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REVIEW

Role of Organ Transplantation in the Treatment of Malignancies – Hepatocellular Carcinoma as the Most Common Tumour Treated with Transplantation

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Abstract There are only few malignant tumours where organ transplantation is the treatment of choice. Transplantation can be considered individually in certain lung carcinomas, unresectable heart tumours, cholangiocellular carcinoma and Klatskin tumour. It is acceptable in unresectable chemosensitive hepatoblastoma, epitheloid haemangioendothelioma, liver metastasis of neuroendocrine tumours and as the most common indication, the early hepatocellular carcinoma (HCC) in cirrhotic liver. Results of liver transplantation (LT) for HCC according to Milan criteria as a "gold standard" are excellent. Time of LT has a great influence on the results. While patients are on waiting list, locoregional therapies may help prevent tumour progress. Living donor LT is an acceptable treatment of HCC. The greatest experience with this procedure is in Asia. Despite the favourable results, LT as the treatment of HCC is debated and raises several questions: regarding indication and expectable outcome. Milan criteria seem to answer this questions although they are too strict. The number and size of HCC foci per se is not sufficient predictor of eligibility to transplantation and for prognosis. Majority of the prognostic factors can be evaluated only after transplantation with pathological examination of HCC. Aim of the present research is to find prognostic factors that are characteristic of biological behaviour of HCC, which can be detected before LT in order to select patients who have the greatest benefit from LT. Re-definition of eligibility criteria is an actual question; an international consensus based on additional prospective studies is required for the "new" recommendation.

Keywords Bridging therapy · Bronchioloalveolar carcinoma · Des-gamma-carboxy prothrombin · Extended criteria · Heart sarcomas · Hepatocellular carcinoma · Living donor liver transplantation · Liver transplantation · Milan criteria · Proliferation signal inhibitor

Abbreviations

AASLD	Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
AU	Arbitrary unit
BAC	Bronchioloalveolar carcinoma
DCP	Des-gamma-carboxy prothrombin
FDG-PET	Fluorodeoxyglucose positron emission tomography
HCC	Hepatocellular carcinoma
INR	International normalized ratio for prothrombin time
LDLT	Living donor liver transplantation
LRT	Locoregional therapies
LT	Liver transplantation
MC	Milan criteria
MELD	Model for end-stage liver disease
UCSF	University of California San Francisco
PEI	Percutaneous ethanol injection
PIVKA	Protein induced by vitamin K absence or antagonist
RFA	Radiofrequency ablation
SHARP	Sorafenib HCC Assessment Randomized Protocol

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SUVmax	Maximum standardized uptake value
TACE	Transarterial chemoembolization
TARE	Transarterial radioembolization
TTV	Total tumor volume

Introduction

Like all medical interventions, organ transplantation has indications and contraindications. General contraindications of transplantation include malignant tumours. Invasive tumour of a recipient waiting for organ transplantation is a contraindication for transplantation because immunosuppressive therapy for protection of transplanted organ would facilitate tumour progress and have adverse consequences to the patient. Depending on the tumour type and properties 2 to 5 years of tumour free survival is required for the patients to re-consider organ transplantation. Such decision should be made individually [1]. For specific tumours there are literature recommendations for the required waiting time. According to the recommendation of the Canadian Society of Transplantation the recommended tumour free waiting time for kidney transplantation, e.g. in ductal carcinoma in situ is 2 years, for invasive breast cancer is 5 years, and for stage III–IV breast cancer kidney transplantation is not recommended [2].

There are some exceptions in malignancies where no recurrencies are anticipated after the therapy thus no waiting time is required prior to transplantation. These include basal cell carcinoma of the skin, in situ bladder cancer, non–invasive papillary tumours of the bladder, and focal, microscopic low-grade, low risk prostate cancer. In case of some other 'in situ' carcinomas the waiting time may be less than 2 years based on individual consideration of the risk [2].

The above information applies to patients with malignant disease waiting for organ transplantation due to chronic organ damage, i.e. the transplantation is not for the treatment of malignancy. However, some exceptions exist where the tumour of a specific organ requires organ transplantation. i.e. transplantation is also the treatment of the tumour.

