A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma

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In patients with colorectal cancer, metastatic spread has long been considered clear evidence of systemic disease for which surgical treatment would be inappropriate. In a minority of patients with liver metastases from colorectal cancer, however, complete removal of tumor is possible while leaving enough liver parenchyma to permit long-term survival. For this subgroup, overwhelming evidence suggests that resection of colorectal liver metastases provides an effective therapeutic approach [1–4] that can cure a substantial proportion of patients and may result in disease-free survival of 20 years or more [5–7].

This article presents basic information on outcome after resection of colorectal liver metastases. Next, it describes the cardinal prerequisites for a favorable outcome after resection of such metastases. The authors then analyze the impact of various prognostic factors on outcome after resection of colorectal liver metastases and discuss contraindications to this surgery.

Basic data on colorectal liver metastases

Incidence of resectable metastases

Approximately 15% to 25% of patients with primary colorectal cancer present with synchronous liver metastases [8], with higher detection rates seen in series in which intraoperative ultrasonography is routinely applied [9–11]. An additional 20% of patients without metastatic disease at the time
of primary tumor resection develop metachronous hepatic tumors, usually within 3 years [12,13]. Approximately one fourth [14] of patients with synchronous or metachronous liver metastases are candidates for liver resection, and in one fifth, complete removal of all macroscopically detectable disease with clear resection margins (a so-called “R0 resection”) is possible [8,13]. Thus, given the approximately 150,000 new cases of colorectal cancer diagnosed in the United States each year [15], 10,000 to 15,000 patients per year are candidates for resection of colorectal liver metastases.

**Overall results of hepatic resection**

Since 1980, single-institution series with more than 100 patients have reported actuarial 5-year survival rates ranging from 18% to 46% after resection of colorectal liver metastases [7,16–38], whereas multi-institutional series have described rates of 21% to 33% [2,39,40] (Table 1). In the authors’ series of 597 patients (hereafter referred to as the Erlangen/Jena series) who underwent resection of colorectal liver metastases with curative intent, the overall 5-year survival rate was 33% [36]. This rate is mirrored by the large-scale study by Fong et al [21], who reported a 5-year survival rate of 36% in 1001 consecutive patients.

The actual 5-year survival rates for patients with a follow-up time exceeding this period were 25% (136 of 551) in the Fong et al [21] series and 33% (159 of 426) in the Erlangen/Jena series [36]. Ten-year survival figures, if recorded at all, are rarely based on a large sample of patients, but in the most recent update of the Erlangen/Jena series, the 10-year survival rate was 24% (based on 60 surviving patients, 56 of whom were free of recurrent disease) [36]. In the Fong series, this figure was 22% [21].

These outcomes are in contrast to the outcomes in patients with unresected metastatic colorectal cancer, in whom survival of 5 years or more is extremely rare [14,19,22,41,42], even in patients who from a current perspective would have been clear candidates for resection [4], and survival beyond 10 years has not yet been convincingly reported. Therefore, these data provide the best presumptive evidence that long-term results after liver resection are not simply from a selection bias [43–45] but from a direct effect of surgery resulting in a change in the natural history of hepatic colorectal metastases [4,5,33,44,46–49].

**Evolution of selection criteria for liver resection**

During the late 1970s, resection of colorectal metastases was proposed exclusively for patients with solitary metastases [16,50]. Ten years later, resection of multiple lesions became increasingly accepted [16,51]. One of the first studies, from the Mayo Clinic in 1984, reported similar survival curves in 104 patients who had solitary lesions resected and 37 patients who had multiple metastases resected, with 5-year survival rates of 25% and
18%, respectively [52]. Even in the late 1980s, however, many authors were still reluctant to advocate surgery for bilateral disease [45, 52–57]. Several analyses of the current authors’ patients have consistently failed to demonstrate any prognostic significance of the number or distribution of metastases (solitary, multiple unilateral, or multiple bilateral) as long as an R0 resection had been accomplished (Fig. 1) [4, 7, 13, 36, 58]. In the mid-1980s, Ekberg et al [59] proposed general contraindications to liver resection based on number of lesions, involvement of other organs, and close surgical resection margins (<1 cm). These factors are now no longer considered contraindications to resection.

