17. Ko S, Nakano H, Shimomura H, et al. Liver transplantation for hepatocellular carcinoma: consideration from the findings on autopsy. Transpl Proc 1996; 28(3):1691-1692.
18. Wong PY, Williams R, Naoumov NV, et al. Clinical course and survival after liver transplantation for hepatitis B virus infection complicated by hepatocellular carcinoma. Am J Gastroenterol 1995; 90(1):29-34.
19. Olthoff KM, Rosove NH, Shackleton CR, et al. Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. Ann Surg 1995; 221:734–743.
20. Stone MJ, Klintmalm BG, Polter D, et al. Neoadjuvant chemotherapy and liver transplantation for hepatocellular carcinoma: a pilot study in 20 patients. Gastroenterology 1993; 104:196–202.
21. Bismuth H, Morino M, Sherlock D, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. Am J Surg 1992; 163:387–394.
22. Majno PE, Azoulay D, Perrin H, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997; 226(6):688–701.
23. Venook AP, Lake JR, Ascher NL, et al. Liver transplantation for hepatocellular carcinoma: results with preoperative chemoembolization. Liver Transpl Surg 1995; 1(4):242–248.
24. Schwartz ME, Miller CM, Guy S, et al. A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 1995; 180(5):596–603.
25. Figueras J, Casais L, Moreno P, et al. Survival after liver transplantation in cirrhotic patients with and without hepatocellular carcinoma: a comparative study. Hepatology 1997; 25(6):1485–1489.
26. Spreafico C, Marchiano A, Regalia E, et al. Chememoembolization of hepatocellular carcinoma in patients who undergo liver transplantation. Radiology 1994; 192:687–690.
27. Ravikumar TS, Steele GD. Hepatic cryosurgery. Surg Clin North Am 1989; 69:433–440.
28. UNOS 1996 Annual Report. United Network for Organ Sharing, Richmond, VA.
29. UNOS 1997 Annual Report. United Network for Organ Sharing, Richmond, VA.
30. Pinna AD, Iwatsuki S, Lee RG, et al. Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. Hepatology 1997; 26(4):877–883.
31. Kar S, Carr BI. Detection of liver cells in peripheral blood of patients with advanced-stage hepatocellular carcinoma. Hepatology 1995; 21(2):403–407.
32. Lemoine A, Debuire B, Bismuth H, et al. Prospective evaluation of circulating hepatocytes by alpha-fetoprotein mRNA in humans during liver surgery. Ann Surg 1997; 226(1):43–50.
33. Yamanaka N, Okamoto E, Fujihara S, et al. Do the tumor cells of hepatocellular carcinomas dislodge into the portal venous stream during hepatic resection? Cancer 1992; 70:2263–2267.

Discussion

DR. ISRAEL PENN (Cincinnati, Ohio): Almost a decade ago I presented data on over 400 patients with hepatomas who were treated by liver transplantation in the 1970s and 1980s. If we exclude incidentally discovered tumors and fibrolamellar hepatomas, the overall 5-year survival was only 18%. Dr. Klintmalm has presented much higher survival figures for patients transplanted in the 1990s. What accounts for these improved results? There are several explanations.

The first, and relatively minor factor, is the overall improvement in the results of liver transplantation for all types of indications in the 1990s compared with earlier series. A much more important explanation is better selection of patients. Instead of offering transplantation to every patient with a hepatoma, we try to exclude those patients with extrahepatic spread. Prior to transplantation, we attempt to evaluate this with CAT scans of the chest and abdomen. In addition, some surgeons do mini-laparotomies or laparoscopies looking for evidence of extrahepatic spread. Finally, when a donor liver becomes available, if preliminary laparotomy demonstrates any extrahepatic spread, the patient is turned down for transplantation and the liver is given to another candidate on the waiting list. The improved results reported by Dr. Klintmalm reflect the influence of better recipient selection. Thus, only 6% of patients in his study had lymph node involvement. Another important factor, that Dr. Klintmalm emphasized, was tumor size less than 5 centimeters. Seventy-one percent of patients in his series had tumors 5 centimeters or less in size. Dr. Klintmalm also emphasized vascular invasion. Only 23% of patients in his series showed vascular invasion. Dr. Klintmalm also stressed the importance of differentiation of the tumor. In his study 87% of patients had grade I or grade II tumors and only 13% had poorly differentiated neoplasms.