Organ transplantation can not always be performed in case of all transplantable organ i.e. 'replacement' of an organ with malignant lesion with a healthy one is not always possible. Thus treatment of *pancreas and small intestinal tumours* is primarily surgical, transplantation is not required, it would not be reasonable. Treatment of *kidney cancer* is also a surgical intervention and kidney transplantation is indicated for the treatment of potential renal failure and not as a tumour therapy. It should be anticipated in case of tumour in solitary kidney, bilateral tumours and malignancy in kidneys with existing impaired function. If renal failure occurs haemodialysis treatment is required, and kidney transplantation is possible only after 2-year tumour free survival. In case of early, small, incidental renal cell carcinoma with good prognosis the waiting time may be shorter or may not be necessary [2]. *Lung cancer*: lung transplantation in case of cancer in end-stage lung is debated; in general, it is not recommended. The objective of a survey involving 67 transplantation centres was to assess the role of lung transplantation in the therapy of bronchogenic carcinoma developed in end-stage lung. In 8.000 lung transplantations bronchogenic carcinoma was observed in the removed lungs of 69 recipients. In 26 cases advanced multifocal bronchioloalveolar carcinoma (BAC) was the primary indication for transplantation. Incidental bronchogenic carcinomas or incidental multifocal BAC were found in the explanted lung of the remaining 43 patients. The 5-year survival of patients with stage I. disease was better (51%) than in stage II and III patients (14%). 26 patients with advanced multifocal BAC had diffuse pulmonary involvement, therefore no surgical resection could be performed; the only treatment option for such patients was lung transplantation. The 5-year survival was 39% which is acceptable when there is no other treatment option. De Perrot et al. demonstrated favourable results of lung transplantation in patients with stage I bronchogenic carcinoma and advanced multifocal BAC [3]. Nevertheless, lung transplant for advanced BAC is currently performed only in a few centres. As there is no international consensus and recommendation, indication of lung transplantation in case of cancer developed in end-stage lung remains to be debated [4]. *Malignant tumours of the heart* are rare; treatment is primarily based on tumour resection. In technically difficult situations, especially tumours of the left atrium, ex vivo resection and autotransplantation might be the solutions. In case of unresectable heart tumours without distant metastases heart transplantation may be considered as a therapeutic option. Until recently there have been only a small number of heart transplantation with tumour indication; two-third of patients died within 1 year due to local tumour recurrence or distant metastases [5–7].

Indication of organ transplantation is the most obvious option in case of *liver tumours*. Theoretically liver transplantation (LT) due to liver tumour may be indicated if LT may provide better long-term survival for the patient compared to the results of other treatment options. LT may fulfil this theoretical requirement in certain conditions. However, LT is not suitable for all liver tumours. Because of the unfavourable experience with LT performed for the treatment of cholangiocellular carcinoma (early recurrence and bad prognosis, 5–15% 5–year survival), this type of liver carcinoma is not recommended for transplantation; this can only be a treatment option in individually selected

patients at early stage [8]. There is a similar situation with hilar cholangiocarcinoma (Klatskin tumour) where LT can be considered in non-disseminated unresectable cases [9, 10]. According to Mayo Clinic protocol patients receive neoadjuvant treatment (external beam radiotherapy with concomitant fluorouracil, Iridium-192 brachytherapy, oral capecitabine), prior to transplantation, patients undergo a staging laparotomy. Only patients with negative staging operations remain eligible for transplantation. If the pathologic analysis of resected specimens confirmed R0, N0 status, the 5-year survival after LT was 82% [11].

LT is acceptable in case of the following tumours: 1. early hepatocellular carcinoma (HCC) in cirrhotic liver, 2. unresectable chemosensitive hepatoblastoma, 3. epitheloid haemangioendothelioma, 4. metastasis of neuroendocrine tumours [12]. Out of these tumours LT is performed more frequently in HCC. In our summary we focus on HCC treatment in more details.

Hepatocellular Carcinoma (HCC)

HCC representing 70–90% of primary liver tumours is one of the most common tumours in the world. It is estimated to cause 0.5 to 1 million of new cases and the same number of death every year [13]. HCC ranked 3rd to 4th place among malignant causes of death but for example in China it is at the 2nd place.

