Clinicopathologic Factors Associated With False-Negative Sentinel Lymph-Node Biopsy in Breast Cancer

To the Editor:

The University of Louisville Sentinel Lymph Node Study (a multi-institutional prospective observational study) has made major contributions to our knowledge about the feasibility, indications, technique, and learning curve for sentinel lymph node (SLN) biopsy in breast cancer. Its particular strength is its breadth; by drawing on the experience of more than 300 surgeons performing more than 4000 SLN biopsy procedures in practice setting ranging from university teaching institutions to rural hospitals, it has been preeminent in establishing that SLN biopsy works in the "real world."

SLN biopsy is falsely negative (FN) in about 5% of node-positive and (depending on the proportion of node-positive cases) in about 2% of all patients. A very large study is therefore required to identify with statistical significance those factors that might contribute to FN results. In a recent report,[1] the Louisville group have addressed this issue and in the process have raised as many questions as answers.

As they have shown before, FN were significantly more frequent when only 1 SLN was removed,[2] a strong argument for removal of all blue and hot SLN, not just the first one. As they have also shown before, FN were more frequent for inexperienced surgeons, and their present data interestingly suggest that the "learning curve" may constitute as few as 4 cases, compared with their earlier estimate of 20 cases.[3] This result matches the experience of others[4] and is consistent with a gradual maturation of the SLN biopsy technique.

Their observation that FN were more frequent for smaller tumors is harder to explain, and is discordant with their earlier finding that the FN rate was unrelated to tumor size.[5] It is equally unclear why FN were more frequent with upper outer quadrant tumors. Finally, their observation that FN were more frequent with the use of immunohistochemical (IHC) staining makes no sense at all; increased pathologic scrutiny of the SLN can only act to *increase* the sensitivity of the examination (thereby decreasing the FN rate). This is confirmed by a detailed collective review of the SLN literature, comparing 27 studies using hematoxylin and eosin staining alone with 8 studies using hematoxylin and eosin plus IHC, with FN rates of 8% and 3%, respectively ($P < 0.006$).[6] Since the Louisville study did not require a standardized pathology technique, it would be interesting to see a direct comparison of all clinicopathologic features for the IHC versus no-IHC cases to see if some other variable could explain this counterintuitive result.

The larger problem may lie elsewhere. Cases with incomplete data automatically "drop out" of multivariate analyses, and this may explain some of the perplexing results above. While their study purports to involve 4116 patients and 3869 successful SLN biopsy procedures by more than 300 surgeons, examination of the data tables indicates that while SLN and axillary node status were known in all cases, tumor size was missing in 33%, and *all* of the other clinicopathologic features were missing in 65% of cases. This pattern of missing data strongly suggests that the University of Louisville data consist of two distinct groups: one (comprising about 1340 patients) in whom complete and detailed information was collected for each case, and another (comprising the remaining two thirds) which recorded the barest minimum of data (SLN and axillary node status only). If, as appears to be the case, the authors are really reporting the results of a minority subset rather than the entire experience of their study, then how can we be sure that this subset is truly representative? Asked another way, are we seeing the collective results of more than 300 surgeons in a broad range of practice settings, or those from a selected subset of surgeons and institutions?

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REFERENCES

1. Martin RC, Chagpar A, Scoggins CR, et al. Clinicopathologic factors associated with false-negative sentinel lymph-node biopsy in breast cancer. *Ann Surg*. 2005;241:1005–1012.
2. Wong SL, Edwards MJ, Chao C, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. *J Am Coll Surg*. 2001;192:684–689.
3. McMasters KM, Wong SL, Chao C, et al. Defining the optimal surgeon experience for breast cancer sentinel lymph node biopsy: a model for implementation of new surgical techniques. *Ann Surg*. 2001;234:292–300.
4. Clarke D, Newcombe RG, Mansel RE. The learning curve in sentinel node biopsy: the ALMANAC experience. *Ann Surg Oncol*. 2004;11(suppl):211–215.
5. Wong SL, Chao C, Edwards MJ, et al. Accuracy of sentinel lymph node biopsy for patients with T2 and T3 breast cancers. *Am Surg*. 2001;67:522–526.
6. Liberman L. Pathologic analysis of sentinel lymph nodes in breast carcinoma. *Cancer*. 2000;88:971–977.

