NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

HCC consensus meeting

Guidelines for the use of liver transplantation in small HCC

Introduction

According to the American Association for the Study of the Liver (AASLD) and the Barcelona Clinic Liver Cancer (BCLC) staging system liver transplantation (LT), radiofrequency ablation (RFA) and liver resection are considered curative treatments for patients with early stage HCC.[1,2] Within Europe 20% of patients undergoing LT do so for the indication of HCC and the rate is continuing to rise in a linear fashion. Although outcomes for LT in HCC show an acceptable survival rate of 62% at 5 years these results are inferior to other indications such as viral, alcoholic and cholestatic cirrhosis which are associated with survival rates of between 69 and 78% at 5 years.[3] In the setting of increasing prevalence of HCC in cirrhosis, organ shortage and inferior outcomes, the role of LT for all patients with HCC can be called into question especially where other treatment modalities exist. This is especially the case for very early or early stage tumours where 5 year survival rates comparable to LT can be obtained using liver resection (LR} or radiofrequency ablation (RFA).

Very early and Early HCC

Current imaging techniques and the use of surveillance ultrasound in high risk groups such as patients with cirrhosis allows for the diagnosis of HCC at an early stage.[4] Using the BCLC classification *very early stage* HCC is defined as a single nodule of <2cm presenting in a patient with well compensated liver cirrhosis (Childs-Pugh A) with a normal performance status. This class is deemed *stage 0* in the BCLC classification and is equivalent to T1 in the UNOS HCC staging system. *Early stage* (Stage A) in the BCLC system comprises tumours of <3cm or 3 nodules all < 3cm in patients with Childs-Pugh A or B and good performance status and is equivalent to T2 in the UNOS staging system. Within *very early* stage and uni-focal *early stage* tumours patients with normal portal pressure and well preserved liver function are considered candidates for LR whereas those with more advanced liver disease or portal hypertension are recommended to undergo LT unless precluded by the presence of co-morbidities, in which case they may be treated with RFA.[1]

Although LR or RFA is recommended first line treatment for patients with very early or early HCC many patients still undergo LT for this indication. The principle advantage of LT over LR or RFA is that it addresses both the treatment of the tumour and the underlying parenchymal liver disease resulting in a decreased risk of cancer recurrence and avoidance of liver failure. The main disadvantage of LT is that it is not immediate therapy and inevitably due to the shortage of donor organs, waiting time can be prolonged thereby exposing patients to the risk of drop out from the waiting list due to tumour progression or acquisition of adverse biological factors such as microvascular invasion (MVI) which may predjudice outcome. Furthermore patients with very early or early stage HCC are generally of robust health, due to well preserved liver function, and

are more often allocated marginal grafts which may also reduce the absolute benefit gained for LT. This is especially true of patients undergoing LT with donation after cardiac death grafts where the outcomes are compromised over and above the negative impact seen by using DCD in other aetiologies.[5] Therefore the optimal treatment of patients with small HCC (very early or uni-focal early stage) is not settled, especially as some series in well selected patients undergoing LR or RFA for small HCC have shown equivalent survival at 5 years to patients undergoing LT. The purpose of this guideline is to provide evidence based recommendations for the management of small HCC in order to 1) Maximise patient benefit and 2) Prevent the unnecessary transplantation.

Liver Resection for very early or early stage HCC

Historically LR has been the primary treatment modality for small HCC. The advantages of LR are that there is limited waiting time; and the tumour specimen is excised and can undergo full pathological assessment, which unlike ablative methods allows an estimate of the risk of recurrence. The drawbacks of LR are the relatively high recurrence rate, operative complications and persistence of the risk of future de-compensation from underlying liver disease.

In large series of patients undergoing LR the 5 year survival rates range from approximately 30 -70% with an operative mortality of typically < 5%,[6] at first glance these survival rates would appear to be inferior to post LT survival however the published series comprise a very heterogeneous group of patients often with disease outside Milan criteria making interpretation of outcomes difficult compared to LT . When analyses are restricted to patients with smaller unifocal tumours long terms results become equivalent to LT.

