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Treatment of hepatocellular carcinoma

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Abstract

Treatment options have largely been selected according to empirical criteria, such as the presence or absence of cirrhosis, number and size of tumors, and degree of hepatic deterioration and taking into account the local technological and economic resources. There are virtually no controlled studies comparing the efficacy of the available treatments, and the substantial heterogeneity of survival between control groups does not allow us to obtain therapeutic evaluation by comparing results of separate trials. The reassessment of treatment outcomes on the basis of intention-to-treat analysis yielded less encouraging figures. Hepatic resection is the primary option for the few patients with a hepatocellular carcinoma arising in a normal liver with well-preserved hepatic function and for patients with a single tumor, compensated cirrhosis and low portal hypertension who are not candidable to liver transplantation. The latter is the best treatment modality for patients with a solitary tumor < 5 cm in diameter or patients with less than three tumors < 3 cm, resulting in a 5-year survival of 75%. Locoregional ablative treatments are curative options for patients with a "resectable" tumor who cannot be offered transplantation or hepatic resection. The 5-year survival is approximately 50% but it copes with a high risk of tumor recurrence. Patients with advanced tumor disease cannot be offered curative treatments but only symptomatic treatments.

Keywords: Hepatocellular carcinoma; Hepatic resection; Liver transplantation; Percutaneous ablation

1. Introduction

Hepatocellular carcinoma (HCC) is often an asymptomatic and slow-growing, single tumor. However, there are HCCs that may develop as multinodular disease and grow fast (Okuda, 1992; Colombo et al., 1991). Since the widespread adoption of abdominal ultrasound scans (US) for screening high-risk patients, the number of patients with small tumors who are potentially operable has more than doubled (Okuda, 1992; Colombo et al., 1991). Nevertheless, it is still not clear whether mortality from HCC has been reduced in parallel. In fact, there is no controlled evidence that any of the available treatments increases the survival of HCC patients. The survival of untreated patients with a single small tumor (< 3 cm) arising in well-compensated cirrhosis (Child's–Pugh A) in one study was 25% at 3 years (Livraghi et al., 1995a).

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2. Selection of patient

Treatment options for HCC patients have been selected on the basis of the local resources and empirical criteria. The latter include the presence or absence of cirrhosis, number and size of tumor nodules, and degree of hepatic deterioration. Because of the wide variability in tumor growth, the predictive power of tumor size and number is weaker than the severity of liver impairment (Okuda et al., 1985).

Staging is a crucial variable in treatment outcome since many therapeutic failures have resulted from faulty patient selection. To assess the size and number of HCC, biphasic elical CT scan and magnetic resonance have been the first-line preoperative investigation, but these procedures may yield false negative results in up to 30% of patients with tumors less than 2 cm (Colombo, 1999). In fact, poorly vascularized small tumors escape detection by contrast enhanced methods, and only a few can be visualized by arterial portography. For staging patients' clinical status, the Child's–Pugh score system provides clinically relevant estimates. The degree of portal hypertension in patients with Child–Pugh A disease is a sensitive predictor of patient survival after resection, and should be included in the work-up of selected patients to be considered for surgical therapy.

3. Patients with normal liver

Hepatic resection is the primary option for the few patients with HCC, normal liver and well preserved hepatic function. In two studies (Ringe et al., 1991; Iwatsuki et al., 1991), the 5-year survival of such patients treated with hepatic resection was approximately 50%, compared to 20% with orthotopic liver transplantation (OLT). The good results with hepatic resection probably depend on the absence of cirrhosis, which allowed for extensive resection of the liver without affecting survival. The poor results with OLT probably reflected some bias in selection of patients, i.e. transplantation in patients with advanced HCC who were judged inoperable with resection. According to the European Transplantation Registry of OLT, 446 patients with HCC without cirrhosis underwent OLT between 1988 and 1994 with 36% 5-year survival. However, many of these patients had chronic viral hepatitis as well as the liver tumor.

4. Patients with cirrhosis and a small tumor

The functional capacity of the liver not involved by HCC is the major factor in these patients' prognosis. Thus, resection of the tumor confers substantial benefit for patients with small tumors and well preserved hepatic function, but leaves the patient at risk of portal hypertension and liver cell failure.

