Therapeutic strategies for synchronous and multiple liver metastases from colorectal cancer

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Abstract

Metastasis in the liver is one of the most critical factors in the prognosis of patients with colorectal cancer. The incidence of synchronous liver metastasis has been found to be approximately 20-25%, but the optimal timing of surgical resection remains controversial. Neoadjuvant chemotherapy has also been found to be beneficial not only for initially unresectable but also resectable synchronous metastases and traditional surgical strategies of hepatic resection with past chemotherapeutic regimens have been used less and less over the past several years. This review will discuss treatments in association with the recently developed chemotherapeutic regimens.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide after lung and breast cancers. It is estimated to account for over one million new cases per year, half of which are fatal.[1] The natural course of CRC will develop metastasis to the liver up to 50% of patients.[2] The incidence of synchronous liver metastasis, commonly defined as liver metastasis occurring within 12 months of the primary colon cancer, has been detected in approximately 20-25% of cases.[3] Expansion of multidisciplinary care with advances in surgical procedure and technique in the past decade has resulted in simultaneous resection being the standard treatment of choice because of its safety and efficiency.[4] However, the optimal timing of surgical resection of synchronous metastasis remains controversial, and guidelines regarding the upper limits of operative indications for synchronous metastases have not yet been defined. In addition, neoadjuvant chemotherapy has also been found to be beneficial not only for initially unresectable but also resectable synchronous metastases.[5,6] After the development of combinations of 5-fluorouracil/folinic acid with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) treatment regimens, a prospective phase II study demonstrated that the response rate was 66%[7] and the maximum resection rate was 82%.[8] Traditional surgical strategies of hepatic resection in accordance with past chemotherapeutic regimens have been used less and less over the past several years. Therefore, this review will primarily discuss treatments in association with the FOLFOX/FOLFIRI chemotherapeutic regimens. Consideration of the timing of hepatectomy and whether it should be performed first or staged, should also take into account the contents and results of recent chemotherapeutic developments.[9] This review will discuss chemotherapeutic strategies involving FOLFOX or FOLFIRI and/or hepatectomy.

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Timing of hepatectomy

Selection for simultaneous or staged hepatectomy

Short- and long-term survival is reported to be worse in synchronous colon and liver metastasis.[10] The surgical indications for resection of synchronous metastasis and the optimal timing of hepatectomy (simultaneous or staged) are still controversial and widely debated.[11] A recent report showed colectomy with hepatectomy to have equivalent short-term outcomes if hepatectomy was minor, whereas major hepatectomy was associated with a doubling of the total severe morbidity rate (36.1% *vs* 17.6%) and a nearly 6-fold increase in mortality (8.3% *vs* 1.4%) in comparison with staged resection.[12] Based on these results, a staged operation for synchronous and multiple hepatic nodules has been recommended with a delay of at least three months after the primary resection. In contrast, other studies showed that simultaneous resection results in similar mortality and morbidity rates but shorter hospital stays than staged operations, despite the fact that both groups have similar operative times, intraoperative blood loss and complications.[9,13] Recent studies also showed simultaneous resection to enhance safety compared with staged operations and recommended that simultaneous resection be performed.[4,14,15] According to the safe-

ty concepts for such surgical procedures, simultaneous colorectal and liver resections have been evaluated as grade C under the recommended guidelines.[16] However, no randomized trials have been reported.

