of the treatment results obtained with chemotherapy to those yielded by surgery is hampered by the differences in patient population.

It is debatable whether local regional therapy is more beneficial than systemic chemotherapy with respect to patient prognosis [39]. Proponents of this method claim for it the high objective tumor response rate of approximately 50%, which is significantly higher than the approxmately 20% achieved by systemic treatment with modulated 5-FU bolus regimens [40, 41]. Some trials also reported a significantly prolonged response duration and time to intrahepatic failure. However, a survival benefit could only be demonstrated in the trials that compared intrahepatic treatment with best supportive care with or without the addition of systemic treatment at some time during the course of the disease [42–44].

The recently reported results achieved with systemic chemotherapy question the value of locoregional treatment. With schedules using infusional 5-FU, a response rate of approximately 40%–50% together with a median survival approaching 20 months [39, 45, 46] was reported. Retrospective analysis of patients with liver metastases only who were nevertheless receiving systemic chemotherapy rather than regional treatment revealed an at least similar outcome with respect to response rate and median survival [39]. This regimen also showed promise when used intraarterially rather than systemically [47]. An ongoing Medical Research Council (MRC) trial in collaboration with researchers from the EORTC is comparing the value of high-dose bi-weekly 48-hour infusional 5-FU given either as HAI or systemically. Locoregional treatment should only be given within the framework of a clinical trial or after failure of systemic treatment in selected patients.

The value of surgery as opposed to chemotherapy in patients with colorectal cancer hepatic metastases was investigated in 24 patients with multiple but resectable liver metastases randomized to complete resection and adjuvant HAI or HAI only [36]. In this small study survival did not improve in patients with resection over that of the cohort treated by HAI only.

To gain a clearer idea of the merits of systemic or locoregional chemotherapy as relative to those of surgical resection in patients with colorectal liver metastases, it might be useful to select patients receiving chemotherapy rather than surgery, according to the prognostic factors designated in the French registry. We identified 50 patients with colorectal cancer hepatic metastases and at least five of the risk factors according to Nordlinger et al. [24]. This group received high-dose infusional 5-FU modulated by interferon or folinic acid [46], and the 50 patients had a two-year survival rate of 28%. It was determined that modulation with folinic acid was more effective than the combination with interferon [46]. A total of 29 patients received this therapy and had a two-year survival rate of 40%, which compares favorably with the patients that underwent surgery (Figure 2).

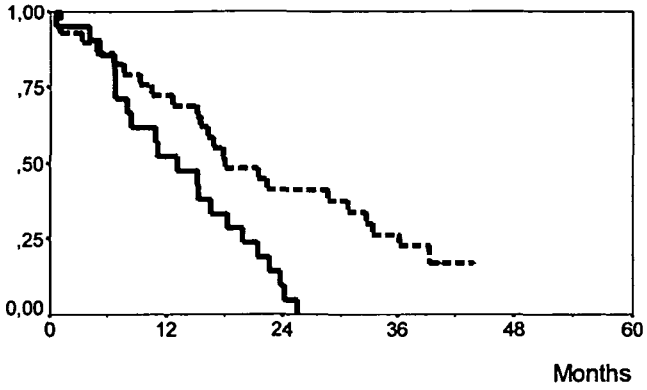

Figure 2. Survival of patients receiving high-dose infusional 5-FU with colorectal cancer metastases confined to the liver and five or more risk factors according to Nordlinger [24]. --- 29 patients receiving weekly 24-hour infusional 5-FU plus folinic acid; — 21 patients receiving weekly 24-hour infusional 5-FU plus interferon.

