Pergamon

*European Journal of Cancer* Vol. 31A, No. 10, pp. 1562–1564, 1995
Elsevier Science Ltd
Printed in Great Britain.
0959–8049/95 $9.50+0.00

0959-8049(95)00080-1

# Editorial

# Why Can't We Cure Primary Liver Cancer?

**P.J. Johnson**

IN A RECENT editorial in this Journal, Shafford and Pritchard characterised treatment of the major form of childhood primary liver cancer (hepatoblastoma) as *A Bit of A Success Story?* [1]. Unfortunately, the treatment of the common adult counterpart, hepatocellular carcinoma (HCC), has a long way to go before receiving such an accolade.

The story of the treatment of HCC can be simply told. Although surgical resection offers the hope of long-term survival, it is an option for only 10–20% of cases. Even among this lucky minority, the tumour will recur rapidly in more than 50% of cases [2]. In high incidence areas, the median survival is less than 3 months. In all areas of the world, survival for more than 1 year from the onset of symptoms is unusual. Non-surgical approaches all have their enthusiastic advocates but are essentially palliative. Responses to systemic cytotoxic chemotherapy do not consistently exceed 20% and are short-lived [3]. Local therapy, including intra-arterial chemo-embolisation [4], percutaneous ethanol injection [5] and selective internal radiotherapy [6], may offer good palliation for selected patients, but have little proven benefit on overall survival. This editorial examines some underlying reasons for this dismal state of affairs, and seeks light at the end of the tunnel.

## WHY IS THE RESECTABILITY RATE SO LOW AND THE RECURRENCE RATE SO HIGH?

Many surgical series are heavily biased by selective referral and give a falsely high impression for the resectability rate. Our own experience at a joint medical/surgical clinic with little referral bias, suggests that the figure for resection with curative intent is no more than 20% and probably closer to 10%. Three interrelated factors, the large size of the tumour at presentation, poor underlying liver function and bilobar or metastatic disease, are responsible. The large size of the tumour makes surgery technically more difficult and is not always related to delay in seeking medical advice; many patients have had symptoms for less than 1 month before diagnosis. The high frequency of associated cirrhosis, at least 75% in most areas of the world [7], contributes to poor liver function and increases the risks of surgery. The presence of cirrhosis also limits the extent of the possible resection because the cirrhotic liver, unlike the normal liver, does not regenerate well.

We should note that surgery itself has never been shown in a controlled study to improve overall survival. However, the fact that, after successful resection, survival curves tend to level out at somewhere between 20 and 40%, strongly argues in favour of surgical resection. The lower figure (20%) is typical when cirrhotic patients are included, the higher figure (40%) is seen in non-cirrhotic subjects. One should not forget that there is a significant postoperative mortality and morbidity after major hepatic resections. A recent study comparing surgical resection against percutaneous ethanol injection (PEI) in small tumours, showed no significant difference in survival at 4 years [5]. However, whereas the survival curve in the resection group is levelling out at this time (4 years), it is still falling in the PEI group. Thus, a fair comment on the role of surgery is that, when possible, it offers a chance of long-term survival at the cost of some short-term morbidity and mortality. Conversely, non-surgical approaches have fewer postoperative complications but also less chance of long-term survival.

There are two theoretical reasons why these tumours recur so frequently after apparently curative resection; either there are residual micrometastases present (intra- or extrahepatic) at the time of resection or a new tumour subsequently develops. The former may be exacerbated by trophic factors released in response to resection that may, in turn, differentially stimulate proliferation of residual microscopic deposits. Not surprisingly, new tumours do develop after surgical resection in the cirrhotic remnant. However, this is probably an uncommon occurrence and likely to contribute mainly to late recurrences.

## LIVER TRANSPLANTATION OFFERS SOME IMPORTANT LESSONS

Early results of transplantation for HCC showed that while most patients did well in the first few months, recurrence was almost inevitable, especially in patients with the typical, large symptomatic tumours [8, 9]. This led to the abandonment of transplantation for HCC in many centres. There is thus clear evidence that extrahepatic metastases are usually present at the time of presentation and that these are the main source of tumour recurrence. It might also be concluded that, if liver transplantation, which is in effect the ultimate form of *local* therapy, is not successful, then all forms of local therapy (embolisation, alcohol injection, etc.) are doomed.

Before becoming too depressed by this line of reasoning, two provisos should be noted. Firstly, in contrast to other forms of local therapy, patients who undergo transplantation receive intense immunosuppression which may encourage the growth of extrahepatic micrometastases. Nonetheless, it is hard to avoid

Correspondence to P.J. Johnson at the Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong.
Received 19 Jan. 1995; accepted 7 Feb. 1995.

the conclusion that the (micro)metastases *are* already established at the time of presentation—unless malignant cells are spread by the surgeon at the time of operation. Secondly, we should also note that local therapies may potentially offer excellent palliation for selected patients. The encouraging results with PEI [5] have already been referred to, and our own experience with selective internal radiation using yttrium$^{90}$ is that response rates of greater than 50% can be obtained, and that the degree of reduction in the levels of the tumour marker α-fetoprotein (AFP), previously only seen after surgical resection, are consistently achieved [6].

