

REVIEW ARTICLE

The Surgical Treatment of Hepatic Metastases in Colorectal Carcinoma

Ulf Peter Neumann, Daniel Seehofer und Peter Neuhaus

SUMMARY

Background: Colorectal carcinoma with hepatic metastases was long considered an incurable disease. Recent advances in surgical treatment have substantially improved the affected patients' prognosis. At first, surgery was only performed in patients whose hepatic tumor burden was small (<4 nodes, <5 cm). Currently, however, the main issue is the feasibility of curative resection of all metastases.

Method: The PubMed literature database was selectively searched for articles with the keywords "colorectal liver metastases," "chemotherapy," and "surgery." Particular attention was devoted to studies of large groups of patients, randomized trials, the German guidelines, and an analysis of the authors' own patient population.

Results: Only 10% to 20% of all patients are candidates for surgical therapy (hepatic resection), as the rest are disqualified either by extensive liver involvement or by extrahepatic neoplasia. A further 10% of patients have hepatic metastases that are primarily considered inoperable, yet later become amenable to surgery after interdisciplinary treatment involving preoperative chemotherapy, portal-vein embolization, two-stage hepatectomy, and/or locally ablative procedures. Chemotherapy is probably beneficial after hepatic resection, although the benefit has not yet been definitively demonstrated by clinical trials. Therefore, chemotherapy should only be given perioperatively in selected cases, when recommended by an interdisciplinary treatment team.

Conclusion: A multimodal approach to the treatment of hepatic metastases of colorectal carcinoma has led to an increase in the number of resections and to an improved long-term survival rate (currently more than 40% at 5 years).

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Colorectal carcinoma is one of the more common types of cancer around the world. In Germany, it is the second most common type, in terms of both incidence (ca. 70 000 new cases per year) and death from the disease (e1).

For patients in UICC stage I (i.e., those who have pT1/2 tumors and do not have any lymph node metastases), the probability of surviving 5 years is 90% (e2). The prognosis of patients in stages II (pT3/4 tumors without lymph node metastases) and III (tumors with lymph node metastases) has improved steadily in recent years: At present, the 5-year survival in these two groups is 80% and 60% (e2). Nonetheless, distant metastases eventually arise in about 20% of patients who are stage II or III at the time of diagnosis (e3). About 35% of all patients already have distant metastases when the diagnosis is made.

Patients with untreated hepatic metastases have a very poor prognosis. In a prospective, observational study carried out on 484 patients from 1980 to 1990, the median time to death was 6.9 months (1).

Adson and colleagues, in the 1970's, were the first to show that patients could be cured by the resection of hepatic metastases (e5). Since then, resection has become established as a standard treatment. For this review, we selectively searched the literature for articles containing the words "colorectal liver metastases," "chemotherapy," and "surgery," paying special attention to studies carried out on larger groups of patients and to randomized clinical trials. The 2008 German guidelines have also been incorporated into the discussion.

