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TOPIC HIGHLIGHT

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Surgical treatment for liver cancer

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Abstract

Primary liver cancer is amongst the commonest tumors worldwide, particularly in parts of the developing world, and is increasing in incidence. Over the past three decades, surgical hepatic resection has evolved from a high risk, resource intensive procedure with limited application, to a safe and commonly performed operation with a range of indications. This article reviews the approach to surgical resection for malignancies such as hepatocellular cancer, metastatic liver deposits and neuroendocrine tumors. Survival data after resection is also reviewed, as well as indications for curative resection.

Key words: Liver cancer; Surgical resection; Indications; Hepatocellular carcinoma; Colorectal liver metastases; Neuroendocrine tumors; Non-colorectal non-neuroendocrine

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INTRODUCTION

Over the past 25 years, hepatic resection has evolved from a high risk, resource intensive procedure with limited application, to a safe and commonly performed operation with broad indications. We have seen a dramatic improvement in perioperative outcome, including reductions in mortality, blood loss, transfusion rates, and hospital stay. These improved perioperative results are largely responsible for the emergence of hepatic resection as a viable and effective treatment option for selected patients with liver tumors. Continued advances in imaging technology, along with a heightened awareness of the clinical and tumor-related variables that dictate outcome, have allowed better preoperative assessment of disease extent and improved patient selection. Advances in other areas, such as minimally invasive and ablative techniques, have increased the treatment options and have had some impact on the approach to patients with liver tumors; however resection remains the most effective therapy. The current status of partial hepatectomy is not the result of any randomised trial demonstrating greater efficacy over another therapy and recurrence rates remain high. Further improvements in survival will require more effective systemic agents and as better adjuvant and neoadjuvant therapies emerge, the results of resection are likely to improve. The indications for its application will then perhaps extend to patients currently considered to have unresectable disease.

PRIMARY HEPATOCELLULAR CARCINOMA

Worldwide, primary hepatocellular carcinoma (HCC)

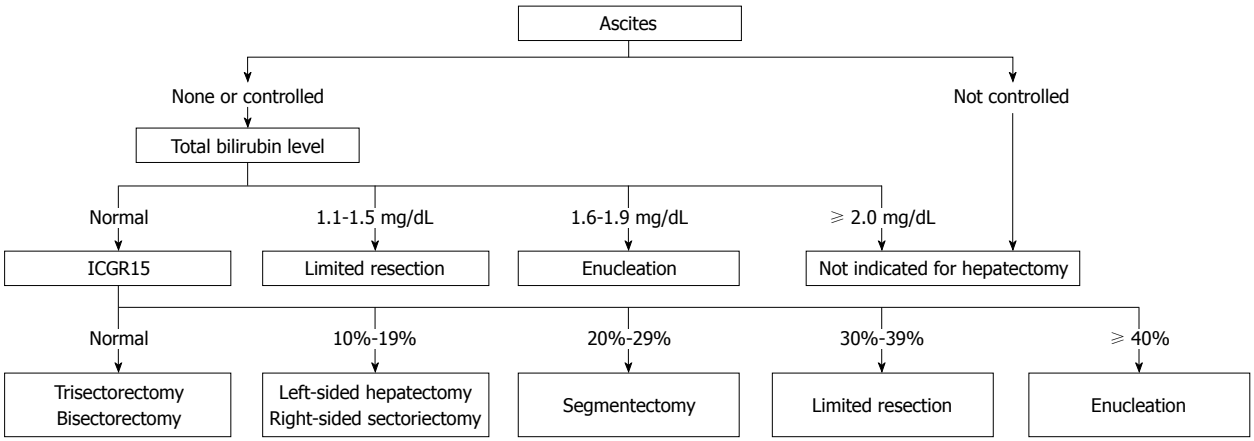

Figure 1 A decision algorithm for the selection of hepatic resection procedure[8].

is among the most frequently encountered solid organ tumors, responsible for approximately 250 000 new cases annually. Previously considered uncommon in western countries, the incidence and mortality related to HCC is increasing, due to the increasing incidence of hepatitis C virus infection. The treatment of HCC, unlike other hepatic malignancies, is often complicated by the coexistence of chronic liver disease and cirrhosis, the presence of which frequently limit treatment options. The only curative treatments are liver resection (LR) or liver transplantation (LT). Improvements in operative technique and postoperative care now mean that a 10% mortality rate for the resection of cirrhotic livers, with up to 30% to 50% 5 years survival rates are to be expected[1].

