CURRENT TREND

Surgical management of liver metastases from gastrointestinal endocrine tumors

Prise en charge chirurgicale des métastases hépatiques des tumeurs endocrines digestives

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Summary  Liver metastases from endocrine tumors can reduce 5-year survival from 90\% to 40\% and, in cases of functional gastrointestinal endocrine tumors, lead to a carcinoid syndrome. Complete resection of cancerous disease should be considered in all cases. Indeed, after hepatectomy, prolonged survival (41—86\% at five years) can be achieved, with low rates of surgery-related mortality (0—6.7\%). Extended liver resection is required in most cases. Percutaneous portal embolization increases the volumetric feasibility of resection, and sequential hepatectomy techniques enable a two-stage resection of both bilobar metastases and the primary tumor. For carcinoid syndrome that does not respond to medical therapy, incomplete resection of liver metastases, by reducing tumor volume, may be indicated to reduce symptoms and halt the progression of carcinoid heart disease. In cases of non-resectable liver metastases in selected patients, liver transplantation can lead to 5-year survival rates as high as 77\%.

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Résumé  La survenue des métastases hépatiques des tumeurs endocrines digestives diminue la survie de moitié et entraîne un syndrome carcinoïde dans le cas des tumeurs endocrines intestinales. L'exérèse complète de la maladie tumorale doit systématiquement être envisagée. En effet, après hépatectomie, la survie peut être prolongée (41—86 \% à cinq ans) et la mortalité opératoire est faible (0—6.7 \%). Il s’agit le plus souvent de résections hépatiques étendues. L'embolisation percutanée de la veine porte permet d'augmenter la faisabilité volumétrique de la résection et les techniques d'hépatectomie séquentielle permettent de traiter en deux temps les métastases bilobaires et la tumeur primitive. En cas de syndrome carcinoïde résistant au traitement médical, une exérèse même incomplète des métastases hépatiques peut être indiquée pour réduire le volume tumoral afin de diminuer la symptomatologie et ralentir l’évolution d’une cardiopathie carcinoïde. En cas de métastases hépatiques

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Introduction

Liver metastases arise from an endocrine tumor in less than 10% of patients [1,2], yet they are frequently the initial manifestation, with more than half the patients with a malignant endocrine tumor also having synchronous liver metastases at the time of diagnosis [2,3]. The development of liver metastases should be considered a major event in the disease course in terms of both quality of life and overall prognosis. Indeed, the 5-year survival rate is around 75—100% for patients free of metastasis, but falls to 40% or less for those with liver metastases [4—8]. In addition to the impact on survival, liver metastases can lead—depending on the histological type and functional capacity—to difficult-to-control hormone production, particularly in cases of large metastatic tumors. This is especially true for midgut and hindgut endocrine tumors, previously termed ‘carcinoid’ tumors. In these difficult therapeutic situations, surgical resection may be proposed to reduce the size of the hepatic metastasis, thereby limiting the amount of serotonin secreted to relieve the patient’s symptoms and slow the progression to carcinoid heart disease [9].

The purpose of the present review is to describe the current indications, modalities and results of surgical treatment of liver metastases from gastrointestinal endocrine tumors.

Histoprognostic classifications

In 2000, the World Health Organization (WHO) proposed a histoprognostic system of classification [10] (Table 1), to which was recently added those proposed by the European Neuroendocrine Tumor Society (ENETS) in 2006 for foregut tumors [1] and, in 2007, for midgut and hindgut tumors [12]. This new classification distinguishes tumor stage from tumor grade. Tumor stage is described according to the TNM system, with liver metastases corresponding to stage M1 or IV. For tumor grading, one of the inadequacies of the WHO classification was that it did not individualize certain well-differentiated tumors presenting with histological signs of aggressiveness, such as a high proliferation index or necrotic foci. The ENETS classification proposes a distinction between grades G1 and G2 for well-differentiated endocrine carcinomas, and adds grade G3, corresponding to poorly differentiated endocrine carcinomas (Table 2). This classification is essentially based on the mitotic index, assessed using the Ki67 antibody (MIB1), and secondarily uses the presence or absence of necrotic foci.

