Chapter 8

Surgical Treatment Strategies and Prognosis of Hepatocellular Carcinoma

Alessandro Uzzau, Maria Laura Pertoldeo, Vittorio Cherchi, Serena Bertozzi, Claudio Avellini and Giorgio Soardo

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http://dx.doi.org/10.5772/55890

1. Introduction

Hepatocellular carcinoma (HCC is the fifth most common cause of mortality worldwide and the third cancer related cause and is responsible for about 1 million deaths yearly [1]. The age-adjusted worldwide incidence is 5.5-14.9 per 100.000 population. In some areas of the world, such as sub-Saharan Africa and Southeast Asia, HCC represents the first cause of cancer death with an incidence of 52 per 100.000. Furthermore, in Europe and USA, HCC incidence has progressively raised in the past decade representing a burden problem.

HCC is one of the few cancers for which a number of risk factors are known in great detail [2, 3]. HCC is almost always (80%) associated with cirrhosis, at least in developed countries, and chronic hepatitis C and B infection, alcoholic cirrhosis and haemocromatosis are some of the established risk factors [4]. The metabolic syndrome related to hypertension, central obesity, diabetes and obesity has been identified as a new risk factor. As a result, screening programs have developed, with the use of ultrasound and α-fetoprotein (AFP), with a hope to increase the chances of diagnosing small HCC and unltimately increase the rate of curability.

Definitive diagnosis relies on the demonstration of a typical vascular pattern per liver imaging techniques (triple-phase CT-scan or MRI) of tumors larger than 2 cm with arterial hypervascularity and venous wash- out. Nodules, smaller than 2 cm, should be rechecked every six months or, if highly suspect, subjected to needle biopsy. It's likely that the study of tumor-specific tissue markers with prognostic value could introduce a systematic use of needle biopsy.

Over the past 20 years, surgical treatment of hepatocellular carcinoma has seen an immense boost and improvement, with good survival outcomes and reduced morbidity and mortality.

Liver resection (LR) and orthotopic liver transplantation (OLT) and ablative therapies are now considered the only potentially curative treatments for this cancer. LR has achieved improvement in survival within the past decade as a result of advances in diagnosis, surgical management of HCC and perioperative care. However, the long-term prognosis remains poor, and the 5-year overall survival rate ranges between 33% and 44%, with a 5-year cumulative recurrence rate of 80% to 100%.

OLT could be viewed as the optimal treatment for HCC that is accompanied by advanced cirrhosis because of the widest possible resection margins for tumour and for a definitive cure of cirrhosis and its related complications. OLT for HCC performed within well-defined oncologic criteria (Milan criteria "reference") has shown long-term results comparable with those of transplantation for non-HCC patients. However, the critical shortage of available donated organs, together with the increasing number of patients awaiting transplantation, makes this therapeutic option available to only a small percentage of patients. Owing to the limited organ supply, many liver transplant centers usually make a selection to resect patients with compensated liver cirrhosis, defined as Child–Pugh A chronic liver disease and resectable tumor and to reserve transplantation for those with impaired liver function (Child-Pugh class B-C) and small oligonodular HCC considered within the currently accepted criteria for transplantation.

Radiofrequency and microwave ablation are relatively new percutaneous techniques in clinical use for HCC, that can produce tumour necrosis. Complete response rates are high in large series if tumour is less that 3 cm in diameter.

This chapter will consider the main surgical techniques for the treatment of HCC in the light of the major guidelines currently available and of personal experience.

Also, we will review HCC prognostic factors, and the particular situation of "large" HCC and the strategy for liver tumours located at the hepato-caval confluence.

2. Surgical approach to HCC

Until two decades ago, prognosis of HCC was considered inevitably poor. Survival values of 54%, 40% and 28% at 1, 3 and 5 years in a group of patients with unresectable HCC were reported [5]. Since then, the therapeutic approach and the prognosis have been significantly modified [6], overall survival rates at 5 yearsreached values of 35-70% for liver resection [7, 8] and 40-75% for liver transplantation, depending on the stratification system of patients [9, 10]. This mainly related to better allocation of patients to current available treatments (OLT, LR, local therapies), enhancement of post-operative care, and treating patients at centers with a high-volume of hepatic surgeries. With regard to LR there has been an improved balance between extent of resection and parenchymal volume spared, a systematic use of intraoperative ultrasound examination (IOUS), and meticulous care to minimize blood loss by mean of intermittent clamping of the portal triad [11], selective clamping, and use of innovative hemostatic tools for dissection as ultrasound dissectors, harmonic scalpel, and argon-beamers.

http://dx.doi.org/10.5772/55890

Side by side, some new techniques, such as portal vein embolization to induce hypertrophy of the remnant liver, and intraoperative radiofrequency (RFA) or microwave (MWA) ablation have allowed it to expand and optimize the surgical offer. HCC occurs in over 80% of cases of cirrhosis. Furthermore, both tumor and cirrhosis contribute to the risk of mortality, and cirrhosis represents a limit for hepatic resection due to the risk of liver failure.

For HCC arising in the setting of healthy liver, it is undisputed that resection represents the first line of treatment; parenchymal resections extended up to 60% of the organ fall within an acceptable risk of post-operative liver failure and mortality.

Conversely, for HCC accompanied by cirrhosis, surgical outcome and prognosis are dependent on the degree of cirrhosis, independent of the tumor stage. In general, considering only the size of the tumor, three categories of HCC could be defined: (<3 cm), -(3-5 cm), a (5-10 cm) and (> 10 cm). The outcome after resection is good in the setting of smaller tumorsand the results after transplantation are optimal for single tumor<5cm or up to 3 tumors, <3cm each (Milan criteria). Furthermore tumor ablation by percutaneous alcohol treatment or RF ablation is optimal for tumors in the first category, and in select cases in the second, not applicable for tumors >5 cm. These results depend on the fact that, with an increase in the tumor size there increases the likelihood of vascular infiltration, poor tumor grading 3-4, satellites nodules, and/or multinodularity which represent (in particular the first two) a strong negative prognostic factors. If it is true that the best results in terms of survival are obtained for single lesion, there is now agreement that multiple nodules, up to 3, and no larger than 3cm can be addressed to transplantation with results similar to those of single tumor < 3 cm. Percutaneous ablative therapies or multiple resections, or resections supplemented by intraoperative ablation also offer discrete survival results in selected cases. The presence of a peritumoral capsule (in the so-called expansive capsulated HCC) represents another favorable prognostic element, while vascular infiltration, both microscopic and macroscopic, even more drastically reduces survival expectancy, because it determines an additional risk of early recurrence. Improved knowledge of the weight of these prognostic factors has led to the development of pathological classification systems very useful for evaluating the prognosis in non-surgical cases. AJCC / UICC pathological classification [12] devotes particular concern to the presence of macroscopic vascular infiltration or infiltration of large venous branches seen on imaging scans, but not to the size of the lesion, which is useful for prognostic purposes. The classification of the American Liver Tumor Study Group [13] also used by the United Network of Organ Sharing (United Network for Organ Sharing - UNOS 2012) [14] takes into account the size and nodularity of HCC tumors and is used to evaluate patients before resection or transplantation.