Indications and decision making for surgical resection

When HCC arises in non-cirrhotic liver, it is often diagnosed when the tumor becomes large and symptomatic. In the absence of diffuse bilobar disease, or extrahepatic metastases, aggressive surgical management is indicated. In this situation, removal of the tumor can be considered as these patients are usually in good general condition and surgical resection tends to involve only tumor mass rather than functional hepatic parenchyma. Although their survival rates are lower than patients with small uninodular tumors, resection is safe and they can expect a 5-year survival rate of up to 39%[2,3].

Most HCCs however occur in patients with chronic liver disease or cirrhosis. This often results in important changes in portal haemodynamics and a reduction in the functional liver parenchyma. The Child-Pugh[4] classification is the most useful tool in evaluating cirrhotic patients with impaired liver function. Other sophisticated techniques for determining hepatic reserve, for example the plasma retention rate of indocyanine green at 15 min (ICG15)[5], preoperative portal pressure assessment[6], and 3-dimensional-CT reconstruction of the liver, can be used in deciding whether to proceed with surgery[7].

Resection of HCC is only considered in Child-Pugh A patients. However, Child-Pugh is only used in cirrhosis and liver damage at resection can vary widely from periportal fibrosis to extensive fibrosis/cirrhosis. Therefore the operating surgeon must modify their technique using as many preoperative investigation results as possible before proceeding. A decision algorithm combining the presence or absence of ascites, total serum bilirubin levels and ICG retention at 15 min has been proposed by Makuuchi *et al*[8] (Figure 1). Patients with ICG15s of 20%-30% and more than 30% can only be subjected to one segmentectomy or limited resection, respectively[9].

Other modalities like hepatic venous pressure gradient have also been proposed. Patients with a gradient below 10 mmHg are eligible for resection and those above 10 mmHg are referred for non-operative management. Factors such as tumor size, the depth and distance of the tumor from the major vessels or the presence of intra-hepatic metastases should also be taken into consideration. Patients with large tumors require careful selection. In clinical practice all patients benefit most from multidisciplinary discussion.

LR for HCC in a cirrhotic liver is contraindicated in the presence of severe liver functional impairment such as ascites, jaundice, Child-Pugh B and C, and liver atrophy. In these cases, there is an increased risk of liver decompensation or failure in the postoperative period. Other factors that preclude resection are the presence of portal vein thrombosis (reflecting extensive disease)[10], lymph node metastases, extra-hepatic localizations and intra-hepatic diffuse disease. All these situations render any treatment palliative. The use of laparoscopic ultrasound as a preoperative assessment tool has further reduced LR rates by as much as 63%[11]. Table 1 summarizes the current indications for curative resection of HCC.

Results after surgical resection

The choice of treatment modality [e.g. hepatic resection, LT, or radiofrequency ablation (RFA)] can influence patient survival and this in turn is governed by the size and distribution of lesions. Improved patient selection leads to optimal survival rates for each subgroup of patients with HCC. The available literature is broadly divided into small (⩽ 5 cm) or 3 or less tumors (⩽ 3 cm)

Table 1 Indication for curative resection of HCC

Early stage HCC
Satisfactory liver function tests
Single nodule ⩽ 5 cm; 3 nodules ⩽ 3 cm
Okuda[59] stage 1 or 2
Child-Pugh[4] A or B
WHO Performance Score 0
No portal hypertension
No portal thrombosis
Normal bilirubin

HCC: Hepatocellular carcinoma.

and large (⩾ 5 cm) tumors, all with differing survival rates. Large multicentre series involving Asia, Europe, USA and France[3,12,13], have demonstrated 3-, 5- and 10-year hepatic resection survival rates of 38%-64%, 36%-41%, and 14%, respectively. Individual centres have published series of 5-year survival rates of 40%-50%[1,14-19], and 10-year survival rates of 8%-17%[16,20,21]. Table 2 shows the survival data for patients who underwent hepatic resection for HCC from large published series. When resecting early HCC, Poon *et al*[22] achieved a 70% 5-year survival rate and a 60% 5-year recurrence rate. Furthermore, when this cohort of patients experienced recurrence, 79% of them were eligible for salvage transplantation. It is important to note the perioperative mortality rates in hepatectomy patients range between 0.9%-6.4% and recurrence rates between 30%-55% (intra-hepatic recurrence being the most likely site)[3,13-16,20,23].