Liver transplantation eliminates both detectable and undetectable tumor nodes and all the preneoplastic lesions in the cirrhotic liver. Moreover, removal of the diseased liver reduces the risk of morbidity and mortality from portal hypertension and liver cell failure. Opposing these "pros" for OLT are several important "cons", i.e. shortage of donated organs, high costs of the procedure, stringent criteria for selection of patients, high risk of early tumor recurrence due to faulty staging of the disease and immunosuppression, and recurrence of hepatitis.

4.1. Orthotopic liver transplantation (OLT)

Overall survival after OLT has improved markedly since the introduction of more precise criteria for patient selection. The best long-term survivors were patients in whom HCC was not the primary indication for OLT but was discovered by chance as a minute nodule during examination of the explanted liver. In Pittsburgh (Iwatsuki et al., 1991), the 5-year survival of 16 such patients who underwent transplantation for chance-discovered HCC was as high as 90%. In Milan, 48 consecutive patients with viral cirrhosis and a single < 5 cm tumor or less than three < 3 cm nodes were treated by OLT (Mazzaferro et al., 1996). The 4-year actuarial survival was 92% for the 35 patients who at the operation were confirmed as having met the selection criteria, com-

pared to 60% for the 13 patients who did not, because they were found to have ancillary nodes.

Though the survival of transplanted patients seems to be largely influenced by tumor size and number, there is no general agreement on the ideal tumor size that entails the least risk of recurrence, mostly because small volume does not mean early biological stage in all cases. Between January, 1988 and June, 1994, the 5-year survival of 834 patients with HCC (7% of total) who were transplanted in 82 European Centers was 39%. This included the 54.5% survival of 176 patients in whom cirrhosis was the primary indication for OLT and 45.5% of 361 cirrhotics in whom HCC was the primary indication.

Vascular invasion by the tumor and perihepatic lymph nodes are thought to be crucial in tumor staging. Unfortunately, vascular invasion can be assessed only during the operation; lymph node assessment can be confidently done only during laparoscopy or laparotomy. In Hannover (Ringe et al., 1991), the overall 5-year survival was 15% in 61 patients with or without cirrhosis who were transplanted between 1974 and 1988, but 56% for patients with solitary small HCC and no lymph node metastases (TNM Stage I–II). Similar results were obtained in Pittsburgh (Iwatsuki et al., 1991): 71 patients with cirrhosis were transplanted and the 5-year survival for those in stages I–II and III was greater than 50%, compared to 11% for stage IV. These data should be cautiously interpreted as TNM staging is poorly applicable to HCC patients. In fact, stage II includes a heterogeneous group of patients, i.e. those with more than one small tumor, a tumor larger than 2 cm without vascular invasion and those with a small tumor with portal invasion that entails a poor prognosis. The most common cause of early death, i.e. within 3 months of OLT, was graft failure. In all studies, the most common cause of late death, i.e. from 3 months after OLT, was recurrence of the original tumor.

Factors associated with short survival after transplantation include distant metastases, lymph node involvement, bilobar tumors, tumor margin involvement, and vascular invasion (Ringe et al., 1991; Iwatsuki et al., 1991). One major obstacle to the interpretation of OLT results is the large differences between transplantation centers in terms of time-lag between candidacy and operation. Reassessment of OLT outcomes on the basis of intention-to-treat analysis has yielded less encouraging figures ($< 50\%$ survival after 2 years) (Llovet et al., 1999).