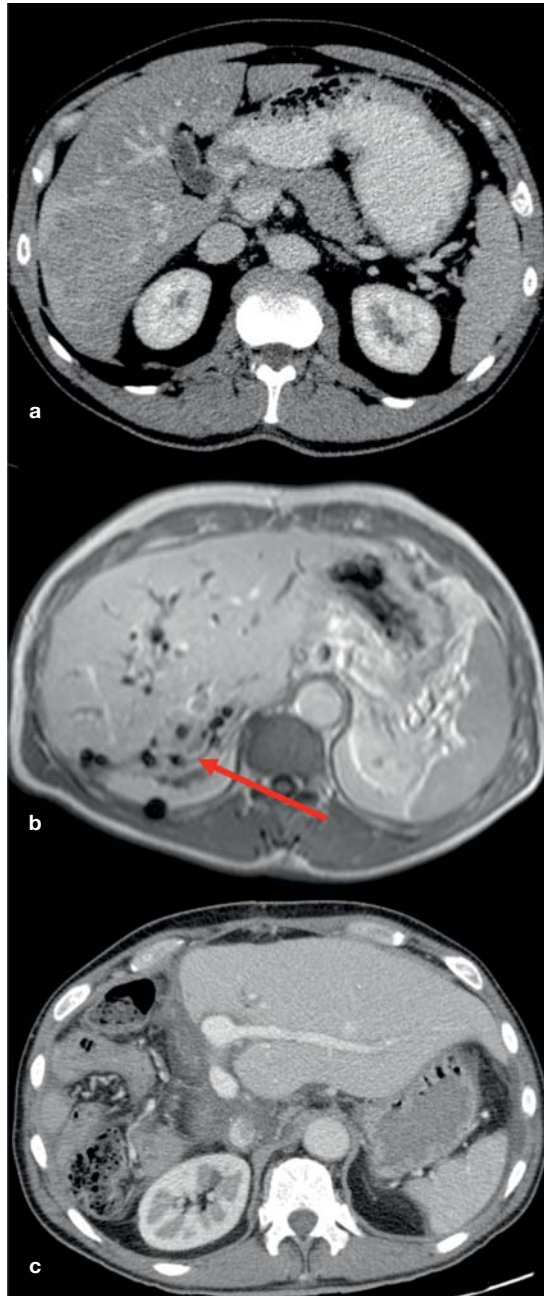
Primarily resectable hepatic metastases

For operable hepatic metastases, hepatic resection is the treatment of choice. The reported 5-year-survival rates that have been achieved after the resection of isolated hepatic metastases with curative intent range from 25% to 50% (1–3, e4, e6–e8). Hepatic metastases, however, are primarily resectable in only about 20% of patients (4). For the remaining 80%, resection is contraindicated by the presence of diffuse hepatic metastases, nonresectable extrahepatic disease, or impaired liver function.

It is now generally accepted that the contraindications for hepatic resection that were defined in the 1980's are no longer applicable. At that time, the

Figure 1:

A man with a metastasis in the right hepatic lobe.
 (a) The metastasis as it appeared before right hemihepatectomy
 (b) Thereafter, tumor recurrence in the resection bed, with obstruction of the remaining bile ducts (see arrow)
 (c) The result after resection of segments 1 and 4, resection of the portal vein bifurcation, and resection of the extrahepatic bile ducts



presence of 4 or more tumor nodules, metastases exceeding 5 cm in size, extrahepatic disease, or a tumor-free resection margin of less than 1 cm (e9) was held to contraindicate hepatic resection. Many subsequent studies have confirmed that these are, indeed, relevant prognostic factors for survival after the resection of hepatic metastases of colorectal carcinoma, yet long-term survival is still possible when hepatic resection is performed despite the presence of these supposed contraindications.

There have also been technical improvements in the treatment of hepatic metastases of colorectal carcinoma. Diagnostic assessment has become

markedly more sensitive through the use of modern types of CT and MRI scanners and the introduction of PET-CT (5, e10–e14). Furthermore, surgical dissecting techniques and the development of potent systemic chemotherapy protocols have been optimized (e15–e18). As a result, 5-year survival rates after the resection of hepatic metastases of colorectal carcinoma have improved markedly (6) (Figure 1). Today, even patients with more than three metastases or with metastases larger than 5 cm in diameter can be cured with appropriate surgical treatment, as Tomlinson et al. found in a recent analysis (7). 102 patients were tumor-free 10 years after the resection of hepatic metastases of colorectal carcinoma, and only one patient among them developed a recurrent tumor thereafter.

Perioperative complications

Hepatic resections can now be performed safely and effectively. The mortality of hepatic resection was about 5% as late as 1990, while recent articles on the subject generally document figures between 1% and 2% (3). This reduction of mortality has been achieved even though the resections themselves have become ever more extensive.