The influence of HCC varies between different areas of the world (Table 1) [14, 15]. The most important risk factor of HCC includes liver cirrhosis that is present in 80–90% of cases. Etiologies and risk factors are summarized in Table 2 [14, 16].

Treatment and prognosis of HCC is primarily determined by the stage of HCC, functional status of liver and performance status of patient [17, 18]. There are different treatment options for HCC [19–22]. The treatment methods according to recommendations of the American Association for the Study of Liver Diseases (AASLD) in 2010 are shown in Table 3 [23]. (The full version of the new guidelines is available on the AASLD Web site at http://www.aasld.org).

Table 1 Incidence of hepatocellular carcinoma in different areas of the world

Number of cases	Countries
20–100/100.000 people/year	Mongolia, Korea, China, Japan, Hong Kong, Thailand, sub-Saharan Africa
10–20/100.000 people/year	Italy, Spain, Latin American countries
5–10/100.000 people/year	France, United Kingdom, Germany
<5/100.000 people/year	United States, Canada, Scandinavia

Table 2 Etiological and risk factors of hepatocellular carcinoma

Viral	chronic hepatitis B and hepatitis C virus infection
Toxic	alcohol, aflatoxin, betel quid, smoking, oral contraceptive
Metabolic	obesity (body mass index >30 kg/m^2), diabetes mellitus, non-alcoholic fatty liver disease
Genetic	hereditary haemochromatosis, alpha-1 antitrypsin deficiency
Immune-related	primary biliary cirrhosis, autoimmune hepatitis

Surgical therapy of HCC includes liver resection and LT. Resection is considered for 15–30% of HCC patients. This is the treatment of first choice for non-cirrhotic patients. However, HCC primarily develops in cirrhotic liver where the possibility of resection is limited due to the risk of post-operative liver failure. The risk of HCC recurrence after resection exceeds 50% and the 5-year survival is below 70%. The underlying cause of high recurrence rate is that the liver cirrhosis as a risk factor of HCC continues to be present after resection [24]. This is why LT might be a more thorough mode of treatment as it simultaneously treat HCC and the underlying disease, that is liver cirrhosis [25].

HCC Therapy—Liver Transplantation

By the 1980's LT has become a routine procedure in the larger transplant centres and HCC was included in the scope of indications for LT based on the previous principle. However, preliminary results were quite bad and characterized by high tumour recurrence (32–54%) and low survival rate (20–40% 5-year survival); the waiting time of patients was more than 1 year. The primary reason of bad results was that transplantation was performed in almost unselected patients (irrespectively of the stage of tumour, with macroscopic vascular invasion, lymph node or extrahepatic involvement indicating bad prognosis) [25, 26].

The stricter selection of patients led to better results in the 1990's. In 1996, Mazzaferro et al. reported 75% 4-year survival after LT due to HCC based on Milan criteria (MC) [27]. These favourable results were confirmed by other authors later. [25, 28–30].

MC outlined in 1996 are now accepted worldwide based on the results. Accordingly, LT may be performed if HCC is a solitary tumour of less than 5 cm or having not more than 3 foci and neither focus is larger than 3 cm, with no macroscopic vascular invasion and extrahepatic tumour growth (Table 4). After LT performed based on MC 5-year