Finally, another HCC tumor parameter, which is critical to treatment decisionsis of the tumor location within the liver and its relationship with vascular structures. This technical aspect isespecially relevant to small tumors that are centrally located, or close to the main portal branches or to the hepato caval confluence, which should be considered for percutaneous therapy or transplantation, given the difficulty of extensive resection in this setting. In addition, other aspects related to the underlying liver disease must be addressed, such as the presence of portal hypertension (with pressures > 10mmHg), or platelets <100,000 that are associated with poor survival outcome following surgery, and increased bilirubin levels.

3. Liver resection and assessment of liver function

Problems to be faced in order to formulate a correct indication to resection are linked to 1) general conditions of the patient, in particular the presence of co-morbidities, 2) stage of the tumor, and 3) presence of advanced cirrhosis and hepatic function status which represent a limiting condition to hepatic resection and a real risk of postoperative liver failure, this being the major cause of mortality.

Liver function in cirrhotic liver is evaluated using different models, none of which is more useful than others in predicting of residual liver function after resection. Child-Turcotte-Pugh (CTP) [15] is the functional classification still widely used in most Western Centers: patients who fall within class A can be submitted to resection, even extended, with a low risk of liver failure, patients in class B are better candidates for non-surgical procedures (such as RFA, or transarterial chemoembolization), while those belonging to class C can only aspire to a transplant (Table 1) if within Milan criteria and good surgical candidates. However, the accuracy of CTP in predicting survival and treatment outcome has been questioned. Furthermore, this classification based only on few functional aspect of the liver is of limited utility in a decisional algorithm that must take into account also pathological aspects of the tumor.

For this reason, attempts have been made to integrate functional aspects of cirrhotic liver and tumor features. An example of these attempts is the Okuda classification (Table 2) [16] which combines tumor burden expressed as a percentage value of liver measure (< 50% or > 50%), with other functional and clinical variables: bilirubin and albumin levels, and the presence of ascites. Okuda's classification is certainly useful for predicting the risk of post-operative complications but not the results of long-term survival. In untreated patients with HCC on cirrhosis, this classification has proved to be highly predictive of survival.

Point	Bilirubin (mg/dL)	**Prothrombin time**	Albumin (g/dL)	**Ascites**	**Encefphalopathy (grade)**
1	< 2	"/> 70%	"/> 3.5	None	None
2	2-3	40-70%	2.8-3.5	Slight	1-2
3	"/>3	< 40 %	< 2.8	Moderate	3-4
Stage	Score				
A	5-6				
B	7-9				
C	≥ 10				

Table 1. Child-Pugh-Turcotte Score

In many Centers, especially Asians, CPT score is supplemented with the indiocyanin green clearance test (ICG) [17, 18]. Indocyanine Green dye is exclusively cleared from the blood by

Criterion	Cut-off	
	+	-
Tumor size (*)	"/> 50%	< 50%
Ascites	Clinically detectable	Absence
Albumin	< 3g/dL	"/> 3 g/dL
Bilirubin	"/> 3 mg/dL	< 3mg/dL
Stage I	No positives	
Stage II	One or two positives	
Stage III	Three or four positives	

Table 2. Okuda staging system. (*) Largest cross-sectional area of tumor to largest cross-sectional area of liver

the liver. A value of ICG at 15 minutes ≤ 14% is considered as predictive of a good functional reserve that allows resection of more than two segments according to Couinaud classification, both in patients in class A as well as for those in CPT class B [17, 19, 20]. Compared to only CPT score, ICG15r offers a prediction of the extent of liver resection [11] (Figure 1).

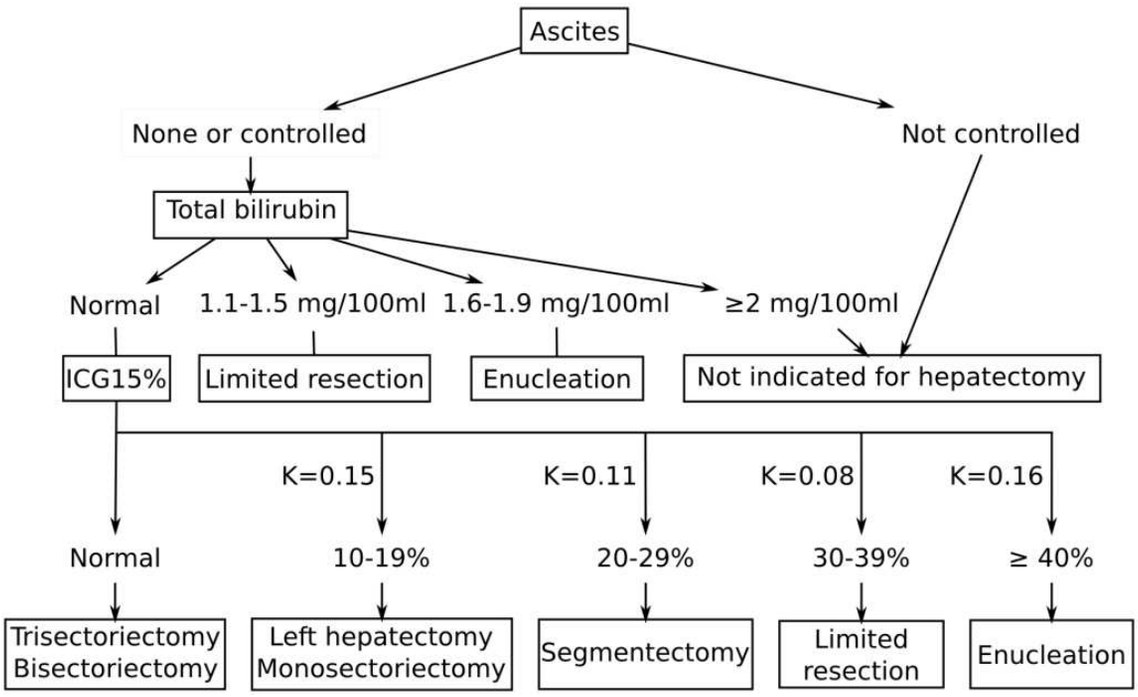

Figure 1. Possible extent of liver resection based on ICGr15 test.

It should be noted that these methods of evaluating liver function do not directly consider the presence and degree of portal hypertension, which instead is withheld as an high risk factor of post-operative morbidity in most Western Centers. Guidelines of the 'European Association of the Study of the Liver (EASL 2005) in fact, strongly recommend to preclude resection to

patients with portal hypertension (PHT) with hepatic venous portal gradient (HVPG) > 10mmHg [5, 21, 22]. According to EASL guidelines, direct measurement of veno-portal gradient is more appropriate than an indirect assessment for the presence of esophageal varices, splenomegaly, and thrombocytopenia [23]. Recently hepatic elastography, which is a measure of the parenchymal "stiffness" would seem to linearly correlate with the values of HVPG, and may be considered as a simple alternative to the direct measurement [24, 25].

Notably, in late 1990s, another classification was proposed, named Barcelona Clinic Liver Cancer (BCLC) staging; which takes into account both variables linked to the tumor, and patient's conditions (CTP), to be also used as a treatment alloction system (Table 3) [5].

BCLC stratifies patients depending on the size and features of the tumor in four categories or stages: early stage (quite broad: single tumor up to 5 cm in diameter or up to three HCC with a diameter of <3 cm), intermediate stage, advanced and terminal stages. For each category, after considering the performance status, values of bilirubin and presence or absence of portal hypertension, each patient is assigned to a specific treatment modality (resection, transplantation, percutaneous treatment (PEI, RF, MW) which should offer the expectation of survival and treatment outcome.