Long-term results after hepatic resection

More than 40% of appropriately selected patients with colorectal carcinoma who undergo the resection of hepatic metastases survive for at least 5 years thereafter (5, 6, 8, 9, e6, e9, e19–e22). This is particularly true of patients whose surgery was performed more recently (Figure 2). As many as two-thirds of patients later develop a recurrent tumor, and half of them have a recurrent tumor in the liver (e23). In one of the largest studies performed to date, which included 1001 patients, Fong et al. showed that the benefit of surgery extends not just to patients who have undergone an R0 resection (5-year survival: 37%), but also to those who have undergone an R1 resection, i.e., a resection with positive margins, up to 20% of whom are still alive 5 years after surgery.

Prognostic parameters

Many different prognostic scores (Table 1) are used to predict the patient’s risk of recurrence and chances of long-term survival on the basis of preoperatively measured parameters. The three most commonly used scoring systems in hepatic surgery are those of Nordlinger, Fong, and Iwatsuki (2, 9, e24). Although these scoring systems differ with respect to certain individual parameters, they share the common feature that a low score (i.e., the presence of no more than a few risk factors) is correlated with a low risk of recurrence, while the chance of long-term survival is less than 10% when all risk factors are present. No preoperatively measurable prognostic parameter can identify with any certainty the patients who will not benefit from surgical treatment. The most important prognostic factor, according to all studies, is a tumor-free resection margin (10, 11, e25, e26).

Hepatic re-resection in case of recurrent tumor

The resection of hepatic metastases of colorectal carcinoma is followed by tumor recurrence in up to two thirds of cases, and about half of these recurrences are found in the liver (12, e23, e27, e28). In general, whenever there is a chance of a curative resection, resection should be considered for recurrent tumors as well. The operative morbidity and mortality of hepatic re-resection in experienced centers are no greater than those of primary resection.

In a study on second operations in 94 patients with recurrent hepatic metastases of colorectal carcinoma, 38% of the patients were alive 5 years after surgery (12). Thus, whenever complete resection of the tumor is possible, surgery is indicated even for patients with recurrent hepatic metastases (Figure 1).

Strategies for improving resectability

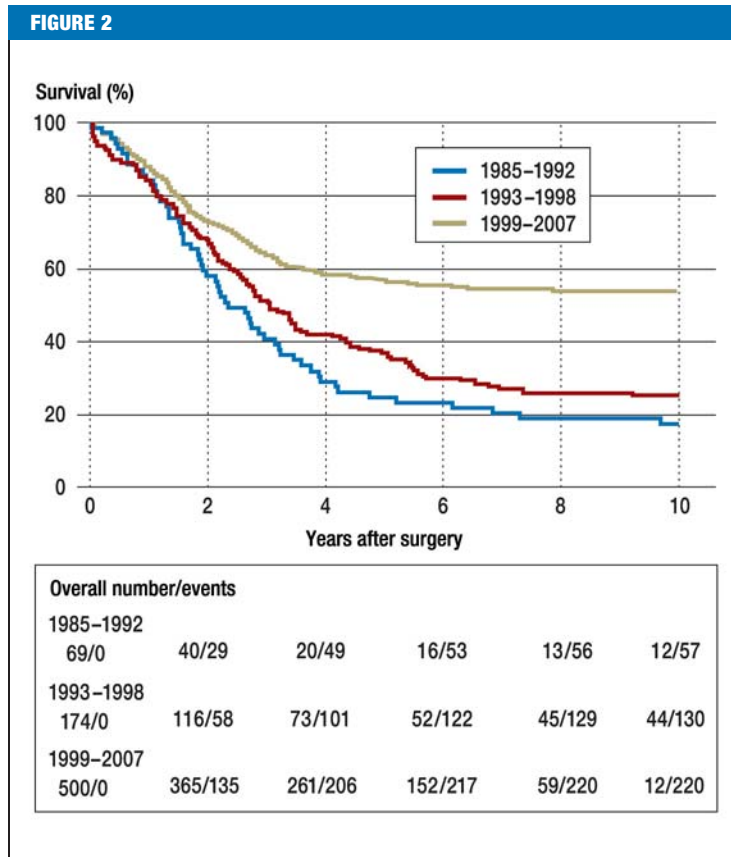
At present, only 10% to 20% of patients with hepatic metastases of colorectal carcinoma can be considered candidates for resective surgery. Opportunities for resection are often limited by an unfavorable anatomical site of the metastasis(-es), poor function of the remaining hepatic parenchyma, and/or the patient's poor general condition. Multiple strategies have been developed in order to increase the percentage of patients whose metastases are resectable.