Table 3 Treatment options of hepatocellular carcinoma

Treatment	Recommendation (AASLD Practice Guideline, 2010)
Liver resection	Patients who have a single lesion can be offered surgical resection if they are non-cirrhotic or have cirrhosis but still have well preserved liver function, normal bilirubin and hepatic vein pressure gradient <10 mmHg
Liver transplantation	Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria. Living donor transplantation can be offered for HCC if the waiting time is expected to be so long that there is a high risk of tumor progression leading to exclusion from the waiting list. No recommendation can be made regarding expanding the listing criteria beyond the standard Milan criteria. Preoperative therapy can be considered if the waiting list exceeds 6 months.
Percutaneous ablation	Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation. PEI and RFA are equally effective for tumors <2 cm. However, the necrotic effect of RFA is more predictable in all tumor sizes and in addition, its efficacy is clearly superior to that of PEI in larger tumors.
Transarterial chemoembolization	TACE is recommended as first line non-curative therapy for non-surgical patients with large/ multifocal HCC who do not have vascular invasion or extrahepatic spread.
Multikinase inhibitor	Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function.
Radioembolization with Yttrium90-labeled	Glass beads has been shown to induce extensive tumour necrosis with acceptable safety profile. However, there no studies demonstrating an impact on survival and hence, its value in the clinical setting has not been established and cannot be recommended as standard therapy for advanced HCC outside clinical trials.
Tamoxifen, anti-androgens, octreotide or hepatic artery ligation/ embolization	Not recommended.
Systemic or selective intra-arterial chemotherapy	Not recommended and should not be used as standard of care.

(*AASDL* American Association for the Study of Liver Diseases, *HCC* hepatocellular carcinoma, *PEI* percutaneous ethanol injection, *RFA* radiofrequency ablation, *TACE*: transarterial chemoembolization)

survival exceeds 70% and the tumour recurrence rate is below 15% [27, 31]. MC results are favourable but only a few HCC patients can comply with those requirements due to the restrictions and get the benefits of LT.

Waiting time is a critical point of transplantation due to HCC. The number of cadaveric donors is below LT requirements; therefore, the waiting time for transplantation is still quite long although transplantation would be urgent. During the 'inactive' waiting period HCC may progress, patients exceed eligibility criteria and may be cancelled from the waiting list (WL) loosing the chance for LT. What are the options to reduce waiting time, the risk of tumour

Table 4 Criteria for liver transplantation for hepatocellular carcinoma

Transplant centre	Cadaveric or living donor	Criteria
Milan (Italy) (1996)	cadaveric	single nodule ≤5 cm, or 2–3 nodules ≤3 cm
UCSF (US) (2007)	cadaveric	single nodule ≤6.5 cm or 2–3 nodules ≤4.5 cm and total tumour diamater ≤8 cm
Milan (Italy) (2009)	cadaveric	number of nodules + maximum diameter (cm) ≤7
Edmonton (Canada) (2009)	cadaveric	total tumour volume ≤115 cm^3 and AFP ≤400 ng/mL
Pamplona (Spain) (2001)	cadaveric	single nodule ≤6 cm, or 2–3 nodules ≤5 cm
Kyoto (Japan) (2007)	living	≤10 nodules, each ≤5 cm and DCP ≤400 mAU/mL
Kyushu (Japan) (2007)	living	all nodules <5 cm or DCP <300 mAU/mL
Multicenter (Japan) (2007)	living	single nodule ≤5 cm, or 2–3 nodules ≤3 cm and AFP ≤400 ng/mL and DCP ≤100 mAU/mL
Seoul (Korea) (2008)	living	≤6 nodules, all nodules ≤5 cm
Seoul (Korea) (2007)	living	nodule ≤5 cm, no number restriction, AFP ≤400 ng/mL
Barcelona (Spain) (2002)	living	single nodule ≤7 cm, multinodular: 3 nodules ≤5 cm or 5 nodules ≤3 cm

(*AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *UCSF* University of California San Francisco)

progress and how to increase the number of LTs due to HCC and improve the results?

Increasing the Number of Donors

There are the following facilities: use of marginal donor livers (extended donor criteria e.g. elderly donor, fatty liver, donation after cardiac death, etc.), split-graft liver transplantation into two different patients, domino liver transplantation and *living donor liver transplantation* (LDLT) [32].

