ANNALS OF SURGERY
Vol. 230, No. 4, 607–612

February 8, 1999

To the Editor:

The prospective randomized study by Lorenz et al[1] reported in the December 1998 issue of *Annals of Surgery* failed to demonstrate any overall survival or other clinical benefits from adjuvant selective intraarterial chemotherapy in patients undergoing curative liver resection for metastatic colorectal tumor. In this study, 226 patients with liver metastases from colorectal cancer were randomized to receive liver resection alone or resection in combination with intraarterial chemotherapy of 5-fluorouracil (5-FU). The authors should be congratulated for this important study. The search for an effective adjuvant therapy is of paramount importance at a time when major liver resection, the only treatment with proven efficacy, is still associated with a high recurrence rate (60%–80%).[2–4] However, this study, which was discontinued due to a high recurrence and mortality rate at the interim analysis, does not rule out a significant benefit for intraarterial chemotherapy. Some aspects of the study design and interpretation of the data require comments.

A more efficacious local effect might have been achieved by using floxuridine (FUDR) instead of 5-FU. Several studies have shown that the local efficacy of FUDR within the liver is superior to 5-FU due to its higher hepatic extraction.[5–8] In addition, the authors indicate that the schedule of intraarterial 5-FU might also be effective against systemic disease. Their intraarterial 5-FU protocol differs from established regimens of long-duration (6 weeks) low-dose infusions of 5-FU or protocols using a short-duration, high-dose schedule. The systemic efficacy of their regimen remains unclear. Therefore, a significant survival benefit for adjuvant intraarterial chemotherapy might have been missed in the study by using a less effective chemotherapeutic regimen.

We are concerned that the percentage of patients with synchronous metastases in this study is rather high (45% for the control group and 36% for the adjuvant treatment group). Synchronous metastases are associated with a less favorable prognosis in some studies.[9,10] We do not perform adjuvant intraarterial treatment in these patients. In addition, intraarterial chemotherapy was not started in 23% of the patients, and only 39% of the patients completed the adjuvant protocol. Furthermore, the authors do not provide data about the median follow-up time of the patients.

Data on the number of patients in each participating center would have been of interest. The high mortality rate of 7.5% in the adjuvant treatment group, including three patients dying from catheter-induced hemorrhage and 5 patients dying from chemotherapy-related complications, may indicate that some participating centers lacked sufficient experience for this protocol.

We would like to point out that, in contrast to the authors' statement, a prospective randomized study evaluating adjuvant intraarterial chemotherapy after curative resection was published by Wagman et al in 1990.[11] These authors used intraarterial FUDR (0.5mg/kg/d) for 14 consecutive days of every month for 12 months and found significantly delayed recurrence, but failed to show a significant increase in patient survival. Lorenz et al[12] (first author of the multicenter study under discussion[1]) also reported in 1997 a prospective study using adjuvant intraarterial FUDR or 5-FU after hepatic resection of colorectal metastases. In this earlier report,[12] in contrast to the recently published series,[1] the recurrence rate was significantly reduced and patient survival significantly prolonged in patients receiving more than 5 cycles of chemotherapy. These two studies[11,12] are not discussed in the present publication. Furthermore, a significant effect on tumor progression[13–15] and survival[16,17] has been shown in some randomized trials using intraarterial FUDR for palliative treatment of liver metastases from colorectal cancer. A critical comparison of the different results available in the literature would have added substantial information to this controversial topic.

In our opinion, a higher local efficacy with fewer systemic side effects could have been achieved by using a drug with high hepatic extraction such as FUDR, with or without folinic acid. Systemic disease should be approached by intensive preoperative diagnostic evaluation, including new techniques like positron emission tomography (PET) scans, to exclude patients with nonresectable disease or extrahepatic lesions. Additional aggressive systemic chemotherapy might be necessary in selected cases. Finally, other types of adjuvant therapy such as immunotherapy may provide additional benefit.[18]

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Table 1. INCLUDED PATIENTS PER PARTICIPATING HOSPITAL

