Identification of Candidates and Selection Criteria

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2.1 Introduction

The liver is the most frequent site of metastases as a result of the portal circulation and up to 60%–80% of patients with a history of colorectal carcinoma, pancreas carcinoma, breast cancer or other tumor types will develop metastases within the liver during the follow-up period [1]. There is no doubt that surgical resection of these metastases is the only potential curative option for these patients and is therefore considered as gold standard. However, due to anatomic or technical reasons or simple inoperability, only 20% of patients are suitable candidates for resection [2]. For patients unable to undergo surgery local ablative techniques like radiofrequency ablation (RFA) or laser- (LITT) or cryotherapy are regarded as alternative potentially curative treatment options; however, only another 20%–25% are candidates [2]. The remaining patients suffer from a more widespread disease within the liver and are therefore not eligible for any local destructive therapy. For those patients, systemic first- and second-line chemotherapy is the only therapeutic option with a mean additional life span of up to 24 months [3], for example, in patients with the history of colorectal cancer. Unfortunately, tumor cells can become resistant against chemotherapy, or patients sometimes suffer from unbearable side effects. In these patients radioembolization (RE) is a useful option to prolong life with a good quality of life.

Hepatocellular carcinoma (HCC) represents one of the most common types of cancer, with more than 1 million new cases worldwide and a dramatic increase in the western world. In most cases, HCC is detected at an advanced stage and frequently liver cirrhosis as an underlying disease is present. Therefore, therapeutic options are limited. Beside resection, liver transplantation is regarded the only curative therapy [4]. However, only 10%–15% of patients are candidates for curative surgery – especially due to the shortage of liver donors. There are no effective systemic treatments [4] to date for these patients and transarterial chemoembolization or RE are therefore the only palliative therapies.

The selection process for patients planned to undergo RE has to take multiple aspects into consideration. The ideal candidate should have liver only or liver dominant disease, no or only few comorbidities and normal lab tests. Further factors influencing eligibility for RE relating to both metastatic and primary tumors of the liver are anatomical situation and factors associated with a high risk of pulmo-

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nary complications. While the normal liver is able to tolerate excessive exposure to toxic agents, such as alcohol and chemotherapy, a liver with pre-existing damage, such as cirrhosis, has a poor reserve for additional toxic chemical or radiation insults. Therefore, there are specific differences in selection of patients suffering from metastases to those suffering from a primary hepatic tumor.

2.2 Liver Function Parameters in HCC and Metastatic Disease

Due to possible toxicities of RE to the liver, it is crucial to exclude patients with a significantly impaired liver function to prevent further deterioration or even function loss of the liver. The most important laboratory parameters to indicate a good liver function include prothrombin time, levels of albumin and total bilirubin [1]. Therefore, all patients who are potential candidates for RE should have lab tests including at least liver function, blood count, prothrombin time and international normalized ratio (INR) during the preparatory examinations. Contraindication for RE include bilirubin of more than 2 mg/dl, AST or ALT of more than five times above normal and significantly altered INR or PTT.

Furthermore, analyzing tumor markers (depending on the tumor type treated – AFP, CEA, CA 19–9 and other relevant markers) for assessment of treatment response during follow-up is recommended.

2.3 Vessel Anatomy

Beside tumor type specific evaluations, all patients have to undergo angiography to determine the anatomy of hepatic vessels and to show changes in flow dynamic. Although discussed in Chapters 4 and 5 in detail, a short summary regarding vessel anatomy and potential contraindication should be given. At minimum, the celiac trunk, the common and proper hepatic arteries, the right and left hepatic arteries, the gastroduodenal artery and the mesenteric artery must to be examined prior to treatment using state-of-the-art angiography and a power injector. Potential contraindications include high grade stenosis or occlusion of the celiac axis with blood supply via the GDA, aberrant vessels supplying the stomach or intestines when they can not be occluded or a blood supply of the tumor to be treated via the phrenic artery. Patient history has to be taken into account, for example prior to surgical intervention with ligation of arteries or implantation of liver ports, which often makes therapy impossible due to high grade stenosis of the hepatic artery or even occlusion of the hepatic artery caused by the catheter of the port.

Tc-99m labelled macroaggregated albumin (Tc-MAA) has to be administered during the preparatory examinations to calculate a potential shunt from the liver to the lung or the intestines. Depending on the shunt volume a reduction of the total dose administered to the liver is necessary or RE is even impossible, if there is a liver-to-lung shunt of more than 20% of the administered dose. A more detailed discussion regarding management of anatomic variants, possible risks and management of aberrant vessels and the impact of Tc-MAA scan on dose calculation is given in Chapters 4–6 and 8.

2.4 Selection Criteria in Metastatic Disease

Secondary metastatic disease to the liver is the most common type of hepatic malignancy with a ratio of 30 to 1 to primary liver tumors [5]. Patients diagnosed with liver metastases unsuitable for surgery have to undergo at least two to three different chemotherapeutical regimens before they can be taken into account for RE. Due to rapid and ongoing changes in chemotherapy, discussing every patient scheduled for RE with an experienced oncologist in order to avoid missing standard regimens is strongly recommended. Another very important fact regarding chemotherapy is to stop therapy at least 2–3 weeks prior to RE to enable a differentiation of subsequent therapeutic response. More important for a stop of the ongoing chemotherapy is that several substances (5-FU, capecitabine, gemcitabine) act as radiosensitizers increasing the risk of radiation induced liver failure [6]. Further factors influencing the eligibility for RE, besides the history of chemotherapy, are the possibility to perform

Table 2.1. Indications for radioembolization

Primary or secondary liver tumor confined to the liver
No surgical options: • Due to lesion size or amount • Due to inoperabilty
No thermal ablative therapy possible
Standard chemotherapies: • Without success • With intolerable side effects
Preserved liver function • Bilirubin less than 2 mg/dl • AST and ALT ≤5× normal • Normal blood coagulation parameters • Albumin ≥3 mg/dl
Good ECOG performance score Karnofsky index ≥60%

surgery or ablative therapies – which are regarded as curative and should be performed whenever possible. The history of arterial infusion therapy via a surgically implanted port or pump is of particular interest, because in these patients the hepatic artery is often altered and catheterization of the hepatic artery may be impossible.