Reply:

In reply to Dr. Cody's concern's regarding incomplete data, Tables 1 and 2 present the data only from with patients with false-negative (FN) and true-positive (TP) results. This total is 1361 patients. The footnote statements at the bottom of both tables state that the number of patients in each category should total 3870. This statement is incorrect, and is the reason for the confusion. In actuality, Tables 1 and 2 are missing only a small number of patients in each category. We apologize for this confusion, and have submitted an erratum that explains this error. Nonetheless, these mistakes affect neither the analysis of the data nor the conclusions reached by this study. Please be assured that the University of Louisville Breast Cancer Sentinel Lymph Node Study is not fundamentally flawed by a preponderance of missing data (as is evident in our numerous other publications).

We agree with Dr. Cody that, in theory, "increased pathologic scrutiny" by IHC analysis of SLN should increase the sensitivity for detection of nodal metastasis and reduce the FN rate. We were therefore surprised at the finding that IHC was, if anything, associated with an increased FN rate. Although we do not have a simple explanation for this finding, it has been checked many times to assure accuracy. The data are the data, and no amount of explanation will change

the results. It is possible that our findings are related to the lack of standardization of IHC performance and interpretation throughout all institutions that were involved in the study. We agree with Dr. Cody that our results do provide more questions than answers regarding IHC, but unless the long-awaited results from two large prospective studies indicate that micrometastases detected by IHC analysis are clinically significant, IHC should not be performed for routine SLN analysis.

The association of upper outer quadrant (UOQ) tumors with an increased FN rate was initially evaluated in a report by Chao et al,[1] which demonstrated a significantly higher FN rate when compared with other tumor locations. This has been a consistent finding during our study. Unlike the finding with IHC, however, the fact that UOQ tumor location is associated with a greater FN rate has an intuitive explanation: injection of radioactive colloid (especially peritumoral injection) in the UOQ often makes gamma probe detection of SLN in the adjacent axilla very difficult because of the high degree of background radiation or "shine through." This tumor location has proved the most challenging for surgeons who are learning SLN biopsy.

We agree with Dr. Cody that the results regarding FN rate and tumor size are in disagreement with our prior report.[2] However, results from large clinical studies are not always constant with increasing sample size. Dr. Cody is familiar with this phenomenon, as the Memorial Sloan-Kettering group initially reported that SLN biopsy was more accurate for T1 tumors,[3] then in a later analysis found that this was not the case.[4] Our prior report included 1436 patients, while the current analysis involves 4131 patients. However, the results are not so dissimilar as they may appear. Our current analysis showed no significant relationship between FN rate and tumor size when categorized by T-stage; tumor size was only significant when you split tumor size into categories of <2.5 cm versus ≥ 2.5 cm. Admittedly, this statistical finding may have little clinical implication.

Regardless, our study indicates that the most practical thing one can do to reduce the FN rate is to increase surgeon and institutional experience with this technique. This allows SLN biopsy to be performed with an acceptable FN rate for most breast cancer patients.

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REFERENCES

1. Chao C, Wong SL, Woo C, et al. Reliable lymphatic drainage to axillary sentinel lymph nodes regardless of tumor location within the breast. *Am J Surg*. 2001;182:307–311.
2. Wong SL, Edwards MJ, Chao C, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. *J Am Coll Surg*. 2001;192:684–689.
3. O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg*. 1998;187:337–338.
4. Olson JA Jr, Fey J, Winawer J, et al. Sentinel lymphadenectomy accurately predicts nodal status in T2 breast cancer. *J Am Coll Surg*. 2000;191:593–599.

Is There Really a Survival Benefit of SDD in Burns?

To the Editor:

We were impressed by the interesting study on selective decontamination of the digestive tract (SDD) recently reported by de La Call et al in a large population of burned patients.[1] We are fully aware of the tremendous work that was required to carry out such a randomized trial. This study addresses an important and unresolved issue. However, after careful analysis of the data, we question some of the authors' conclusions.