Neoadjuvant chemotherapy before hepatectomy should be considered to reduce intrahepatic recurrence, even if the tumors are resectable.[17] Pre- or postoperative FOLFOX chemotherapy *versus* surgery alone in patients with *resectable* liver metastases was evaluated in the final report from the European Organization for Research and Treatment of Cancer (EORTC) 40983 randomized trial.[5] According to these results, chemotherapy was found to be significantly better than surgery alone at inducing 3-year progression-free survival (42.4% *vs* 33.2%, P=0.025). The study proposed the establishment of a new standard whereby pre-operative chemotherapy is to be performed even if the tumor is resectable. However, the use of oxaliplatin has caused concern because its use might worsen pre-operative liver function.[18] Resection of both intra- and extra-hepatic metastases should be considered if all metastatic sites can be completely resected and the disease is controlled by chemotherapy.[19] A recent report showed that neoadjuvant FOLFOXRI administered for 3-6 months is actually safe,[20] and no consensus exists concerning operative mortality and morbidity rates.[21,22] Even in the case of repeat hepatectomy, the operation itself was reported to be safe and to offer survival benefit.[23] In cases of recurrence, 70% were observed within 12 months after the initial liver operation, with 92% observed within 24 months,[24] and for disease isolated to the liver, repeat hepatic resection led to favorable patient survival.[25,26] The criteria for the selection of patients for hepatic re-resection included the ability to achieve an R0 resection, the disease-free interval, solitary recurrences and operative risk. The 5-year disease-free survival rate after repeat hepatectomy was almost the same as that achieved after initial hepatectomy (26% *vs* 25%).[27]

Recently recommended strategy

A *reverse strategy* has been proposed for patients with advanced synchronous colorectal cancer metastases, and in particular for patients in whom the primary tumor is located in the rectum.[28] According to this report, pre-operative chemotherapy is followed by resection of the colorectal metastases and then by resection of the colorectal primary in a second operation. The risk for progression of metastases while the patient is undergoing treatment for the primary tumor is a cause for concern. In some patients, colorectal cancer metastases become unresectable during this interval because the delay until the resection of metastases is frequently longer than three months.[29] The major limitation of this strategy is that extensive resections, including major or extended hepatectomy, are associated with increased mortality and severe morbidity rates (up to 8% and 36%, respectively) when combined with resection of the primary tumors.[30] A recent study of the feasibility and safety of this reverse strategy demonstrated morbidity and mortality rates of 19% and 0%, respectively, and a 3-year overall survival rate of 83%.[28] Another study showed the reverse strategy to be associated with postoperative morbidity and mortality rates of 31% and 4%, respectively, and a 3-year survival rate of 79%.[11] The new reverse approach includes the risk that during the period between chemotherapy and liver resection the primary tumor might become obstructive. This rare possibility can easily be solved by performing the Hartmann procedure; studies show that this *liver first* approach is a safe procedure that brings satisfactory results.[31] The primary tumor can be left in place without the need for resection in patients with stage IV disease who received palliative systematic chemotherapy for advanced unresectable metastatic disease.[32] In this report, among 233 patients with advanced stage IV colorectal cancer, only 26 patients (11%) had symptoms related to the primary tumor, which was similar to the 15% rate seen in the subset of patients with rectal primaries left in place. The reverse strategy might not be considered in patients with an initially circumferential obstructive tumor. However, in most patients, this strategy is appropriate because it establishes early control of stage IV disease both systemically and in the liver, and it is also associated with an effective response in the primary tumor.[33] These concepts might be critical and it is expected that a series of clinical studies will be planned.

Concepts emerging from basic studies

Hepatocyte growth factor/scatter factor (HGF/SF) and its receptor, c-Met, are well known to relate to liver regeneration. Its overexpression or activation has also been studied in the progression of CRC;[34] therefore, the c-Met pathway is believed to play a critical role in the carcinogenesis of CRC. A report of clinical cases demonstrated that liver metastasis was significantly higher in the group with high expression of c-Met. However, in CRC cases with liver metastasis, despite high-grade immunodetection of c-Met activity in the primary tumor, these cases changed to low-grade activity in liver metastasis sites. An experimental mouse study also showed that expression of c-Met decreased from culture conditions to metastasis with time and tumor size dependency.[34]

Recently, some novel concepts for cancer growth and invasion have been derived from epithelial-to-mesenchymal transition (EMT), whereby a cancer cell changes its cellular phenotype from a local growing type and acquires an invasive and/or metastatic ability.[35] EMT has been well recognized at the invasive margins of cancer masses, but not in localized tumors. After migrating to sites distant from the primary tumor, mesenchymal-epithelial transition (MET) is also associated with