Use of LDLT in the treatment of HCC was encouraged partly by the urgent condition caused by the tumour and that in some countries (e.g. in Asia where HCC is one of the most common tumours) the number of cadaveric LTs is very low due to religious and cultural reasons (cadaveric organ donation rate <5/million population/year) thus in addition to liver resection LDLT may give a chance for the treatment of patients [33]. Advantages of LDLT include that in case of an eligible donor it allows transplantation, it may reduce waiting time thereby decreasing the risk of HCC progress and post-transplantation tumour recurrence [25]. The available results are favourable; the 5-year survival is above 70% when MC is met. However, tumour recurrence rate is higher than expected; based on the results from Asian centres it is 15–29% [34, 35]. It is assumed that due to the shorter waiting time with LDLT compared to cadaveric transplantation the tumour biological behaviour can be assessed less accurately and therefore there is a higher probability of LT due to a more aggressive HCC thereby increasing the chance of tumour recurrence. The other cause may be that factors affecting the transplanted liver lobe and stimulating its growth also promote tumour cell growth [36]. An other explanation may be that for LDLT MC is not met so strictly and sometimes only gross vascular involvement and extrahepatic tumour growth are considered as contraindications [37]. There is higher recurrence rate in case of HCC exceeding MC.

In the work by Todo et al. the 3-year patient survival was 78.7% within the MC, while in case of tumour exceeding MC it was 60.4% [31, 35, 38, 39].

Disadvantage of LDLT includes the risk of surgical complications for the healthy donor. Different publications report various data thus donor morbidity rate is 0–100% with median of 16.1%, and the mortality rate is 0.1–1%. During LDLT the interest of both the donor and the recipient should be considered. The purpose is to avoid health damage of donor with adequate survival result of the recipient [40, 41].

Influence of HCC in Determination of Patient's Order on Waiting List

MELD (Model for End-stage Liver Disease)-score determines the severity of liver disease based on INR (international normalized ratio for prothrombin time), serum bilirubin and creatinine levels as well as it has predictive value regarding the probability of death on the liver transplantation WL. Patients are ranked in the WL based on their MELD-score; a higher score represents more severe disease and ranks the patient higher on the list. At the time of HCC diagnosis majority of patients has low MELD-score based on their liver function; thus, despite malignant disease, such patients are ranked lower on WL thereby adversely increasing the waiting time due to the risk of tumour progress. In 2002 the United States changed this prioritization policy and in calculation of MELD-score it considered HCC with more points in case of an MC-compliant tumour stage. Patients with T1 lesions (single tumour <2 cm) were automatically allocated a MELD score of 24 points and those with T2 tumour (T1 < but within MC) 29 points. Thus patients with tumour could be ranked higher on WL thereby decreasing the waiting time and the number of patients cancelled from the list due to tumour progress reduced by half, and the rate of patients transplanted due to HCC increased from the previous 4.6%–7% to 18–22% [25, 42]. This of course affected the LT chances of non-tumour patients on the WL. Moreover, in 33% of T1 tumour patients no tumour was found in the removed liver i.e. pre-operative HCC diagnosis was erroneous; thus these patients received LT earlier without established reason. Therefore, allocation was changed and now HCC patients with stage T1 disease are allocated a MELD-score corresponding to the status of their liver and for a stage T2 tumour 22 points are allocated and the score is increased every 3 months [40, 43].

HCC Treatment during Waiting Period

LT is one option to treat HCC but the time of transplantation can not be guaranteed. The treatment of HCC patient on WL is justified partly by the unpredictable waiting time and partly by the fact that during the waiting period HCC progress may occur and in case of a tumour exceeding the criteria patient will drop out from the list. As a consequence patient will loose the opportunity to LT and efficient oncological treatment. Primarily locoregional therapies (LRT): radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) and transarterial chemoembolization (TACE) are recommended and widely used in practice as bridging therapy. Between a third and a half of HCC patients receive such therapy (Fig. 1). However, there are no results available from prospective, randomized studies that would confirm LRT benefits (prevention of dropout, reduction of HCC recurrence after LT). Relevant publications reported nowdays could not confirm the benefits of TACE or RFA [40, 44]. However, LRT may have complications with major complication rate of 5–8%, and mortality after TACE of 2.5% [40, 45].