The observed reduction of mortality in SDD recipients is likely to be caused by factors other than SDD. Indeed, considering the classic determinants of burn mortality, especially age,[2] the placebo group appears to be more severely injured. The age difference between groups was nearly significant ($P = 0.06$), which may have a substantial impact on expected mortality. In addition, the surface of the burns tended to be larger with slightly more inhalation injuries in the control group: this corresponds potentially to 3 points on "Ryan's score." Indeed, elderly patients with inhalation tend to die early, which was typically the case in this study: 5 placebo patients died during the first week (before any expected effect of SDD), and further 6 during the second week. As these factors have a major impact on survival of severe burn patients,[2] the reported mortality rate difference may disappear after adjustment, which was not apparently done in the study, where only raw mortality was reported.

The conclusion that SDD reduces the incidence of pneumonia in severe burn patients should also be modulated. According to the data, SDD reduced only the pneumonia defined by the authors as "primary endogenous." As the median time to the first pneumonia episode was 3 days, this effect can be almost exclusively attributed to the intravenous administration of a third generation cephalosporin (cefotaxime) for 4 days after admission.[3] Although included in most SDD regimens, considering its potential negative impact on the ecology of microorganisms,[4] the choice of a third-generation cephalosporin for initial prophylaxis remains questionable. This may have contributed to the high rate of multiresistant microorganisms reported "secondary pneumonia were invariably caused by MRSA or AGNB."

In contrast, SDD had no impact on pneumonia defined as "secondary endogenous." Although 17 days was the median delay before their development, the microorganisms isolated strongly suggest that the oropharyngeal and digestive application of nonabsorbable antimicrobials only have a limited effect restricted to *Pseudomonas aeruginosa*. The absence of effect on bloodstream and on wound infections, which are typically caused by enteral microorganisms,[5] scored by the authors as "secondary endogenous" also suggests that SDD was of limited efficacy.

As in other studies, SDD may have promoted the emergence of MRSA-related pneumonia.[6,7] In addition, the microbiologic profile reported in the patients suggests that infection prophylaxis and control might be improved in this particular burn unit, contrasting with the concept of SDD promoted by one of the coauthors of the study.[8]

Accordingly, we wonder if both the title and conclusions of the study are appropriate, since they may constitute an

Post-scriptum: Predicted mortality in Table 1 probably refers to reference 18 (Ryan) and not to reference 16 (van Saene).

overinterpretation of the data. As a consequence, we will continue to refrain from systematic SDD in burn patients admitted into our specialized ICU until more data are provided.

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REFERENCES

1. de La Call MA, Ceredá E, Garcia-Hierro P, et al. Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract: a randomized, placebo-controlled, double-blind trial. *Ann Surg*. 2005; 241:424–430.
2. Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. *N Engl J Med*. 1998;338: 362–366.
3. Bornstain C, Azoulay E, De Lassence A, et al. Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clin Infect Dis*. 2004;38:1401–1408.
4. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. *JAMA*. 1996;275:234–240.
5. Mayhall CG. The epidemiology of burn wound infections: then and now. *Clin Infect Dis*. 2003;37:543–550.
6. Gastine H, Wolff M, Delatour F, et al. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics: the French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med*. 1992;326: 594–599.
7. Verweast C, Verhaegen J, Ferdinande P, et al. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med.* 1997;25:63–71.
8. Van Seane HKF, Petros AJ, Ramsey G, et al. All great truths are iconoclastic: selective decontamination of the digestive tract moves from heresy to level 1 truth. *Intensive Care Med*. 2003;29:677–690.

Reply:

We read the letter by Eggimann et al and are pleased to have the opportunity to clarify their interpretation of the results of our randomized controlled trial to asses the efficacy of SDD in severely burned patients.[1]

We agree that there was an imbalance in the distribution of some variables related to mortality between test and control groups. Therefore, we reported in the sections Statistical Analysis (p. 426) and Results (p. 427; paragraph Mortality) the crude risk ratio of mortality [0.33 (95% confidence interval [CI], 0.13–0.85)] and the adjusted risk ratio using a multivariate Cox regression model [0.25 (95% CI, 0.08–0.76)]. Apparently, Eggimann et al ignored these data. The mortality data were adjusted using expected mortality,[2] and similar results were obtained after adjusting using variables usually included in the predictive models of mortality (age, body surface burn, full-thickness burn, and inhalation): risk ratio, 0.27 (95% CI, 0.09–0.85). Therefore, the conclusion about the impact of SDD on mortality is clinically and statistically correct.