Rationale for surgery

Although endocrine tumors are thought to be slow-growing, the majority of patients with liver metastases die within five years of diagnosis [3]. In addition, liver metastases can themselves be a source of two types of complications via compressive effects, related to the size and number of metastatic tumors, and/or hormonal effects, related to inappropriate secretion of serotonin, gastrin and, more unusually, insulin. Therefore, surgery may be proposed for two reasons: to achieve a cure by complete resection (R0) or transplantation; or as a palliative treatment when symptoms fail to respond to medical treatment. In the latter situation, and unlike virtually all other situations in oncological hepatic surgery, incomplete hepatic resection (R1 or R2) may be a rational solution because of the slow-growing nature of these tumors, and of well-differentiated G1 or G2 tumors in particular.

In the specific case of endocrine tumors of the foregut as elements of a multiple endocrine neoplasia type-1 (MEN-1) syndrome, the role of surgery is more controversial, especially for Zollinger—Ellison syndrome, which accounts for 60% of MEN-1 syndromes involving a functional pancreatic endocrine tumor [13]. Resection of foregut tumors cannot be expected to definitively normalize gastrinemia, as biochemical recurrence is a constant in MEN-1 tumors [14]. Furthermore, excess acid secretion can be controlled by antisercretory medication in more than 98% of patients for periods as long as 22 years [15]. Moreover, although there have been reports of a slowing of metastases after surgery of the primary tumor [14,16,17], there is no strong argument favoring hepatectomy for MEN-1 patients with liver metastases.

Non-surgical treatment

Thus far, no randomized study has compared surgical resection of liver metastases of endocrine tumors with techniques for in-situ destruction such as radiofrequency ablation, cryotherapy or ethanol injection. Of these three techniques, most of the clinical experience has involved radiofrequency ablation for liver metastases [18—22]. Its use is, however, limited by the high rate of local recurrence [23,24] and by the fact that lesions greater than 5 cm in size, or those lying close to large vessels or bile ducts, are not suitable for this technique. Nevertheless, it can be used as a complement to surgery in a treatment that combines resection and intraoperative radiofrequency ablation [20], or as an alternative to resection in patients with non-resectable tumor or after previous hepatic surgery [25]. In the series reported by Mazzafera et al. [21], the 1-, 2- and 5-year survival rates of 63 patients treated exclusively with laparoscopic radiofrequency ablation were 91%, 7% and 48%, respectively.

Trans-arterial chemoembolization (TACE) is also proposed for liver metastases of well-differentiated gastrointestinal endocrine tumors. In two recent series using this technique, the 5-year survivals were 83% and 50%, respectively [26,27]. Nevertheless, the sole study comparing TACE with resection
Table 1  Histoprognostic classification of endocrine tumors from the World Health Organization (WHO), 2000 [10].

<table>
<thead>
<tr>
<th>Low-grade endocrine tumor</th>
<th>Intermediate-prognosis endocrine tumor</th>
<th>Well-differentiated endocrine carcinoma</th>
<th>High-grade endocrine carcinoma</th>
<th>Mixed endocrine/exocrine tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size &lt; 2 cm, well-demarcated, &lt; 2 mitoses/2 mm²; No vascular invasion;</td>
<td>Size &gt; 2 cm, &gt; 2 mitoses/2 mm²;</td>
<td>All low-grade tumors with local macroscopic invasion and/or metastases</td>
<td>Small-cell endocrine carcinomas;</td>
<td>Composite tumors</td>
</tr>
<tr>
<td>In gastrointestinal tumors: no involvement of the musculosa (or the serous in the appendix); No metastases</td>
<td></td>
<td></td>
<td>Large-cell endocrine carcinomas;</td>
<td>Combined with amphicrine tumors</td>
</tr>
</tbody>
</table>

showed a benefit with resection of a 70% 5-year survival compared with 40% for TACE [28].

Resectability of liver metastases

As liver metastases are numerous and often rather large, their surgical resectability is a primary concern. Once it has been established that curative or cytoreductive resection is indicated, resectability can be determined from two factors: anatomical feasibility and volumetric tolerance. A multidisciplinary discussion involving a liver surgeon and a radiologist is required to validate the decision.

Anatomical feasibility

The number-one rule for partial hepatectomy is to ensure that enough liver parenchyma with a satisfactory blood supply (hepatic artery, portal vein, hepatic vein) and biliary drainage remains after surgery. Thus, tumors that have invaded the three hepatic veins or the portal bifurcation cannot be resected unless complex venous reconstructions are feasible. Similarly, bilateral involvement of the secondary biliary confluence is a contraindication for resection when a biliodigestive anastomosis to the remaining ducts cannot be constructed. However, except for such cases of vascular and biliary contraindications, ‘hyperextended’ hepatectomy that leaves behind only one sector of the liver (the posterolateral sector, left lobe) is possible, provided that the remaining liver volume is adequate and of sufficient quality. Combined resections are also possible for multiple tumorectomy or multiple anatomical resection.