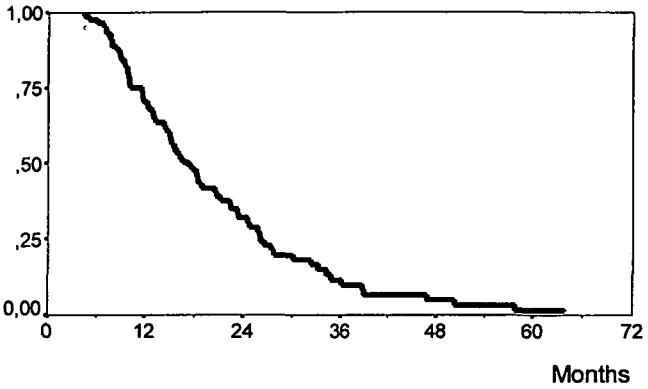

Figure 3 Survival of 94 patients receiving locoregional chemotherapy via the hepatic artery for colorectal cancer metastases confined to the liver and five or more risk factors according to Nordlinger [24].

Another cohort of 94 patients received regional therapy via the hepatic artery as described previously [48]. This group of patients also matched the high-risk group according to Nordlinger (Figure 3). The two-year survival rate of 33% is very close to the one reported for individuals with hepatic resection. These data are remarkable because they were obtained in patients for whom surgery was not suitable because of extensive non-resectable disease.

Discussion

About 50% of patients with colorectal cancer are cured by surgery alone. Patients with tumor involvement of regional lymph nodes additionally benefit from adjuvant systemic chemotherapy. Patients with resectable liver [24] or lung metastases [49] can, according to the retrospective reports, expect a five-year survival (not disease-free survival) rate of about 30% and with an R_0 resection of about 15% [50].

To compare the relative effectiveness of surgery and locoregional or systemic chemotherapy in patients with isolated liver metastases is difficult because the patient cohorts differ substantially. Individuals suitable for surgery are generally referred to specialized centers and represent a highly selected subgroup with technically or medically operable liver lesions that are preoperatively rigorously staged and further selected at laparotomy to exclude extrahepatic spread. Fong et al. [10] found that 10% of patients for whom liver resection was planned actually had extrahepatic disease detected only at laparotomy. In patients who did not qualify for resection due to more widespread disease, but for whom locoregional chemotherapy was deemed suitable, the incidence of extrahepatic tumor detected at laparotomy was 20%–25% [51–53]. If we consider successful surgery as a 'response' to treatment surgeons have a failure rate of only about 10% in selection of possible responders prior to treatment, while medical oncologists fail well over 50% of the time. Although cure of malignancy is claimed for surgical resection of colorectal liver metastasis, the survival curves do not show a plateau even after a follow-up period of 5 or more years. Nevertheless, resection of liver metastasis is a safe procedure which is associated with low mortality in specialized centers. Even if the patient is not cured the quality of life is generally high after resection and only reduced postoperatively for six to 10 days if no complications occur, while patients given chemotherapy will be treated for several months. Therefore, surgery is the treatment of choice for patients with good prognostic factors.

Whether surgery should be considered the preferred treatment also in patients with a strong chance of recurrence remains to be demonstrated. Our retrospective data indicates that these patients may also be adequately treated by systemic chemotherapy.

Another interesting experience has been reported by Bismuth et al. [54]. A total of 330 patients with colorectal cancer liver metastases were initially unresectable for various reasons and underwent the systemic application of 5-FU, folinic acid plus oxaliplatin. A radical resection was possible in 53 patients. The cumulative three- and five-year survival rates were 54% and 40%, respectively. This experience reflects the superior activity of the new generation of chemotherapies for patients with colorectal cancer. We should therefore consider chemotherapy a powerful tool within a multidiciplinary concept for patients with metastatic disease. The combination of systemic chemotherapy and excellent surgery appears to be a promising approach. Therefore, a German–French trial of combined preoperative chemotherapy followed by surgery in patients with high-risk hepatic metastases (Nordlinger score >4) has been initiated under the auspicious of the EORTC.

It is to be hoped that identification of subgroups, by the use of molecular markers or specific properties of tumors such as thymidilate synthase expression, will render it possible for us to individualize the treatment of this heterogeneous disease.

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