Center	n
University Hospitals	
Berlin-Steglitz	2
Berlin-Virchow	7
Bonn	1
Dresden	1
Frankfurt	58
Giessen	9
Homburg/Saar	1
Jena	1
Köln	1
Leipzig	12
Magdeburg	14
Marburg	2
Münchene r. d. Isar	5
München-Grosshadern	17
Regensburg	7
St. Gallen	9
Würzburg	19
General Hospitals	
Erfurt	2
Esslingen	7
Frankfurt-Höchst	5
Fürth	6
Gera	29
Göppingen	8
Leipzig-St. Georg	1
Traunstein	1
Trier	1
Total	226

Authors' Reply:

We are pleased to receive the pertinent and relevant comments from Drs. Clavien, Selzner, and Morse.

As a center in Germany working since 1982 on regional treatment along with a group including several university clinics and major hospitals, our multicenter randomized open controlled clinical trial was designed to test the hypothesis that an adjuvant hepatic arterial infusion (HAI) chemotherapy with 5-fluorouracil (5-FU) and folinic acid (FA) in a defined dose and schedule may be effective after complete resection of colorectal liver metastases. This trial contributes to evidence-based medicine.

The primary endpoint was survival time. An increase of 50% in median survival time was specified to be a detectable difference with a power of 80%. The trial does not rule out a statistically significant benefit in survival time for this HAI chemotherapy. However, the upper 95% confidence limit for the hazard ratio shows that it is unlikely to improve median survival time by more than 15%, and the lower 95% confidence limit for the hazard rate shows that the risk of death is probably higher, by up to a twofold rate. Furthermore, in this trial it was unlikely to achieve significance, even if there would be an increase in median survival time of 50%. Moreover, in secondary endpoints there were no beneficial trends of clinical relevance. In view of the data presented on toxicity, we conclude that an increase in median survival time of no more than 15% is clinically of minor relevance compared to the possibility that the adjuvant therapy may be harmful.

We ourselves were completely unhappy with the interim results of our randomized trial. But there was no other way than to stop accrual for this trial and report the negative results as fast as possible. The publication of this trial—even when the final analysis is still underway—was urgent because adjuvant treatment after liver resection is unfortunately being routinely performed in some clinics[2,3] despite lack of evidence.

Nevertheless, there might be more effective adjuvant chemotherapeutic regimens. However, today controlled clinical trials furnish no evidence of efficacy for any regimen investigated. Several possible reasons for the failure of HAI 5-FU/FA were already mentioned in the discussion of the article. Further special issues were criticized in Clavien's comment.

The main criticism was that HAI 5-FU/FA was used in the study instead of HAI 5-fluoro-2-deoxyurdine (FUDR). The administration of HAI 5-FU/FA was based on our own experiences and on other regional European or Japanese experiences in palliative treatment. In these trials HAI 5-FU with or without FA demonstrated a 48% to 78% response rate.[1,5,11,14,15] The randomized HAI FUDR studies mentioned by Clavien et al reached the same range of response but failed to provide proof of a benefit in survival time *versus* a control group with a regular systemic treatment. This has been already discussed in at least two meta-analyses.[4,8,9]

A randomized multicenter trial of the German Cooperative on Liver Metastases which compared HAI 5-FU/FA, HAI FUDR, and intravenous (IV) 5-FU/FA showed a longer time to progression and an overall survival time for HAI 5-FU/FA *versus* FUDR. Especially in patients with a tumor volume of less than

25% in the liver, the time to progression was doubled to 12 months, whereas in the HAI FUDR regimen, only 6 months were recorded. Besides the local effect (response rate of HAI 5-FU/FA 43%, HAI FUDR 42%), a considerable systemic effect can be postulated because the appearance of extrahepatic disease in the HAI FUDR group of 40.5% was reduced to 12.5% after HAI 5-FU/FA.[6]

Even if the mode of 5-day continuous 5-FU infusion is not used in general for the treatment of metastases of colorectal cancer, there is evidence that the regimen is at least as effective as the Mayo or Machover regimen.[9]