4.2. Hepatic resection

Hepatic segmentectomy and subsegmentectomy are the technical procedures of choice. The best results in terms of both short-term and long-term survival were for patients with a single tumor less than 2 cm in diameter. In 347 Japanese patients, the 5-year survival rate was as high as 60.5% (Tobe and Arii, 1992). Stepwise analysis showed the most valuable prognostic factor was portal involvement followed by tumor number, α-fetoprotein (AFP), tumor size, and cirrhosis. The best predictive combination of three factors was AFP, tumor size and number of tumors (The Liver Cancer Study Group of Japan, 1994). Metachronous multifocal tumorigenesis is another mechanism by which HCC may recur after resection, in the absence of portal metastases. In a series of 102 patients with tumors smaller than 3 cm, without venous invasion or intrahepatic metastases, recurrence was recorded in 68% 5 years after resection (Adachi et al., 1995). The Cox proportional hazard model indicated serum albumin and transaminases as independently associated with recurrence, suggesting that the state of the underlying liver parenchyma was a key factor in neocarcinogenesis. In fact, survival of patients undergoing hepatic resection is influenced not only by the tumor size and invasiveness, but also by the functional status of the liver expressed as the Child's–Pugh score. The 3-year cumulative survival was 50% for 78 Japanese patients with a single tumor and Child's A status, 35% for 26 with Child's B status and 0 for three with Child's C status (Nagasue and Yukaya, 1989). For 72 European patients, these figures were 51% for Child's A patients and 12% for Child's B–C (Franco et al., 1990) (Table 1). In patients with compensated cirrhosis, portal hypertension is the most reliable predictor of survival after resection: patients with a small tumor and less than 10

Table 1
Three-year survival of patients with a small HCC treated by hepatic resection, according to the degree of hepatic impairment expressed by Child's Pugh classes (A, B and C)

Liver stage (Child–Pugh)	Nagasue and Yukaya (1989)		Franco et al. (1990)	
	Number treated	% Alive	Number treated	% Alive
A	78	50	54	57
B	26	35	14	
			+	12
C	3	0	4	

mmHg hepatic venous pressure gradient had more than 50% 5-year survival whereas patients with higher gradients survived less (Bruix et al., 1996).

By "intention-to-treat" analysis, the 5-year survival of 35 patients with normal bilirubin and low portal hypertension who were treated by hepatic resection was 74% compared to 25% for the 42 patients with worst predictors. The comparison of OLT results in the same Center demonstrated that resection was superior to OLT for patients with good predictors. The latter treatment, in fact, gave 2-year survival of 54% due to prolongation of the waiting list from 62 to 162 days, causing the number of drop-outs to rise from 0 to 8 (Llovet et al., 1999). Thus, hepatic resection should be offered to carefully select patients with HCC who cannot be treated by OLT in the short-run.

5. Patients with cirrhosis not eligible for surgery

This is a vast category of patients with advanced age, deteriorated liver function, large tumors, tumors in strategic positions or associated clinical conditions which contraindicate surgery.

5.1. Percutaneous interstitial treatments

US-guided treatments include tumor injection with absolute ethanol (PEI), 50% acetic acid or hot saline, or tumor thermoablation with radiofrequency, microwaves or laser. In uncontrolled studies, survival was largely influenced by liver function, size and number of tumors. The 5-year survival of 293 Italian patients with Child's A cirrhosis and less than 5 cm tumor who were treated with PEI was 47%, compared to 29% for 149 with Child's B cirrhosis, and associated with a low risk of severe complications (1.7%) and mortality (0.1%) (Table 2). However, tumor disease recurred in virtually all treated patients, more often in those with high levels of serum AFP and those without peritumoral capsule or with cirrhosis (Livraghi et al., 1995b). In 60 randomly selected patients with tumors smaller than 3 cm and compensated cirrhosis, injection with 50% acetic acid (PAI) was superior to ethanol in terms of 2-year cancer-free survival (92 vs. 63%, $P = 0.02$), being particularly active in patients with hypervascular tumors (Ohnishi et al., 1996). The 3-year survival of patients treated with PEI was half that previously reported in comparable patients for tumor size and liver function, indicating that data on survival analyzed by intention-to-treat were less encouraging than previously thought. In a prospective randomized study of 86 patients with compensated cirrhosis and small HCC, radiofrequency was superior to PEI in terms of complete tumor necrosis (90 vs. 80%), and number of treatments (1.2 vs. 4.8), but it caused more complications (9.5 vs. 0%) (Livraghi et al., 1999).