Volume limitations

The capacity of non-pathological liver to regenerate after hepatectomy is good, which means that a large proportion of the hepatic parenchyma may be removed; indeed, leaving 25% or even 20% of the functional liver tissue may be sufficient [29–31]. However, in the context of liver metastases from endocrine tumors, the ratio of remnant functional liver to the initial total liver tissue may be difficult to estimate because of the high number and size of tumor nodules, the volume of which should not be included when determining the volume of the total liver. To overcome this problem, there is a validated volumetric ratio that does not consider the total liver volume, but uses total body weight instead [32]. It has been demonstrated that there is a risk of fatal postoperative liver failure when the remaining functional liver ratio falls to less than 0.5% of total body weight.

Multiple-array computed tomography (CT) of the liver is usually applied to measure liver volumes, but other imaging techniques, such as ultrasonography, have also been evaluated for this purpose [33]. When the predicted volume of functional liver is either less than 20–25% of the total liver or less than 0.5% of total body weight, most authors recommend attempting to induce hypertrophy in the remaining functional liver via portal embolization to reduce the risk of postoperative liver failure and increase the tolerability of postoperative complications. The most common situation is a right hepatectomy that extends to segment IV, with prior percutaneous embolization of the right portal branch. Atrophy of the right liver and compensatory hypertrophy of the

Table 2  Histological grades of gastrointestinal endocrine tumors from the European Neuroendocrine Tumor Society (ENETS), 2006–2007 [11,12].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic index (10 HPF)a</th>
<th>Ki67 index (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt; 2</td>
<td>≤ 2</td>
</tr>
<tr>
<td>G2</td>
<td>2–20</td>
<td>3–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

a 10 high power field = 2 mm²; at least 40 fields evaluated in zones with the highest mitotic density.
b MIB1 antibody; % of 2000 tumor cells in zones with the highest density of cells with labeled nuclei.
Hepatic endocrine metastases

Figure 1  Two-stage hepatectomy for bilobar liver metastases: (A) resection of the primary tumor is associated with tumorectomy to clear the left lobe, with ligature of the right portal branch to bring about hypertrophy of what will be the remaining left lobe; and (B) right lobectomy, made possible by the increased volume of the left lobe.

left are generally observed within three to six weeks. The procedure is feasible in nearly 100% of patients [34] and, in our experience, enables a mean gain in volume of 47%, thus increasing the volumetric feasibility for resection of hepatic metastases from 22% to 72% (unpublished data).

When liver metastases are bilobar, two-stage hepatectomy may be a useful alternative to portal embolization [35]. The technique enables the successive treatment of the left liver metastases followed by those in the right liver, with ligature of the right portal branch in the first stage of the hepatectomy to induce hypertrophy of the left lobe during the time interval between the two operations. Another advantage of the method is that it separates the morbidity of the two hepatectomies, and associates the less complicated hepatic procedure with concomitant resection of the primary tumor (Fig. 1).

Finding the primary tumor and extrahepatic extension

In most patients, liver metastases appear before identification of the primary endocrine tumor, which is often small, despite the fact that, in many cases, the liver metastases are rather large. An attempt to find the primary tumor should always be undertaken. Cancer resection of midgut tumors should be proposed in all cases, even in the presence of metastatic spread, as these tumors can lead to intestinal obstruction or mesenteric ischemia related to retractile mesenteritis or compression of the mesenteric veins. When the primary tumor is symptomatic, resection of midgut tumors enables reduction of symptoms in 70–100% of patients [36,37]. In addition, in at least two retrospective series, resection of the primary tumor in metastatic patients increased their median survival from 69 to 139 months [38], and from 48 to 89 months [39], respectively.

Localization of the primary tumor can be achieved with abdominopelvic ultrasonography, endoscopic ultrasound, thoracoabdominopelvic CT, upper or lower gastrointestinal endoscopy and opacification techniques, depending on the nature of the symptoms or the histology of the liver metastases on percutaneous biopsy. Whatever the location, somatostatin receptor scintigraphy (SRS) should always be performed in the search for the primary tumor. Over the past 20 years, this exploratory technique has largely replaced hormonal assays in portal venous blood. Its sensitivity for the detection of primary endocrine tumors ranges from 52% to 89% [40—46]. The approximate localization of the primary tumor by SRS can guide further exploration with a videocapsule, or more invasive explorations via enteroscopy or endoscopic ultrasonography. Indeed, SRS should also be proposed as a first-intention exploration in the search for extrahepatic spreading, then completed with positron emission tomography (PET) coupled with CT. The impact of somatostatin-labeled PET–CT (68Ga-DOTATOC) on therapeutic strategies has recently been demonstrated [47].

