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To the Editor:

We read with great interest the two recent publications by Neoptolemos and colleagues on the ESPAC-1 trial of adjuvant therapy for resectable adenocarcinoma of the pancreas.[1,2] We congratulate the authors on completing a randomized trial for a disease that has proven difficult to study. We agree with the authors that patients who undergo an incomplete resection resulting in a positive margin are at increased risk for disease-specific mortality. We are concerned, however, over the conclusion of the manuscript published in this journal–that an R1 resection (microscopically positive margins) occurs exclusively because of the underlying biology of the tumor (namely, "a biologically more aggressive cancer") and is independent of patient selection and surgical technique. Concerns over how this conclusion was reached include the following:

1. The authors need to clearly state whether they did or did not have a standardized system of pathologic assessment of surgical specimens, and if they did, how they monitored for quality control. This information is not present in either manuscript. The data presented in Table 3 suggest that the pathologic evaluation of surgical specimens may have been incomplete. Only 77 (76%) of 101 margin-positive patients and 333 (76%) of 440 margin-negative patients were included in the multivariate analysis. Although not stated, it is implied that the remaining patients (nearly 25%) were excluded from analysis, presumably because pathologic data were not evaluable or incomplete.
2. Among the 101 patients with positive resection margins, only 48 were randomized in the 2×2 factorial design. Interpretation of the analysis of the other 53 patients is limited because nonrandomized treatments were not standardized. Furthermore, information on the treatment received by these patients was not provided.
3. The 25th percentile of follow-up in the 227 living patients is given as 1 month (interquartile range, 1–25 months). Thus, 56 (25%) of 227 patients had no more than 1 month of follow-up. This seems high and suggests a lack of maturity of follow-up.
4. It is not clear why the authors performed separate analyses in margin-positive (R1) and margin-negative (R0) patients. In both Tables 2 and 3, the effects of clinical and tumor characteristics on survival are presented separately for the two groups defined by margin status. Thus, there is interest in assessing whether the effects of the clinical and tumor characteristics vary according to margin status. The statistically appropriate analysis for addressing this question is to assess the significance of an interaction (or product) between margin status and each study factor in a model including both margin-positive and margin-negative patients (this is equivalent to the test of heterogeneity reported for the treatment effects).
5. In Table 3, an initial variable selection was performed to identify significant "independent" predictors of survival duration. However, more appropriate would have been an analysis that adjusts the apparent effect of margin status on survival for any confounding from all study factors. This requires including all variables in the analysis regardless of their significance. Both the univariate (unadjusted) and multivariate (adjusted) hazard ratios for the effect of resection margin status on survival should be given along with 95% confidence intervals.

The authors' conclusion that a microscopically positive margin following pancreaticoduodenectomy reflects tumor biology (and is independent of preoperative staging or surgical technique) is not as secure as suggested in their manuscripts.[1,2] It is important to acknowledge the limitations of their study that may impact their analysis and conclusions. These may include the lack of standardized pathology assessment, the lack of protocol-mandated pathology quality control, limitations imposed on the analysis by incomplete data, and technical aspects (outlined above) of the statistical analysis itself.

In patients with adenocarcinoma of the pancreatic head or uncinate process, the most common site of margin positivity following pancreaticoduodenectomy is the retroperitoneal (also termed mesenteric or uncinate) margin adjacent to the proximal 3 to 4 cm of the SMA. A positive retroperitoneal margin may result from: 1) poor patient selection for pancreaticoduodenectomy–for example, surgical resection in patients with tumors that extend to the SMA, usually a result of poor-quality preoperative imaging; 2) failure of the surgeon to separate the specimen from the retroperitoneum in the immediate periadventitial plane of the SMA, an error that can be prevented with proper surgical technique; or 3) the infiltrative nature of pancreatic adenocarcinoma. The latter factor is related to the underlying biology of pancreatic cancer. However, patient selection and surgical technique are under the immediate control of the surgeon and probably have little to do with subtle variations in the biologic behavior of individual tumors.