Preoperative chemotherapy ("down-staging")

When hepatic metastases of colorectal carcinoma are unresectable, systemic chemotherapy is indicated. About 20% of metastases respond to treatment with 5-fluorouracil (5-FU) and folic acid (4). When these are used in combination with newer drugs, such as oxaliplatin or irinotecan (CPT-11), the response rate rises as high as 60% (e29). Folprecht et al. reviewed the available studies on the "down-staging" of hepatic metastases of colorectal carcinoma and found that resection rates are correlated with response rates (4).

The first major clinical series of this type was published in 1996 by Bismuth et al. (13) and updated in the years thereafter (14, e30). The 5-year-survival was 40% (95% confidence interval: 33% to 68%) and was thus comparable to that of patients with primarily resectable hepatic metastases.

Further studies and retrospective analyses on this subject are listed in Table 2. A major bias in the studies of neoadjuvant chemotherapy published to date arises from patient selection. In the available prospective studies of patients with "isolated" hepatic metastases (i.e., no extrahepatic metastases), the criteria for non-resectability differ from one study to another and are often poorly defined. The hepatotoxicity of all currently used chemotherapeutic drugs argues against their use as neoadjuvant treatment for patients with primarily resectable hepatic metastases. Oxaliplatin can cause sinusoidal obstruction ("blue liver"), while irinotecan can induce fatty liver or steatohepatitis (e31–e34). These changes are associated with significantly more



Patient survival (Charité, Berlin) after the resection of hepatic metastases of colorectal carcinoma, displayed as a function of the time of resection

frequent perioperative complications. Vauthey et al. found that steatohepatitis after irinotecan use is associated with a significantly higher 90-day mortality (15).

Portal-vein embolization

In some cases, the resection of one or more hepatic metastases is technically feasible, yet cannot be performed because the amount of liver tissue remaining after resection would be too small. To minimize the risk of postoperative hepatic insufficiency, ipsilateral hepatic atrophy and contralateral hepatic hypertrophy can be induced preoperatively by selective embolization of the hepatic portal vein, or else by ligation of the branch of the portal vein that leads to the hepatic lobe containing the metastasis. Portal-vein embolization should always be considered when the residual hepatic volume without it would be less than 30% of the normal size of the liver, and when at least two contiguous hepatic segments are free of metastases. For technical surgical reasons, the left lateral segments 2 and 3 are particularly suitable for this approach. As long as the liver is not cirrhotic, portal-vein embolization results in a 40% to 60% hypertrophy of the contralateral hepatic lobe. It remains unclear at present whether the stimulus

TABLE 1

Prognostic factors for long-term course after the resection of hepatic metastases of colorectal carcinoma

| Author | Number of patients | Tumor size | Number | Synchronous/metachronous | Tumor-free interval | Stage of primary tumor | Preop. CEA | Type of resection |
|----------------|--------------------|------------|--------|--------------------------|---------------------|------------------------|------------|-------------------|
| Minagawa (e45) | 235 | - | + | - | - | + | - | - |
| Cady (e 46) | 244 | - | + | - | - | - | + | |
| Iwatsuki (e24) | 305 | + | + | + | + | + | | + |
| Scheele (e47) | 469 | + | - | + | | + | + | + |
| Jonas (3) | 660 | - | + | | - | + | | + |
| Jaeck (e6) | 747 | - | - | | - | + | - | - |
| Fong (2) | 1001 | + | + | | + | + | + | + |
| Nordlinger (9) | 1568 | + | + | + | + | + | + | - |

