

Which liver metastases are resectable?

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Introduction

The concept of resectability of liver metastases of colorectal cancer has changed considerably over the last decade. The aim of resection of liver metastases is to render the patient free of all metastatic disease. This is limited on the one hand by the presence of extrahepatic (unresectable) tumour manifestations which need to be ruled out by adequate preoperative staging and intraoperative assessment. On the other hand, with regard to the liver itself, there has been a paradigm shift of resectability criteria. While in the past resectability was thought to be limited by the number, size, and location of metastases, it has become clear that metastases are resectable, irrespective of number, size and location, as long as an adequate functional future liver remnant (FLR) remains. With recent advances in surgical technique like portal vein embolisation (PVE) and two-stage hepatectomy, many patients with metastases who were previously thought to be unresectable proved to be resectable instead. Furthermore, advances in systemic chemotherapy have enabled resection after downsizing of lesions which were deemed unresectable due to size or location prior to chemotherapy. Scoring systems may help to assess the prognosis of patients after resection of liver metastases. Their role in deciding upon resection or systemic chemotherapy in a given patient has not and probably cannot be assessed prospectively. In view of these uncertainties it seems easier to define unresectability than to positively define resectability in a dynamically changing field. Furthermore, other areas of uncertainty exist, particularly in those patients where the number and distribution of metastases is known to confer a limited prognosis despite radical resection which may also be achieved by systemic chemotherapy. Assessment of the role of adjuvant chemotherapy after radical resection of liver metastases is not within the scope of this review.

Irresectability

Irresectability should be the mirror image of resectability. However, since the criteria of resectability

have changed considerably during the last years, it comes as no surprise that criteria of irresectability also vary widely. Biasco and colleagues, in their recent review, list 'multiple bilobar metastases, ill-located lesions affecting the main hepatic blood vessels such as portal vein, hepatic artery and vena cava/suprahepatic vessels, and portal vein thrombosis' as contraindications for liver surgery [1]. Poston, however, in his earlier review only lists as absolute contraindications, uncontrolled primary disease and wide-spread hepatic involvement with foreseeable inadequate liver function post resection while caudate lobe lesions, tumours invading the vena cava, involvement of the hepatic vein confluence, bilobar lesions, and size are viewed only as relative contraindications [2].

Pre-operative staging

Exact determination of number and location of liver metastases is essential for the planning of surgery. This is best achieved by helical contrast-enhanced computer tomography (CT) or, alternatively, contrast-enhanced magnetic resonance tomography (SPIO-MRT). Using state-of-the art CT technology for patient selection Figueras and colleagues achieved a resection rate of 91% (235 of 259 patients scheduled for hepatic resection in curative intent) [3]. The role of three-dimensional imaging using CT-generated data in the management of colorectal liver metastases is less clear [4]. While this technique helps greatly in planning hepatectomy in the setting of live-donor liver transplantation [5], its role in assessing the future liver remnant (FLR) in planned resection of CRC metastases has not been systemically and prospectively evaluated. Histological verification of suspected metastases is strongly discouraged in patients with resectable disease since needle-track deposits are common after biopsy of suspected colorectal metastases [6], and these patients have reduced survival following hepatectomy [7].

The presence of extrahepatic disease is best ruled out by FDG-PET [8]. Indeed, it could be shown that the long-term results of liver resection for CRC metastases were improved when FDG-PET was used

systematically for pre-operative patient selection [9]. Whether response to chemotherapy assessed by serial FDG-PET measurement of standard uptake volumes (SUV) may be a prognostic indicator of long-term prognosis after resection of CRC metastases remains to be investigated. Along the same line, the assessment of metastases after chemotherapy with regard to the question of pathological complete response (CR) as opposed to remaining vital tumour tissue is still unresolved [10].

While the use of staging laparoscopy with or without intraoperative laparoscopic ultrasound has been explored by some investigators [11,12], it is not generally recommended. First staging laparoscopy may be technically impossible due to dense adhesions in patients with metachronous liver metastases and second, even after staging laparoscopy, the patient may still be found to be irresectable.