Stadio	Tumor features	Clinical features
Stage A (EC early)		
A1 PST 0	Single tumor	Portal hypertension absent, normal bilirubin levels
A2 PST 0	Single tumor	Portal hypertension present, normal bilirubin levels
A3 PST 0	Single tumor	Portal hypertension present, abnormal bilirubin levels
A4 PST 0	3 nodules less than 3 cm	Child Pugh A-B
B (EC intermediate) PST 0	Multinodular	Child Pugh A-B
C (EC advanced) PST 1-2	Vascular infiltration and extrahepatic extension	Child Pugh A-B
D (EC end stage) PST 3-4	Any	Child Pugh C

Table 3. BCLC staging system (Barcelona Clinic Liver Cancer). PST: performance Status Test.

Notably, the American Association for the Study of the Liver guidelines (AASLD) [26], adopted BCLC HCC staging. The Asia-Pacific Association for the Study of the Liver (APASL) [27] maintained a bolder position: it does not evaluate a "functional reserve", and even puts a limit in the presence of portal hypertension, reflecting different development experience in Eastern Centers. The gap between the two guidelines is expanded even more if it considers the tumor burden, in fact AASLD guidelines recommend liver resection only in the presence of a single HCC, while APASL guidelines allows resection if HCC is confined to the liver, if the portal

trunk is patent and the resection technically feasible, verbatim "Liver resection is a first-line curative treatment of solitary or multi-focal HCC confined to the liver, anatomically resectable, and with satisfactory liver function". This recommendation is obviously very different from that of the AASLD, verbatim "Patients who have a single lesion can be offered surgical resection if they are non-cirrhotic or have cirrhosis but still have preserved liver function, normal bilirubin and hepatic vein pressure < 10 mm Hg".

Thus, HCC staging and treatment allocation reflect a certain methodological variability [28] determined by ethical and social influences, and different practical needs of the different health care systems worldwide, which ultimately produce center-specific selection criteria.

4. Indication to liver resection

Resection for HCC is placed on the basis of two preliminary "technical" considerations:

1. Amount of liver function reserve and value of residual liver volume (RLV).
2. Anatomical location and extent of the tumor.

Single HCC below 5 cm, or multifocal HCC (not more than three tumors) without vascular invasion and with limited dimensions (<3 cm each), offer very good survival results that reach 50% at 5 years [29–31], and up to 70% at 5 years in a category of patients with normal bilirubin values and absence of portal hypertension [5]. In view of these results, there is a rather frequent disease relapse, estimated in terms of 50% at 3 years, 70% at 5 years and > 80% at 10 years [29–32]. Since these hopeful survival results (in particular for single HCC < 3 cm) were consistent with those of percutaneous ablation therapies, and slightly lower than those of transplantation, the choice of the procedure essentially depends on the experiences of the treating center [26].

The best results in terms of survival and low disease recurrence are offered by transplant specially in cases with established cirrhosis, even if, on a basis of "intention-to-treat" comparison the difference tends to be closer [33]. However, the option of liver transplantation is clearly limited by the shortage of organs supply. In 2010, based on the Organ Procurement and estimated Transplantation Network (OPTN), average waiting list time ranged from 140 days for American Indians up to 651 days for Hispanics [34]. Depending on the wait time period and the selection criteria used, the dropout rate for patients with HCC awaiting LT ranged between 12% and 38% [10, 35–37], and was essentially linked to tumor progression. Therefore, for early stage HCC transplantation should be reserved for those patients with poor liver function (eg CPT class C), and/or with evidence of portal hypertension. Since the report from Mazzaferro on the results of liver transplantation in a very well defined category of HCC, with actuarial 4-year overall survival of 85% and disease-free survival of 92%, subsequently confirmed by others, the "Milan criteria" [9] has marked an important turning point towards a more homogeneous transplant indication. Subsequently, other centers [38] have attempted to expand these criteria with fairly consistent results. However, the favorable results of transplantation for HCC within the Milan criteria must be considered very carefully, because it may be influenced from a selection bias. In fact, stratifying patients for factors other than

size (for example for the presence of vascular invasion), survival curves between OLT and LR showed a similar trend [39]. Many high volume centers for HCC treatment reported that patients eligible for OLT (within the Milan criteria), but subjected to liver resection showed 5-year actuarial survival rate of about 60-70%, [6, 8, 40–45], in particular in a subgroup of patients without vascular invasion [39, 42–48].

Taking into account these observations, it seems appropriate to offer hepatic resection to patients with preserved liver functions who may be also eligible for transplantation, thanks to the rapidity of care, the greater simplicity of resection compared to transplant, and the lower rate of post-operative morbidity and mortality. Furthermore, it must be considered that transplant exposes patients to the risk of toxicity and potentially fatal infections related to immunosuppressive therapy, and predispose to the development of "de novo tumors".

In contrast, as previously mentioned, resection is associated with a higher recurrence rate (50-70% at 5 years) given the persistent background defect of the underlying liver disease that led to HCC development in the first place. Liver recurrence could be managed surgically (with a re-resection) in selected cases, or through the use of percutaneous ablative therapies, or by mean of “salvage transplant”. Recurrences rates are lower if tumors are within the Milan criteria could benefit after orthotopic liver transplant as well as from split liver transplantation (SLT), the latter, using of a portion of liver from a living or dead donor, allows a more rapid access to liver transplantation. Two recent studies showed 5-year survival, morbidity and recurrence rate after salvage transplant to be similar to OLT performed as first choice [41, 49].

Recurrence is influenced in part by HCC pathological criteroa such as satellites nodules, vascular invasion, and poor histologic grading G3-G4. Translational research aimed at identifying molecular characteristics of HCC predictive of high risk of recurrence will be promising to avance this area of clinical challenge. Thus far, different chemoterapeutic agents have been tested in the adjuvant setting to reduce the recurrence rate. However, the small numbers of patients and the confounding variables did not lead to conclusive results.

The evidence gained to date for reducing the risk of recurrence has been linked to the surgical technique details. In particular, during the exploratory time, intraoperative ultrasonography should be systematically used for the correct evaluation of the position of the lesion, for the exclusion of further lesions not identified at pre-operative imaging, and yet for a correct evaluation of the vascular anatomy (Figure 2). It is estimated that 22 to 35% of the planned resections could change as a result of the IOUS examination.