Later on, HAI 5-FU/FA was used instead of HAI FUDR to avoid local toxicity such as chemical hepatitis or biliary sclerosis. In randomized studies, the rates of chemical hepatitis range from 45% to 70% and the rates of biliary sclerosis from 3% to 25%.[12] Reports of toxicity in the adjuvant setting are rare. In a pilot study, however, we observed biliary sclerosis in two of 12 patients after adjuvant HAI FUDR for 14 days. In one patient, this was noted unfortunately only 12 months after cessation of the adjuvant 14-day HAI FUDR treatment. Progressive liver failure with untreatable cholangitis but no tumor recurrence led to liver transplantation in this patient.[7] Similar to these two cases, five additional fatal cases of biliary sclerosis were reported by Wagman after resection of solitary metastases and adjuvant HAI FUDR.[17]

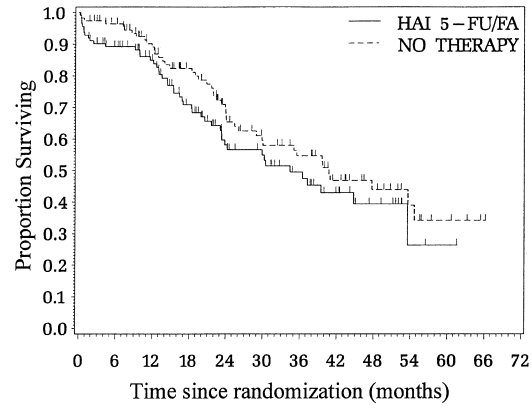
These cases of local toxicity known in Germany made it impossible to use HAI FUDR as an adjuvant treatment in a multicenter trial in the presence of active 5-FU/FA treatment options.

Clavien et al recommend exclusion of synchronous liver metastases from adjuvant HAI chemotherapy because of the inferior prognosis. To date, many retrospective patient series have been analyzed in order to find important prognostic factors. Only three of 19 showed that synchronous liver metastases have a significant negative influence on the prognosis.[10]

In spite of these results, we cannot understand the argument not to include patients with synchronous metastases in HAI chemotherapy studies despite their being associated with a less favorable prognosis. One may argue in an adjuvant setting, and possibly also in a palliative setting, that the less favorable the prognosis, the greater is the need for treatment.

In the case of complex treatments—especially in the combination of surgery and postoperative adjuvant chemotherapy—variations of the planned treatment are normal. A multicenter trial with different levels of experience increases these rates. Therefore, besides the intent-to-treat analysis, an as-treated analysis was performed to rule out overlooking the possibility that the positive influence of the treatment was hidden by the rate of patients who were never treated. This, however, also failed to produce a benefit. Due to the nature of an interim report, in some patients adjuvant treatment was started but had not yet been completed at the date of the evaluation of the interim analysis, and this explains the high rate of premature terminations.

We provided full information on the follow-up times of the patients in the central Figure 1 because times were marked in the survival curves when censored. Furthermore, the numbers of patients at risk were presented every 6 months. A median follow-up time of about 20 months can be discerned from Figure 1. The exact value is 608.5 days. The value of median follow-up is of less importance and can lead to misinterpretation or to misuse, because it combines aspects of the presented survival times of patients and of the presented time schedule of



Patients at risk (| censored)

HAI 5-FU/FA	113	91	76	57	38	32	24	16	9	2	1	0	0
NO THERAPY	113	100	81	67	49	39	33	22	15	8	4	1	0

Figure 1. Cumulative overall survival after liver resection by treatment group ("intention to treat"): resection only *vs.* adjuvant hepatic arterial infusion with 5-fluorouracil/folic acid (HAI 5-FU/FA) for 5 days every 28 days for 6 months (P = 0.1519).

recruitment up to the time of the analysis. Thus it is very difficult to interpret this measure at the time of an interim analysis.

The number of patients per center ranged from 1 to 58 (median 5.5, average 8.7 patients) and may indicate different experience. Table 1 lists the participating centers with the number of recruited patients for each center up to December 31, 1996.

There might be some question as to where this data would be of interest, for example in subgroup analyses. Subgroup analyses which are not planned at the beginning of a trial are analyses to generate, not confirm, hypotheses, and they are subject to the final analysis at the end of the trial and not at the date of the interim analysis.