Disease recurrence

Microscopic vascular invasion, fibrosis and underlying cirrhosis have been consistently shown to be independent risk factors for decreased overall long-term survival in multivariate analysis[3,13-16,21,24,25]. Multiplicity and size of tumors (> 5 cm) are also negative predictors of prognosis. Margin positivity is associated with local recurrence[1,26], however the absolute width of the margin is less important[27,28]. Poon *et al*[22] also demonstrated in their paper that recurrence is most likely disseminated by both the portal venous system for intra-hepatic metastases and multicentric carcinogenesis for multi-segmental metastases, while proportionally less recurrence occurs locally. Therefore the authors propose that the presence of venous invasion and satellite nodules, factors that are incorporated in the pathological tumor-node-metastasis staging system, are more important predictors of recurrence irrespective of the margin status[29]. A surgeon's technique and the extent of tissue dissection has been shown to indirectly influence survival, as blood transfusion perioperatively predicts poor prognosis in multivariate analysis[18,24,29]. With regards to percutaneous RFA, the preliminary results from a recent nationwide study involving 7185 patients from multiple centres in Japan showed that surgical resection was a significant negative factor for recurrence as compared with RFA, however there was no difference in the overall survival rates[30].

LT

LT can have the benefit of being curative and treating any underlying cirrhosis, however there are many contraindications to transplantation, as well as a worldwide shortage of suitable allografts. Comparing orthotopic LT to LR in cirrhotic patients with small (⩽ 3 cm) uninodular or binodular metastasis, the 3-year disease-free survival rate without recurrence is significantly better in the transplant group (83% *vs* 18%)[31]. Mazzaferro *et al*[32] first published their results in 1996 where the 4-year survival rates post-transplant in selected patients with isolated small tumors (⩽ 5 cm) or two to three nodules ⩽ 3 cm were up to 75%. Since their landmark publication, LT is universally accepted as the first line treatment for patients who fulfil the Milan criteria.

The use of LR in the presence of cirrhosis is limited because of significant morbidity, which could be related to the laparotomy itself[33], and high recurrence rates. However, LT is also limited due to the shortage of organ donors[34] and the resultant risk of tumor progression with increased waiting times[33]. Controversy still remains over the treatment of patients with preserved liver function who could tolerate LT or resection. Therefore the use of primary resection followed by salvage transplantation (if required) for intrahepatic HCC recurrence has been proposed as an acceptable approach in such patients[34,35]. Some authors recommend the use of other neoadjuvant antitumoral procedures during the waiting time to LT, such as transarterial chemoembolization, percutaneous RFA or percutaneous ethanol injection. Whilst effective, they have the disadvantage of not being able to perform a full pathological examination of a surgical specimen, which allows assessment of prognostic factors of HCC (i.e. microvascular invasion, satellite nodules, tumor differentiation and molecular markers of recurrence), thereby further helping the transplant decision-making process[33].

SECONDARY TUMORS

Colorectal liver metastases (CLM)

Stage IV colorectal carcinoma is by far the most common indication for hepatic resection in Western countries. However no single consensus exists on the indications for surgical resection. Surgery is the treatment of choice in patients with colorectal cancer, but over half of all patients develop liver metastases. It has been postulated that because haematogenous spread usually occurs in a stepwise fashion, initially to the liver, with subsequent intra-hepatic spread *via* the portal vein and further spread to the systemic circulation, surgical resection of isolated hepatic metastases from colorectal cancer may be curative. The natural history of colorectal cancer is variable, with a median survival without treatment of only 8 mo. Patients with isolated metastases have a better prognosis than those with more extensive metastatic disease[36]. However few patients with liver only metastases survive for 5 years. Around 20%-30% of these are potentially

Table 2 Survival data for patients who underwent hepatic resection for HCC and colorectal liver metastases