TABLE 2

Resection rates of initially unresectable hepatic metastases after down-staging by preoperative chemotherapy

| Author | Year | Number of patients | Regimen | Response rate (%) | Resection rate (%) | 5-year survival (%) |
|------------------------------------|------|--------------------|---|-------------------|--------------------|---------------------|
| All patients | | | | | | |
| Bismuth (13) | 1996 | 53 | FOLFOX | - | 16 | 40 |
| Adam (e30) | 2004 | 1104 | FOLFOX | - | 12.5 | 39 |
| Masi (e48) | 2006 | 74 | FOLFIRIFOX | 71.6 | 25.7 | 36.8 |
| Isolated hepatic metastases | | | | | | |
| Giacchetti (e49) | 1999 | 151 | FOLFOX | 58.9 | 38.4 | 58 |
| Pozzo (e50) | 2004 | 40 | FOLFIRI | 47.5 | 32.5 | - |
| de la Camara (e51)* | 2004 | 212 | FOLFIRIFOX | 64 | 43 | - |
| Quenet (e52)* | 2004 | 26 | FOLFIRIFOX | 73 | 54 | - |
| Alberts (e53) | 2005 | 42 | FOLFOX | 59.5 | 33.3 | - |
| Ho (e543) | 2005 | 40 | FOLFIRI | 55 | 10 | - |
| Folprecht (e55) | 2008 | 109 | FOLFIRI + Cetuximab FOLFOX + Cetuximab | 75 | 42 | 58 |

FOLFOX, folic acid, 5-FU, oxaliplatin;
FOLFIRIFOX, 5-FU, irinotecan, oxaliplatin;
FOLFIRI, 5-FU, irinotecan.
* data currently available only as an abstract

to hypertrophy that portal-vein embolization provides might also accelerate the growth of tumor nodules (16, e35). In any case, the data regarding morbidity, mortality, and long-term survival are comparable to those of standard hepatic resections (16, e36–e39).

Two-stage hepatic resection

A further way of enabling curative resection of patients with extensive bilobar hepatic metastases of colorectal carcinoma is so-called two-stage hepatic resection (17, e40–e42). This technique is suitable for patients with bilateral hepatic metastases who can undergo neither

complete tumor resection, nor tumor resection combined with a local ablative procedure, because of the risk of postoperative hepatic insufficiency. Most, but not all, of the tumor burden is resected in a first operation, and then the remaining tumor nodules are resected in a second one, after liver tissue has regenerated. The decision whether to operate in one or two stages depends on the quantity and quality of the extra-tumoral hepatic tissue (Figure 3). The second operation is usually performed three to four weeks after the first, to allow time for the residual liver tissue to become adequately hypertrophic.