There are 55 RCTs on SDD and 10 meta-analyses of SDD-RCTs. All but two meta-analyses have demonstrated a significant survival benefit in patients receiving SDD using parenteral and enteral agents. There was an impact on mortality, but not significant as the sample size was too small in the Kollef[3] and Safdar et al[4] meta-analyses. Despite the consistent survival benefit of SDD in its entirety, the latest fad of the SDD antagonists concerns the relative contribution of the parenteral and enteral components to the reduction of morbidity and mortality. The 55 RCTs were not designed to assess the relative effect of the two major components of SDD. Our conclusion [last but one paragraph of the article, p. 429] "Whether the prevention of primary endogenous infections by the parenteral cefotaxime component only reduces the mortality to the same extent as the full SDD protocol, can only be answered in a RCT in which parenteral cefotaxime is compared with enteral polymyxin/tobramycin/amphotericin B" is in line with the results of all SDD trials and meta-analyses. But uncertainty of the weight of the parenteral and enteral contribution does not justify withholding a treatment that saves lives.

Eggimann et al question the choice of third-generation cephalosporin, cefotaxime, as parenteral component of SDD. They believe that cefotaxime selects multiresistant aerobic Gram-negative bacilli [AGNB] and methicillin-resistant *Staphylococcus aureus* [MRSA], due to its disregard for the patients' ecology. The parenteral and enteral antimicrobials of the SDD protocol mainly target AGNB. The recent Dutch RCT, the largest to date with approximately 1000 patients, evaluated cefotaxime and polymyxin/tobramycin/amphotericin B on antimicrobial resistance among AGNB as the primary endpoint.[5] The Amsterdam RCT demonstrated that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of SDD patients compared with 26% of control patients with a relative risk of 0.6 (95% CI, 0.5–0.8). Fair enough, the SDD prophylaxis is not active against MRSA. Of the 55 RCTs on SDD, there are 5 RCTs[6–10] conducted in ICUs where MRSA was endemic at the time of the trial, so they report a trend toward higher MRSA carriage and infection rates in patients receiving SDD. However, cefotaxime was not used in the French RCT.[6] Cefotaxime was given to both arms, test and placebo, in the Barcelona[7] and Cape Town[8] RCTs. The Innsbruck investigators gave intravenous ciprofloxacin.[9] The Belgian RCT used cefotaxime.[10] These data suggest that the enteral component exerts selective pressure rather than the parenteral cefotaxime.

SDD was designed in the early 1980s, when MRSA was not such a widespread problem. Nowadays, MRSA is a global problem, in particular, in intensive care units such as our burn ICU. The addition of enteral vancomycin to the classic SDD is required to control MRSA in ICUs with endemic MRSA.[11,12] Enteral vancomycin was introduced into our burn ICU on the strength of the data of this RCT in severely burned patients.[1] The relative risk of acquiring MRSA at any site was 0.22 (95% CI, 0.15–0.34), and in the lower airways 0.07 (95% CI, 0.03–0.19), without the emergence of vancomycin-resistant enterococci or *S. aureus* with intermediate sensitivity to vancomycin.

Eggimann et al made a valid point about the relative failure of SDD [25%] in preventing secondary endogenous infections due to AGNB. We believe that this is an important finding that in severely burned patients the efficacy of SDD in not 100%. The fourth paragraph of the section Discussion [p. 428] describes the possible causes of the SDD failures in this particular severely ill patient population.

Our RCT demonstrates that, at present, the best available evidence is that SDD saves 1 burn patient for every 5 treated without harmful side effects. From an ethical point of view, withholding a life-saving therapy would be unacceptable to our patients.