The most recent developments, including new strategies such as portal vein embolization to enlarge the liver remnant [60–62] and neoadjuvant

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of resectiona (R category)</th>
<th>No. patients</th>
<th>5-y survival, %</th>
<th>Median survival, mo</th>
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<td>All</td>
<td>280</td>
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<td>NS</td>
</tr>
<tr>
<td>Gayowski et al, 1994 [23]</td>
<td>All</td>
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<td>280</td>
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<td>Jenkins et al, 1997 [28]</td>
<td>All</td>
<td>134</td>
<td>25</td>
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<td>Yamamoto et al, 1999 [38]</td>
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<td>51</td>
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<td>38</td>
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<td>Kokudo et al, 2001 [29]</td>
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</tr>
<tr>
<td></td>
<td>0</td>
<td>473</td>
<td>41</td>
<td>44</td>
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</tbody>
</table>

| Multi-institution series      |                                |              |                 |                     |
| van Ooijen et al, 1992 [40]   | All                            | 118          | 21              | NS                  |

Abbreviation: NS, not specified.

a All, all resections performed (curative and noncurative), including R0, R1, and R2.
Fig. 1. Influence of number and distribution of colorectal liver metastases on survival in 473 consecutive patients undergoing curative (R0) resection between 1961 and 1998 and followed up through January 1, 2000. Operative mortality is excluded. (Adapted from Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
chemotherapy to shrink tumor size and reduce cell viability [63], were
developed to increase the proportion of patients in whom resection was
technically possible.

**Current analysis of prognostic factors**

*Prime prognostic factor: completeness of tumor removal*

R0 resection, defined as complete removal of all macroscopically
detectable disease and negative microscopic resection margins, is the most
important determinant of outcome (Fig. 2). In the early Erlangen/Jena
experience, survival after histologically nonradical procedures followed the
same course as did survival with best clinical care without surgery [64]. The
Ohio State University also published identical survival curves for patients
with incomplete resection and no resection [65]. Further reports distinguis-
ching between histologically nonradical operations (ie, in which the margins
are involved; so-called “R1 resection”), operations in which gross tumor is
left behind (so-called “R2 resection”), and procedures with a clear resection
margin, even of minimal extent (R0 resection), have demonstrated long-term
survival only in the latter subgroup (Table 2) [7,13,23,28,33,66–70]. This
effect is also reflected in the slightly better results reported in the five series
in Table 1 that included exclusively R0 resections.

Only Fong et al [20,21] have reported substantial long-term survival rates
in patients with involved resection margins: 17% at 5 years in 65 patients
and, more recently, 20% at 5 years in 106 patients. In contrast to the
International Union Against Cancer guidelines, however, which define R1
resections as those in which the margin is microscopically involved, a margin
of less than 5 mm was considered an R1 resection in this series (Y. Fong,
personal communication).

Considering the impact of a negative resection margin on prognosis, the
detailed analysis of prognostic indicators should be restricted to patients in
whom R0 resections were achieved and should exclude operative mortality.
This policy of statistical evaluation was constantly applied to the current
authors’ analyses to minimize the confounding effects of such factors as
surgical mortality and positive margins on outcome.

**Demographic and personal features**

In most publications, gender does not significantly affect outcome in
patients undergoing resection of colorectal liver metastases [4,7,
21,28,30,31,33]. Age may influence operative risk and patient selection but
is unlikely to influence survival at 5 years in those who survive the early
postoperative period [13,20,30–33,45,53–55,57,71–73].

After 10 and 15 years, however, age-related competing risks result in a
statistically significant inferior survival for older patients [36]. Similarly,
Performance status not only serves as a selection criterion but also affects prognosis [36, 74], as do preoperative weight loss and albumin level [75].

**Primary tumor features**

The following features have all been described as being associated with inferior outcomes: location in the rectum [7, 76], greater depth of infiltration according to the pathologic tumor category [77], mesenteric lymph node metastases [17, 20, 21, 30, 31, 47, 52, 55, 58, 78–83], and poor differentiation [7, 84]. A recent analysis from Fong et al [21], however, revealed identical survival rates, of 35%, in 743 patients with colon tumors and 258 patients with rectal tumors, and these results must be considered relevant given the large number of patients involved. Because primary tumor effects are more pronounced in patients with synchronous metastases, such differences in results between series may be partially attributable to differences in the ratio of synchronous versus (late) metachronous lesions [7, 28, 37, 39, 54, 65, 71, 85–87].