Scoring systems

Based upon retrospective analysis of large single institutional series [13] or multicentre-databases [14], scoring systems have been developed which take into account various factors such as age, interval between resection of the primary tumour and occurrence of liver metastases, number and size of lesions and levels of tumour markers. These scoring systems have not yet been used to prospectively stratify patients into various treatment strategies. The score developed by Fong has been verified by other independent investigators [15].

Based upon the absence or presence of prognostic factors it may be envisaged that patients with favourable prognostic factors (e.g. a solitary metastases less than 5 cm appearing more than a year after resection of the primary tumour with negative CEA) should undergo immediate resection while those with negative prognostic factors (e.g. multiple metastases with the largest exceeding 5 cm with bilobar distribution appearing within a year of resection of the primary and a CEA >200 ng/ml) should first be treated by systemic chemotherapy even though resection might seem technically feasible. However, such an individualised approach is not supported by any prospective data. The most relevant prognostic factor in both scoring systems is achievement of a negative resection margin. Thus every effort should be made to achieve negative resection margins.

Intraoperative assessment

Intraoperatively, the number and location of metastases within the liver is best determined by bimanual

palpation and intraoperative ultrasound (IOUS) after mobilisation of the liver from its ligamentous attachments. Systematic lymphadenectomy is not carried out systematically. In prospective studies with systematic lymphadenectomy 10–20% of all patients undergoing liver resection for CRC metastases were found to have positive lymph nodes near the hilum, along the hepatoduodenal ligament or even up to the celiac axis. All macroscopic enlarged and altered lymph nodes should be removed. It could be shown that patients with lymph node metastases along the hepatoduodenal ligament may to some extent benefit from concomitant hepatic resection while those patients who are found to have positive lymph nodes along the coeliac axis do not seem to benefit from hepatic resection [16]. Extrahepatic disease by itself does not preclude hepatic resection provided it is radically resectable [17].

Number of metastases

While it is undisputed that the number of metastases is correlated to the prognosis after radical resection, there is no uniform agreement as to the cut-off number of lesions where hepatic resection would be futile, provided a radical resection can be achieved. Scheele reported that the presence of five or more independent metastases adversely affected resectability based upon an analysis of 1718 patients with liver metastases treated at a single centre from 1960 to 1992. While in patients with five to seven metastases curative resection was an exceptional event, it was never possible in patients with nine or more lesions [18]. In a retrospective analysis of a consecutive series of 484 liver resections carried out for CRC metastases, Malik and colleagues from Leeds could show that the cut-off seems to be eight metastases (not four as was often stated before) [19]. Pawlik reported on 159 consecutive patients with four or more metastases who were treated at MD Anderson Cancer Centre. The median number of metastases was five (ranging up to a maximum of 14 lesions). Only a relatively small proportion of patients were treated by resection alone (29%), and even fewer by radiofrequency ablation (RFA) alone (7.5%). The majority of patients were treated by combining resection with radiofrequency ablation (63.5%). With this approach a 5-year actuarial survival rate of 50.9% could be achieved, with a disease-free survival (DFS) of 21.5% [20]. Thus, the number of metastases alone does not limit resectability.

Size of metastases

Although metastases exceeding 5 cm do confer a reduced prognosis after resection compared to those of lesser size, a cut-off value for resection does not exist. Hamady and colleagues from Leeds analysed their experience with 484 liver resections performed during an 11-year period (1993–2003). In particular, they compared the survival of those patients with metastases up to 8 cm with those with metastases greater than or equal to 8 cm in diameter. In addition, a further subgroup of giant metastases (>12 cm) was analysed separately. Five year survival rate of patients with <8 cm lesion compared to those with lesions \geq 8 cm was 42% versus 38%. Patients with metastases exceeding 12 cm in diameter still had a 5-year survival of 29% and DFS of 38% [21]. Thus, size alone does not preclude resectability of liver metastases.