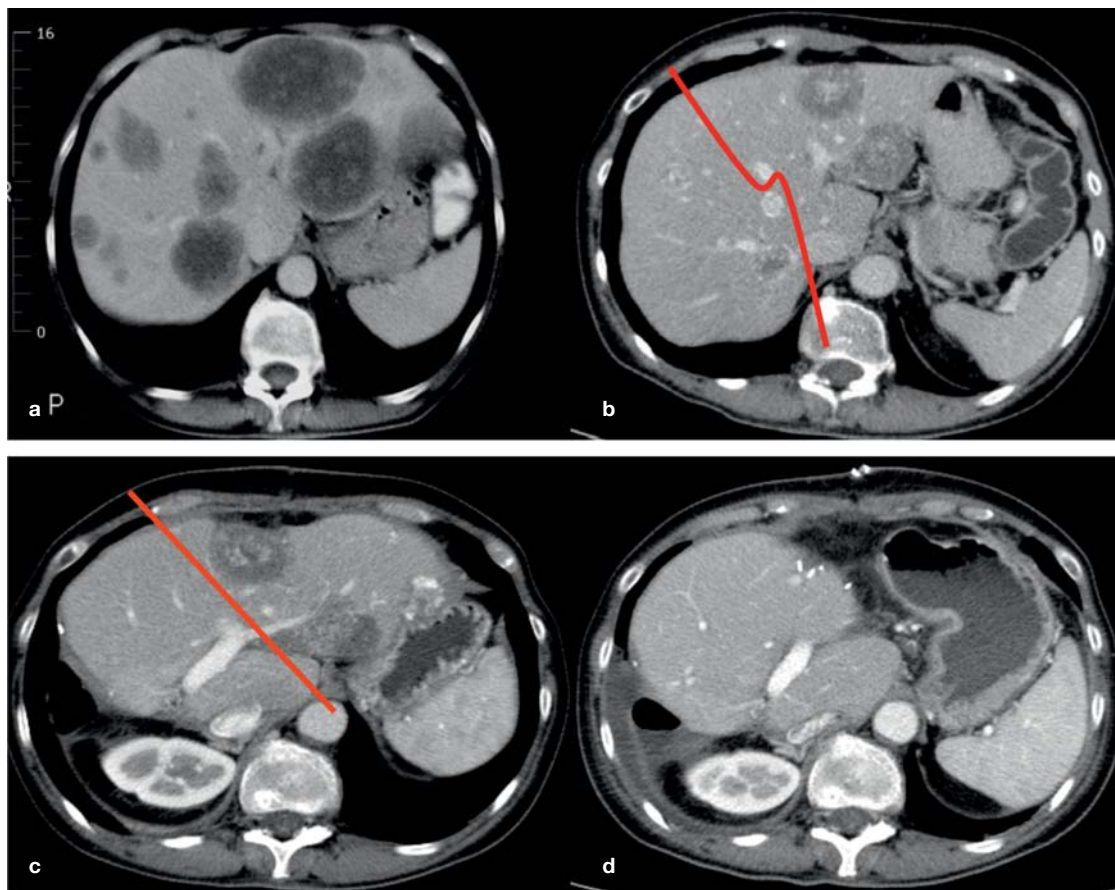


Figure 3: CT findings in a woman with hepatic metastases. (a) Multiple hepatic metastases (b) Surgical treatment became possible after down-staging by chemotherapy (c) First, a right hemihepatectomy was performed (d) Six weeks later, after regeneration of the left hepatic lobe, the left lateral hepatic segments were resected

Local tumor destruction and hybrid techniques

In recent years, local ablative methods such as cryotherapy and radiofrequency ablation (RFA) have come into more common use for the *in situ* destruction of hepatic metastases. Among these methods, RFA has been studied the best. It can be performed percutaneously, laparoscopically, or at open surgery and is currently used for tumors up to 5 cm in diameter.

Lencioni et al. recently reported a multicenter study of 423 patients with a total of 615 metachronous metastases of colorectal carcinoma who were treated with RFA. The average tumor size was 2.7 cm (18). In this patient group, 25% had local tumor progression, and the 1-, 3-, and 5-year survival rates were 86%, 47%, and 24%. These figures correspond to those of Abdalla et al., who found that tumor progression is more probable after RFA than after surgical resection (19, e43). In general, RFA is associated with low morbidity and mortality. As no prospective data are yet available for a comparison of local ablative techniques to hepatic resection with curative intent, the procedure cannot be recommended as an alternative to hepatic resection, though it does play a role as an additional, complementary method of achieving complete tumor destruction in patients whose lesions are not otherwise R0-resectable.

New criteria for resectability

Currently available data have led to a change in the indications for resecting hepatic metastases of colorectal carcinoma. Previously, the indication was based on tumor-biological and clinical characteristics. The new criterion is the feasibility of complete resection of both intra- and extrahepatic disease.