HCC tend to permeate portals pedicles causing "anatomical" metastases or tumor thrombi that in turn are responsible of liver metastases (Figure 3). For this reason, many surgeons prefer to perform anatomical segmental or sub-segmental resections rather than atypical or wedge resections to ensure the inclusion of any microscopic satellite nodules, and tumor segmental embolization [50]. The advantage of anatomic resections remains valid, even in cases of multifocal lesions, as an alternative to extended resections such as hepatectomy or extended hepatectomy, given the advantage of preserving the hepatic functional reserve [51]. In the case of small centrally located HCC, and/or HCC proximal to major vascular pedicles, extensive resections are required [52], but alternatively bi- or three-segmentectomy whenever feasible,

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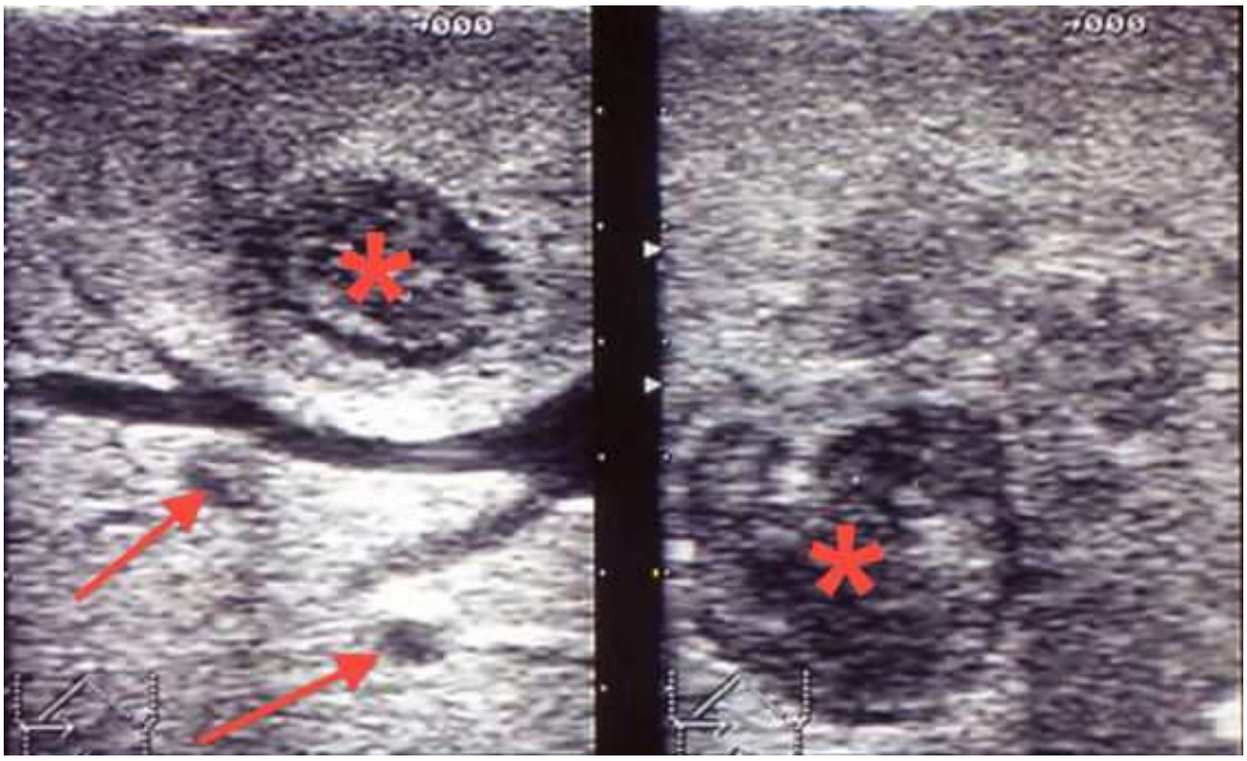

Figure 2. Intraoperative ultrasound examination showing a small HCC of 2 cm (star mark) located in the eighth segment and two minimal HCC (5 and 4 mm) (arrows) in the contiguous seventh segment. The planned resection of the eight segment was changed to a bisegmentectomy of 7+8.

offers the same oncologic advantage, and at the same time allows a second surgical approach in case of relapse. Central resection (segments 5, 8, and 4), anterior-central resection (segments 4b and 5), posterior-central resection (segments 4° and 8), and lateral-superior bisegmentectomy (segments 7 and 8), and inferior-right bisegmentectomy (segments 6 and 5) represent an economic alternatives to standard right hepatectomy.

The segmental nature of the liver has been reported by Bismuth [53] who described eight segments, each of which is provided by an independent artero-portal and biliary pedicle. Segments are easily identified by anatomical landmarks, or through the intraoperative ultrasonography study of the portal branches distribution. A clear segmental demarcation could be obtained through by ultrasound-guided direct puncture and flushing of the portal branch with intravenous dye (methylene blue) tattooing the liver surface corresponding to the perfused district; using small bilumen-catheters equipped with inflatable balloon, and the Seldinger technique it is possible to simultaneously tattooing the liver surface (Figure 4) and occluding the vascular lumen in order to stop blood flow to the segment, minimizing blood loss, and theoretically reducing the risk of retrograde embolization from the tumor.

In general HCC ≤ 3cm can be treated with a segmentectomy, or with sub-segmentectomy, HCC 3-5 cm with segmentectomy eventually extended to contiguous subsegments, HCC> 5 cm may require more extensive resections in order to provide a free margin from neoplasm of at least 1 cm (Figure 5).

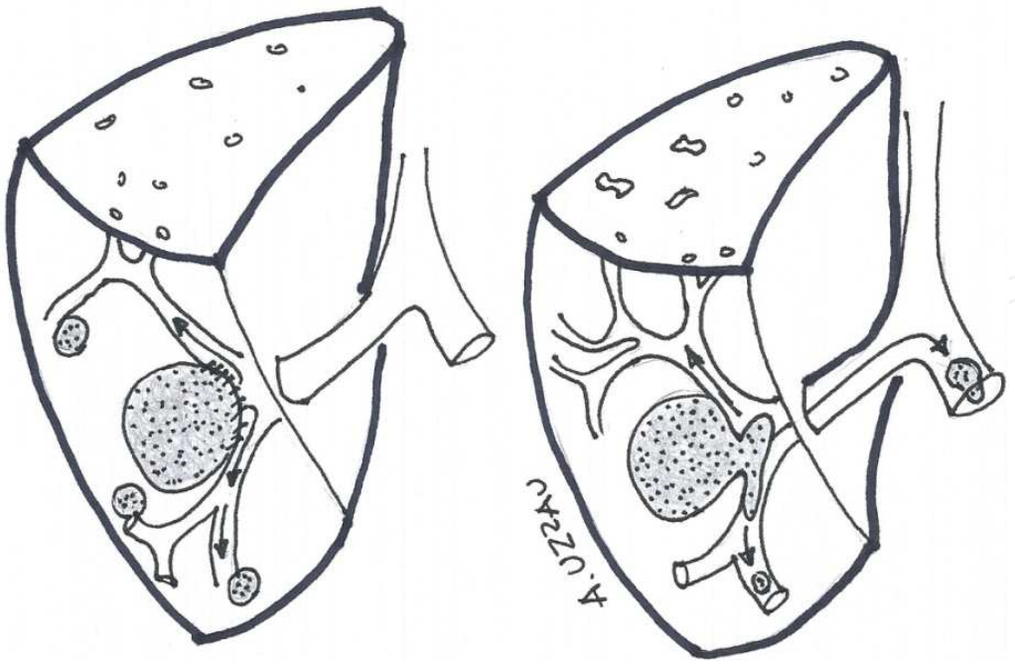

Figure 3. Modality of intrahepatic spreading of HCC. Tumor infiltrating sub-segmentary portal branches and delivering tumor cells to the perifery (intra-segmental diffusion) (left). Tumor thrombus has invaded a portal pedicle and becomes a source of dissemination at distance (intra- extra-segmental diffusion) (right).