If the recruiting phase of the trial had not been stopped, a 30-day mortality rate of 7.5% might have been questioned in the adjuvant treatment group as being unacceptably high with respect to reported rates. Although a "high" mortality rate of 7.5% alone cannot indicate that some participating centers lacked the experience required by the protocol, one might have tried to reduce this rate by closing recruitment in "bad" centers. In view of reported rates of up to 10% from retrospective studies, one might have classified a center as "bad" if the one-sided statistical test rejects the null hypothesis that the 30-day mortality rate is less than or equal to 10% at a significance level of 5% (no adjustments for multiple testing 26 centers).[13] None of the centers would then have been classified as "bad" from the interim analysis. Nevertheless, in every multicenter study there can be centers with insufficient experience with respect to the protocol.

The overall mortality rates of a randomized multicenter study on liver resection are not very often published to date. The reported rate of less than 3% in patients not treated by means of postoperative adjuvant HAI demonstrated the good quality of the participating surgeons, because the mortality rate in other multicenter trials reached a rate of 7.6%.[16]

Wagman's work is well known to all the authors and was mentioned and discussed several times in the introduction and the discussion of the criticized article.[17] However, Wagman's study never had a chance to give clear information to the

scientific community because several approaches were investigated. Most of the patients were not resected, had multiple metastases, and received palliative arterial or systemic treatment (70/91 patients). Furthermore, for each indication, the number of patients was far below what today is regarded as necessary.

This trial was not designed to test hypotheses with a procedure adjusting for multiple comparisons. Furthermore, there were no power calculations to determine a sample size. P values therefore have to be interpreted descriptively with the objective to generate and not to confirm hypotheses. Confidence intervals for the impact were not calculated. It would be an overinterpretation of study data, therefore, to conclude that Wagman et al found statistically significantly delayed recurrence and that they failed to show a statistically significant increase in patient survival.

Only six patients with resection of a solitary metastasis were compared to only five patients with resection of a single metastasis and postoperative adjuvant treatment. The subgroup of 10 patients with resection of multiple metastases and adjuvant treatment is not statistically compared to each of the previous groups. Furthermore, the method of randomization (by phone? by fax? directly by a randomization list or other means?) is not described in detail. We did not classify this study as a randomized trial to test the hypothesis that adjuvant chemotherapy may be effective after complete resection of colorectal liver metastases.

Our overall intention in publishing the interim results was not to abolish additional treatment in patients with resected liver metastases but to generate further research and support further prospective studies. We are grateful for the critical comment by Clavien et al and support the urgently needed critical but honest discussion about appropriate adjuvant treatment after liver resection.

Our aim remains to improve survival in patients with liver metastases and we would be glad to go this way together and provide evidence-based therapies for our patients. We initiated a feasibility study of a neoadjuvant treatment before liver resection using 5-FU/FA/oxaliplatin in resectable patients with a high risk of recurrence. This study was sponsored and approved by the review board of the German Cancer Society.

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To the Editor:

With interest we have read the article of Fernández-del Castillo et al[1] in which they describe their results on debridement and closed packing with stuffed Penrose drains for necrotizing pancreatitis. They claim the lowest reported mortality rate with these results. In our opinion, their superior outcome is merely a result of patient selection than their treatment strategy.

The only information about the severity of disease is provided by the APACHE II score. The mean and median APACHE II scores of the patients in this study was 9, and represented the state of the patients 24 hours before surgery. In the original study by Knaus et al,[2] an APACHE II score of 5 to 9 in postoperative patients was related to a mortality rate of less than 5%. In a study

by Wilson et al,[3] no deaths occurred in patients with pancreatitis who had a mean APACHE II score of <10. Ranson or Glasgow criteria are not recorded in the present study, and although the authors mention the importance of contrast-enhanced CT scans, a CT-based score such as the CTSI[4] is not given. Therefore, the severity of disease and extent of necrosis can not be quantified. Moreover, only 45% of the patients needed postoperative intensive care support. All these data indicate that most patients were not severely ill.