R0-resectable hepatic metastases, in patients without any extrahepatic metastases, should be resected. As the determination of resectability is becoming ever more complex, all patients with hepatic metastases of colorectal carcinoma should be presented to an experienced hepatobiliary surgeon before the beginning of treatment. Postoperative hepatic function can be predicted more precisely with the aid of CT volumetry. This technique enables prediction of the remaining volume of hepatic tissue after surgery to within 10% of the actual value.

Metastases are considered resectable when the following criteria are met:

- exclusion of a non-resectable extrahepatic tumor manifestation,
- parenchymal involvement <75%,
- <3 hepatic veins and <7 hepatic segments involved,
- no hepatic insufficiency, no Child B or C cirrhosis,
- no severe accompanying diseases.

TABLE 3

Randomized studies on (neo-)adjuvant chemotherapy and resection of hepatic metastases of colorectal carcinoma

| Author | Year | Number of patients | Regimen | Disease-free survival | Overall survival |
|-----------------|------|--------------------|---|--|--|
| Lygidakis (e56) | 2001 | 62 / 60 | resection + immunotherapy + 5-FU vs. resection + HAI immunotherapy + 5-FU | – | 5 years: (p = 0.05) 73% vs. 60% |
| Lorenz (21) | 1998 | 113 / 113 | resection vs. resection + HAI 5-FU / LV | median: 14.2 vs. 13.7 months (n.s.) | median: 34.5 vs. 40.8 months (n.s.) |
| Kemeny (20) | 2005 | 74 / 82 | resection + 5-FU vs. resection + HAI FUDR + 5-FU | median: 17 vs. 31 months (p<0.05) | 10 years: (n.s.) 27.2% vs. 41.1% |
| Portier (22) | 2006 | 86 / 85 | resection vs. resection + 5-FU / LV | 5 years: (p = 0.028) 50% vs. 33% | 5 years: (p = 0.13) 51% vs. 42% |
| Mitri (23) | 2008 | 140 / 138 | resection vs. resection + 5-FU / LV | median: 18.8 vs. 27.9 months (p = 0.058) | median: 47.3 vs. 62.2 months (p = 0.095) |
| Nordlinger (25) | 2008 | 182 / 182 | resection vs. resection + perioperative FOLFOX | 3 years: (p = 0.058) 28.1% vs. 35.4% | NA |

5-FU, 5-fluorouracil; LV, leucovorin; HAI, intra-arterial infusion in the hepatic artery; FUDR, floxuridine; NA, data not available; n.s., not significant; FOLFOX, folic acid, 5-FU, and oxaliplatin

Metastases are considered nonresectable or marginally resectable when an R0 resection is not possible. Metastases are also considered marginally resectable in the setting of, for example, extrahepatic tumor manifestations, technical impediments to surgery, or inadequate expected residual liver mass. For these patients, intensified preoperative chemotherapy can be considered. The feasibility of secondary resection should be evaluated at each re-staging under chemotherapy.

Accompanying chemotherapy

There is no longer any doubt that patients benefit from hepatic resections that are performed with curative intent. The current discussion concerns the question whether they also benefit from accompanying adjuvant or neo-adjuvant chemotherapy.

The first encouraging data on adjuvant chemotherapy after hepatic resection were published by Kemeny et al., who compared local intra-arterial therapy combined with systemic 5-FU chemotherapy to adjuvant treatment with 5-FU alone. A trend was found toward improved progression-free survival in the group that additionally received regional therapy (37.4 versus 17.2 months, p = 0.06) (20, e44). Nonetheless, the overall survival was no better in this group. This finding could not be replicated in a German study of intra-arterial chemotherapy administered in the hepatic artery (21) (Table 3).