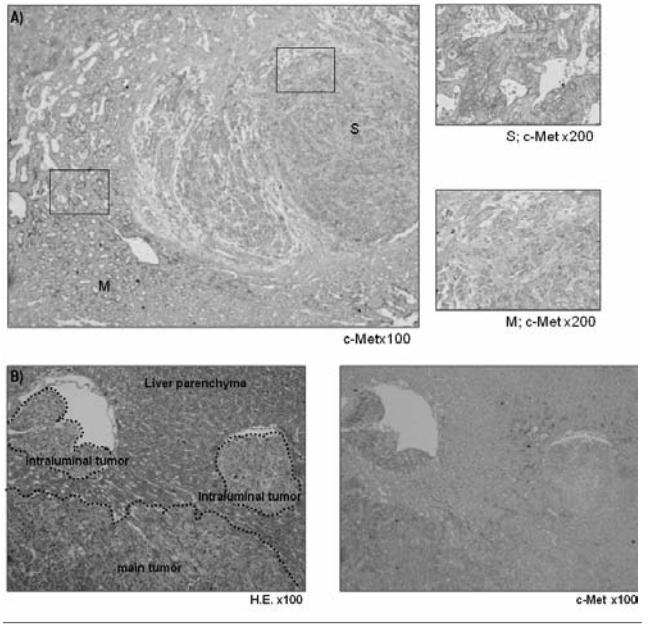

Figure 1. c-Met expression in liver metastatic sites. A) In the main tumor, c-Met expression was reduced in the central area but remained at high levels in satellite lesions. B) In the peripheral area of the main tumor, c-Met expression was diminished in the space completely occupied by vessels, but remained high in the space devoid of vessels.

increases in mass-building activity.[36] HGF itself is well known as a SF,[37] and is involved in the regulation of not only cell growth but also cell motility and morphology.[38] Carcinoma cells with HGF/SF have already been demonstrated in relation to EMT,[39] suggesting that primary CRC cells with highly expressed c-Met gain motility due to HGF/receptor activation for progression to the vessels and/or distant organs. Therefore, it seems that the HGF/c-Met system mediates cancer progression from local expansion to distant area metastasis via the process of EMT, and is down-regulated in mass formation at secondary sites via the process of MET.

Further studies using immunohistochemistry have added to these results (Figure 1). The expression of c-Met was clearly reduced in satellite lesions, despite expression remaining high in the central area of the same tumor. Even within single tumors, there was a difference in c-Met expression whereby it was increased in the growing invasive periphery but decreased in the established central regions. There may be a concern that as a treatment for metastastic liver tumors, hepatectomy could induce tumor growth in the residual liver.[40] As serum levels of HGF increase following hepatectomy, the suggestion that this could prompt the growth of c-Met over-expressing colorectal cancer cells has been discussed.

Clinical studies

Some specific factors have been identified that give indications for the treatment policies required.[9] Hepatectomy should be selected first if the resection can be performed safely and with a possibility of cure, with no limit on the size or number of tumors. However, where curative resection is not performed for reasons such as the presence of tumors in other organs, chemotherapy should be selected first, and the timing of possible radical hepatectomy immediately planned.[9]