Another important consideration is whether the tumor was discovered incidentally when the liver was removed at the time of transplantation. We showed that incidental tumors had a 57% 5-year survival, compared with only 18% in patients with hepatomas known to be present prior to transplantation. Dr. Klintmalm's series is very unusual in that 40% of the patients had incidentally discovered tumors. Also, he did not observe a difference in survival between the incidentally discovered tumors and those known to be present prior to transplantation. This is a very, very surprising finding. Surgeons, who have transplanted large numbers of patients having hepatomas, have usually found that those with incidentally discovered tumors have a far better outcome than those with known hepatomas, because most incidental tumors tend to be small and have a favorable prognosis.

Dr. Klintmalm showed no difference in 5-year overall survival of patients with incidental compared with known hepatomas. However, what is much more significant, is what were the actual recurrence rates in these two groups of patients? Also, I would like to know what were the 5-year tumor-free survival rates of the incidental hepatomas compared with those known to be present prior to transplantation? One more question. What was the overall perioperative mortality in the two groups of patients in this series, because this does impact on the long-term survival as well.

DR. GORAN B. KLINTMALM (Dallas, Texas): First of all, the number of incidental tumors in this material is high. I suspect that, since these are fairly recent patients, many centers stopped doing transplantation for known hepatic tumors, and that is why we see such a high representation of incidental tumors compared to previously presented studies.

I think also as a result of previous reports from single-center studies, we have become kind of nihilistic regarding incidental tumors, saying, well, they do so much better anyway, so we don't need to treat them. Consequently, they were less likely to receive postoperative chemotherapy. And that may be one of the answers for the absence of survival difference between incidental and nonincidental tumors, but this is only speculation.

As far as preoperative mortality, I do not have the data. This is what was reported to the registry. And of course we have no way of finding out if the centers have patients that died within 30 days and didn't report them. Again, that is one of the weaknesses of a registry.

DR. RONALD W. BUSUTTIL (Los Angeles, California): I have basically four questions. One is related to what Dr. Penn said. You showed in the data that tumors greater than five and those that have vascular invasion have a worse prognosis than those that are small and do not have vascular invasion. Yet in your incidental tumors, they were smaller and they had a lesser degree of vascular invasion. How come they don't do better? Number 2, the degree of differentiation you mention has a significant prognostic impact on survival. What you are telling us is that we should be biopsying these tumors. I am a little nervous about doing that, because we have done it with patients that have been referred to us and we find that they have got cancer growing out of their biopsy sites. Is that not a concern?

The third question is, do you have any data on cholangiocarcinomas? This is a controversial issue, but I do think that some of these patients should be candidates for transplantation. And did you look at that?

The final question is, clearly, if we take the conventional wisdom of all that has been reported over the past five years, patients who have more than stage II tumors probably ought to have some adjuvant chemotherapy, transplantation alone is not good enough. Do you have any data from your registry that looks at the aspects and the types of adjuvant chemotherapy that these patients used?

DR. GORAN B. KLINTMALM (Dallas, Texas): As far as the incidental, it is a similar question to that of Dr. Penn. It is inexplicable at this time why this is. The treatment question is an important one, and may be the important one. We have looked at the issues about size and vascular invasion just like you mentioned. And in incidental tumors, you see it less frequently, but still they do die with recurrence from tumor. And it may well be that those few that have the aggressive tumors grow out faster. Again, that is something that with the growth of the registry we will have bigger numbers to look into.

As far as grade, yes, we, like you and everybody else here, have been adamant in advising against biopsy in those patients. The observations made by Williams a long time ago that tumor recurrences occurred in the needle track I think was very important. However, these are the data. And really the big question here is, does the grade have an impact and importance for the response to the adjuvant therapy? With 50% only being treated with adjuvant chemotherapy and with the plethora of treatments available, we simply didn't have big enough groups to make a valid analysis at this time. And that is, of course, really what this registry is aimed at, and hopefully we will one day get those answers. Cholangiocarcinomas, yes, we have 71 patients as of September last year. And when we have more of those, certainly I will report them as well.