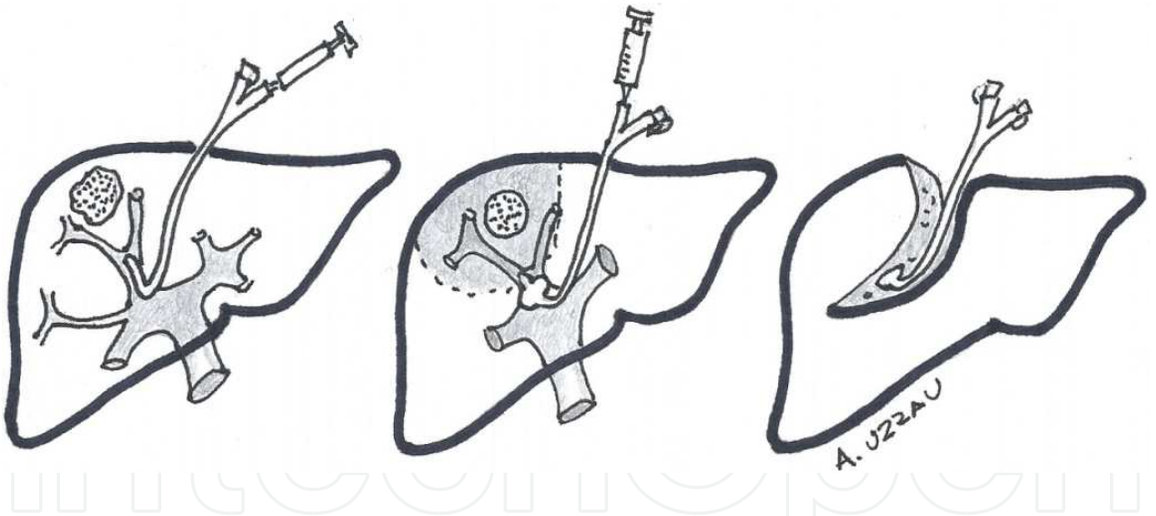

Figure 4. Technic of tattooing liver segment. Staining a segment through a bilumen catheter introduced according to Seldinger technique, after direct puncture under US guidance of a segmental portal pedicle (left). Blood flow occlusion inflating the balloon (optional) (center). Division of the parenchyma in segmental ischemic condition (left).

With regard to the definition of the so-called "high-risk HCC", it is still controversial. The high-risk HCC could be defined as:

1. "large", those > 5 cm in diameter (Figure 6). Large HCC increases the risk of vascular infiltration, worsening the prognosis. Even 10 years ago, 5-year survival after resection was no more than 33%. Today survival rate for large HCC without vascular infiltration are reported to be about 70% at 5 years [54] and 45% for so-called "giant HCC" (> 10cm) [55].

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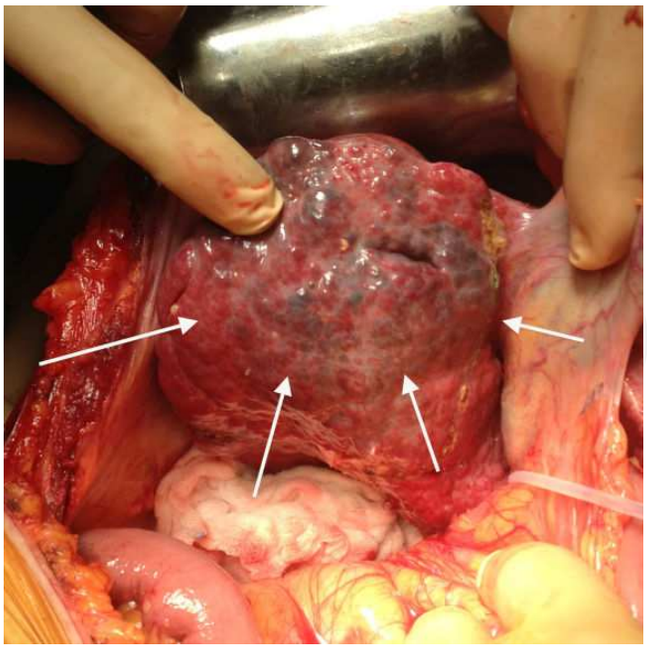

Figure 5. Tattooing of sub-segment of the fifth segment for a small HCC deeply located.

2. "multifocal tumors". Multifocality was considered for a long time as a contraindication to surgical approach, since it is associated with a poor prognosis. The only feasible treatment within the limits of small dimensions (3 nodules < 3cm each) is liver transplantation. However, many patients do not fall within the selection criteria and about 20% of those selected experience progression and dropout from the waiting list. Thus, surgical resection for patients with preserved liver functions may be the only curative option for multifocal HCC. Global survivals from 29.9% to 58% are reported at present, depending on the selection criteria [56, 57].

3. "macroscopic portal/hepatic vein involvement". This condition indicates the worst prognosis with a life expectancy of a few months in the absence of treatment.

In general, resectability for high-risk HCC is considered in absence of extrahepatic disease (lymph node metastasis or extrahepatic hematogenous spread and contiguous organs involvement), and in presence of preserved liver function. Due to the size, number, location and vascular involvement of the tumor, major resections or multiple resections are required, and are often associated with vascular reconstruction procedures. Limits to indication are the percentage value of the estimated remnant liver, and feasibility of vascular reconstruction. This configure a complex liver surgery that exposes at significatively higher morbidity/mortality risk and different survival rates depending on specific Centers selection and influenced by three main prognostic factors: grading, vascular infiltration, and size of the tumor. However, if resection is technically feasible, long-term survival for these patients is better than second-line therapy as trans-arterial chemo-embolization (TACE) [58, 59].

For multifocal and bilobar HCC although there are no randomized trials,there is anevidence of cohort studies that rported successful resection in select cases [60, 61]. Resection can be

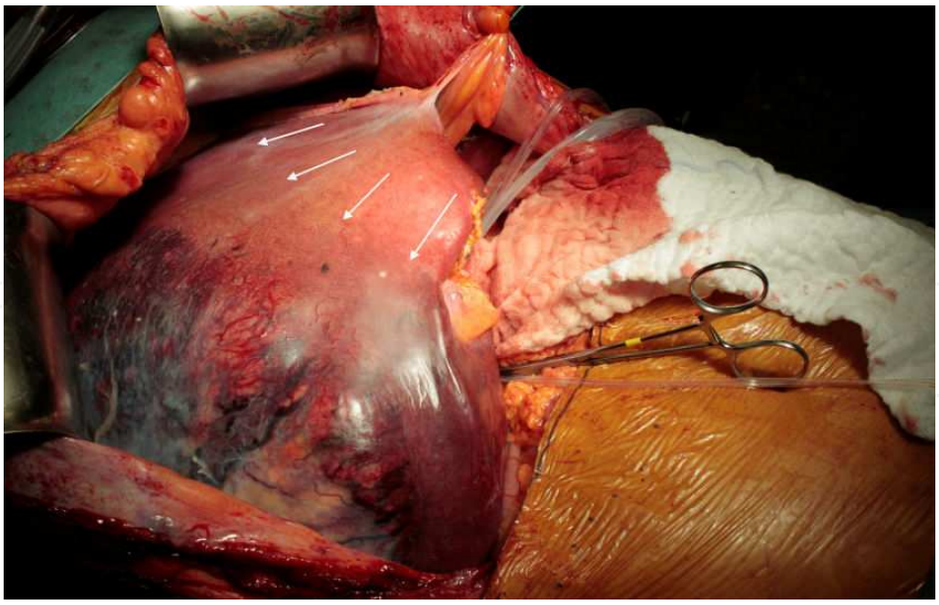

Figure 6. A case of very large, or so-called "giant HCC" which measured > 30 cm in diameter and weighted 5 Kg, involving the entire right hepatic lobe. The tumor did not involve the portal trunk and the left lobe was hypertrophic. Note the ischemic demarcation line (arrows) after selective right pedicle clamping.

combined with intraoperative ablation (RFA) expanding the rate of curability. Overall 5 years survival between 39% and 58% for large, multifocal and vascular infiltrating HCC [57, 58, 62–65] compared with the results of TACE overall survival of 24-63% at 2 years, and lowest rate of survival at 5 years [66–68].