There is also some good news from the transplantation experience. The most recent evidence is that patients with *small tumours* (less than 5 cm in diameter) do extremely well with transplantation, especially when they are detected while asymptomatic [10, 11]. Thus recurrence in such patients is uncommon, and long-term survival of greater than 60% can be expected. As noted above, this is in stark contrast to the experience with large symptomatic tumours. While one doubling time, from 5 to 10 cm in diameter may be an insignificant period in the life of a particular tumour, evidently something occurs during this time that has a severe adverse effect on the survival of the host. The problem is, of course, that tumours are very seldom detected while small and amenable to such forms of treatment.

A specific, histologically defined variant of HCC, fibrolamellar HCC (FLC) [12], should also be mentioned. The characteristic histological features are large polygonal tumour cells arranged in trabecular formation and surrounded by layered stromal fibrosis. This rare variant arises in adolescents and young adults, has no bias towards males and is not associated with AFP expression or cirrhosis. Because of a higher resectability rate and a more indolent clinical course, it has a better prognosis than the common type of HCC. The 5-year survival rate is in the order of 30%, but the tumour is still ultimately fatal in most cases. Here the report by Ellis and associates (pp. 1594–1598), which includes 2 patients with FLC both of whom had partial responses to their ECF regimen (epirubicin, cisplatin and 5-fluorouracil infusion), is encouraging and certainly warrants further study [13].

Thus on the basis of the aforementioned, the answer to our original question, *"Why can't we cure liver cancer?"* is two-fold. Firstly, we seldom detect tumours while small, and amenable to surgery. Secondly, there is no particularly active systemic therapy to complement effective local therapy.

## THE WAY FORWARD—EARLY DETECTION

The solution to the first problem should be early detection. At first sight, HCC is the ideal tumour for which to screen and thereby establish early diagnosis. The high risk populations are known (hepatitis B carriers and/or those with cirrhosis), and we have good screening tools, ultrasonography and estimation of the serum AFP. The observations that small tumours do well with liver transplantation (and most likely with simple surgical resection) suggest that we may have an effective local treatment. Indeed, there is evidence that as more small tumours are detected, so the long-term survival rate improves [14]. Despite these persuasive theoretical arguments, screening has not yet been convincingly proven to be cost effective. The reasons probably differ around the world. One is that ultrasonography probably needs to be carried out at very short time intervals, approximately every 3 to 4 months, and this imposes enormous practical difficulties for most populations. A second problem is that the high risk groups are seldom identified *before* the tumour develops, i.e. only a minority of subjects are known to have cirrhosis or be hepatitis B virus carriers before presenting with tumour. A third reason is that the specificity of the AFP test is low.

An elevated AFP level (> 10 ng/ml) can be expected in 60–70% of cases of HCC. However, modestly raised levels of AFP (10–500 ng/ml) can also be seen in patients with benign liver disease (cirrhosis or chronic hepatitis). Since it is this group of patients that are being screened for HCC, and the small tumours that we are seeking often also express serum AFP levels in the range, evidently the AFP test must have a very low specificity for HCC. Several attempts have recently been made to overcome this problem. The AFP expressed by different types of disease (i.e. benign as opposed to malignant liver disease) may express AFP characterised by different sugar chain structures [15]. Thus by using lectin binding assays it is possible to distinguish "benign" from "malignant" AFP even at low concentrations [16]. However, this approach is time consuming and has not yet entered routine clinical practice in most countries. Another simpler method is to identify HCC-specific variants by isoelectric focusing. This approach seems to allow very early diagnosis, perhaps even before the tumour can be detected by physical means [17].

## THE WAY FORWARD—EFFECTIVE SYSTEMIC THERAPY AND PREDICTION OF METASTASES

Useful systemic therapy, with a role similar to that used so effectively in childhood liver cancer, remains elusive. As noted above, doxorubicin, the most active cytotoxic agent, has a response rate of only 15–20%, and in only 5% will the response rate be complete [3]. Moreover, these responses are usually brief and have not been shown to significantly improve survival. Nonetheless, even if there are no drugs that are effective on a macroscopic tumour, it might be worthwhile trying our best available therapy in an adjuvant role, i.e. immediately before or after apparently complete surgical resection. Attempts have been made to detect circulating tumour cells, which may be predictive of haematogenous spread. The approach is to use polymerase chain reaction (PCR) techniques to detect circulating mRNA for albumin of AFP. Since these are unique to hepatocytes, their detection in the blood should at least indicate the potential for metastases [18, 19]. One could foresee that it might then be feasible to identify those patients most suitable for resection and those who might benefit from adjuvant therapy.

## CHOLANGIOCARCINOMA

So far, this editorial has confined itself to the commonest of the malignant primary liver tumours, HCC. Cholangiocarcinoma is much less common and may be subdivided into the intrahepatic (or peripheral) type and the hilar type. The former behaves in a similar manner to HCC, except that it is not associated with cirrhosis and does not express AFP. Treatment, however, has been equally disappointing. Again the ECF regimen described by Ellis and associates, which reports a response rate of 40% in a wide range of biliary tract tumours (cholangiocarcinoma, carcinoma of the ampulla and carcinoma of the gallbladder), is worthy of further study. The problems associated with the hilar cholangiocarcinoma are quite different and lie outside the scope of this review.

