Review Articles

Surgical management of hepatic metastatic disease

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ABSTRACT

In Europe, liver metastases are the most common malignomas of the liver. The majority of metastases are due to colorectal cancer. Radical surgical resection, if possible, is the treatment of choice. Radical resection of metastases from wilms-tumor, carcinoids, carcinoma of the breast, hypernephroma, adrenal tumors, malignant melanoma, leiomyosarcoma and gastric cancer may improve long time survival, however knowledge is too small for giving general directions. Local destructive therapies are only beneficial when a total necrosis of the tumor is reached. Indications for this treatment are quite rare. Both, systemic and local chemotherapy offers only palliation with little influence on long time survival. Adjuvant and neo-adjuvant chemotherapy is applicated under study conditions with encouraging results. Chemoembolisation of metastases might be useful in individual cases.

Keywords: Liver metastases, surgical treatment, prognosis.

In Europe, the incidence of liver metastases is much higher than the incidence of primary malignomas of the liver. Due to the high incidence of colorectal cancer and its tendency to spread into the liver these metastases are the most common liver malignancies in Europe. The kind of therapy depends on the type and extent of the tumor, the quality of the liver tissue and the general condition of the patient. In general, metastases can be treated by surgical resection or local destruction and by systemic or local chemotherapy. The optimal choice and combination of these treatment modalities requires experience, co-operation between different specialities and appropriate diagnostic methods to determine the extent and course of the disease. To judge the success of treatment, knowledge about the natural course of the disease is necessary. Due to the lack of prospective studies the comparison between treated and untreated patients with the same state of disease and same risk profile is often difficult to perform.

Diagnosis of hepatic metastases. Commonly liver metastases are detected during the staging of the primary cancer or during the follow up. Liver tumors found by incidence or due to their symptoms are less frequent. Tumor marker, liver enzymes and ultrasound are the methods for follow up screening. Prospective studies indicate that serial serum Carcinoembryonic antigen (CEA) assays are the most effective screening mechanism for the detection of subsequent colorectal liver metastases.[1] Eighty-five to 90% of patients with colorectal hepatic metastases have an elevated CEA. Whether because of symptoms, an elevation in serum CEA, or based on a follow-up scan or ultrasound, the diagnosis of hepatic metastases is suggested, further diagnostic studies are related to potential therapeutic options. If systemic chemotherapy is to be recommended, only a baseline imaging of the liver is necessary. However, if hepatic resection is under consideration, a complete extent of disease evaluation is required. For the preoperative evaluation of intrahepatic disease computerized tomography (CT) scan with bolus contrast (IV dynamic) provides a reasonable assessment. Improved delineation may be obtained

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by visceral angiography and dynamic portography CT.[2] The kind of diagnostic studies for evaluation of extrahepatic disease depends on the primary tumor. For a complete staging of colorectal metastases a detailed history and physical examination, chest CT, colonoscopy and abdominal CT is required. Pelvic CT may be included if appropriate.

Liver resection. Indication: Complete resection of liver metastases of colorectal cancer provides the best long-term survival. This has now been confirmed beyond doubt in numerous studies.[3-5] Decreased morbidity and mortality after liver resection and an increased knowledge about prognostically relevant factors have lead to the widening of the indications for resection of colorectal liver metastases. As long as complete removal is possible, resection is the best choice of treatment even in bilobular disease, recurrent metastases or liver metastases in combination with solitary lung metastases. The relatively small percentage of completely resectable metastases however makes multimodal therapeutic strategies potentially necessary. The value of neoadjuvant chemotherapy for colorectal metastases, with the aim of making non-resectable tumor resectable, is discussed controversely. On one hand, some groups present good results,[6] on the other hand there is the potential risk of liver damage due to aggressive chemotherapy prior surgery. For some other entities (breast cancer, malignant melanoma) the indication for neoadjuvant chemotherapy is undisputed.

A partial tumor resection might be indicated in symptoms untreatable by other methods (pain due to capsule tension, cava compression, bleeding), and influence on long time survival cannot be expected. Due to lack of experience, indication for resection of non-colorectal metastases is more uncertain. The absence of generally accepted guidelines makes an individual approach necessary. Improved survival can be expected after radical resection of metastases from hypernephroma or carcinoid. In individual cases a positive effect is achieved after resection of metastases from breast cancer, adrenal cancer, malignant melanoma, sarcoma and stomach. Even for metastases of pancreatic cancer a positive effect has been described in the literature.[7]