**Table 2**

Impact of type of resection on prognosis after resection of colorectal liver metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of resection (R category)</th>
<th>No. patients</th>
<th>5-y survival, %</th>
<th>Median survival, mo</th>
</tr>
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<tbody>
<tr>
<td>Ringe et al, 1990 [33]</td>
<td>0</td>
<td>119</td>
<td>27</td>
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<td></td>
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<td>38</td>
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<td>1/2/X</td>
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<tr>
<td>Sugihara et al, 1993 [70]</td>
<td>0a</td>
<td>109</td>
<td>48</td>
<td>—</td>
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<tr>
<td></td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>17b</td>
</tr>
<tr>
<td>Henne-Bruns et al, 1993 [68]</td>
<td>0</td>
<td>66</td>
<td>37</td>
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<td>187</td>
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<td>0</td>
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<td>1/2</td>
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<td>2</td>
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<td>89</td>
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<td>18</td>
<td>6</td>
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<td>36b</td>
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<td>0</td>
<td>21b</td>
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<td>15</td>
<td>—</td>
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<td></td>
<td>1/2</td>
<td>7</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Fong et al, 1997 [94]</td>
<td>0</td>
<td>361</td>
<td>43</td>
<td>—</td>
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<td></td>
<td>1/2</td>
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<td>17</td>
<td>—</td>
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<td>473</td>
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<td></td>
<td>1/2</td>
<td>109</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>

**Abbreviations:** X, no R classification documented.

* Only patients without extrahepatic disease.

* Estimated from graph.

* Calculated from tables.
Metastases

Multiple tumors [4,47,52,57,78,81,88] and a bilobar distribution [31,59] both seem to be of minor prognostic importance after R0 resection. The variable impact of these features in reported series may be from an increase in number of nonradical procedures as the extent and complexity of the resection increase with bilobar involvement [17,20,21,38,65,89].

Less attention is usually paid to satellite metastases. This may reflect their relatively low incidence, of 14% to 24% [7,38,59,90], and the difficulty in defining lesions as either “independent” or “satellite.” The current authors have defined a satellite metastasis as follows: (1) one that is located in the same Couinaud segment as the main nodule or within 2 cm from the main nodule and (2) with a diameter at presentation of less than half the diameter of the larger nodule, or 4 cm or less if the metastasis is associated with a giant main lesion [58]. In fact, all but two of the authors’ satellite metastases have measured less than 1 cm in diameter. From this definition, satellite metastases proved, in the authors’ 1996 multivariate analysis, to be the most important single adverse prognostic factor [7], although they were less powerful in the recent update [91]. Satellite metastases were also significant in other series [32,34,59,92]. Because satellites develop as a result of local distribution via portal vein infiltration, they may indicate an adverse tumor biology with a higher potential for vascular invasion leading to spread, regardless of whether the main lesion is single or multiple [7]. In the Erlangen/Jena series, the proportion of subsequent pulmonary metastases was doubled in patients with satellite nodules, which may reflect invasion of hepatic venous branches as well [13].

This observation was in contrast to early data from Cobourn et al [93] and Langer [56] who found satellite nodules to have no prognostic impact when they accompanied otherwise solitary metastases. More recently, however, authors from the same group described a significant difference in 5-year survival after resection of solitary lesions in patients with and without satellite metastases (16% and 47%, respectively) [37].

In contrast to the number of metastases, the “tumor burden” is usually a significant indicator of prognosis [33]. Tumor burden may be defined by the maximum diameter [21] or by the percentage of liver volume replaced by tumor [19,30,69,88,94–97]. There was only one anecdotal 5-year survivor among 18 patients with greater than 50% of the liver volume replaced by tumor in Doci et al [19] and just one 5-year survivor among nine such patients in the current authors’ series (Fig. 3) [36]. Nevertheless, other reports have failed to demonstrate a significant influence of tumor burden on survival [31,37,57,65,72,95].

Histopathologic features, such as fibrous pseudocapsule formation [38], the degree of fibrosis around the metastases [32,38,98], single-node versus confluent-node growing pattern of individual lesions [97], infiltrative versus expansive pattern of growth [98], invasion of portal and hepatic vein
Fig. 3. Survival after R0 resection according to the proportion of liver volume replaced by tumor. Only one patient with more than 50% of the liver volume replaced by tumor survived for 5 years, and this patient eventually died of recurrence. Operative mortality is excluded. (Adapted from Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
branches [38], peritumorous lymphocyte infiltration [98], and cell proliferation–related markers [99] may contribute independently to a better assessment of prognosis. In a recent Japanese series [31], vascular and biliary invasion both failed to influence prognosis.