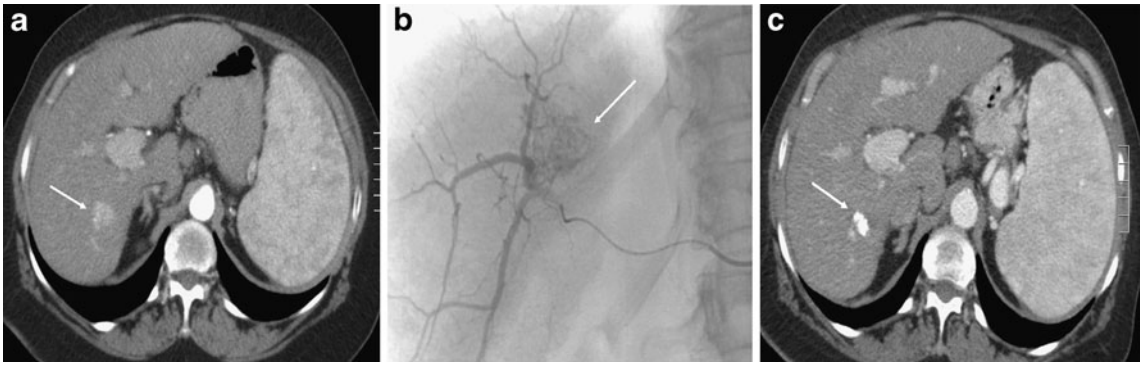

Fig. 1 "Bridging therapy" of hepatocellular carcinoma (HCC) with transarterial chemoembolization (TACE) **a**: Contrast enhanced CT examination shows tipical arterial enhancement of a HCC nodule (*arrow*), **b**: Superselective TACE with microcatheter, good Lipiodol uptake (*arrow*) **c**: Control CT examination shows dens Lipiodol retention (*arrow*) and decreased tumor size

According to a survey in the US LRT used as a treatment of T1 HCC increased the mortality rate of patients on WL by deteriorating liver function [46]. LRT is primary considered in patients where there is high risk of tumour progress even within a short waiting time or in case of low risk when the waiting time is more than 6 months [40, 47]. Prospective controlled studies are needed to assess the role of LRT prior to LT. Liver resection is also considered as a bridging therapy which is surgical treatment of tumour in patients with compensated liver cirrhosis, on WL. Of all bridging options resection provides the best tumour control. Histology of the resected tissue may provide important information about the prognostic value for both the biological nature of tumour and liver status [31].

Additionally, there are other new, promising options for the treatment of patients on WL. Clinical data have shown that external beam radiotherapy has excellent local tumour control [48]. Selective internal irradiation with Yttrium-90 microspheres (trans-arterial radioembolization—TARE) can also be suitable as bridging therapy [49].

In the SHARP trial the multikinase inhibitor sorafenib has demonstrated efficacy in the management of advanced HCC [50]. Its use for delaying HCC progression prior to LT also seems reasonable. Based on their work Vitale et al. concluded that sorafenib neoadjuvant therapy is cost-effective compared to no therapy for T2-HCC patients waiting for liver transplantation, particularly for median times to transplant under 6 months [51]. However, whether or not sorafenib is suitable for bridging therapy, and how the antiangiogenic effect of sorafenib affects post-LT surgical complications remain to be debated and further well-designed studies are needed to answer these questions [52, 53]. Based on preclinical data Rowe also noted that neoadjuvant treatment with sorafenib, rather than slowing disease progression, may increase tumour invasiveness and metastatic potential during therapy and the recurrence of HCC after liver transplantation [54].

Consideration of treatment of patients on WL from the aspect of LT is understandable. However, oncological considerations should also be assessed in such decisions since if the patient is left untreated and he/she drops out of WL due to HCC progress, the patient will be deprived of the possibility of both the LT and LRT that could provide survival benefit.

By downstaging through treatment of HCC exceeding Milan criteria (TACE, or combined modalities) patient may fulfil the criteria again. The questions are that who can be on WL and after how much waiting time. It is recommended to include primarily the patients with stable tumour status (stable disease) even 3–6 months after the treatment and having less aggressive tumour behaviour and less chances of post-transplant recurrence [52, 55, 56].

LT after Liver Resection—Salvage Therapy

Approximately 25% of HCC patients is eligible for liver resection and LT as well. Possibility of liver transplantation is limited; therefore, when the conditions are fulfilled liver resection is recommended, particularly in elderly patients. In case of HCC recurrence after liver resection LT is a valid treatment option under specific conditions. The rate of complications is higher after such "salvage" LT but the results are comparable to the primary LT [57]. Salvage transplantation may be offered to patients at the onset of recurrence, provided their are eligible for LT (age, Milan criteria, and time to recurrence >12 months) [52].