Location of metastases

Bilobar metastases not only confer inferior prognosis compared to unilobar metastases but also pose particular challenges with regard to planning the resection. Combining RFA with resection may be one solution [20]. Other strategies include two-stage hepatectomy (2-SH) or portal vein embolisation (PVE) (vide infra). Today, the presence of bilobar metastases is no contraindication for liver resection.

Future liver remnant

The biggest concern in liver surgery is preservation of an adequately sized future liver remnant (FLR) with arterial and portal blood supply, biliary drainage and preserved hepatic venous outflow. In an undamaged liver, 70–80% of the liver volume can be safely resected, leaving an FLR of 20–30%. The French Practice Guidelines for resection of metastases distinguish between Class I and Class II resections:

- Class I resection: evident resectability – right or left hepatectomy or less with removal of four segments or less and leaving a FLR of 40% or more
- Class II resection: possible resectability – extended resections removing five or more segments, leaving a FLR of less than 40%.

Peri-operative mortality is higher in class II resections and has to be weighed against the potential oncological benefit [22]. Since the size and function of the FLR is of utmost importance, strategies to increase the FLR have been developed.

Increasing the size of the future liver remnant

The FLR may be increased by use of portal vein embolisation (PVE) of the tumour bearing part of liver thus inducing hypertrophy of the contralateral remaining part of the liver. PVE increases the FLR from 19–38% pre-embolisation to 32–46% of the total liver volume (TLV) at the time of surgery 24 to 63 days after the procedure with a resection rate of 63% to 100% of patients embolised [23]. PVE seems to be superior to portal vein ligation [24]. When PVE did not result in a sufficiently large FLR, Gruttadauria and colleagues have described the use of sequential arterial embolisation to provide a further stimulus for hypertrophy of the FLR [25]. Until more experience becomes available this procedure should remain experimental. Another strategy to increase the size of the FLR is two-stage hepatectomy (2-SH). With this approach, the main tumour bearing lobe of the liver is removed first, thus allowing for the remaining lobe to hypertrophy and enable removal of residual metastases in the remaining lobe 4–6 weeks after the first hepatectomy. It is apparent that two scenarios have to be distinguished: a FLR that is free of metastases but appears to be too small and a relatively small FLR with some metastases in addition. The latter scenario is much more difficult since it is, as of yet, unresolved whether metastases remain stable or increase in size during the (desired) hypertrophy following resection or PVE. It could be shown that administration of chemotherapy during the phase of regeneration is principally feasible although it impedes hypertrophy to some extent [26].

Presence of extrahepatic disease

The presence of extrahepatic disease does not preclude liver resection per se as long as all lesions can be resected radically [17].

Preoperative chemotherapy (downsizing)

Since the pioneering work of Bismuth and his group in Villejuif it could be shown that modern systemic chemotherapy may downsize metastases that were previously thought to be irresectable and allow for resection at a later point in time. This is always downsizing and never downstaging since the tumour stage remains UICC stage IV, i.e. metastatic disease. Secondary resectability may be achieved in 24% to 54% of patients with hepatic metastases only and in 1–26% of non selected patients with metastatic CRC,

depending highly upon the response rate of the employed chemotherapeutic regime [27]. If these patients are radically resected, their prognosis approaches the prognosis of patients who are resected primarily [28].