Recently, Delis [69] compared a group of 59 patients within the UCSF (abbreviation needs to be defined..) liver transplant criteria (single tumor ≤6.5 cm, or three or fewer tumors of which the largest ≤4.5 cm and the sum of the tumor diameter ≤8 cm) [38] and another group of 27 pateints who exceeded these criteria: all patients underwent hepatectomy or extended hepatectomy with no mortality, but with higher rates of complications in the group that exceeded the UCSF criteria. 1, 3 and 5 years disease-free survival were 66%, 37% and 34%, respectively, in the first group and 56%, 29% and 26%, respectively, in the second group ($p < 0.01$), and the rate of recurrence was significantly higher in the second group, 74% vs 69% ($p < 0.002$). Vascular invasion was a strong predictive factor of intrahepatic and distant recurrences. Therefore, major vascular invasion is considered a contraindication to surgery and transplant in many surgical centers. Ikai [62] reports results of 66% and 43% 5-year survival in HCC with and without vascular infiltration, and found better survival values for the cases with tumor invasion of the portal branches of 2nd and 3rd order compared with invasion of the portal trunk or main branches, or contralateral infiltration. The recurrence rate was high (percentage??), but a considerable proportion of cases may be candidates for re-resection or ablative treatments. In the presence of tumor invasion of the portal trunk, 5-year survival of 26.4% is reported (thrombosis with portal infiltration) and 28.5% ($p = .33$) (without portal infiltration) [70]. According to some authors pre-treatment with TACE before resection can increase the global values of 5-year survival up to 42% that is a value significantly higher than 7% observed in non resected patients [71]. Resection and reconstruction of the portal trunk or

of the main portal branches represent a very small percentage of the total resections, but they impose considerable technical difficulty because they require mobilization of the portal vein to the pancreas, an accurate posterior skeletonization, and dissection of the contralateral portal pedicle before the venotomy.

In the presence of hepatic veins involvement resection also extended to venous segments is accompanied by global survival at 1 and 3 years of 88% and 50% respectively, with mortality rates of 12% [72]. These are very selective indication procedure, which must be addressed at highly skilled centers in the hepato-biliary-pancreatic surgery.

In conclusion, for high-risk HCC there are no guidelines supported by strong scientific evidence at the moment, but nevertheless, resection is offered more frequently in both Eastern and Western Centers as well as in Academic Centers with a high volume of liver surgery [73–75].

5. Technical details

Major resection, defined as the resection of more than two segments (on liver with chronic disease), does not involve particular risks of liver failure in patients with preserved functional reserve (CTP class A), which can tolerate even more extensive resections, such as right or left hepatectomy. However, except for cases of large HCC where the resected liver accounts for a small proportion of functioning liver parenchyma, in other cases it is appropriate that a greater hepatectomy is replaced by more limited resections, allowing to reduce the risk of postoperative liver failure, and maintaining the chance of a new intervention in case of recurrence.

As aforementioned, the choice of a segmental resection is standard because it reduces the incidence of early complications, such as seromas, abscesses and in particular biliary leak. This aspect should not be underestimated since postoperative infection could lead to increased risk of liver failure.

An adequate knowledge of the vascular anatomy of the liver, the improvement of surgical technique and post-operative care have allowed to extend resections for large tumors, select cases of majorvascular involvement, saving the functioning segments, such as the salvage of segment 6 to preserve the portal postero-inferior pedicle, or reconstructing hepatic vessels in order to avoid vascular congestion of residual segments and/or sectors (Figure 7). Vascular reconstruction can be of direct-type as hepato-caval, or with prosthetic interposition (generally Gore-Tex), or venous segment interposition (portal or gonadal). This procedure can be performed with direct vascular control, or with ex-vivo technique using veno-venous bypass. Vascular reconstructions have the main purpose of avoiding the congestion of segments that have no other way of direct outflow [76]. For these techniques a complete study of vascular distribution preoperatively with CT-angiography and intraoperatively by mean of ultrasonography is mandatory.

Intraoperative bleeding represents a further technical problem., In fact, blood loss affects both the patient outcome in the short term, as well as the long-term survival and relapse. In the case

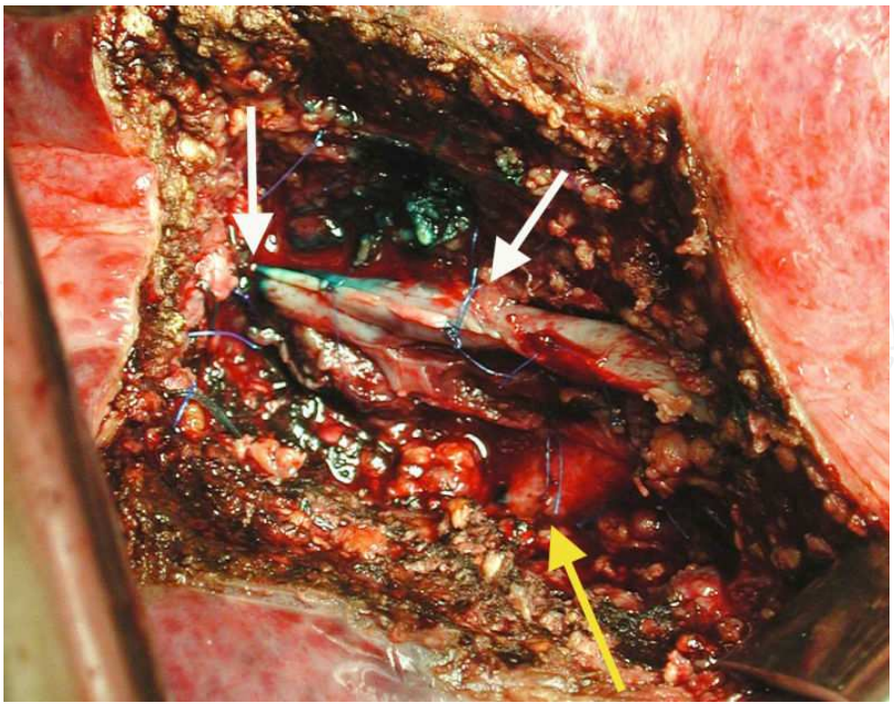

Figure 7. Direct reconstruction of the middle hepatic vein (white arrows) after resection of HCC situated between segment 8 and 4a. The yellow arrow indicates the upper segmental branch for segment 8.

of cirrhotic patients, bleeding is a cofactor of liver failure. Currently in high volume centers for liver surgery, 50-70% of resected patients do not require blood transfusions.