Extension of Criteria

Based on Milan criteria LT is indicated in case of early HCC. Only few patients can comply with these criteria. The question is whether the eligibility criteria can be extended to give chance for LT to more HCC patients without substantial changes in results. The good post-LT patient

survival data of patients who were considered to be within MC based on radiological examinations but were confirmed to be outside MC based on pathological examinations, was the basic concept of extension of criteria [58, 59]. Several work teams are trying to find a solution to this problem, one of the most well-known criteria were recommended by the San Francisco Transplant Team (University of California, San Francisco—UCSF) indicating transplantation in cases exceeding tumour size of MC (Table 4). After analysis of data from 467 patients underwent liver transplantation due to HCC Duffy et al. have found that results with UCSF criteria do not significantly differ from that with MC, the 5-year patient survival was 75% [60, 61]. The UCSF criteria have become accepted. Milan work team also dealt with the possibility of extension of criteria. Based on the evaluation of 1,112 patient's data exceeding MC in a multicenter, retrospective analysis the "up-to-seven" criteria were defined. These criteria are based on the number of tumours and the size of the largest focus. The sum of the two values can not be more than 7. E.g. one nodule of 6 cm (1+6), or five nodules up to 2 cm (5+2). With these criteria—if no microvascular invasion was present in the tumours—the 5-year patient survival was 71.2% [62]. As this criterion was based on post-LT pathological findings Sotiropoulos concluded that "the up-to-seven criteria are illusive and not applicable in clinical practice" as a prognostic model [63]. Total tumour volume (TTV) can be determined from the number and size of foci (TTV). A new criterion can be established by considering TTV and alpha fetoprotein (AFP) together. In case of TTV of ≤115 cm^3 associated with an AFP serum level of ≤400 ng/ml 3-year patient survival is equivalent to the survival of patients within MC [64].

Extension of eligibility criteria should be considered with special care also in case of living donor liver transplantation, and the group of HCC patients beyond Milan criteria, who would benefit from LDLT should be specified. The MC have been reliable guideline for LDLT for a long time. Asian centres had the greatest experience in LDLT therefore it is not surprising that primarily these centres work on extension of MC or determination of different criteria using a broader analysis of prognostic factors in addition to tumour number and size. Ito et al. reported that in patients with HCC focus number ≤10, tumour size ≤5 cm, and des-gamma-carboxy-prothrombin level ≤400 mAU (arbitrary units)/ml (Kyoto criteria), the 5-year patient survival after LDLT is 86.7%, while in patients with HCC exceeding these criteria 5-year patient survival was 34% only [35, 65]. Many Asian centres use their self-developed criteria [35, 66–70]. Western countries are also open to change. However, Silva has concluded that there are currently insufficient data to recommend more liberal criteria selection as a standard of care [40, 71].

Both Western and Eastern transplant teams deal with extension of criteria for LT due to HCC and achievement of more and more favourable results in cadaveric and living donor liver transplantation. Although at the present time, MC remain the only universally accepted and continously validated criteria, it is the individual decision of each transplant centre which criteria to use (Table 4).

Theoretically the extension of the scope of HCC indication may provide LT as an option for more patients but this puts more emphasis to the problems of donor shortage, organ allocation, prioritization (tumour and non-tumour patients), and waiting time.

Role of Prognostic Factors Characterizing Biological Behaviour of HCC in Determination of Eligibility for Liver Transplantation