Table 3  Major published series of hepatectomy for endocrine metastases.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patients (n)</th>
<th>Symptoms (%)</th>
<th>5-year recurrence rate</th>
<th>Surgery-related mortality (%)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Que et al. (1995) [60]</td>
<td>74</td>
<td>90</td>
<td>60%</td>
<td>2.7</td>
<td>73% at 4 years</td>
</tr>
<tr>
<td>Dousset et al. (1996) [59]</td>
<td>17</td>
<td>88</td>
<td>59%</td>
<td>0</td>
<td>46% at 4 years</td>
</tr>
<tr>
<td>Chen et al. (1998) [58]</td>
<td>15</td>
<td>—</td>
<td>67%</td>
<td>0</td>
<td>73% at 5 years</td>
</tr>
<tr>
<td>Chamberlain et al. (2000) [3]</td>
<td>34</td>
<td>90</td>
<td>—</td>
<td>6</td>
<td>76% at 5 years</td>
</tr>
<tr>
<td>Jaeck et al. (2001) [57]</td>
<td>13</td>
<td>—</td>
<td>31% at 3 years</td>
<td>0</td>
<td>91% at 3 years</td>
</tr>
<tr>
<td>Sarmiento et al. (2003) [54]</td>
<td>75</td>
<td>96</td>
<td>76%</td>
<td>1.3</td>
<td>61% at 5 years</td>
</tr>
<tr>
<td>Elias et al. (2003) [56]</td>
<td>47</td>
<td>—</td>
<td>70% at 10 years</td>
<td>4.7</td>
<td>71% at 5 years</td>
</tr>
<tr>
<td>Norton et al. (2003) [55]</td>
<td>16</td>
<td>50</td>
<td>—</td>
<td>0</td>
<td>82% at 5 years</td>
</tr>
<tr>
<td>Touzios et al. (2005) [53]</td>
<td>18</td>
<td>50</td>
<td>—</td>
<td>5.5</td>
<td>72% at 5 years</td>
</tr>
<tr>
<td>Musunuru et al. (2006) [52]</td>
<td>13</td>
<td>37</td>
<td>39% at 3 years</td>
<td>—</td>
<td>83% at 3 years</td>
</tr>
<tr>
<td>Gomez et al. (2007) [51]</td>
<td>15</td>
<td>—</td>
<td>34%</td>
<td>6.7</td>
<td>86% at 5 years</td>
</tr>
<tr>
<td>Hibi et al. (2007) [50]</td>
<td>21</td>
<td>57</td>
<td>76%</td>
<td>0</td>
<td>41% at 5 yearsa</td>
</tr>
<tr>
<td>Eriksson et al. (2008) [20]</td>
<td>42</td>
<td>—</td>
<td>24%</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Landry et al. (2008) [49]</td>
<td>23</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td>75% at 5 years</td>
</tr>
</tbody>
</table>

a  73% with curative resection.
Results of curative liver resection

First-intention complete resection of the tumor should be considered in cases of well-differentiated endocrine tumors (grade G1 or G2) [48]. This is because the results of several non-randomized studies have demonstrated the benefits of complete resection of liver metastases with evidence of longer survival, which was better than that observed in the natural history of the disease or in patients given non-surgical treatments [3,20,49—60]. The main studies of hepatectomy for endocrine metastases are presented in Table 3. These were retrospective series of small populations, and generally included both complete and palliative resections. In addition, the origin of the primary tumor was variable, with some studies even including liver metastases from bronchopulmonary endocrine tumors, known to have the poorest prognoses [50]. Nevertheless, most of the studies demonstrated differences in survival between patients who had undergone curative hepatic resection and those who had incomplete resection or non-resectable metastases [20,49—51,54,56].

At the cost of mortality rates of 0—6% and despite the high 5-year recurrence rate (> 50%), overall survival after curative resection ranges from 47—91%. Other than tumor differentiation, independent preoperative factors for a poor prognosis include pancreatic tumor, non-functional primary tumor, presence of multiple and/or bilobar liver metastases, and invasion of greater than 75% of the hepatic parenchyma [3,56,61].