To limit blood loss, Pringle maneuver or clamping the portal triad are the technique most commonly used. Intermittent clamping of the hepatic hilum is preferred in cirrhotic patients compared to continuous clamping aimed to limit ischemia/reperfusion damage. Typically, clamping that determines a state of warm ischemia, is prolonged in cirrhotic up to 15 minutes. In the case of prolonged resection times clamping can be repeated with periods of unclamping (reperfusion) of 5 minutes (intermittent clamping). To limit the risk of ischemia/reperfusion damage many surgeons employ the technique of pre-conditioning, which consists of 10 minutes clamping followed by 10 minutes reperfusion, which precedes the definitive clamping. Pre-conditioning is believed to adapt liver parenchyma to warm ischemia thus reducing the damage of ischemia/reperfusion. In fact, there is much evidence of this advantageous use of the pre-conditioning in animal studies. However, evidence from few clinical studiesdoes not conclude potential definite benefit in humans [77–79].

An elegant and effective alternative to the Pringle maneuver is vascular direct control by means of ligation and division of the portal and arterial branches of the hepatic lobe to be resected if a hepatectomy is planned, or its selective clamping in the course of segmental resections; thus maintaining blood flow to the contralateral lobe. The selective exclusion of blood flow is confirmed by a change in color (ischemic demarcation) on the surface of the liver lobe excluded. Typically, if resections are performed with vascular control outset, the hepatic vein drainage is identified and secured too, thus causing a total parenchymal ischemia. Under certain

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favorable circumstances of anatomical dissection (easy hilum), inflow vascular control can also be obtained on second order branches (sectorial pedicles) determining a super-selective ischemic control.

Clamping of the hepatic vessels is generally employed during major resections, while it is not necessary if a small segmental resections, or wedge and laparoscopic resection are carried out [80–82].

The interruption of the blood flow from the hepatic pedicle effectively reduces bleeding during transection; however, bleeding could still results from the hepatic veins branches. To limit this further source of bleeding, it is useful to conduct resection under low value of central venous pressure (PVC) at less than 5 mmHg, and to place the patient in 20-25° Trendelemburg decubitus. The value of CVP in fact is reflected both at the level of the hepatic veins as well as at the sinusoidal compartment level, and blood volume lost during resection well correlates with the value of CVP [83–86].

Intraoperative control of bleeding is further optimized by the use of different instruments of parenchymal dissection, all aimed at containing bleeding from venular or sinusoidal origin. Classical hepatic dissection is carried out through parenchymal crushing by means of the Kelly or Klemmer clamps (crushing clamp technique): clamp pressure fractures the parenchyma leaving uncovered blood vessels that, depending on the size, are secured by mean of coagulation device or sutures or clips. Alternatively one can employ tools that divide the parenchyma in a gentler manner, through the ultrasonic dissector (ultrasonic dissection - CUSA-), bipolar current instruments (LigaSure), or radio frequency device (Harmonic Scalpel), to list a few examples. Although simple to use, the usefulness of these instruments is not clearin terms of blood saving or shorter time of resection[87].

Another technical consideration related to expanding the possibility ofresection even in those cases in which the total liver remnant volume is < 30% in healthy liver or < 35-40% in cirrhotic liver is expected, which are the limits generally accepted to contain the risk of postoperative liver failure [88, 89]. It is in fact possible to increase the volume of the hepatic remnant through the mechanism of liver lobe induced hypertrophy occluding the contralateral portal branch, the so-called portal vein embolization (PVE). This procedure is generally carried out under local anesthesia, through the puncture of a portal branch under ultrasound guidance or by fluoroscopy, which is then occluded by different embolizatin materials. This technique determines a volumetric increase of the residual lobe of about 8 to 12% over the time of about 20-30 days. After PVE, the percentage of patients undergoing surgery ranges from 62 to 100% according to recent studies [90, 91].

6. Indication to orthotopic liver transplantation

Since 1968 the "European Liver Transplant Registry" (ELTR) records all data of liver transplants in 145 centers across Europe. These data give an overview on what is the trend of transplants in Europe during each period.

Both the number of centers and the number of liver transplants gradually increased, but after an exponential growth until the 80s, they reached a plateau that was maintained as shown by recent data (ELRT) with about 5800 liver transplants performed per year across Europe. Cirrhosis was the most common indication for liver transplantation (52%) rate, followed by primary tumors of the liver (14%, HCC 12.1%).

Indication for liver transplantation have significantly changed over time. Subsequently, the rate of liver transplantation for increased to 20% in late 1990s. Between 2000-2010, two groups of indications have increased: primary tumors of the liver (16%), especially HCC, and cirrhosis (53%), especially alcohol related (20%).

Transplantation for HCC has thus become a therapeutic approach more commonly used in Europe where it accounted for 25% of all indications for liver transplantation. Improvement of survival of cirrhotic patients given by the pharmacological control of HBV and HCV, has led to an increased rate of survival and lower rate of recurrent HCC. In fact, HCC has gradually become the most common complication in cirrhotic patients. In the last three years the number of patients with HCC in transplant list has grown dramatically: more than 30% in France, 26% in Europe, 34% in the United States [92, 93].

7. The role of liver transplant from living donor

Living donor liver transplantation (LDLT) is a practice used mainly in Asia, where orthotopic organs are not readily available. Its use was later extended to other countries, mostly in Europe and North America to compensate for the shortage of organs and the long time on the waiting list which leads to patients' death, or dropout for medical reasons or progression of cancer beyond acceptable transplant criteria.

The main requirement of the transplant from a living donor is the "donor safety", namely the protection of the donor. Although the risks of this intervention in specialized centers are very low, the incidence of death of the donor ranges from 0.15 to 0.30%, but can reach up to 0.50%. The concept of "double equipoise" was proposed to describe the balance that must be maintained between the benefits related to the survival of the recipient and the risk of morbidity/mortality of the healthy donor. For example, in Europe and North America transplantation for acute liver failure from a living donor is not accepted, as the mortality of the recipient in such cases is higher. Some studies have suggested a higher risk of tumor recurrence related to liver regeneration after transplantation using a hemiliver from living donor compared to cadaveric whole liver. Other studies have shown no significant differences related to the type of graft used, and the only risk factor appeared to be related to the timing of transplantation from a living donor (fast-tracked patients), a short interval between the diagnosis of HCC and transplantation whaich can lead to a greater risk of tumor recurrence in the short term related to the fact that the biological behavior of HCC has not yet fully manifested. For these reasons, it is generally required to have a wiat time ofat least three months between the diagnosis of HCC and transplant before offering a graft from a living donor. The transplant from a living donor is acceptable if the 5-year survival is

http://dx.doi.org/10.5772/55890

comparable to that of patients transplanted from cadaveric donor. The use of cadaveric donors in the event of failure of the graft is generally accepted. The need for re-transplantation is still very low however, and the survival after re-OLT is high. In patients transplanted for HCC from a living donor within regionally accepted criteria, re-transplantation for graft failure using a cadaveric liver is also possible and accepted by the scientific community. If the transplant from a living donor had been done over the criteria, re-transplant from a cadaver is not recommended [94–98].

8. Inclusion criteria

Currently, in many countries, the eligibility criteria for transplantation for HCC follow "Milan criteria" [9]:

- the presence of a single tumor of less than or equal to 5 cm in size;
- up to three tumors of size less than or equal to 3 cm;
- absence of extrahepatic or lymph node metastases;
- absence of tumor thrombosis of the portal veins, or hepatic veins per liver imaging.