Table 2
Five-year survival of patients with cirrhosis and tumors smaller than 5 cm treated by percutaneous ethanol injection (Livraghi et al., 1995b)

Liver stage (Child–Pugh)	Number of patients	% Alive
A	293	47
B	149	29
C	20	0

Table 3
Randomized controlled studies of transarterial embolization therapy in patients with advanced HCC

Author (year)	Rx	Number of patients	One-year survival		*P*-value
			Treated (%)	Controls (%)	
Pellettier et al. (1990)	TACE	42	24	31	ns
GETCH (1995)	TACE	96	62	44	ns
Pelletier et al. (1998)	TACE	73	51	55	ns
Bruix et al. (1998)	TAE	80	70	80	ns

TAE, transarterial embolization without chemotherapy.

5.2. Transcatheter arterial chemo-embolization (TACE)

TACE through the femoral artery leads to ischemic necrosis of the tumor and allows hepatic arterial injection of antitumor agents, which increases the local concentration of drugs and reduces systemic side effects. Mixing such anticancer drugs as doxorubicin, cisplatin or mitomycin C with Lipiodol, an iodized oily agent that remains selectively in tumors for long periods, may enhance the anti-tumor effect. This approach often gave an objective response, but significant prolongation of median survival has not been demonstrated.

In a large multicenter study in France involving 79 patients with unresectable HCC, TACE reduced tumor growth, but did not significantly improve survival (Pellettier et al., 1990) (Table 3). It remains to be assessed whether TACE prolongs the survival of patients with Child–Pugh A cirrhosis and one small HCC. TACE is contraindicated for patients with venous tumor supply, advanced liver deterioration, complete thrombosis of the portal vein trunk, renal failure or extrahepatic metastases.

5.3. Other palliative treatments

Systemic chemotherapy has been widely used to treat inoperable HCC, but the response rate is very low (20%). In the only randomized controlled trial (Lai et al., 1988), doxorubicin not only failed to prolong survival but also caused fatal complications due to cardiotoxicity in a number of patients. The possible sex hormone-dependence of HCC and the presence of tumor hormone receptors have suggested a potential for hormonal manipulation of tumor growth, particularly using anti-estrogens. However, in a large study of Spanish patients with inoperable HCC (Castells et al., 1995), treatment with the anti-estrogen Tamoxifen did not improve survival or the quality of life, compared to placebo.

Palliative radiotherapy for pain reduction has been attempted by whole liver irradiation at 25 Gy over 5 or 6 weeks, which is considered the minimum required to control HCC (Nagata et al., 1992). Proton radiation therapy is more active and better tolerated than conventional radiotherapy of the liver, but it requires expensive equipment. An analysis of 83 patients treated with proton radiotherapy showed 19% had a complete response compared to 50% with a partial response and 31% without any appreciable benefit (Matsuzaki et al., 1994). The quality of life was unaffected in most patients, and only three developed liver failure after radiotherapy.

Coagulonecrosis of tumor tissue can be achieved by inserting microwave electrodes into the tumor under US guidance or laparoscopy and general anesthesia (Kanai et al., 1996). After 100-W application, tumors 3–7 cm in diameter underwent necrosis in 30 min.

In the future, gene therapy may offer new hopes to many patients with so far untreatable HCC. Tumor cells may be transfected with viruses that can transfer genes to facilitate cell suicide or to make cells more responsive to antiviral drugs (Seki et al., 1994).

6. Conclusions

Hepatic resection is the treatment of choice for the few patients with HCC developing in normal livers. This treatment is recommended also for cirrhotic patients with small tumors having normal values of bilirubin and low indices of portal hypertension who cannot be treated by OLT. Whenever possible, OLT would be the best chance of cure for carefully selected patients with cirrhosis and a single tumor less than 5 cm in diameter or fewer than three < 3 cm tumors. In cirrhotic patients with well-preserved liver function who cannot be surgically treated, PEIT appears to be effective. However, prospective comparison of the cost/efficacy of resection versus PEIT is required, though controlled trials in patients with HCC are difficult to perform for both ethical and practical reasons. The role of chemotherapy in preventing early tumor spread during therapy is unclear.

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