Comparing synchronous and metachronous metastases, most authors have found superior results for metachronous lesions [7,13,28,58,70,83,88,100], but others have seen similar outcomes for these two types of metastases [37,47,54,57,59,78,81,101]. This again may reflect a different treatment approach in patients with synchronous lesions. In some reports, patients with synchronously detected lesions who underwent delayed liver resection had outcomes similar to those of patients with metachronous lesions, whereas patients with synchronously detected lesions who underwent liver resection at the time of resection of the primary tumor had worse 5- and 10-year survival rates than patients with metachronous lesions [28]. In the current authors’ series, the survival rate was reduced by almost 50% [36], which likely reflects improved patient selection rather than any oncologic advantage of a waiting period. Centers with the general concept of delayed resection and groups that are not involved in primary treatment of colorectal cancer and therefore treat predominantly patients referred after colorectal resection in other hospitals are unlikely to confirm a better outcome in the metachronous group. A few authors reported extremely poor results in patients who underwent resection of synchronous liver lesions [28,83] and therefore either generally question the value of resecting synchronous metastases [102] or restrict this procedure to treatment of solitary lesions [26]. In a report from the Mayo Clinic, however, synchronous presentation of metastases was associated with a superior prognosis [34]. Synchronous presentation of metastases should not affect the decision to operate but may influence the timing of resection, particularly in patients at high risk for recurrence. In the Erlangen/Jena series, when only metachronous metastases were analyzed, no survival differences were detected between patients with disease-free intervals of 12 or fewer months, 13 to 24 months, and more than 24 months [7]. There was also no survival difference in other series comparing patients with disease-free intervals of more or less than 12 months [2,28,65,72].

**Therapeutic approach**

Most authors have failed to detect any significant difference in outcome between anatomic and nonanatomic procedures [27–32,65,69,88,94–97], whereas others have reported superior results for minor resections, usually performed in a nonanatomic manner [19,72]. In the Erlangen/Jena experience, the anatomic approach reduced the incidence of R1 resections [64,103]. Even within the R0 group, however, survival with the anatomic technique was significantly better than survival after nonanatomic resections. Among
anatomic procedures, there was no difference between standard resections and more sophisticated segment-oriented procedures [7,36,84]. This superiority of major anatomic procedures was also described by other investigators [83,104,105].

Blood loss, intraoperative hypotension, and the need for blood transfusion have all been reported to reduce survival rates [27,32,34,72,83,106–108], but in the largest series available [21], this effect disappeared when operative mortality was excluded. Only a few series, however, have proved an independent impact of blood loss, intraoperative hypotension, and blood transfusion on prognosis in a multivariate analysis [32,40]. Others have found no effect, even when using a univariate approach [20,28,30,69,76,88,94–97,109,110]. It is therefore unclear whether blood transfusions per se impair prognosis or simply reflect a more complex procedure, required with a greater tumor load, and less favorable “tumor biology.” In the current authors’ series, 5- and 10-year survival rates both dropped by 10% per 1000 mL of blood lost during surgery in the univariate analysis, paralleled by the negative effect of intraoperative transfusions of blood and fresh-frozen plasma. In the multivariate analysis, however, only administration of fresh-frozen plasma was independently associated with worse prognosis [66].

Other factors have been evaluated and found to significantly affect prognosis in many series. These include preoperative carcinoembryonic antigen levels to indicate tumor aggressiveness (Fig. 4) [20,21,31,36,67,89,111,112], number of involved liver segments [74], and length of operation time [108]. More sophisticated markers, such as tumor ploidy [89,113–115], oncogene expression, and tumor suppressor gene expression [116], may further improve patient selection or allocation to multimodal strategies. In a recent analysis, however, only p53 predicted intrahepatic tumor relapse, whereas other factors, such as DNA content and the genetic markers c-myc, c-erbB-2, epidermal growth factor receptor, H-ras, proliferating cell nuclear antigen, nm23, and even coexpression of multiple markers, did not predict survival after potentially curative resection [117].

**Potential contraindications to liver resection**

In their landmark article published in 1986, Ekberg et al [59] proposed three general contraindications to liver resection for metastatic colorectal cancer: the presence of four or more metastases, the presence of additional extrahepatic disease, and a resection margin of less than 1 cm.