Indications for palliative resection

Symptoms related to tumor volume

Because of their slow progression, liver metastases from endocrine tumors can reach a considerable size. In certain cases, the size and location of one or more of these tumor masses can lead to compression of the bile ducts or neighboring organs. While it is not uncommon to observe locally dilated bile ducts, bile duct obstruction is not, in itself, a valid reason for undertaking palliative hepatic surgery, as progression to secondary biliary cirrhosis or recurrent cholangitis is unusual. Similarly, palliative resection is rarely proposed for abdominal pain or for compression of a neighboring organ.

Symptoms related to hormone secretion

Uncontrolled hormone production is the main reason for proposing palliative liver resection, particularly for hepatic metastases of endocrine tumors. Tumor reduction is often proposed for liver metastases of midgut endocrine tumors when serotonergic symptoms fail to respond to maximum medical therapy. Surgical reduction is considered effective when the resected tumor volume reaches 90% of the total tumor volume [62] and there are no extra-abdominal metastases. Under the same conditions, palliative hepatic surgery can be proposed for functional foregut endocrine tumors. On the other hand, colorectal endocrine tumors, which are rarely functional and often associated with extrahepatic metastases, are generally not a good indication for cytoreductive liver surgery [48].

Carcinoid heart disease

Carcinoid heart disease develops in more than 50% of patients with carcinoid syndrome [63]. The 4-year survival rate of patients with moderate-to-severe ventricular dilatation is around 20% versus 40% in patients free of right-ventricular dilatation [64]. In a series of 77 patients at the Mayo Clinic [65], among those eligible for hepatectomy, hepatic surgery undertaken to reduce tumor size improved patient survival, which was partly explained by the slower progression of their heart disease. On multivariate analyses, liver resection was an independent factor for non-progression of carcinoid heart disease (OR = 0.29, P = 0.03).

Liver transplantation

Replacement of a diseased liver should not constitute a curative treatment for metastatic diseases. Nevertheless, since metastases of endocrine tumors have a slow progression and remain totally within the liver, they may constitute—at least theoretically and within the limits of grafts availability—a therapeutic indication for liver transplantation. Initially considered a salvage or palliative treatment for non-resectable liver metastases of endocrine tumors, liver transplantation is now proposed for certain candidates, and can result in a 5-year overall survival of 70% and 5-year recurrence-free survival of 50% [66]. Several cases of liver transplantation for liver metastases of endocrine tumors have been published, albeit usually as part of a small, single-center, series or as case reports [59,67—85]. A meta-analysis of some of these cases was done in 1998 [86]. The largest series of liver transplants for liver metastases of endocrine tumors was the multicenter French study, coordinated by Le Trent et al. [87], which reported on 85 cases with an overall survival of 47% and a recurrence-free survival of 20% at 5 years. The study also highlighted several factors predictive of a poor prognosis that can be identified before transplantation, thereby enabling better patient selection. Multivariate analyses identified these following factors: the need for supramesocolic exenteration in association with the graft; liver metastases from the foregut; and the presence of hepatomegaly, defined arbitrarily as more than 20% increase over the theoretical liver volume. The 5-year survival of patients whose primary tumor could not be identified was not significantly different from those with a primary gastrointestinal tumor (55% versus 65%, respectively).

In 2007, Mazzafierro et al. [66] proposed a set of guidelines for the selection of candidates for liver transplantation known as the ‘Milano criteria’ (different from the Milano criteria established for hepatocellular carcinoma). These guidelines emphasized the requirement for a specific diagnosis of endocrine tumors, and considered patients who had well-differentiated endocrine tumors with low-grade malignancy, established on the basis of mitotic and proliferation indices, as eligible for liver transplantation. Also, overexpression of Ki67 (> 10%) is associated with a high risk of recurrence after liver transplantation [78]. Similarly, MIB1
uptake more than 5% is another factor indicating a poor cancer prognosis after liver transplantation [88]. In other words, liver transplantation can be considered for ENETS grade G1 tumors, and only with reservation for G2 tumors, but is certainly contraindicated for G3 tumors. Another selection criteria proposed by Mazzaferro et al. [66] concerns the location of the primary tumor. Only patients with liver metastases from cancer-resected primary tumors lying entirely within the drainage territory of the portal vein are eligible for liver transplantation. This excludes endocrine tumors of the esophagus and rectum, as well as of the lungs, and thyroid and adrenal glands. In addition, two other selection criteria were similar to those reported by the multicenter French study mentioned above—specifically, the degree of hepatic tumor invasion (the cutoff set empirically at 50% of the liver) and previous resection of the primary tumor, with stable tumor disease for six months prior to liver transplantation—which consequently rules out concomitant liver transplantation and resection of the primary tumor.