The authors state that 56% of the patients had infected necrosis at operation. These data cannot be compared with other investigations, because infected necrosis is a generally accepted indication for surgery only if proven by preoperative positive fine-needle aspiration. Positive percutaneous aspiration was done in 15 patients (23%), which is remarkably lower than the recent series by Tsiotos et al (44% culture-positive fine-needle aspirate).[5]

The patients were operated upon after a median of 31 days (mean 56 days), while 42% were operated after 6 weeks. Therefore we think the majority of patients underwent surgery for complications of necrotizing pancreatitis, rather than acute necrotizing pancreatitis, and we question if this approach is the best for this category of patients. Twenty-five patients (39%) underwent operation because of "persistent pancreatitis," described as failure to thrive because of persistent abdominal pain, low-grade fever, or inability to eat. The need for surgery in these patients is questionable. There is no evidence that surgical management will improve outcome for this indication.[6,7] Any other surgical technique or conservative treatment might have given equivalent results.

We emphasize the need for uniform definitions of necrotizing pancreatitis and its complications[8] to make interinstitutional comparison possible. We favor the excellent results of Fernández-del Castillo et al, but most patients were not operated because of severe acute necrotizing pancreatitis. Therefore we must be careful with the conclusions of the authors.

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May 5, 1999

Authors' Reply:

We have read with interest the comments of Willemsen, Bleichrodt, and Girbes regarding our paper on surgical treatment of necrotizing pancreatitis. They challenge our better operative outcomes, claiming that the good results in this study are due to patient selection.

First of all, we would like to emphasize that this report is based on 64 *consecutive* patients, and include all patients with necrotizing pancreatitis that required surgical treatment by the authors over the 80-month period. Patients with pancreatic pseudocysts who underwent either internal or external drainage were specifically excluded.

Willemsen et al argue that the mean APACHE score of 9 indicates a lesser severity of disease, and make reference to a study by Wilson et al where no deaths occurred in patients with pancreatitis who had a mean APACHE II score of less than 10. Willemsen et al must realize that a median APACHE score of 9 implies that 50% of patients will have a higher score, and that we cannot compare patients with pancreatitis who require surgery with those who don't. Furthermore, the APACHE II score in our study was obtained 24 hours before surgery; because it is our practice to delay surgery whenever possible, allowing the patient to stabilize and the score to decline, the lower score additionally underscores the *initial* severity of the pancreatitis. Postoperative intensive care needs cannot really be compared, inasmuch as ICU usage is partly a matter of the surgeon's "style" and institutional practice, and tends to be used sparingly at our institution. The fact is that our series shows a remarkably low mortality for a situation that has traditionally been associated with a worse outcome. As a point of comparison, the study by Tsiotos et al to which the correspondents make reference had a mean APACHE II score of 10, and a mortality of 25%.

We disagree with their statement that a positive percutaneous aspiration is required to consider infection an indication for surgery. The presence of gas within the necrosis is almost always indicative of infection and thus replaces the need for fine-needle aspiration. Furthermore in our experience, patients with sterile necrosis who are acutely ill benefit from necrosectomy, which our results show can be accomplished with similar operative benefit in sterile as in infected necrosis. The contention that operative intervention leads to infection of previously sterile necrosis is without importance, insasmuch as we saw no complication consequent to this contamination.

We do acknowledge that 42% of our patients were operated on 6 weeks after inception of pancreatitis, and that many of these did not have infected necrosis. However, inclusion of these patients (who are usually less sick and have a lower APACHE II score) does not account for our better results, because comparison to those operated earlier than 6 weeks shows no significant difference

in surgical outcomes. We do agree that selective rather than universal debridement is appropriate.

We disagree strongly that the need for surgery in patients with "persistent pancreatitis" is questionable, and would like to know what Dr. Willemson and colleagues propose to do for patients such as these. We do see many patients with sterile necrosis who never require surgery, but all those operated on in this series had been hospitalized continuously or recurrently for this problem. The benefits of the necrosectomy and debridement are very evident in these patients: one of the important messages from our experience is that unnecessary delays are incurred in many patients who continue to be symptomatic from the burden of necrotic tissue. They are not offered surgery on the basis that their necrosis is sterile and the assumption that a debridement is associated with high morbidity and mortality. Our good experience does not support that belief.

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