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REFERENCES

1. de la Cal MA, Cerda E, García-Hierro P, et al. Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract: a randomized, placebo-controlled, double-blind trial. *Ann Surg*. 2005;241:424–430.
2. Smith DL, Cairns BA, Ramadan F, et al. Effect of inhalation injury, burn size, and age on mortality: a study of 1447 consecutive burn patients. *J Trauma*. 1994;37:655–659.
3. Kollef M. The role of selective digestive tract decontamination on mortality and respiratory tract infections: a meta-analysis. *Chest*. 1994; 105:1101–1108.
4. Safdar N, Said A, Lucey MR. The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis. *Liver Transpl*. 2004;10:817–827.
5. de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet*. 2003;362:1011–1016.
6. Gastinne H, Wolff M, Delatour F, et al. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics: the French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med*. 1992;326: 594–599.
7. Ferrer M, Torres A, Gonzalez J, et al. Utility of selective digestive decontamination in mechanically ventilated patients. *Ann Intern Med*. 1994;120:389–395.
8. Hammond JM, Potgieter PD, Saunders GL, et al. Double-blind study of selective decontamination of the digestive tract in intensive care. *Lancet*. 1992;340:5–9.
9. Lingnau W, Berger J, Javorsky F, et al. Selective intestinal decontamination in multiple trauma patients: prospective, controlled trial. *J Trauma*. 1997;42:687–694.
10. Verwaest C, Verhaegen J, Ferdinande P, et al. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med*. 1997;25:63–71.
11. Silvestri L, Milanese M, Oblach L, et al. Enteral vancomycin to control methicillin-resistant Staphylococcus aureus out-break in mechanically ventilated patients. *Am J Infect Control*. 2002;30:391–399.
12. de la Cal MA, Cerda E, van Saene HK, et al. Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant Staphylococcus aureus in a medical/surgical intensive care unit. *J Hosp Infect*. 2004; 56:175–183.

Prevention of Intra-abdominal Adhesions Using the Antiangiogenic COX-2 Inhibitor Celecoxib

To the Editor:

We read, with avid attention and close interest, the carefully performed study of Greene et al,[1] demonstrating that perioperative COX-2 inhibitors may attenuate adhesion formation in an experimental murine model. This seems entirely in keeping with the known antiangiogenic effects of these drugs and the up-regulation of COX-2 that is known to occur in adhesion-associated tissues and, especially, fibroblasts. However, we are somewhat concerned that the authors did not extrapolate further from their realizations that adhesion formation is "like all types of wound healing" and that "it may aid in healing" and include formal assessment of surgical wound healing in their protocol. This omission is particularly apparent given that the authors admit awareness of the fact that other antiangiogenic agents have been previously precluded from further investigations as anti-adhesion agents because of their effects on wound healing among other problems. Additionally, there exists a considerable body of literature that suggests that COX-2 may function more in a pro-restorative role after tissue injury than in a purely pro-inflammatory capacity. In particular, these anti-inflammatory agents in general (and COX-2 inhibitors in particular) are known to delay the healing of gastric ulcers[2] as well as intestinal mucosal injuries[3] and bone fractures[4] and have also been shown (by our own group[5] and others[6]) to markedly affect the integrity of colonic anastomoses in experimental settings similar to that used in this current study. Furthermore, this specific area of concern regarding their safety can be expanded to include the authors other contentions that "celecoxib and rofecoxib are known to be safe even when taken in high doses chronically" and that "clinical trials (now) need to be performed to confirm the (their) beneficial properties in reducing intra-abdominal adhesions." Unfortunately, it has been recently realized that exactly the opposite is true, and the considerable cardiovascular toxicities induced by these agents have led to the withdrawal of rofecoxib and labeling precautions being ascribed to other related compounds.[7,8]

In defense of the authors, however, it may well be that (rather than selective referencing or incomplete background research) their study has been superseded by clinical and experimental realizations that have occurred sometime between its initial submission and entry in to the public domain (a consideration supported by their most recent reference listed being from 2003). Acknowledgment of this lag-time in the section devoted currently to corresponding author details may go some way toward facilitating a reader's appreciation of the current relevance of experimental findings. However, in cases such as this, when manuscripts are, perhaps, more significantly undermined but by their lack of an up-to-date discussion of the clinical relevance of their hypothesis than by their study design or analytical performance, it would seem prudent allow the authors a late right of review of their manuscript or, at least, a prefacing statement to avoid misleading conclusions to be transmitted to the casual reader.