As far as adjunct therapy, 48% only received therapy. And I think that is unwarranted. This is a disease that is difficult and very hard to treat. This report would suggest that every patient with a hepatocellular carcinoma should have adjuvant therapy, incidental or not.

DR. RONALD W. BUSUTTIL (Los Angeles, California): But did the adjuvant therapy make a difference in those that you looked at?

DR. GORAN B. KLINTMALM (Dallas, Texas): What I am saying is that I looked at it—I have virtually all the drugs used, given pre, post, intra, embolization, et cetera, and when you divide those 200 patients who have received adjuvant therapy, the groups are simply too small to allow a meaningful discussion.

My finding was that the incidentals are less likely to have vascular invasion, less likely to have poor differentiation. But they did have it. And it may well be that it was those tumors that recurred. We simply don't have enough of those patients yet to be able to make that crucial analysis.

DR. SHUNZABURO IWATSUKI (Pittsburgh, Pennsylvania): I congratulate Dr. Klintmalm for his large registry of hepatoma patients treated with transplantation. We did not join this registry because we had more than 100 patients in our data base when the registry began in 1992, and also because we had some concerns about the registry format. Our own data base now contains more than 300 patients of hepatoma, and last week we presented our results with these cases at the annual meeting of the Society of Surgical Oncology. As shown in this slide, tumor-free survival correlated extremely well, not only by univariate, but also by multivariate analysis, with 1) tumor size, 2) tumor distribution, 3) vascular invasion, and 4) lymph node metastasis. Dr. Klintmalm's registry analysis could not find any of those critical factors in pTNM stage to be significant by multivariate analysis. I looked for some possible explanations in Dr. Klintmalm's abstract. Although he registered 410 patients, single or multiple data were missing for 10% to 20% of the registry cases. If these missing multiple data were distributed at random in the 410 patients, I calculated that only about 88 patients had the complete set of data which would be essential for multivariate analysis. Thus, although the number of registry cases exceeded ours, the number available for a valid multivariate analysis was significantly smaller. In addition, prognostic risk factors for any malignant tumor are best examined by tumor-free survival. Dr. Klintmalm used patient survival whereas we used tumor-free survival as our end-point. This is the second reason for the difference between the two studies. I believe that the missing data can still be collected, making the registry a reliable source of information for an important publication. The registry format should be improved by including the tumor margins and the degrees of vascular invasion.

Finally, detailed pathological findings should be reexamined by a group of expert pathologists to ensure accuracy. It should be noted that only 23% of the patients in the registry had vascular invasion, an incidence that appears to be much too low in comparison with other single center reports, considering the size of the tumors recorded in the registry.

DR. GORAN B. KLINTMALM (Dallas, Texas): This supports that Dr. Iwatsuki's studies from Pittsburgh contain some of the hallmark information about hepatic tumors in transplantation. The analysis we just saw is one of the most important ones we have seen from a single center, if not the most important. What I showed during the presentation was the Cox Regression Analysis, including the histologic grade. On this slide I have the Cox Regression without the histologic grade. If you exclude histologic grade, you actually get data that supports your finding, so you should be happy.

DR. JOHN S. SPRATT (Louisville, Kentucky): I just have a comment. That is, he shows that differentiation is significant. If he had the proliferative index of these neoplasms, he would find that there is a random variation in the proliferative index. If you then convert that to the growth rate, you will have a log normal variation in growth rates. Some of these tumors are so indolent that they, as well documented in the literature, live 15 to 20 years with the cancer.

The thing is, you can't use truncated survival rates like 5-year

survival rates and come up with any significant conclusion about the biological variation of the behavior of these neoplasms. So I would encourage all the students of this area not to get hooked up on 5-year survival rates. Fixed end-point survival rates truncate data and shut out a lot of useful information on the natural histories of these neoplasms.