It is crucial to assess and rule out active extrahepatic spread, respectively. RE is based on the difference in blood supply to tumor tissue, almost completely supplied by the liver artery, and normal liver tissue, supplied nearly completely by the portal vein. Therefore, the effect of RE is exclusively confined to the liver and liver directed RE does not influence extrahepatic metastases and therefore, in patients with extensive extrahepatic spread, a systemic approach must be taken into account. However, stable osseous metastases in breast cancer are regarded as an exception from this rule – due to the normally long lasting progression of these metastases and their lack of influence on patients' life expectancy. The most important aspect in the selection of patients for RE is their actual clinical condition measured using the ECOG performance status or the Karnofsky score. Patients with a clearly reduced performance status are at higher risk to develop severe side effects, including radiation induced liver failure [5, 7]. Patients not fulfilling the criteria mentioned above should either be rejected for RE or should only be selected as candidates, if there is consent in an interdisciplinary tumor board regarding the potentially beneficial effect of the therapy in these special cases.

2.5 Selection Criteria in Hepatocellular Carcinoma

HCC most often occurs either in viral (HBV, HCV) or nutritive toxic caused cirrhosis. Due to the underlying cirrhosis patients often present with additional symptoms like portal hypertension, limited liver function, ascites or even portal vein thrombosis. Furthermore, many patients have already undergone different treatments like TACE, RFA or surgical resection. In these patients the degree of hepatic compromise must be taken into account to avoid treatment effect on liver reserve, which potentially accelerates liver failure. Risks versus benefits of each therapeutic regimen have to be discussed on an individual basis taking the higher risk for iatrogenic liver failure in this tumor entity compared to metastatic disease into account. Goin et al. [8] were able to show that the best pretreatment indicator for potential complications after therapy – beside the total amount of radiation dose – is the total serum bilirubin. In a risk stratification analysis, Goin et al. [9] could identify at least seven so-called risk variables strongly associated with 3-month mortality. The risk factors include liver dependent and independent factors. Liver dependent factors include the infiltrative pattern of HCC, bulky disease, transaminases (AST and ALT) elevated more than five times above normal values, a tumor volume of more than 50% of the liver volume and albumin less than 3 g/dl. The combination of any of those factors was shown to further increase the risk of severe complications. The liver independent factors causing a higher mortality are diagnosis of non-HCC and a lung dose more than 30 Gy. Each factor belonging to the liver dependent factors was associated with a

Table 2.2. Risk stratification when treating HCC (modified from [9]) – risk factors associated with significantly higher morbidity and mortality after radioembolization

Infiltrative growth of HCC
Bulky disease
AST or ALT >5× ULN
Tumor volume more than 50% of liver volume
Albumin less than 3 mg/dl
Bilirubin more than 2 mg/dl

3-month mortality of up to 50%. In addition, Goin et al. [9] described a 49% risk of death within 3 months after treatment if one of the risk factors mentioned above is positive, compared to a risk of 7% if none of the risk variables is positive before treatment. Therefore, the ideal patient for RE should have biopsy proven HCC confined to the liver, less than 50% of the liver infiltrated, should have bilirubin less than 2 mg/dl, no ascites, an albumin level above 3 g/dl, uncompromised coagulation and no hepatic encephalopathy [8, 9]. In other words, the patient should fulfill the criteria for Okuda stage 1, CLIP 2 or Child-Pugh class A. Furthermore, surgical resection or a possible transplantation should be ruled out and patients' overall condition should be comparable to at least Karnovsky level ≥ 60.

Portal vein thrombosis without cavernous transformation and hepatopetal flow is a well known and accepted relative contraindication for other types of transarterial therapy (e.g. TACE). However, there is controversy as to whether the same exclusionary criteria should be applied for the selection of patients for ^{90}Y microsphere treatment. The size of the spheres (20–60 μm) leads to an obliteration of the arteriolar bed. However, the relative percentage of obliteration is small and for this reason the alteration of vascularity and the overall embolic effect is minimal [10]. Therefore, the infusion of microspheres should be without complication in patients with this condition, as recently shown in a small cohort of patients [10]. However, until now, portal vein thrombosis is listed as a contraindication according to the package inserts of SIR-Spheres® (Sirtex Medical, Lane Cove, Australia) and Theraspheres (MDS Nordion, Kanata, Canada).

2.6 Conclusion

Patient selection for SIRT has to be made on an individual base and is very challenging. Therefore, the establishment of an interdisciplinary team consisting of at least an interventional radiologist, an oncologist, a liver surgeon and a nuclear medicine specialist is crucial for the success of the therapy. Furthermore, an exact evaluation of patient history, lab tests and Karnofsky or ECOG index need to be performed to rule out an unacceptable high risk and in order to guarantee the best tailored therapy for each patient.

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