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Reply from the Authors:

We thank Evans, Hess and Pisters for their comments regarding our recent publications,[1,2] and would like to respond to their specific queries:

Table. Cox proportional hazards model including all clinical and tumour characteristics

Variable	Levels	β	se(β)	χ^2	P	HR (95% CI)
All Patients (n = 345,235 deaths)						
Resection margin	neg, pos	0.246	0.177	1.94	0.163	1.28 (0.91–1.81)
Sex	F, M	0.051	0.146	0.12	0.724	1.05 (0.79–1.40)
Age	continuous	0.017	0.007	5.71	0.017	1.02 (1.00–1.03)
Nodal involvement	no, yes	0.351	0.141	6.18	0.013	1.42 (1.08–1.87)
Tumour grade	well, mod, poor	0.401	0.115	12.15	<0.001	1.49 (1.19–1.87)
Max. tumour size	continuous	0.101	0.037	7.45	0.006	1.11 (1.03–1.19)
Past smoker	never, past	−0.176	0.171	1.06	0.303	0.84 (0.60–1.17)
Present smoker	never, present	−0.180	0.190	0.89	0.345	0.84 (0.58–1.21)
Preop. diabetes	no, yes	0.181	0.169	1.14	0.285	1.20 (0.86–1.67)
Local invasion at op.	no, yes	−0.283	0.190	2.22	0.137	0.75 (0.52–1.09)
Involved adjacent structures	no, yes	0.123	0.139	0.77	0.379	1.13 (0.86–1.49)

1. As a European randomized controlled trial (RCT) in 11 countries, it was not the intention of ESPAC-1 to undertake central pathology review, as all centers relied on expert local gastrointestinal pathologists. At the time of interim analysis of treatment effects, patients with missing surgical data were excluded from the Cox regression analysis. Missing data were randomly distributed across all treatment groups and in equal proportions between R0 and R1 groups - 107 (24%) of 440 R0 patients and 24 (24%) of 101 R1 patients. Thus, prognostic variables were based on an initial model consisting of over 410 patients with pancreatic ductal adenocarcinoma and 66% deaths. Patients were *prospectively stratified* on the basis of resection margin status, before randomization for treatment (or not). There is no other such comparable prospective data set.
2. *All* patients were randomized to treatment! A strength of the trial was the pragmatic design that represents "real-life" clinical practice providing results applicable to the wider population. The patient and disease characteristics of the patients in the three randomization options were all similar. The only selection was in those patients having one of the single randomizations as opposed to the double randomizations (of each patient) in the 2 × 2 design. Patients undergoing one of the single randomizations to a specified treatment (or none) could be allocated treatment specified in the second randomization option or specifically to have that treatment denied ("background treatment"). The pooling of patients is according to their randomized treatment. "Background treatment" refers to the second treatment (or no treatment) after the first randomization. In the case of patients randomized through the 2 × 2 option, this "background treatment" is also randomized. In the case of patients randomized through the single randomization option, "background treatment" (or none) is allocated from the second randomization option. Overall analyses were stratified by both randomization option and "background" therapy to protect against any selection bias. ESPAC-1 was analyzed on an intention-to-treat basis.
3. These interim data were based on 314 deaths, making the data static for 58% of all patients and the reason why we agreed to analyze at this time point. Indeed, 56 living patients (which translates to 11% of all patients) had follow-up ≤ 1.3 months. The data, although not complete, were mature enough to investigate specific prognostic factors, because 56 (25%) of alive patients also had follow-up ≥ 24.9 months. A further analysis of treatment effects is planned for April 2002 with minimum of 2 years follow-up.
4. Prognostic variables were selected using the complete data set. As explained in the paper,[2] we did not re-analyze R0 and R1 patients separately in terms of selection of prognostic variables but rather fitted the global Cox model to the two sub-groups of data. The most important findings were that resection margin status was only prognostically important in the absence of tumor grade, nodal status, and the reduced significance of age for R1 patients (unlike R0 patients, whose risk increased with increased age). Including resection margin status and interactions with other variables in the "base" Cox model of all patients did not provide any additional explanation of the variability in the data (i.e., test of interaction not significant). Similarly, the interaction term of resection margin status and tumor size was not statistically significant when included in the alternative model of these two main effects.
5. The hazard ratio (heart rate) for risk of death by resection margin status in Figure 2 was omitted in error in the published version of our paper. The increased risk for R1 compared with R0 patients has heart rate = 1.36 (95% CI: 1.08–1.98). HRs for all variables adjusted for the effect of resection margin status and other significant factors were calculated in a Cox Regression model based on 345 patients and 235 (68%) deaths (see Table). Resection margin status is not significant in the presence of grade of disease and nodal status. The importance of nodal status is reduced (albeit still highly significant) and the influence of tumor size is increased when adjusted for resection margin status in the model. The effects of tumor grade and age remain unchanged. This model does not maximize use of the data, as inclusion of nonsignificant variables increases the number of patients excluded through missing data.