After LT and immunosuppression the progress of recurrent HCC is rapid and has fatal consequences despite oncological treatment. Because the possibility of recurrency and organ shortage it is important that those patients are included on WL and registered for LT who have the lowest risk for recurrency and the best expected survival [72]. To achieve this goal, evaluation of the characteristic prognostic markers of HCC is important. Tumour stage (number and size of foci) which is the basis of the most criteria systems is an important prognostic factor and is related to the probability of vascular invasion and HCC recurrence but it is alone insufficient for the assessment of aggressiveness of HCC. Additionally, the tumour stage established by preoperative radiological examinations does not always match with pathological results. Both false positive result, particularly in case of T1 tumours and underestimated tumour stage compared to the pathological findings may occur. Rate of difference can be as high as 30% [40, 73]. One can get a more accurate picture of the nature of HCC based on tumour grading, microvascular invasion, tumour necrosis, microsatellite tumour, capsule invasion. However, this information is available only from the pathological examinations after LT. In general, the biopsy substance of HCC is not sufficient for complex examination, particularly in case of larger, multifocal tumours with heterogeneous structure. Tumour resection is an exception as in such cases the entire tumour can be examined [31]. The efficiency of LRT, whether partial or complete necrosis occurred inside the tumour, can also be assessed by pathological examination after LT.

AFP is a tumour marker detectable prior to LT but its value is abnormal only in half of HCC patients. It prognostic value is limited. In patients with serum AFP of >500 ng/ml or where serum AFP level increases rapidly there is a higher risk of HCC recurrence, even if they meet MC [64]. A retrospective analysis has shown that an increase in AFP level exceeding

15 μg/L/month in patients on WL is associated with low patient survival rate after LT thus AFP progression could be a pathological preoperative marker of tumour aggressiveness [74]. However, pre-LT bridging treatment affects AFP levels, thus the prognostic validity of AFP is questionable in such cases [63].

The additional known tumour marker of HCC is des-gamma-carboxy-prothrombin (DCP), an abnormal prothrombin protein which is a product of low or point mutation induced insufficient γ-glutamyl carboxylase activity of HCC cells. DCP—also known as 'protein induced by vitamin K absence or antagonist-II' (PIVKA-II)—is the prognostic factor of HCC. DCP positive HCC is more aggressive compared to DCP negative HCC. Serum level above 300 mAU/mL correlates with histological vascular invasion and DCP could be a strong prognostic indicator [40, 75–77].

A novel option for establishment of HCC prognosis before LT is the ^{18}F-FDG PET. In the studies by Lee et al. it was shown that ^{18}F-FDG PET is an independent and significant prognostic factor for tumour recurrence in LT for HCC, with a cutoff $Tumor_{SUVmax}$/normal-$Liver_{SUVmax}$ of 1.15. The 1-year recurrence free survival rate above cutoff was markedly different from the rate below cutoff (97% vs. 57%) [78].

Immunosuppressive Therapy

Immunosuppressive therapy prevents organ rejection after LT, but has a disadventageous oncological effect, as it may facilitate HCC recurrence. Immunosuppession in patients underwent LT is generally based on calcineurin inhibitor (cyclosporin, tacrolimus). To reduce recurrence risk of HCC the introduction of proliferation signal inhibitor (rapamycin and its derivates) is recommended, because of their antiproliferative effect [79]. In animal studies combination of rapamycin and sorafenib inhibited the growth of metastatic HCC xenograft. Combination of the two agents seems promising in the treatment of HCC patients and prevention of HCC recurrence after liver transplantation [80]. The beneficial effects have already been reported in case studies [81, 82].

Conclusion

Organ transplantation has limited role in the treatment of malignant tumours. Transplantation is individually considered in the treatment of certain lung tumours or unresectable heart tumours but there are no accepted international guidelines for their routine application. The role of organ transplantation is more definite in the treatment of liver tumours particularly in HCC. LT is an option for the effective treatment of HCC developed in association with liver cirrhosis. Survival results achieved with Milan criteria are excellent—considering treatment of malignant disease—and there are only slight differences compared to the results of non-tumour patients underwent liver transplantation. The time to LT is a critical and important factor regarding the results. Treatment of patients on WL and usefulness of bridging therapy to prevent tumour progress are debated in terms of LT but leaving a tumour patient without treatment because of the hope of LT is similarly debatable. Living donor LT has become accepted in the treatment of HCC and it is used in increasing number of patients primarily in Asia. Re-definition of eligibility criteria for LT is an actual question; however, an international consensus based on additional research results and prospective studies is required for the "new" recommendation considering prognostic aspects and facilitating the selection of ideal patients in terms of the results.

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