	Number of patients	Morbidity (%)	Mortality (%)	Recurrence (%)	DFS 5 yr (%)	Survival (%)			
						1 yr	3 yr	5 yr	10 yr
Hepatic resection for HCC									
Ng *et al*[3]	784	23	2	34	40	88	76	58	NA
Esnaola *et al*[12]	586	NA	4	NA	NA	NA	NA	36	14
Wayne *et al*[13]	249	NA	6	NA	NA	NA	NA	41	NA
Shimozawa *et al*[16]	135	25	2	82	30	NA	73	55	18
Ercolani *et al*[17]	224	36	NA	42	27	83	63	43	NA
Borie *et al*[25]	107	NA	6	NA	NA	NA	NA	33	NA
Zhang *et al*[24]	412	NA	3	71	26	80	53	30	NA
Hepatic resection for colorectal liver metastases									
Gomez *et al*[50]	501	NA	4	87	13.4	NA	NA	62	NA
Arru *et al*[45]	297	17	1	NA	NA	91	51	28	17
Aoki *et al*[44]	187	NA	NA	74	19	NA	49	30	22
Fong *et al*[26]	1001	NA	3	NA	NA	89	57	37	22
Kato *et al*[60]	585	NA	NA	NA	NA	NA	NA	33	NA
Mala *et al*[61]	137	NA	3	NA	NA	NA	NA	29	NA
Rees *et al*[42]	107	3	1	NA	NA	94	56	37	NA

DFS: Disease free survival; NA: Not available.

resectable and the selection criteria for surgery are constantly changing[37,38]. Chemotherapy is palliative when used alone, but can prolong survival in inoperable disease. Used in combination with surgery it may prolong time to recurrence after resection or downsize to resectability in patients previously judged inoperable[39]. With regards to percutaneous RFA, a recent systematic review by Stang *et al*[40] found that RFA of unresectable CLM is a useful adjunct to surgery and/or chemotherapy and can prolong time without toxicity and survival.

Surgical resection of hepatic metastases can be undertaken safely in the majority of patients and the median postoperative 30 d mortality is 2.8%[26]. The most common reported causes of postoperative death include hepatic failure, postoperative haemorrhage and sepsis.

The outcome of resection of colorectal liver metastasis is encouraging, with postoperative mortality in large series ranging from 0.2%-3.5%[26,41-45]. The 1-year overall survival rate is 89%-97%[26,42,46]; while the 5-year survival rate ranges between 15%-50%[26,41,45,47-49]. Five years disease free survival rates are on average 19% in radically resected patients. Some studies with longer follow-up periods report a 10-year overall survival rate of 17%-33%[14,44,45]. The rate of complication in individual studies is more variable, ranging from 3%-17%[42,45]. The recurrence rate with 5-year period of follow-up is consistent around 62%-74%[44,50].

The factors which are predictive of poor prognosis include poor tumor differentiation[44,45,50], increasing size and number of metastases[26,42,44,50], Dukes' staging, presence of extra-hepatic metastasis (other than resectable pulmonary metastasis), elevated carcinoembryonic antigen (CEA) levels and positive nodal status. Fong *et al*[26] summarised the above with the Clinical Risk Score which includes 5 risk factors (size of metastasis > 5 cm, extrahepatic metastasis, disease-free interval between primary tumor to diagnosis of metastasis, multiple metastasis and CEA level greater than 200 ng/mL). A score of 5 is predictive of poor prognosis, whilst patients with 0-2 are more likely to have favourable outcomes. Gomez *et al*[50] also recently demonstrated in their paper that increased inflammatory markers and number of blood transfusions perioperatively are related to the early development of recurrence. Table 2 shows the survival data for patients who underwent hepatic resection for CLM from published large series.

Neuroendocrine tumors (NET)

Cytoreductive therapy is effective in the management of metastatic NET to the liver, independent of their functioning status[51]. In functioning tumors, clinical endocrinopathies are relieved in most patients and this response usually lasts for several months. Major morbidity and mortality are not greater than the average complication rate for resection for non-neuroendocrine metastatic tumors at major centres; therefore surgical outcomes appear to justify operative intervention[51]. Patients whose primary tumor can be controlled, whose metastases outside the liver are limited, and who have a good performance status are candidates for resection. Directed anatomic and non-anatomic hepatic resections and RFA therapy can effectively reduce the amount of active disease, thereby improving hormone control and patient survival, with very low morbidity and mortality in comparison to other tumor types[51]. A full symptomatic response in up to 90% patients with a median overall survival of 48 mo adds many months of symptom-free survival to the lives of most patients. In many patients undergoing a major hepatic resection, concurrent resection of the primary tumor is also performed[51]. Resection in selected patients is not more complicated or risky than resection for other metastatic tumors. In addition, endocrinopathies do not increase anaesthetic or operative risk in selected populations. The best post-operative

results are the product of managing these patients over time, becoming familiar with their clinical syndromes and ensuring the early detection of both local recurrence and the development of resistant disease.