The selection criteria for liver transplantation are summarized in Table 4, and liver transplant outcomes are presented in Table 5.

**Table 4** Selection criteria for candidates for liver transplantation.

<table>
<thead>
<tr>
<th>From Mazzaferro et al. [66]</th>
<th>From Le Treut et al. [87]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological proof of low-grade endocrine tumor, with or without carcinoid syndrome</td>
<td>Hepatomegaly ≤ 120% of theoretical liver volume</td>
</tr>
<tr>
<td>Primary tumor lies entirely within drainage territory of the portal vein (pancreas and gut from distal stomach to pelvic colon)</td>
<td>Well-differentiated endocrine tumor</td>
</tr>
<tr>
<td>Surgical curative resection of primary tumor and all extrahepatic disease before transplantation</td>
<td>Non-duodenopancreatic primary tumor</td>
</tr>
<tr>
<td>Intraparenchymatous metastatic spread involving ≤ 50% of liver</td>
<td></td>
</tr>
<tr>
<td>Stable tumor disease for at least 6 months before transplantation</td>
<td></td>
</tr>
<tr>
<td>Age ≤ 55 years</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5** Major series of liver transplantation for endocrine metastases.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patients (n)</th>
<th>Origin(^a)</th>
<th>Symptoms (%)</th>
<th>Overall survival</th>
<th>Recurrence-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lehnert (1998) [86]</td>
<td>103(^b)</td>
<td>Int 36 DP 0 U 0</td>
<td>42</td>
<td>47% at 5 years</td>
<td>24% at 5 years</td>
</tr>
<tr>
<td>Rosenau et al. (2002) [78]</td>
<td>19</td>
<td>Int 8 DP 10 U 0</td>
<td>90</td>
<td>80% at 5 years</td>
<td>21% at 5 years</td>
</tr>
<tr>
<td>Cahlin et al. (2003) [89]</td>
<td>10</td>
<td>Int 4 DP 7 U 0</td>
<td>40</td>
<td>80% at 1 year</td>
<td>50% at 3 years</td>
</tr>
<tr>
<td>Florman et al. (2004) [71]</td>
<td>11</td>
<td>Int 3 DP 7 U 0</td>
<td>100</td>
<td>36% at 5 years</td>
<td>9% at 5 years</td>
</tr>
<tr>
<td>Frilling et al. (2006) [84]</td>
<td>15</td>
<td>Int 7 DP 7 U 0</td>
<td>100</td>
<td>67% at 5 years</td>
<td>48% at 5 years</td>
</tr>
<tr>
<td>van Vilsteren et al. (2006) [85]</td>
<td>19</td>
<td>Int 7 DP 11 U 0</td>
<td>32</td>
<td>87% at 1 year</td>
<td>77% at 1 year</td>
</tr>
<tr>
<td>Olausson et al. (2007) [82]</td>
<td>15</td>
<td>Int 4 DP 10 U 0</td>
<td>60</td>
<td>90% at 5 years</td>
<td>20% at 5 years</td>
</tr>
<tr>
<td>Mazzaferro et al. (2007) [66]</td>
<td>24</td>
<td>Int 24 DP 0 U 10</td>
<td>58</td>
<td>90% at 5 years</td>
<td>77% at 5 years</td>
</tr>
<tr>
<td>Le Treut et al. (2008) [87]</td>
<td>85</td>
<td>Int 31 DP 40 U 14</td>
<td>58</td>
<td>47% at 5 years</td>
<td>20% at 5 years</td>
</tr>
</tbody>
</table>

\(^{a}\) Of primary tumor; Int: intestinal; DP: duodenum or pancreas; U: unknown.

\(^{b}\) Review of the literature from 1981 to 1997.

The development of liver metastases constitutes a major adverse turning point in the disease course of endocrine tumors. However, complete surgical resection of these tumors can lead to prolonged survival and should be discussed for all patients. The currently available surgical and radiological techniques enable extended resection of the liver parenchyma, allowing the complete resection of even multiple large or bilobar liver metastases. For patients with a carcinoid tumor resistant to medical treatment, the usefulness of palliative resection should be examined if at least 90% of the tumor volume can be removed. For selected patients with non-resectable liver metastases, liver transplantation may be proposed.

**Conflict of interest statement**

No conflict of interest.

**References**


Hepatic endocrine metastases