The overall 5-year survival rate and median survival time (MST) for

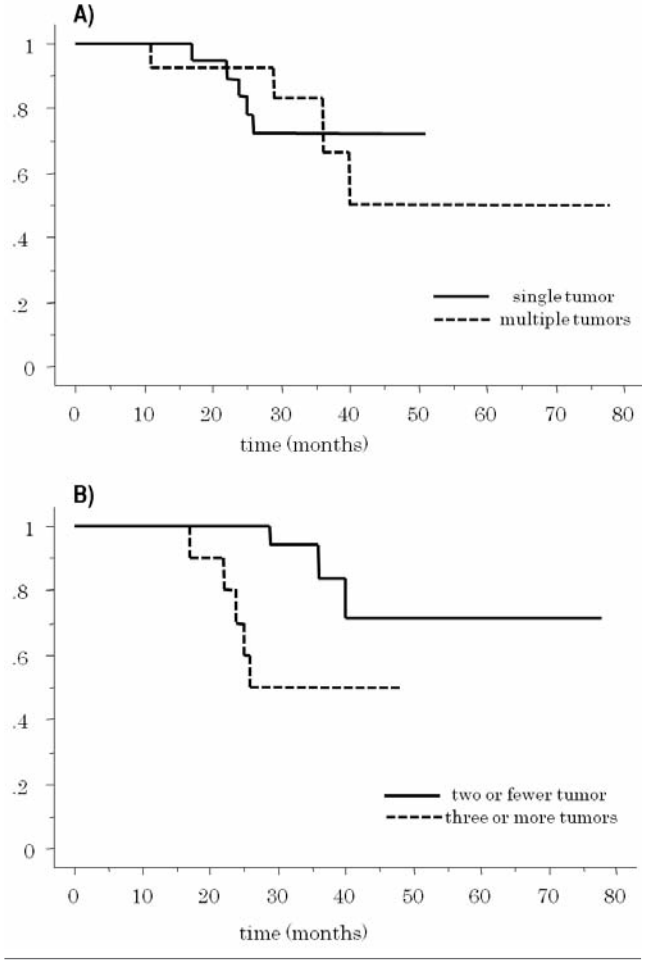

Figure 2. Clinical outcomes compared for tumor numbers. A) Among all patients studied, the 3-year survival rate and median survival time (MST) of patients with a single tumor (continuous line, 72% and 37.9±16.8 months; N=12) were similar to those of patients with multiple tumors (dotted line, 65% and 28.2±13.1 months; N=25). B) The 3-year survival rate and MST of patients with two or fewer tumors (continuous line, 83% and 36.6±14.0 months; N=18) were significantly better (P=0.0127) than those of patients with three or more tumors (dotted line, 65% and 24.0±13.6 months; N=19).