After complete removal of the primary tumor, LT seems to be very attractive as a means of eradicating metastatic NET. Unfortunately, there is very sparse evidence for any benefit of LT over LR. Current indications for LT include those with unresectable disease, no extrahepatic or resectable extrahepatic metastatic spread, progressive hepatic metastases, refractory symptoms to medical therapy or interventional procedures, and deposits exhibiting Ki-67 levels < 10%[52,53]. It has also been suggested that LT should be reserved for patients with non-carcinoid (i.e. non-serotonin secreting) tumors, as the overall survival may be better than LR alone. In a recent article by Frilling *et al*[53], the 5-year tumor free survival was 48.3% amongst the 16 Type Ⅲ (disseminated metastatic spread) patients that they transplanted. They concluded that LT for metastatic NET achieves excellent long-term palliation for highly selected patients[54]. Current methods to detect the spread of NET disease that were not readily available in the past, such as magnetic resonance imaging (MRI) and indium-111 pentetreotide (Octreoscan), may decrease the application of LT and allow for a better selection of candidates. The option of LT is still open for improvement and is dependent on organ availability and better staging of the disease.

Metastases from NET are hypervascular thus favouring the application of MRI as the single imaging method. MRI not only evaluates the location and characteristics of the lesions, but also determines their relationship with major vessels and bile ducts. Spiral CT scan has also been used extensively in the past with acceptable results. Indium-111 pentetreotide functions on the basis of somatostatin receptors present in these tumors, but its use has not been established definitely in the work-up of these patients. The best use of indium-111 pentetreotide is in the evaluation of disease beyond the primary and liver locations, for example to exclude bone metastases. Its use therefore will likely affect the preoperative work-up of candidates for operative management.

In general, surgery is appropriate for patients with metastatic NET for the following two reasons: (1) many of them still have the primary tumor in place and resection should be undertaken to avoid acute complications and (2) the addition of adjunctive ablative therapies to surgical resection accomplishes the control of ⩾ 90% of the bulk of the tumor. It is important to note that even when complete resections are performed the recurrence rates for metastatic NET are extremely high (76% *vs* 91% for incomplete resection at 5 years)[55]; overall 5-year recurrence rates are up to 88%[51]. In practical terms, patients with metastatic NET are seldom cured. The best hope physicians can offer these patients is an extended survival period with minimal endocrine symptoms and decreased requirements of somatostatin analogues[51].

Non-neuroendocrine, non-colorectal liver metastases (NCNN)

The role of metastasectomy for colorectal and neuroendocrine liver secondaries is well established. Significant palliation and survival have been reported after aggressive surgical resection. The indication for the surgical resection of liver secondaries from NCNN tumors is less well defined. In the past, patients with metastatic liver disease were not considered curable and their life expectancy was limited. However, progress in chemotherapy has spurred the development of surgical strategies to cope with patients presenting with liver secondaries from other primary tumors. Diversity of tumor types and a wide variation in available adjuvant treatment schedules makes it difficult to draw conclusions from the published data, but LRs have been performed for metastatic spread from gastrointestinal stromal tumor, renal, lung, thyroid, parotid haemangiopericytoma, ovarian, cervical, Ampulla of Vater, pancreatic and melanoma primaries to name a few. Survival is directly related to the nature of the primary tumor. Reports to date suggest no survival advantage in resection of liver metastases from oesophageal, stomach, small intestine or pancreas. Indeed, 3 and 5 years survival rates for resected metastatic breast tumors are 53.9% and 24.6%, genitourinary tumors 50.4% and 37.8%, and leiomyosarcoma 63% and 36%, respectively[56-58].

CONCLUSION

Surgical resection is the mainstay of treatment for primary and secondary liver tumors. With the recent increased use of newer surgical techniques, for example laparoscopic LR using RFA for the transection of the liver parenchyma, morbidity and mortality rates from this surgery have improved. Patients with HCC meeting the local criteria for transplantation should be considered for this. Alternatively, if LT is not an easily accessible option or the patient is ineligible for transplantation, then hepatic resection and/or other antitumor treatments should be considered. The use of cytoreductive surgery in metastatic NET may successfully control symptoms and prolong survival. For patients with CLM, hepatic resection remains the best treatment option. The results for the resection of NCNN metastases are not as encouraging and are dependent on the tumor of origin.

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