Technique. Extent and location of the metastases, the quality of the liver and the general condition of the patient have to be considered before embarking on liver resection. Assessment of the metastases is preoperatively performed by portal enhanced CT. For intraoperative assessment, especially for ascertainment of the tumor location relative to the liver segments and large vessels, intraoperative ultrasound is used. Patients history, laboratory results (Asparate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, - Glutamyltransferase, bilirubin, cholinesterasis, clotting factors and Monoethylglcinexylidite test) and

if in doubt a biopsy of the parenchyma are relevant for estimating the liver quality. If an extended liver resection is planned the volume of the liver and the volume of the remaining liver should be estimated by CT prior to surgery. At least 25% of parenchyma should remain after resection. If the estimated remaining volume is too small for a resection, expandation of the remaining parenchyma is possible by ligation of the contralateral main portal branch 4-6 weeks prior to resection. Complete tumor removal is essential for increasing survival. The main problems in achieving adequate clearance arise with very large tumors impinging on the vena cava or hepatic veins or on intersectorial vascular boundaries or central hilary structures. However, wedge resections for tumors larger than 3 cm in size and apparently situated peripherally in the liver may be problematic. Adequate clearance is often compromised in the depth of the wedge, particularly over the anterior surface of the right lobe. It has been demonstrated that wedge resections carry high local recurrence rates and that anatomically based resection yields better results.[5] Extreme care should be taken that, at the point of closest parenchymal transection, the liver does not tear open and split along the tumor-liver interface at the time of transection.

The major hazard of hepatic resection is bleeding, particularly from the hepatic veins and inferior vena cava. This is especially likely to occur during major resection for high and posteriorly placed tumors where there is little clearance between the tumor margin and the passage of the hepatic veins into the vena cava or with any tumor lying closely adjacent to the inferior vena cava. For these types of tumors vascular exclusion techniques (total vascular exclusion) or even in-situ perfusion of the liver may be necessary.

Results. Due to its curative potential, radical resection is the therapy of choice for colorectal metastases, even in progressed cases. However even in experienced centers only 20% to 30% of all patients with colorectal metastases are radically resectable. The stage of the primary cancer, size and number of metastases, presence of extrahepatic metastases and the size of the resection margins are prognostic factors after resection of colorectal metastases. Other factors like tumor free interval, number of affected liver segments, extent of resection, age and sex of the patient are disputed.[8] Difference in long term survival between radical resection and palliative chemotherapy decreases with increasing extent of metastases (Figures 1 & 2). The indication for adjuvant chemotherapy after radical resection of extended metastases is presently under investigation. In our own patient collective 3-year survival after radical liver resection is 47% and 5-year survival is 36%. The morbidity after liver resection is 26% (11% pleura effusions). The mortality is 2%. There is good correspondence
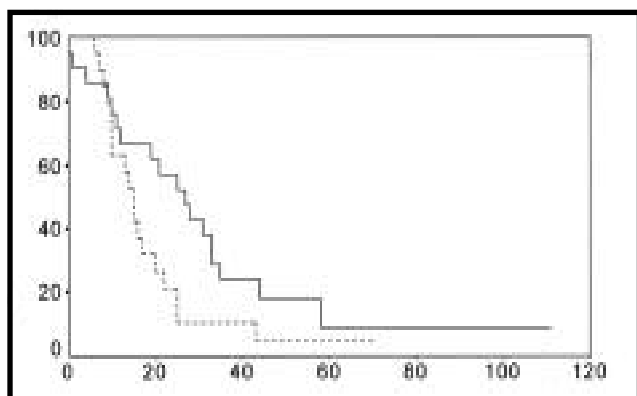
Figure 1 - Patients with 3 or more liver metastases treated in the Hepatobiliary Department of the University of Hamburg between 1986 and 1996 (n=107). Kaplan-Meier analysis with comparison of patients with radical resection (continuous line) and palliative treatment (interrupted line) of patients shows no significant difference in long term survival (p=0.29).
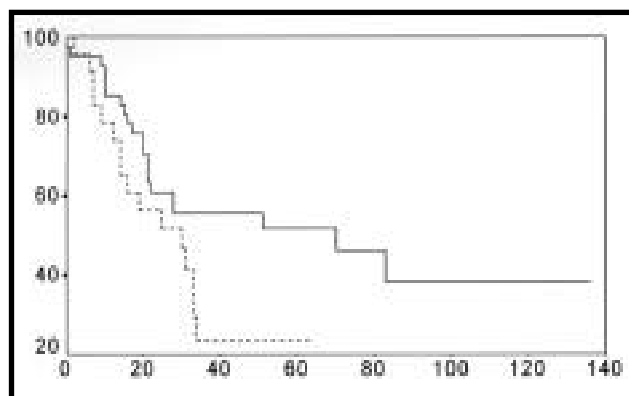

Figure 2 - Patients with 1 or 2 liver metastases treated in the Hepatobiliary Department of the University of Hamburg between 1986 and 1996 (n=195). Kaplan-Meier analysis with comparison of patients with radical resection (continuous line) and palliative treatment (interrupted line) of patients shows significant difference in long term survival (p=0.0001).

between our results and results described in the literature (45-43% and 33- 23%).[3,4]

Liver transplantation. Liver transplantation for therapy of liver metastases is not indicated. The only exceptions are metastases from carcinoids. Due to their small malignant potential, transplantation might be an option when all other modalities are failing.