There are currently two further options for systemic chemotherapy: neo-adjuvant and adjuvant postoperative chemotherapy. For adjuvant chemotherapy, data are only available on 5-FU based treatment. Portier et al., in the AURC 9002 trial, describe an improved 5-year tumor-free survival of 33.5% among patients receiving adjuvant 5-FU bolus therapy, compared to 26.7% treated with resection alone (22). These 5-FU

patients' overall survival was no better than that of their counterparts without 5-FU, but the study size was, in any case, inadequate to detect a moderate benefit. An unplanned subgroup analysis revealed that patients with a greater tumor burden (diameter >5cm, or 3 or more tumor nodules) survived longer if they received adjuvant chemotherapy. Likewise, a pooled analysis of a number of studies, including the FFCD study, found a trend toward a benefit from adjuvant 5-FU treatment, in terms of both progression-free survival and overall survival (23). These data appear promising, especially because there have been further improvements in chemotherapeutic regimens since they were published. Further evidence that adjuvant 5-FU treatment confers a survival benefit after the resection of hepatic metastases of colorectal carcinoma comes from a cohort study of 792 patients by Parks et al. (24): The median survival time was 47 months, compared with 36 months without 5-FU.

This year (2010), Nordlinger et al. have published the results of the EORTC 40 983 trial, in which neo-adjuvant therapy with FOLFOX (folic acid, 5-FU, and oxaliplatin) before and after hepatic resection was compared with resection alone. There were 182 patients in each of the study's two groups (with and without neo-adjuvant therapy). The declared study endpoint of a significantly improved progression-free 3-year survival was not met in the intent-to-treat analysis. Tumor-free survival was 28.1% after surgery alone and 35.4% in the FOLFOX group (25). The study did, however, show a significantly improved tumor-free 3-year survival when all patients whose data could be completely evaluated were taken into account (as opposed to the intent-to-treat analysis). Data on overall survival are currently unavailable. It should also be mentioned that the chemotherapy group had a higher rate of postoperative

complications, but their postoperative mortality was no higher.

Thus, in our view, preoperative chemotherapy should remain reserved, at least for now, to patients whose hepatic metastases are marginally resectable. This group includes patients whose tumor burden is high because of multiple hepatic metastases and extrahepatic tumor manifestations. Our view is founded on the documented survival benefit that can be achieved in patients who have a large burden of initially unresectable hepatic metastases by down-staging their tumors with chemotherapy, in order to render them resectable.

Conclusion

The results of surgical treatment of metastatic colorectal carcinoma have improved markedly in recent years. The reasons for this include developments in medical imaging, in perioperative and surgical treatment, and in chemotherapy, with the introduction of potent new protocols. Clinicopathological factors such as tumor size, number of tumor nodules, and extrahepatic tumor manifestations no longer contraindicate hepatic resection. The main consideration at present is the need to achieve a complete R0 resection. Accompanying chemotherapy should be considered, especially for patients with an unfavorable risk profile. Neoadjuvant chemotherapy is reserved for patients with marginally resectable metastases. The resectability or non-resectability of hepatic metastases is a matter that must be evaluated by a surgeon who is experienced in the treatment of hepatic metastases.

Conflict of interest statement

Prof. Neumann has received study support, lecture honoraria, and reimbursement of travel expenses from Merck and study support and reimbursement of travel expenses from Roche, Astellas, and Novartis. PD Dr. Seehofer states that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

KEY MESSAGES

- Hepatic resection is the standard treatment of resectable metastases of colorectal carcinoma. 5 years after such procedures, 40% of patients are still alive.
- In view of the improved surgical, radiological, and oncological treatments that are now available, all patients for whom a complete resection is possible (even those with extrahepatic involvement) should undergo resection.
- Interdisciplinary treatment approaches can raise the percentage of patients who are candidates for resection by approximately 10%.
- No standard protocol currently exists for systemic chemotherapy accompanying hepatic resection.
- Patients with synchronous, unresectable, or potentially resectable hepatic metastases should be treated in a center for hepatobiliary surgery.

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