DR. GORAN B. KLINTMALM (Dallas, Texas): Thank you. I appreciate that comment and I agree with it. This I think is the answer to Dr. Iwatsuki's question. This is a Cox analysis on tumor characteristics but excluding the information on histological grade. Dr. Iwatsuki did not include that data from his single center analysis.

As you see here, if you look at recurrence survival, independent factors important for outcome are positive nodes, vascular invasion, tumor size, and bilobar spread. And, suddenly, we have data that are very conforming with Dr. Iwatsuki's data. Of course, Dr. Iwatsuki's is much better controlled.

And as you see here, 261 patients all had these data. If you look for overall patient survival, vascular invasion alone was the only independent indicator of survival, and with the negative factor 1.9.

So, Dr. Iwatsuki, I agree with you. I think that the factors you have analyzed are important. What I bring up is histological grade. That may be something we overlooked in the past that we need to take into the algorithm when planning our therapy.

DR. MURRAY F. BRENNAN (New York, New York): As the focus is on grade and vascular invasion, both of which are highly subjective analyses, has the pathology been reviewed uniformly by a central pathology bank?

DR. GORAN B. KLINTMALM (Dallas, Texas): No. And as I say, that is sort of one of the drawbacks with the registry. Because this is data reported from all these 21 countries and 53 institutions.

DR. MURRAY F. BRENNAN (New York, New York): But you could get the slides and have them reviewed. And as they are the dominant factor in your analysis, I think you have to do that.

DR. GORAN B. KLINTMALM (Dallas, Texas): If I get an NIH grant to help support this work, yes.

DR. MURRAY F. BRENNAN (New York, New York): And secondly, before everybody takes adjuvant chemotherapy for hepatoma and convinces you to do it, I am unaware of any interpretable study in any country that has ever shown a survival benefit for chemotherapy for hepatoma.

DR. GORAN B. KLINTMALM (Dallas, Texas): I agree with that and I am aware of that. This is why I think that, as far as I know, this is the only registry which can provide some insight into what may be effective therapy. Today we don't have any other mechanism to find out, unfortunately.

DR. CHARLES M. MILLER (New York, New York): It is a very nice presentation. It sheds light on a difficult multi-factorial nature of doing these analyses. Just a simple question. Did you look at indication for transplant, whether it be for tumor or chronic end-stage liver disease. Number 2, did you determine recurrence-free survival of the incidentals versus the non-incidentals? Because they die of different reasons.

DR. GORAN B. KLINTMALM (Dallas, Texas): The last answer first. Yes, we did. I have recurrence-free survival on virtually every factor we looked at here, but I don't have time to show them. As far as the exact numbers for incidental and non-incidental for recurrence, I don't have it off the top of my head but I could certainly provide it for you.

DR. CHARLES M. MILLER (New York, New York): Did you look at the indication for transplantation, whether it be actually for tumor or for other indications leading to end-stage liver disease?

DR. GORAN B. KLINTMALM (Dallas, Texas): Yes. Sixty percent received a transplant for the indication of hepatocellular carcinoma.

DR. CHARLES M. MILLER (New York, New York): Was there a difference in tumor-free survival?

DR. GORAN B. KLINTMALM (Dallas, Texas): And I agree with that comment again. And if NIH gives me support, I will do it.

DR. FRANK C. SPENCER (New York, New York): I want to compliment Dr. Klintmalm for his efforts with establishing and maintaining a central registry. This is a true labor of love; so "don't shoot the messenger." A central registry should have much scientific value because few centers will accumulate enough individual data to be statistically valid. The classical international neurological study demonstrating the limited benefit from anastomosis of the superficial temporal artery to the middle cerebral artery for cerebral ischemia is a classic example. The major handicap with a central registry, of course, is to obtain comparable data. The obvious question, as Dr. Murray Brennan and others have asked, is the validity of the histologic grading. An independent review would seem indicated.

Separately, I noticed in one of the initial slides that a number of patients died "free of tumor." What did they die from?

DR. GORAN B. KLINTMALM (Dallas, Texas): The first results slide I showed, where we compared the survival with UNOS data, we all know that patients with transplantation die from other causes than tumors, especially if they don't have a tumor. They die from rejection, from recurrent disease, from infections. And that is the other 50%.