Locally destructive therapies. Percutaneous image-guided therapies for hepatic neoplasm's can be divided into two categories: 1) direct intra-tumoral injection of compounds such as ethanol, hot saline and acetic acid in an attempt to induce cellular death, and 2) thermally mediated techniques such as radio frequency ablation (RF), interstitial laser photocoagulation (ILP), microwave therapy or cryotherapy. Most of the experience exists with the use of percutaneous ethanol injection (PEI), RF and cryotherapy. The results of PEI in patients with hepatic metastases are less promising than those seen in the patients Hepatocellular carcinoma. These differences likely stem from the fact that metastases lack a defined capsule and are not surrounded by cirrhotic, fibrotic liver. As a result, ethanol cannot be easily contained within the lesion, and hence the lesion is inadequately treated. This extra-tumoral ethanol may also result in an increase in associated adverse events.[9] Another disadvantage is that safety margins cannot be induced due to the dependence on morphologic barriers like a tumor capsule. The principle of tissue destruction by thermical noxes is better suited for liver metastases. Cryosurgery is a well-established therapeutic option. During surgery or in recent time, even percutaneously a cryoprobe is placed with ultrasound guidance. The probe is perfused with liquid nitrogen, necrosis is induced by freezing the tissue. A newer approach is the induction of health by radio frequency. This new method is minimally invasive, but can only induce

necroses up to 4 cm. Locally destructive therapies are indicated if complete ('R$_0$') liver resection cannot be performed but complete local destruction seems possible. These cases are very rare as most irresectable tumors are too large or too numerous for local destruction as well. Another indication is the simultaneous use of tissue resection and destruction or the use for treatment of tumor recurrence after liver resection. The indication for ablation of tumor residuals after chemotherapy is under investigation. There is only little knowledge about the results after ablation of non-colorectal metastases.

Systemic chemotherapy. Systemic chemotherapy for metastatic liver disease is a palliative treatment option. Its influence on survival is only small but chemotherapy with little side effects might improve patients' condition by tumor regression. Chemotherapy can induce downstaging in a few patients and might change an irresectable into a resectable situation. Because of the risk of liver cell damage, the indication for neoadjuvant chemotherapy is disputed in colorectal liver metastases. An adjuvant chemotherapy might prolong survival after resection of tumors with a high risk of recurrence.[10] Adjuvant chemotherapy after resection of colorectal metastases is used within studies. In non-colorectal metastases indication for chemotherapy has to be proven individually. Tumors with a high response rate (i.e. breast cancer) should be treated by chemotherapy before surgery. 5-Fluorouracil (5-FU) is the substance with the greatest response rate in treatment of colorectal liver metastases. Using monotherapy, tumor regression is observed in 7% to 18% of the cases. The time of survival is 4 to 6 months. An increased effect can be achieved by applying a higher dosage, however this is connected with a rising percentage of side effects. The combination of different substances can lead to

an improvement in effects. The best known combination is 5-FU with folinic acid. Response rate to this combination is 30%, mean survival 12 months.[11] Newer, more effective agents are being tested.

Local chemotherapy. A local intra-arterially applicated chemotherapy is possible in patients with irresectable liver metastases without any extrahepatic tumor. Extrahepatic tumor spread is an absolute contraindication. Therefore, appropriate investigations (chest and abdomen CT, bone szintigraphy, possibly endoscopy) have to be performed to exclude the presence of extrahepatic tumor. Due to the anatomic variation of the arterial supply of the liver an angiography has to be performed. Local chemotherapy leads to a high concentration of the cytotoxic drugs within the liver, whereas the systemic concentrations are low due to the first-pass effect. This gradient of concentration is especially high in 5-FU and 2-deoxy-5-fluorouridine (FUDR). Due to this gradient high response rates with low systemic toxicity can be achieved. Disadvantages are the loss of systemic effects and the need for surgical intervention to place the catheter. Different therapeutic modalities are used. Intermittent infusion of 5-FU is as well used as the continuous infusion of FUDR. The results of the different schemes are similar. The response rates are between 30% to 80%. Depending on the extent of the tumor and the quality of liver perfusion, mean survival is between 12 and 16 months.[12,13] This influence on long time survival is not significantly different to systemic chemotherapy.[14]

Chemoembolisation. During chemoembolisation a mixture of an emboligenic and a cytotoxic substance is injected selectively into the arterial tumor supply. A selective dearterialisation of tumor tissue and a high long lasting concentration of the applied cytotoxic drug in the tumor tissue should be induced. The effects in treatment of metastases are disputed. The response rate is only 15% to 22% with a mean survival of 8 to 11 months.[15,16] Better results can be expected in embolisation of neuroendocrine tumors. Carcinoid metastases show complete regress of symptoms in 70% and partial regression in 30% with a mean survival of 24 months after embolisation.[17]

In conclusion, metastatic liver disease puts surgeons and physicians into a difficult situation. With the present state of knowledge, complete (R$_0$) resection should be strived for since it offers the best survival chance for patients. For those tumors that are very chemosensitive or that are not R$_0$ resectable chemotherapy, with the aim of downstaging the tumor should be attempted. Innovative approaches to the problem of non-resectable liver metastases are being developed and should become routine in the coming years.

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