## THE FUTURE

In the West where HCC is relatively rare, there is the prospect that early diagnosis can be achieved in those patients known to

have cirrhosis and who are carefully followed up. Such patients may be offered liver transplantation or resection with the prospect of a successful outcome. In high incidence areas, hepatic transplantation is not a realistic option. It is not that the skill is lacking but the sheer size of the problem, the reluctance of many cultures to consider organ donation and the high prevalence of hepatitis B virus (HBV) infection that makes transplantation for HCC an impractical approach. At our local clinic, we see between 5 and 15 new cases each week and at least half of these are terminally ill at presentation. A further 25% will already, although in better general condition, have inoperable tumours. For some of these patients, and many other patients worldwide, we may now be able to offer useful palliation. However, this needs to be backed up with effective systemic treatment if we are to have a real impact on survival. There is little prospect of this at present. In many parts of the world, where HCC is related to HBV infection, it is likely that the problem will start to fade over the next generation with the advance of immunisation against HBV. However, in Europe and Japan, where most HCC is related to chronic hepatitis C virus infection (where the prospect for a vaccine is remote) or chronic alcoholism, a long-term solution is not in sight.


1. Shafford EA, Pritchard J. Hepatoblastoma—a bit of a success story? *Eur J Cancer* 1994, **30A**, 1050–1051.
2. Lai E C-S, Ng I O-L, Ng M M-T, *et al.* Long term results of resection for large hepatocellular carcinoma: a multivariate analysis of clinicopathological features. *Hepatology* 1990, **11**, 815–818.
3. Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future directions. *Cancer Treat Rep* 1988, **15**, 1–31.
4. Bismuth H, Morino M, Sherlock D, *et al.* Primary treatment of hepatocellular carcinoma by arterial chemoembolization. *Am J Surg* 1992, **163**, 387–394.
5. Castells A, Bruix J, Bru C, *et al.* Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology* 1993, **18**, 1121–1126.
6. Lau W-Y, Leung W-T, Ho S, *et al.* Treatment of inoperable hepatocellular carcinoma with intrahepatic-arterial yttrium-90 microspheres—a phase I & II study. *Br J Cancer* 1994, **70**, 994–999.
7. Johnson PJ, Williams RJ. Cirrhosis and the aetiology of hepatocellular carcinoma. *Hepatology* 1987, **4**, 140–147.
8. O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. *Ann Surg* 1988, **207**, 373–379.
9. McPeake J, Williams R. Liver transplantation for malignancy: the current position. In Terblanche J, ed. *Hepatobiliary Malignancy*. London, Edward Arnold, 1994, 596–618.
10. McPeake JR, O'Grady JG, Zaman S, *et al.* Liver transplantation for primary hepatocellular carcinoma: tumour size and number determine outcome. *J Hepatol* 1993, **18**, 226–234.
11. Iwatsuki S, Starzl TE, Todo S, *et al.* Experience in 1000 liver transplants under cyclosporine-steroid therapy: a survival report. *Transplant Proc* 1988, **20** (suppl. 1), 498–504.
12. Craig JR, Peters RL, Omata M. Fibrolamellar carcinoma of the liver: a tumour of adolescents and young adults with distinctive clinicopathologic features. *Cancer* 1980, **46**, 372–379.
13. Ellis PA, Norman A, Hill A, *et al.* Epirubicin, cisplatin and infusional 5FU (ECF) in hepatobiliary tumours. *Eur J Cancer* **31**, 1594–1598.
14. Zhou X-d, Yu Y-q, Tang Z-y. Advances in surgery for hepatocellular carcinoma. *Asian J Surg* 1994, **17**, 34–39.
15. Sato Y, Nakata K, Kao Y, *et al.* Early recognition of hepatocellular carcinoma based on altered profiles of alpha-fetoprotein. *N Engl J Med* 1993, **25**, 1802–1806.
16. Du M-Q, Hutchinson WL, Johnson PJ, Williams R. Differential alpha-fetoprotein lectin binding in hepatocellular carcinoma: diagnostic utility at low serum levels. *Cancer* 1991, **67**, 476–480.
17. Burditt L, Johnson M, Johnson PJ, William R. Detection of hepatocellular carcinoma-specific alpha-fetoprotein by isoelectric focusing. *Cancer* 1994, **74**, 25–29.
18. Matsumura M, Niwa Y, Kato N, *et al.* Detection of alpha-fetoprotein in mRNA, an indicator of hematogenous spreading hepatocellular carcinoma, in the circulation: a possible predictor of metastatic hepatocellular carcinoma. *Hepatology* 1994, **20**, 1418–1425.
19. Reid AE, Liang TJ. Tumor marker for metastasis: searching for an abnormal needle in a haystick. *Hepatology* 1994, **20**, 1631–1634.