Problems with this study were the small number of patients who met these criteria and the inclusion of nonradical procedures. Nevertheless, the “Ekberg criteria” have frequently been quoted by subsequent authors [2,71,77,81]. In turn, the presence of one to three liver metastases, irrespective of unilateral or bilateral distribution, that can be removed with a margin of 1 cm or more became generally accepted as a clear indication for liver resection as long as extrahepatic disease was not present at the same time.
Fig. 4. Survival after R0 resection according to the preoperative carcinoembryonic antigen level. Operative mortality is excluded. (Adapted from Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
Number of metastases

Since Ekberg et al’s study [59], several authors have reported long-term success in patients with four, five, or even more independent hepatic lesions. Nordlinger et al [57] described 14 patients in whom five or more metastases were removed with clear margins. Their survival followed the same course as seen in 36 patients who had two, three, or four metastases resected.

In Fong et al [20], 5-year survival rates were 24% in 68 patients with four or more metastases resected, 31% in 140 patients with two or three metastases resected, and 47% in patients with solitary lesions resected. Despite the significant influence of number of metastases on outcome, the authors did not see an argument for excluding patients with four or more lesions from resection. In Minagawa et al [31], 5- and 10-year survival rates among 53 patients with 4 to 13 resected lesions were 32% and 29%, respectively.

In the most recently published update of the current authors’ experience, no survival difference was found between patients who had one to three versus four or more independent metastases completely removed (R0 resection). The group with four or more metastases comprised 48 patients, 18 of who were alive at the time of the report. Seventeen of the patients had survived more than 5 years, and 15 of these without recurrent disease (Fig. 5) [36]. In this analysis, only 6 of 473 patients initially surviving a curative resection had eight or more metastases resected; however, 3 of these 6 patients were alive at the end of observation and 2 were 5-year survivors (Fig. 6) [36]. Because of the improvements in diagnostic preoperative imaging techniques and the variations in biology of hepatic colorectal metastases, an operative decision based only on the number of lesions that can be resected with curative intent seems premature. Regardless, the number of patients who actually had curative resection of four or more metastases remains small.

Extrahepatic disease

A well-accepted contraindication to liver resection is the presence of extrahepatic disease [23,26,34,40,118–120]. In Adson et al’s [16] initial report published in 1984, no patient with extrahepatic disease survived beyond 5 years, and the actual 2- and 3-year survival rates were 36% and 11%, respectively, which was significantly lower than the rates of 72% and 63%, respectively, for patients without extrahepatic involvement. Hughes et al [80] reported a 5-year overall survival rate of 20% with extrahepatic disease, but 5-year disease-free survival was only 4%. In Fong et al [21], a 5-year survival rate of 18% was observed among 88 patients with extrahepatic tumor, half of whom had direct invasion of other structures and half of whom had discontiguous extrahepatic spread. In the Erlangen/Jena series [36], 17 of 51 patients with extrahepatic disease and a follow-up time of more than 60 months have become 5-year survivors, and 3 patients have meanwhile survived free of disease for more than 10 years (Fig. 7). In these patients, extrahepatic tumor consisted of either locally recurrent disease, direct tumor
Fig. 5. Survival after R0 resection according to the number of independent liver metastases removed (≥4 vs 1–3). Operative mortality is excluded. (Adapted from Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
Fig. 6. Survival after R0 liver resection by number of metastases resected. Operative mortality is excluded. (From Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
Fig. 7. Survival after R0 liver resection in patients with and without extrahepatic tumor. Operative mortality is excluded. (Adapted from Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
invasion of adjacent structures, or one or two pulmonary metastases [36]. Elias et al [121] reported a 5-year disease-free survival rate of 33% among 11 patients in whom either lung metastases \( n = 5 \) or hilar nodes \( n = 6 \) were removed at the same time as the hepatic resection. Two studies suggest that extended survival is possible when hepatic resection is combined with cytoreductive tumor excision of limited peritoneal carcinomatosis and intraperitoneal chemotherapy [122,123].

Some recent articles on repeat hepatic resection have reported 5-year disease-free survivors among patients who underwent resection of both liver and lung metastases or both liver metastases and locally recurrent disease [7,13,95,124–126]. These reports indicate that although extrahepatic disease is rarely completely resectable, some carefully selected patients may still be considered for surgical treatment.

**Resection margin**

The factor most influenced by the surgical approach is the margin of clearance. There is general agreement that a margin of 1 cm or more is preferable [68,71,80]. There is consensus that determination of margin width must not be based on palpation of the liver but rather should be guided by routine application of operative ultrasonography [89,127]. Further, anatomic procedures, such as segmentectomies according to Couinaud’s terminology instead of nonanatomic wedge excisions, are recommended because anatomic procedures are more likely to achieve satisfactory margins [103].