The tumor should be considered unresectablebased on the location, major vessel involvement, or if the tumor is multifocal or the patient has advanced cirrhosis (Child class B or C) [9, 99].

The expansion of the Milan criteria with the criteria of San Francisco (1 nodule < 6.5 cm in diameter or multiple nodules of 4.5 cm in diameter with the sum of the diameters < 8cm) had mixed results in terms of survival (survival at 5 years of 50%); for patients with HCC outside the limits of the criteria of Milan, the survival tends to decrease mainly in the recurrence of disease. Survival that is reduced to less than 50% at five years after transplantation is considered not acceptable. Given the scarcity of available organs, many countries circumscribe selection of patients exclusively to the Milan criteria. In practice, the problem of the shortage of organs is the principal factor influencing the indications for transplantation. Therefore, it became mandatory to tranplant only patients who can reach an adequate survival.

The "United Network of Organ Sharing or UNOS" has rejected the use of CTP classification to prioritize HCC patients on the waiting list, who may have an increased risk of mortality while on the waiting list. The MELD system became the standard method for assessing the clinical severity of a patient potentially candidate for liver transplantation. It is based on a numerical score that takes into account the levels of serum creatinine, total bilirubin and INR. The score is calculated according to the formula:

9.57*log (creatinin mg/dl) + 11.2*log (INR) +3.78*log (Bilirubin mg/dl) + 6.43

This formula calculates the risk of 3-months mortality. Patients with high scores have priority on the waiting list for transplantation [100].

The limit above which a patient can be enrolled into a waiting list is of MELD 15; whenever the MELD is less than 15 the risk of the transplantation is certainly greater than the risk of mortality by three months in the absence of transplantation. Since patients with HCC often have a MELD < 15 and therefore a lower priority of transplantation, UNOS considered to assign all patients with HCC (T1-T2) a MELD of 22, regardless of the actual state of liver disease. This, however, several others factors are still considered.

In addition to the number and size of lesions (Milan criteria) and serum creatinine, bilirubin and INR (MELD score), great importance is also given to the values of the α-FP. Although there is not a cut-off default, in patients with cirrhosis and HCC, if α-FP levels is increasing by more than 15 microg / L per month, liver transplantation is associated with a 5-year survival of less than 54%. Consequently, α-FP is considered a marker of related HCC aggressiveness and therefore should be considered to select potential candidates [101].

9. Prognosis

The main causes of death after liver transplantation are:

- Perioperative generalized morbidity causes such as multi-organ failure, cerebrovascular, cardiovascular, pulmonary and renal complications (29%).
- Recurrence of the primary disease (20%), especially tumors (11%).
- Sepsis (18%), especially bacterial (9%).
- Technical complications (5%), especially bleeding and vascular disorders (3%).
- Rejection (4%), especially chronic (3%).

Intraoperative death and liver failure represent 3% of all deaths.

Over the past 10 years there is a decrease in mortality in the range of 16%.

Survival after transplantation account for 82% at 1 year, 71% at 5 years, 61% at 10 years, 51% at 15 years and 43% at 20 years.

Survival has improved over the time reaching 85% at one year in 2004, compared to 76% in 1990-1994 to only 33% in 1985 (please list reference(s)..). This improvement over the time is most evident in liver transplantation for liver tumor.

From 1988 to 2009, 5-year survival was statistically higher for patients with cirrhosis (72%) than in patients with primary liver cancer (52%). During the last 10 years, post transplant survival for cirrhosis and liver cancer tended to approach (73 vs. 64%).

Moreover, a recent multicenter study from Europe showed that cumulative 1 and 5 year survival for patients transplanted for HCC on cirrhosis is 86% and 70% respectively in patients within the Milan criteria. Patients beyond the Milan criteriahad an average overall 5-year survival of 61.5% (correct?) [92, 102].

Etiology of liver disease and (n. TX)	Years (1999-2009)			
	1 year actuarial survival (%)		5 years actuarial survival (%)	
	Graft (%)	Pazient (%)	Graft (%)	Pazient (%)
Acute hepatic failure (3449)	70	76	62	69
Colostatic disease (4675)	83	89	74	81
Congenital biliary pathology (2167)	84	90	79	87
Cirrhosis (25424)	81	85	69	73
Primary liver tumors (7640)	81	83	61	64
Metastatic tumors (361)	77	83	50	55
Metabolic diseases (2866)	82	87	72	79
Budd Chiari (400)	76	81	66	73

Table 4. Patients and graft survival over the last 10 years (adat from European studies of liver transplant for HCC (correct?). Modified from [92]

10. Follow-up and treatment of recurrence

The main concern for patients subjected to liver transplant for HCC is recurrence that occurs in 8 to 20% (reference). Recurrence usually occurs within the first two years and is associated with a median survival of less than one year from the time of diagnosis (range 7-18 months). The adoption of α-FP assay and imaging (ultrasound, CT and MRI) every six months in the course of the follow-up has resulted in early detection of recurrence, allowing for a possible treatment to more than 1/3 of the cases.

Recent studies have tried to identify the role of post-transplant adjuvant therapy, but results, while highlighting a benefit in terms of overall survival and disease-free interval, are not conclusive because of their variability in terms of chemotherapeutic regimen, dosage, inclusion criteria and end points.

Sorafenib is a tyrosine kinase multi-targeted inhibitor, approved for treatment of patients with advanced HCC. However, its use post-transplant is not permitted outside of clinical trials. Loco-regional therapies for HCC recurrence (RF, TACE) and resection have been used in patients with limited burden of disease and appear to be useful in selected cases. In conclusion, the HCC recurrence after transplantation provides surgery for resectable lesions or through loco-regional therapies or systemic therapies (including Sorafenib) for unresectable lesions. Liver re-transplantation for HCC recurrence is not established [103–106].

11. Summary

Surgical treatment of HCC has evolved over the last 20 years due to improvements in surgical technique, anesthesiologist care and in particular to more appropriate criteria for carrying out resection or liver transplantation. Using systematic screening of at-risk groups has increased the detection of HCC at an early stage, potentially curable.

Survival rates following HCC surgical treatments, which were disappointing in the past, are very high today exceeding 50% at 5 years, both with resection as well as with transplantation in the category of single and small HCC. The choice between transplant and resection is eventually related to liver function that may be compromised by coexisting cirrhosis, and the availability of grafts that is currently lacking.

The biggest flaw of hepatic resection remains its high rate of relapse of the disease. In part, due to true recurrence, and partly due to the emergence of new HCC. In this situation it is possible to consider a transplant rescue, a second resection or local therapy options if the disease is limited to the liver, or systemic therapies if metastatic.

A most relevant concern remains that of high risk HCC for which transplantation is precluded. In this category of HCC resection with very strict indications can still meet a decent expectation of survival.

Author details

Alessandro Uzzau[1*], Maria Laura Pertoldeo[1], Vittorio Cherchi[1], Serena Bertozzi[1], Claudio Avellini[2] and Giorgio Soardo[1]

*Address all correspondence to: alessandro.uzzau@uniud.it, alessandrouzzau@gmail.com

1 Department of Clinical and Experimental Sciences, University of Udine, Italy

2 Department of Biological and Medical Sciences, University of Udine, Italy

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