Liver resection after chemotherapy

Liver resection after previous chemotherapy poses special challenges since depending upon the regime used, structural and functional alterations of the non-tumour bearing liver tissue have been observed. For oxaliplatin based regimes, this is predominantly (but not exclusively) sinusoidal obstruction resulting in the macroscopic appearance of the 'chemo-blue liver' while irinotecan may lead to predominantly (but not exclusively) fatty degeneration of the liver and steatohepatitis, also termed 'chemotherapy associated steatohepatitis (CASH)'. Vauthey and colleagues observed, in their series of 406 liver resections for CRC, an increased 90-day mortality in patients with steatohepatitis (14.7% versus 1.6%) [29]. The use of preoperative percutaneous liver biopsy to allow for risk stratification and therapeutic decisions is currently under investigation. By contrast, Welsh and colleagues reviewed the single institution experience of Basingstoke comprising 750 consecutive liver resections performed for CRC metastases. They compared 252 patients who had received preoperative neoadjuvant chemotherapy with a comparable group of 245 patients without pre-op chemotherapy. Surgery lasted longer and blood loss was increased in patients after chemotherapy, while postoperative mortality and morbidity was similar between both groups. However, the incidence of surgical complications was higher when the interval between termination of chemotherapy and surgery was less than 4 weeks [30].

Apparent complete response in preoperative imaging

The remarkable successes of systemic chemotherapy have led to the question of how to deal with an apparent complete response in imaging when planning a liver resection. It appears that a 'true', i.e. pathologically proven CR is rare, although there is still conflicting evidence according to the incidence of true CR. In a retrospective analysis, Benoist reported a true pathological CR of 17% [31]. On the other hand, Taylor from the MSKCC reported a true CR of 63% (pathological CR 37% plus enduring clinical CR 26%) [32], while Wicherts from Paul Brousse reported a pathological CR in only 31 of 791 patients (4%) [33].

While this issue is unresolved, it is recommended that the initial CT scans are taken into consideration when planning resection after chemotherapy [34] and that all visible 'scars' should also be removed as far as possible.

Response to therapy as a prognostic indicator

Whether response to chemotherapy is a prognostic indicator is still unresolved. Data from Adam's group showed that patients who progressed under chemotherapy had a reduced prognosis compared to patients who were resected after documented response to chemotherapy [35]. On the other hand, data from Neuhaus' group refuted this observation [36]. In case of doubt, resection should also be attempted in these patients as long as the lesions seem resectable. Whether other measurements of response such as FDG-PET measured response with SUV's may help in the future with therapeutic decisions is unresolved [37].

Classic versus expanded criteria for liver resection

Poston in his excellent review juxtaposes traditional selection criteria for liver resection (no more than three metastases, unilobar disease, small tumour <5 cm, metachronous detection of metastases, resection margin >1 cm, no extrahepatic disease, patients younger than 65 years, and no portal nodal involvement) with the more liberal approach adopted today where the aforementioned are only relative contraindications [2]. Figueras and colleagues analysed their own series of 545 liver resections for metastatic CRC in 501 patients over a 15 year period comparing 'classic indications' with 'expanded indications'. Expanded indications were defined as lesions exceeding 10 cm ($n=14$), bilobar disease ($n=194$), four or more metastases ($n=140$) and/or extrahepatic disease ($n=73$). Thus defined, 52% of patients fell into the group of extended indications. The 5 and 10-year survival between both groups differed significantly: 45% versus 34% at 5 years and 36% versus 24% at 10 years ($p=0.0009$). Still, given these results which compare favourably with results reported from other series in classic indication, the authors duly conclude that patients should not be denied the option of liver resection only for the fact that their lesions are beyond classic, older criteria of resectability [38].

Outlook to the future

There has been a paradigm shift in definition of resectability. In the past, resectability was defined by what was to be removed. Currently, resectability is defined by what will be left behind after resection of metastases [37]. However, even using a conservative estimation of resectability, population-based studies in Europe show a severe underutilisation of hepatic resection as a therapeutic modality for CRC metastases [39,40]. Improvement in surgical technique together with increased experience has led to a widening of indications for liver resections for CRC metastases. Simultaneously, the progress with systemic therapy has enabled resection in patients who were previously thought irresectable. Given the high incidence of CRC with approximately 50% of patients developing liver metastases at some stage, the future is likely to show an increased demand for highly specialised liver surgery rather than rendering it obsolete. This, however, will only happen successfully in a concerted multidisciplinary team effort bringing together surgeons, medical oncologists and radiologists.

Conflict of interest statement

None declared.

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