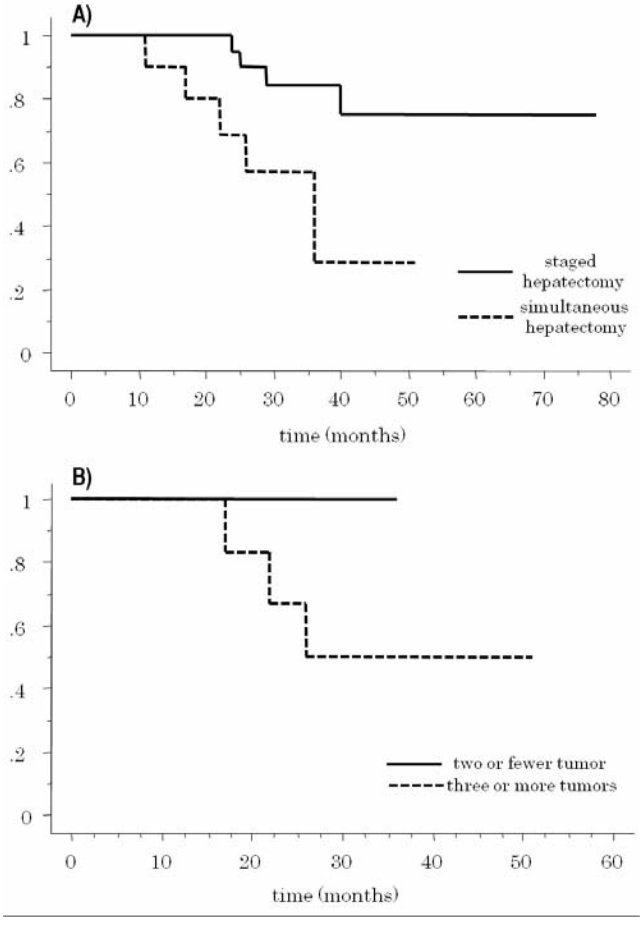

Figure 3. Clinical outcomes for simultaneous hepatectomy. A) For patients in whom synchronous liver tumors were detected, 3-year survival rate and median survival time (MST) after staged hepatectomy (continuous line, 82% and 34.5±14.9 months: N=16) were significantly better (P=0.0467) than those after simultaneous hepatectomy (dotted line, 29% and 23.9±13.6 months; N=10). B) Furthermore, despite the MST (29.7±8.5 months) after simultaneous hepatectomy for a single tumor being similar to that for multiple tumors (23.4±15.7 months) for patients with two or fewer tumors (continuous line; N=6) the MST (34.8±11.0 months) was significantly longer than for patients with three or more tumors (dotted line, 17.0±9.9 months; N=10).

patients in our recent study[41] were 61.2% and 31.0±15.2 months, respectively. Of these patients, the 3-year survival rate (55%) and MST (28.4±15.4 months) of patients in whom synchronous liver metastasis was detected were clearly poorer than those of patients with metachronous tumors (100% and 39.9±10.8 months). Among all patients studied, the 3-year survival rate and MST in patients with a single tumor were similar to those of patients with multiple tumors. However, these indicators were significantly better (P=0.0127) for patients with two or fewer tumors than for patients with three or more tumors (Figure 2). Furthermore, in patients in whom synchronous liver tumors were detected, the 3-year survival rate and MST after staged hepatectomy were significantly better than those after simultaneous hepatectomy (P=0.0467), and the MST for patients with two or fewer tumors was significantly longer than that for patients with three or more tumors (Figure 3). The MST after simultaneous hepatectomy for a single tumor (29.7±8.5 months) was similar to that for multiple tumors (23.4±15.7 months). In contrast, after staged hepatectomy, the MSTs for patients with these factors were similar (single *vs* multiple tumors, 40.7±18.3 months *vs* 30.8±11.6 months; two or fewer *vs* three or more tumors, 37.1±15.1 months *vs* 26.1±16.2 months). According to another report, patients with one or two liver metastases had a similar prognosis, and those with three or more lesions had a significantly decreased 5-year survival, from 28% to 13% (P<0.01).[42] In a recent review,[43] a significantly worse rate of disease-free survival after curative resection for liver metastases was seen in patients with positive lymph node metastases, synchronous development timing, tumor-free interval of less than 12 months, presence of extrahepatic disease, and higher numbers of tumors. With regard to tumor number, the difference between two or fewer and three or more tumors was more critical for disease-free survival than that between one and two tumors (P=0.001 *vs* 0.082) and there was no clear difference when the cut-off point for tumor number was set at four. Another recent study also found three independent factors that were predictive of disease recurrence: three or more metastases at diagnosis, initial unresectability, and simultaneous colorectal surgery with hepatectomy.[44] Therefore, it appears that tumor number is important for patient survival, and a cut-off point set at two tumors may be reasonable for accepting primary hepatectomy.

Conclusions

Clinical features of CRC indicate that the overexpression of c-Met is closely associated with liver metastasis. In liver metastatic lesions, although a comparative reduction in c-Met expression correlates well with tumor growth, there is still a relatively high expression at invasive sites. Therefore, hepatectomy might be selected if cancer can no longer be detected by microscopic examination. According to clinical studies, neoadjuvant chemotherapy improves the prognosis for patients with synchronous liver metastases. Particularly in patients with one or two tumors, primary hepatectomy will induce a favorable outcome with a diminished likelihood of tumor in the remnant. In contrast, where there are three or more tumors, it is best to plan staged hepatectomy, even if it is technically possible to remove these tumors in one procedure. Treatment strategies for CRC patients with liver metastases should involve the consideration of appropriate combinations of chemotherapy and surgery.

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