Given the overwhelming significance of a clear margin [89], the question arises as to a minimal surgical margin, such as the 1 cm proposed by Ekberg et al [59]. In the current authors’ previous publications, patients with a margin of 10 mm or more had better outcomes than those with clear but more limited margins in the univariate analysis, but this was not confirmed in multivariate regression analysis [7,58]. In the authors’ recent update, even the univariate effect completely disappeared, paralleling reports by Fong et al [20] and Kokudo et al [29]. Among patients with a follow-up time exceeding 60 months, 46 of 130 patients with resection margins of 0 to 4 mm were 5-year survivors, and 34 of 86 patients with resection margins of 5 to 9 mm were 5-year survivors (Fig. 8) [36].

In the large-scale series reported by Elias et al [128], the width of the resection margin, 0 to 4 mm versus 5 to 9 mm, failed to significantly influence prognosis even in univariate analysis; the same was true in the report by Nakamura et al [95]. In the updated Lund experience [32], 5-year survival rates were 31% in patients with margins greater than 10 mm and 22% in patients with 1- to 10-mm margins. A similar result was seen in a Pittsburgh study, where 95 patients with resection margins of greater than
Fig. 8. Survival after R0 resection according to the margin of clearance. Operative mortality is excluded. (From Scheele J, Altendorf-Hofmann A, Grube THW, et al. Resection of colorectal liver metastases: which prognostic factors should govern patient selection? Chirurg 2001;72:547–60.)
1 cm had only slightly better overall survival (42% versus 32%) and disease-free survival (29% versus 25%) at 5 years than 92 patients with margins of 1 cm or less [23].

**Lessons from multivariate analyses**

Results of multivariate analyses are summarized in Table 3. Some authors [20,21] included nonradical procedures, in an approach resembling a sort of “intention to treat” analysis. In consideration of the paramount importance of completeness of tumor removal on long-term tumor control and survival, most authors included only R0 resections (inclusion criterion). This type of method for multivariate analysis clearly questions margin size as a factor of prognosis—Ambiru et al’s [17] series is the only exception—as long as only negative margin resections are included in multivariate analysis (see Table 3). In the current authors’ series, in which a negative margin was of paramount importance (see Fig. 2), the ranking of various characteristics by relative importance demonstrates that both treatment variables and tumor biology determine outcome (Table 4).

**Current criteria for exclusion: a personal view**

Liver resection is almost always contraindicated if adequate preoperative imaging and careful operative re-examination indicate that not all detectable tumor can be removed. Tumor debulking may be exceptionally justified in the occasional patient in whom symptoms from a (large) metastatic lesion can be relieved by resection [16,59].

A second absolute contraindication to liver resection is the presence of hilar metastases [2,13,31,34,59,119]. This was a rare finding in the Erlangen/Jena series (7 of 597 patients), Hughes et al’s [2] collected series (24 of 859 patients), the recent report from Mayo Clinic (9 of 280 patients) [27], and Minagawa et al’s study [31] (6 of 235 patients). Using radioimmunoguided surgery, detection of microscopic lymph node involvement within the hepatoduodenal ligament, the celiac axis, and the para-aortic region may be possible [109], but the clinical significance of such “micro-metastases” is still unclear. In Nakamura et al [95], two patients with positive hilar lymph nodes remained disease-free at 49 and 66 months, respectively. Both patients had undergone repeat liver resection. It is not specified whether these metastases were macroscopic or microscopic. A recent extensive review identified 145 node-positive patients who underwent resection of colorectal liver metastases. There were five survivors at 5 years, with one patient free of disease, two with tumor recurrence, and two with unknown disease status [129]. The issue of hilar lymph nodes in hepatic colorectal metastases is specifically addressed in another article in this issue.

