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## DISCUSSION

DR. ENCKE (Frankfurt, Germany): Thank you for this presentation and your large figures. I can only add our own small experience. I can confirm that the mortality and morbidity are extremely low, mortality was zero in our series and we had a morbidity rate of 13%. However, we only had 24 patients with isolated liver metastases as recurrences and we only operated in these patients. We do not perform an operation in those with extrahepatic disease. We reached a prolongation of survival for our second repeat hepatectomies in comparison to the group where it could not perform such an operation, but after 60 months, they all died finally, too. So we did not find this difference between those who lived longer in your series with second repeat hepatectomy in comparison to those with a first hepatectomy.

DR. JEEKEL (Rotterdam, The Netherlands): My question is also related to the inclusion of the patients with extrahepatic disease. I was curious in the last paper about the cryosurgery and now again you included the extrahepatic disease patients in your group. We would not treat those patients in my country. I think it is interesting you do, but if you exclude those patients, we have the 5-year survival of the overall group about 48% to 50%, which is not so different from the overall group of Dukes' A-B-C patients. So, why are these results so extremely good? Do you use other treatment as well as chemotherapy? I presume that you used chemotherapy as well, and I think it is very important to note that and to include it in your data. Is there any way to do this in a prospective manner, to use chemotherapy in addition to your treatment?

DR. BROELSCH (Hamburg, Germany): Congratulations for an excellent presentation. Many data were, however, actually difficult to follow. One question relates to the occurrence of extrahepatic disease. Does this extrahepatic disease occur after the first resection? Was it associated with intrahepatic recurrence preceding the second resection? I would agree with H. Jeekel

that in a situation in which extrahepatic tumor growths develop secondarily in patients, a lot of arguments are required to proceed with a second or a third partial hepatectomy. Do you include into your procedure the resection of or the hepatoduodenal ligament as well? My last question relates to the time interval: It seems to be that the only determinant really predicting good outcome is the absence of extrahepatic disease and the interval occurring between the first resection and then perhaps a second resection. If I understand this right, the interval between the first and the second resection becomes necessary and becomes the real determinant of prognosis because by observing the interval, we are catching here the biological dynamic of the tumor growth as well. The determinant between the first and the second resection is another interval and do you calculate the interval beginning each hepatectomy anew?

DR. COLLIN (Oxford, United Kingdom): Probably the main characteristic determining survival for many tumors is the inherent rate of growth. I would expect slow growing tumors would take a long time to manifest recurrence, and it is not surprising that one of the best determinants of survival after second hepatectomy is the length of time from the first resection. Did you study the tumor to determine how histologically active they were?

DR. MOORE (Boston, Massachusetts): For all who have been watching the wonderful work being reported here, particularly under Professor Bismuth, it is very impressive to see the tremendous investment of time and thoroughness in a surgical problem that has always been regarded as unapproachable.

Dr. Adam mentioned that some of these patients had pulmonary resections also, which is certainly a special aspect and I wonder if any of the 34% long-term survivors had also had resection of pulmonary metastases?

DR. ADAM (Closing Discussion): I would like to thank the discussants for their questions and their kind comments.

Dr. Encke and Dr. Jeekel raised the important point whether patients with extrahepatic disease should be considered for repeat liver resections. Although the common attitude was indeed to exclude these patients from further surgery, we decided to re-explore the indications for re-hepatectomy, provided that all the extrahepatic tumor was resectable, this because of the increasing efficacy of our chemotherapy protocols. As previously mentioned, we have at present no survivor at 5 years among the 14 patients who presented synchronous extrahepatic disease at the time of a second hepatectomy, and extrahepatic tumor was significantly associated with lower survival on univariate analysis. However, I think that the number of patients is still too small to draw definitive conclusions: Extrahepatic disease was not independently associated with lower survival on multivariate analysis, and the mean follow-up in this group was less than 2 years as opposed to 3 years for the whole series, probably because of the more recent policy of accepting these patients for repeat resection. We do not take, therefore, our results as proof that we should abandon this option, even if I agree that the survival is lower in this group than in patients with no extrahepatic disease. On an individual record, I can add that among the 14 patients, 2 survived more than 4 years and 1 more than 3 years after the repeat hepatectomy.

Dr. Encke said that he did not see in his patients with repeat liver resections a clear survival benefit after 5 years. Our experience is different and our data suggest that the benefit is at least equal to the one provided by the first liver resection. For calculating the 41% survival at 5 years, we took into account the survival from the time of second hepatectomy. If we consider the survival from the time of first liver resection, the 5-year survival raises to 54%.

Dr. Jeekel asked about associated chemotherapy. When a liver recurrence was diagnosed, a majority of patients received systemic chemotherapy before the repeat liver resection. Only if the recurrent tumor was small, solitary, without extrahepatic disease, and occurred late after first liver resection, surgery was performed straight away, but this was rare. In the majority of cases, we were faced with patients either with multinodular or large recurrences, sometimes with extrahepatic disease and a repeat liver resection often difficult to perform for technical reasons. In these cases, our policy was to give preoperative systemic chronomodulated chemotherapy combining 5-FU, folinic acid, and oxaliplatin (a non-nephrotoxic platinum complex). This can also be regarded as a way to exclude from repeat resection those patients who have a really uncontrollable form of the disease, flaring up in a short period of time. After the repeat resection, all patients were given at least six courses of the same protocol as adjuvant chemotherapy. I do not know if this associated chemotherapy explains by itself the results we obtained, but obviously it was an important factor to control the disease before resection and to achieve a better patient selection.

Dr. Broelsch commented on the problem of extrahepatic disease and its occurrence before or after a repeat liver resection. The 14 patients that I mentioned before were patients in whom the extrahepatic disease was present at the same time as the hepatic recurrence. These were mainly patients with celiac metastatic lymph nodes, peritoneal deposits, ovarian, or pulmonary metastases, and extrahepatic resection was part of the strategy of attempting tumor eradication. After repeat hepatectomy, extrahepatic metastases developed *de novo* in other patients.

Accordingly, 12 patients of the series who were submitted to pulmonary resection for lung metastases appeared *after* the second liver resection. Two of these patients are presently alive and disease free more than 5 years after the repeat hepatectomy. I have no clear cut answer to give to the question whether we should proceed or not to resect patients with concomitant or subsequent extrahepatic disease. I can only say that on an individual basis, it seems justified to do so.

With regard to the interval between the first and the second hepatectomy, this was usually longer than the time from the first hepatectomy to the diagnosis of recurrence because the majority of patients underwent neoadjuvant chemotherapy. I believe that the interval between the first hepatectomy and the recurrence is probably a better index of the biology of the tumor. I should add that this interval was only considered between the first and the second procedure but not between the second and further resections because the end point of this study was survival after a second liver resection.

Dr. Collin asked about the histologic activity of the tumor and its prognostic value. We did not perform any specific study on tumor activity and on the rate of tumor growth, but

the discovery on the specimen of a total or a subtotal necrosis of the tumor after preoperative chemotherapy was a factor of good prognosis in our experience. Other factors may also be important, and we recently performed in patients undergoing a first resection an analysis on the prognostic value of the mutant form of the P53 protein in the liver metastases. Positivity of mutant P53 was associated with poor survival

after resection, as previously shown for primary colorectal tumors.

Dr. Moore asked whether there are any long-term survivors after resection of liver and pulmonary metastases. We indeed have three patients who lived more than 5 years after repeat liver resection and pulmonary resection, of whom two are currently disease free.