Until very recently there was a general perception that patient prognosis was mainly determined by resection margin status. The ESPAC-1 data (from 541 patients stratified by resection margin status and randomized to treatment according to specific clinical protocol) has provided a unique opportunity to explore the strength of resection margin status in the presence of other possible prognostic factors.

Resection margin status is a significant prognostic factor that requires more investigation. Our interesting discovery was that resection margin status was only statistically prognostic in the

absence of tumor grade and nodal status. The analysis argues that resection margins may be significantly linked to these histologic factors but appears to be independent of tumor size. This invoking and interesting analysis was hypothesis-generated and exploratory but was based on robust, mature data collected from patients treated according to a predefined, agreed clinical protocol. The model will be tested on an independent validation set of patients with resected pancreatic ductal adenocarcinoma randomized in the ESPAC-3 trial. We strongly advocate including patients with R1 tumors in future RCTs of adjuvant chemotherapy but both randomization and analysis should be stratified by resection margin status to account for the more aggressive biology.

It is of course obvious that patient selection and surgical technique are under the immediate control of the surgeon and probably have little to do with subtle variations in the biologic behavior of individual tumors. These observations are hardly relevant to the novel and important finding that it is the *biology* that determines an R1 resection margin. While we are always interested in opinion, it would be valuable to see a similar analysis undertaken in other large series. Thereby we could confirm or refute the present hypothesis and in the process learn more about pancreatic cancer.

We hope that Evans, Hess, and Pisters now better understand that a 2×2 factorial design produces a highly efficient and statistically very powerful trial. The ESPAC-1 trial has clearly and unequivocally rejected the survival value of adjuvant chemoradiotherapy for pancreatic cancer, suggested a role for adjuvant chemotherapy, demonstrated that it is worthwhile treating patients with an R1 margin, and identified biology as a major determinant of tumor cell spread to the resection margin.

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To the Editor:

We read with interest the paper by Liu et al., entitled "Patient evaluation and management with selective use of magnetic resonance cholangiography (MRC) and endoscopic retrograde cholangiopancreatography (ERCP) before laparoscopic cholecystectomy (LC)."[1] The authors' goal of "a reduction in redundant and unnecessary diagnostic testing" is commendable; practicing in a similar teaching hospital environment, we share their objective. However, in reviewing the authors' data, we remain unconvinced of the merits of preoperative MRC.

We applaud the authors' ability to predict patients at high risk of common bile duct (CBD) stones; 93% of their "extremely high risk" patients (group 1) did, in fact, have CBD stones. However, we submit that their treatment algorithm advocates redundant and, therefore, unnecessary diagnostic testing. In addition to preoperative ERCPs, the authors performed 37 MRCs, 12 of which were abnormal (with one false-positive); there was one false-negative study. They also performed 52 intraoperative cholangiography (IOC) studies, of which only 2 were abnormal. Thus, the authors performed 25 unnecessary MRCs (5.7% of the overall group) and 50 unnecessary IOCs (11.4% of the overall group). Despite all this testing, 3 patients (0.9% of the "untested" group 4) returned postoperatively with CBD stones.