Presence of extrahepatic disease at other sites has been considered an absolute contraindication to resection [23,26,40,47,95,118–120]. Contiguous
Table 3
Indicators of prognosis after resection of colorectal liver metastases by multivariate analysis (literature review)

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Stage</th>
<th>Grade</th>
<th>Synchron</th>
<th>Size</th>
<th>Number</th>
<th>Bilateral</th>
<th>Satellite</th>
<th>EHD</th>
<th>CEA</th>
<th>Chemo</th>
<th>Anatomic</th>
<th>Transfus</th>
<th>Hypotens</th>
<th>Margins</th>
<th>R0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doci et al, 1991 [78]</td>
<td>N</td>
<td>Y</td>
<td>NI</td>
<td>N</td>
<td>Y°</td>
<td>N</td>
<td>N</td>
<td>NI</td>
<td>NI</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>IC</td>
</tr>
<tr>
<td>Van Ooijen et al, 1992 [40]</td>
<td>N</td>
<td>N</td>
<td>NI</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>NI</td>
<td>Y</td>
<td>NI</td>
<td>NI</td>
<td>N</td>
<td>Y</td>
<td>NI</td>
<td>IC</td>
<td>IC</td>
</tr>
<tr>
<td>Doci et al, 1995 [19]</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y°</td>
<td>N</td>
<td>N</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>NI</td>
<td>Y</td>
<td>IC</td>
<td>IC</td>
</tr>
<tr>
<td>Scheele et al, 1995 [84]</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>Y</td>
<td>NI</td>
<td>IC</td>
<td>IC</td>
<td>IC</td>
</tr>
<tr>
<td>Fong et al, 1997 [20]</td>
<td>N</td>
<td>N</td>
<td>NI</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>N</td>
<td>N</td>
<td>Y</td>
<td>NI</td>
<td>IC</td>
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<tr>
<td>Rees et al, 1997 [69]</td>
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<td>N</td>
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<td>Fong et al, 1999 [21]</td>
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</tr>
<tr>
<td>Minagawa et al, 2000 [31]</td>
<td>N</td>
<td>Y</td>
<td>NI</td>
<td>N</td>
<td>Y</td>
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<td>N</td>
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<td>IC</td>
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<tr>
<td>Kokudo et al, 2001 [29]</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>Y</td>
<td>Y</td>
<td>NI</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
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<td>NI</td>
<td>N</td>
<td>IC</td>
<td>IC</td>
<td>IC</td>
</tr>
<tr>
<td>Lise et al, 2001 [30]</td>
<td>N</td>
<td>Y</td>
<td>NI</td>
<td>N</td>
<td>Y</td>
<td>N</td>
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<td>N</td>
<td>NI</td>
<td>Y</td>
<td>IC</td>
<td>IC</td>
<td>IC</td>
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<tr>
<td>Scheele et al, 2001 [36]</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
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<td>N</td>
<td>Y</td>
<td>NI</td>
<td>IC</td>
<td>IC</td>
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</tr>
</tbody>
</table>

Abbreviations: CEA, carcinoembryonic antigen level; chemo, chemotherapy; EHD, extrahepatic disease; hypotens, hypotension; IC, inclusion criterion (only R0 patients included in multivariate analysis); synchron, synchronous; transfus, blood transfusions required; NI, not investigated; Z, N, no statistical significance; Y, statistical significance.

° Extent of liver involvement instead of size.

Blood loss instead of transfusion.

Within 12 months from primary tumor, better results for the synchronous group.

Better results for 3 or more versus 1 metastasis.