For instance in the early report by Poon et al patients with Childs-Pugh A cirrhosis undergoing LR for unifocal tumours had a 5 year disease free survival of 40% and an overall 5 year survival of 72%.[7] Size of the tumour is also an important determinant of survival. In a report of 169 patients solitary HCC undergoing resection Shi et al demonstrated a 5 year survival of 74% which improved to 100% in the group of patients with tumours < 2cm.[8] In a more recent study of 543 patients comprising cohorts from both the east and west the overall survival was 60% at 5 years in patients with tumours 2 cm or less regardless of whether they underwent anatomic or non anatomic resection.[9] The utility of resection for patients with HCC < 2cm has also been confirmed in a large series from two western centres which demonstrated that 5 –year survival rates of 63% can be obtained with limited morbidity and mortality, results in patients with the absence of portal hypertension (platelet count > 150,000 mm^3) and < 2cm HCC were excellent with 5 year survival in excess of 80%.[10]

There are no randomized controlled trials comparing LR to LT for small HCC and the impact of drop out on the wait list due to tumour progression hampers the direct comparison of the two treatment modalities. Using intention to treat analysis (ITT) can give a more accurate representation of the role of LR in small HCC. Llovet et al demonstrated that the 5 year ITT survival of patients with childs-pugh A cirrhosis undergoing LR for small (median diameter 33mm) was 51% which compared unfavourably to patient undergoing LT for similar stage disease. However when the analysis was restricted to patients with optimal characteristics (absence of clinically significant portal hypertension and a normal bilirubin level) the 5 year survival was 74% which compared well with the 5 year ITT survival of 69% in the patients undergoing

LT.[11] In a more recent ITT analysis from Spain, no difference in long term (5 and 10 year) survival was noted between patients undergoing LR for tumours < 2 cm compared to those undergoing LT. This study is notable for the fact that the waiting time for LT was quite short (88 days) which had the effect of minimizing drop out from the wait list.[12] It is conceivable that in centres with longer wait times that the use of LR may indeed be advantageous especially if waiting times are prolonged for more than 4 months.[13]

These data show that for patients with 2 cm HCC outcomes following LR are at least equivalent and in well selected patients (normal biochemisty and absence of portal hypertension) may even be superior to LT.

RFA for very early or early HCC

In the current BCLC algorithm RFA is proposed for the treatment of small HCC where the patient is not a transplant candidate. Similar to LR for small HCC, RFA is also immediate therapy but as opposed to LR, RFA is associated with less procedural morbidity and costs.[14] However RFA can be associated with increased rates of local recurrence due to incomplete ablation due to the failure to ablate a wide enough area which is especially apparent in the treatment of tumours > 3cm.

In a series of 100 patients with tumours < 2cm who were potentially operable treated with RFA as primary therapy the 5 yr survival was 68.5% comparing favourably with LT and LR.[15] Compared to LT in a markov model the use of RFA for patients with tumours < 2 cm was more cost effective than LT and results in the same average survival time.[16] The direct comparison of RFA and LR has been studied in only 3 randomised trials involving relatively small numbers of patients.[17,18] The results of these studies are conflicting reflecting in part the inclusion criteria of HCC up to 5 cm, multiple nodules and variations in the severity of liver disease. However a common theme is that RFA is associated with decreased recurrence free survival and after prolonged follow up LR is associated with better overall survival. Observational studies containing more patients allow stratification on tumour size. In a study by Peng et al RFA was associated with lower disease free survival compared to LR but overall 5-year survival (71.9% RFA, 62.1% LR) was similar despite the fact that patients undergoing RFA were older and had more advanced liver disease.[19] Similar results were reported by Wang et al who using propensity matching found that in patients with a single tumour <2cm the 5 year survival rates for LR and RFA were 91.5% and 72% respectively.[20] Taken together these data suggest that in well selected patients with very early stage (<2cm HCC) RFA is associated with at 5 year survival at least as good as LR. One disadvantage of RFA over LR in the management of patients who are potentially LT candidates is the inability to obtain pathological examination of the specimen. Histological analysis of the resection specimen has been proposed as a mechanism of selection of candidates for salvage LT however this area is controversial.

RFA is however, advantageous in patients who may be candidates for LT in that it does not alter their suitability for type/quality of donor organs.

Recommendation

Very early stage (Stage 0) HCC

Patients with very early stage HCC may not derive survival advantage from LT
LT is not recommended for patients with very early stage HCC
Patients with very early stage HCC can be effectively treated with LR or RFA
LR is preferable in patients with well compensated disease with the absence of portal hypertension as it affords the opportunity for histological examination of the specimen

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