We have proposed the routine use of intraoperative ultrasonography (IOUS) to screen for CBD stones.[2] We performed IOUS in 248 consecutive patients undergoing LC. In our experience, IOUS obviates the need for most diagnostic studies. IOUS identified all cases of CBD stones, with no false-positive examinations. We found unsuspected stones in 2 (0.8%) patients, similar to Liu et al.[1] If we project our experience to Liu et al., they would have eliminated the need for all 37 MRCs and 50 IOCs, and identified all 3 cases of unsuspected CBD stones. Furthermore, we[2] and others[3] are successful in extracting the majority of CBD stones laparoscopically. Thus, with the ability to intraoperatively identify and extract CBD stones in a minimally invasive fashion, preoperative ERCP may prove unnecessary even in "extremely high risk" patients.

Liu et al. point out that over $5 billion is spent annually to treat gallstone disease. IOUS allows one to reliably detect CBD stones with minimal expense, without any apparent detriment to patients. While MRC appears to be a promising modality for biliary imaging, we fail to recognize a role for this expensive screening test in patients with gallstone disease.

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Reply from the Authors:

We thank Dr. Biffl and Dr. Moore for their comments and welcome the opportunity to respond. As stated, there has been no consensus reached regarding the optimal strategy in diagnosis and treatment of choledocholithiasis during the laparoscopic era.[1,2] Our group's preference is to diagnose and eliminate common bile duct stones (CBDS) before laparoscopic cholecystectomy (LC). The routine application of endoscopic retrograde cholangiopancreatography (ERCP) for all patients with possible CBDS results in unnecessary preoperative ERCP in up to 75% of patients.[1] The routine use of a noninvasive imaging modality, such as magnetic resonance cholangiography (MRC) before LC, effectively identi-

fies patients who may benefit from therapeutic ERCP. However, this approach results in excessive MRC usage.[3] The goals of the study were to develop patient management strategies that would reduce the occurrence of non-therapeutic ERCP, avoid the intraoperative and postoperative discovery of CBDS, and improve the utilization of MRC. The results of treatment of 440 patients with our selective patient management strategies were reported.[2]

Dr. Biffl and Dr. Moore indicated that the routine use of intraoperative ultrasonography (IOUS) allowed one to detect CDBS with minimal expenses, without any apparent detriment to patients. They suggested that this type of management strategy would lead to the reduction, if not the elimination of all preoperative imaging studies. By design, such an approach would lead to the elimination of preoperative imaging. However, it is pertinent to point out that their proposed approach would shift the burden of diagnosis and treatment of CBDS to the intraoperative and postoperative environments. An valid comparison of outcomes between our management strategies and the one proposed by Dr. Biffl and Dr. Moore should include analysis of intraoperative expenditures, time utilization, patient satisfaction, the number of laparoscopic and open common bile duct explorations (CBDE), postoperative ERCP, and remedial operations performed based on these strategies.

As indicated, the group at the Denver Health Medical Center has had extensive experience with IOUS.[4] It is important to note that the accuracy of IOUS in diagnosing CBDS is highly operator dependent and may be associated with a learning curve, consisting of 20 to 40 examinations.[5] In a recent review, the reported sensitivity of IOUS for CBDS ranged from 71 to 96%.[5] Based on these statistics, the use of this approach would result in the reliance on postoperative ERCP for the clearance of missed-CBDS. With the reported success rate of therapeutic ERCP ranging from 75 to 92%,[1] scenarios involving remedial operative therapy would become possible. Although Drs. Biffl and Moore indicated thatlaparoscopic management of CBDS is highly successful in their hands, the success rate of laparoscopic CBDE has been reported to range between 80 and 85%.[6] The failure of laparoscopic CBDE would potentially result in open CBDE in 15 to 20% of the treated patients.

We believe that the differences between our treatment approach and the one proposed by Drs. Biffl and Moore are influenced by resources and technical expertise available at the respective institutions. We believe that our treatment proposal provided effective strategies for those who may prefer to manage CBDS before LC, and we thank Dr. Biffl and Dr. Moore for sharing with us effective management strategies from their institution.

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