Table 4
Indicators of prognosis after R0 resection of colorectal liver metastases by multivariate analysis (Erlangen/Jena series)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favorable</th>
<th>Poor</th>
<th>P value</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrahepatic tumor</td>
<td>Absent</td>
<td>Present</td>
<td>0.0000</td>
<td>2.19</td>
<td>1.58–3.05</td>
</tr>
<tr>
<td>Hypotensive periods</td>
<td>Absent</td>
<td>Present</td>
<td>0.0001</td>
<td>1.62</td>
<td>1.27–2.07</td>
</tr>
<tr>
<td>Resection technique</td>
<td>Anatomic</td>
<td>Nonanatomic</td>
<td>0.0002</td>
<td>2.06</td>
<td>1.41–3.00</td>
</tr>
<tr>
<td>Metastasis diameter, cm</td>
<td>&lt;5</td>
<td>5</td>
<td>0.0002</td>
<td>1.67</td>
<td>1.27–2.19</td>
</tr>
<tr>
<td>Grade of primary tumor</td>
<td>“Low risk”</td>
<td>“High risk”</td>
<td>0.0003</td>
<td>1.65</td>
<td>1.25–2.18</td>
</tr>
<tr>
<td>Satellite metastases</td>
<td>Absent</td>
<td>Present</td>
<td>0.0069</td>
<td>1.58</td>
<td>1.14–2.21</td>
</tr>
<tr>
<td>PN category, primary tumor</td>
<td>pN0</td>
<td>pN1,2</td>
<td>0.0260</td>
<td>1.36</td>
<td>1.04–1.79</td>
</tr>
<tr>
<td>Use of fresh-frozen plasma</td>
<td>No</td>
<td>Yes</td>
<td>0.0307</td>
<td>1.31</td>
<td>1.03–1.68</td>
</tr>
<tr>
<td>pM category, primary tumor</td>
<td>pM0</td>
<td>pM1</td>
<td>0.1240</td>
<td>1.23</td>
<td>0.95–1.61</td>
</tr>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis diameter, cm</td>
<td>&lt;5</td>
<td>5</td>
<td>0.0000</td>
<td>1.73</td>
<td>1.34–2.25</td>
</tr>
<tr>
<td>Extrahepatic tumor</td>
<td>Absent</td>
<td>Present</td>
<td>0.0000</td>
<td>1.88</td>
<td>1.37–2.58</td>
</tr>
<tr>
<td>Hypotensive periods</td>
<td>Absent</td>
<td>Present</td>
<td>0.0010</td>
<td>1.48</td>
<td>1.17–1.87</td>
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<tr>
<td>Resection technique</td>
<td>Anatomic</td>
<td>Nonanatomic</td>
<td>0.0043</td>
<td>1.71</td>
<td>1.18–2.47</td>
</tr>
<tr>
<td>Grade of primary tumor</td>
<td>“Low risk”</td>
<td>“High risk”</td>
<td>0.0063</td>
<td>1.46</td>
<td>1.11–1.91</td>
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<tr>
<td>pN category, primary tumor</td>
<td>pN0</td>
<td>pN1</td>
<td>0.0159</td>
<td>1.37</td>
<td>1.06–1.77</td>
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<tr>
<td>Location of primary tumor</td>
<td>Colon</td>
<td>Rectum</td>
<td>0.0188</td>
<td>1.33</td>
<td>1.05–1.69</td>
</tr>
<tr>
<td>Use of fresh-frozen plasma</td>
<td>No</td>
<td>Yes</td>
<td>0.0264</td>
<td>1.31</td>
<td>1.03–1.66</td>
</tr>
<tr>
<td>pM category, primary tumor</td>
<td>pM0</td>
<td>pM1,2</td>
<td>0.0381</td>
<td>1.32</td>
<td>1.02–1.71</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

* High risk, adenocarcinoma grade III/IV, mucinous adenocarcinoma, signet ring cell carcinoma; low risk, all others.


Tumor invasion of adjacent structures must be differentiated from other types of recurrence. Direct tumor infiltration usually affects the diaphragm, or rarely, the retrohepatic vena cava, the hilar vessels, or the extrahepatic bile duct. These latter findings are often associated with other negative prognostic factors, such as a large tumor mass or poor differentiation. By following an aggressive policy of wide en bloc resection, long-term disease-free survival may still be possible. In the Erlangen/Jena series [36], patients with direct tumor invasion had only a moderate impairment of prognosis, with 5-year survival rates of 33% compared with 43% in the absence of extrahepatic tumor (see Fig. 7). This view has been confirmed by Miyazaki et al [130], who reported 1- and 5-year survival rates of 64% and 22%, respectively, in 16 patients who underwent combined liver and vena cava resection. Similarly, the current authors would pursue resection in patients with resectable local recurrence and limited lung metastases [131–134]. Tumor at any other site, such as an adrenal metastasis, an omental deposit, nodules on the small bowel, or limited peritoneal spread, is rarely amenable to an R0 resection, and in the authors’ experience, even occasional apparent
R0 removal with subsequent adjuvant chemotherapy has resulted in early recurrence of unresectable disease [7].

**Future perspectives**

Only a minority of patients with colorectal liver metastases are candidates for resection, but, in this subset, resection is clearly warranted. Significant therapeutic progress in patients with colorectal liver metastases overall requires the development of effective therapy for patients with unresectable disease. Adjuvant and neoadjuvant strategies using new chemotherapeutic agents, refined immunotherapy protocols [135], preoperative chemoembolization, radioimmunoguided surgery [109], ex situ and ante situ resection [136,137], or the combination of resection and local tumor destruction [138,139] need further evaluation. Moreover, the less invasive therapeutic alternatives currently under development, such as MRI-guided laser destruction [140–142], percutaneous radionuclide injection, and laparoscopic interventions, may complement, or even replace, conventional surgery in selected patients [143,144].

**References**