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REFERENCES

1. Greene AK, Alwayn IP, Nose V, et al. Prevention of intra-abdominal adhesions using the antiangiogenic COX-2 inhibitor celecoxib. *Ann Surg*. 2005;242:140–146.
2. Jones MK, Wang H, Peskar BM, et al. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. *Nat Med*. 1999;5:1418–1423.
3. Morteau O, Morham SG, Sellon R, et al. Impaired mucosal defense to acute colonic injury in mice lacking cyclo-oxygenase-1 or cyclo-oxygenase-2. *J Clin Invest*. 2000;105:469–478.

4. Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. *J Bone Miner Res*. 2002; 17:963–976.
5. Cahill RA, Sheehan KM, Scanlon RW, et al. Effects of a selective cyclo-oygenase-2 inhibitor on colonic anastomotic and skin wound integrity. *Br J Surg*. 2004;91:1613–1618.
6. Mastboom WJ, Hendriks T, van Elteren P, et al. The influence of NSAIDs on experimental intestinal anastomoses. *Dis Colon Rectum*. 1991; 34:236–243.
7. Garner SE, Fidan DD, Frankish RR, et al. Rofecoxib for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2005;1:CD003685.
8. Juni P, Nartey L, Reichenbach S, et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet*. 2004;364:2021–2029.

Reply:

Recent revelations about unwanted side effects of COX-2 inhibitors have received much publicity since the submission of our manuscript in November 2003. Specifically, it appears that the long-term use of COX-2 inhibitors increases the risk for adverse cardiovascular events.[1–3] Our studies in small animals showing that COX-2 inhibitors inhibit intra-abdominal adhesions, presumably through their antiangiogenic and antifibroblastic propertve not yet been translated to humans. As a result, we can only speculate about how our conclusions relate to the current events regarding COX-2 inhibitors.

It appears that the risk of cardiovascular events in humans taking COX-2 inhibitors is associated with the type of COX-2 inhibitor, the population taking the drug, duration of exposure, and the dose of the drug. For example, patients taking rofecoxib have a greater risk of myocardial infarction compared with patients receiving celecoxib.[4] Elderly patients as well as patients with comorbidities such as rheumatoid arthritis, colorectal cancer, and coronary artery disease also have an increased risk of cardiovascular events while taking COX-2 inhibitors.[1,3,5,6] Higher doses of celecoxib are associated with a greater chance of adverse cardiovascular events.[3,6] Finally, most studies have shown complications only after the long-term use of COX-2 inhibitors over several months.[1–3,6]

While COX-2 inhibitors increase the risk for adverse cardiac events, they do not appear to inhibit wound healing. Evidence suggests that COX-2 inhibitors can selectively inhibit adhesion formation and weaken colonic anastomosis.[7,8] This paradigm is also illustrated among other angiogenesis inhibitors. For example, endostatin inhibits tumor growth but will not inhibit wouing or liver regeneration.[9] Vasostatin does not affect wound healing at doses sufficient to inhibit tumor growth.[10] Furthermore, we have not appreciated wound healing difficulties in animals treated with COX-2 inhibitors.

Because all drugs have a toxicity profile, their risks must be weighed against the potential benefits to the patient. Patients at risk for adhesions may be a new cohort particularly suited for COX-2 inhibitors because of a potentially low risk to benefit ratio. First, because the peritoneal lining is reepithelialized within 6 days, and only 10 days of treatment was required to obtain long-term adhesion prevention in our study, human subjects would not appear to require long-term COX-2 inhibitors to prevent adhesions. Second, it is likely that routine doses of COX-2 inhibitors would be required for efficacy in humans, thus minimizing the increased risk of cardiovascular events associated with high doses used for treating diseases such as rheumatoid arthritis. Third, different COX-2 inhibitors may possess better risk to benefit ratios for treating adhesions. For example, current evidence suggests that celecoxib would be superior to rofecoxib for the treatment of adhesions. Not only did we find celecoxib to be more efficacious in preventing adhesions compared with rofecoxib, presumably because of the superior antifibroblast activity of celecoxib, but in humans celecoxib also has a lower toxicity profile than rofecoxib.[4]

In conclusion, COX-2 inhibitors have a potent ability to prevent adhesion formation in mice. If COX-2 inhibitors are proven to be equally effective in reducing adhesions in humans, then these drugs could become routine perioperative prophylaxis for patients undergoing surgical procedures. However, the likelihood of an adverse cardiovascular event with a COX-2 inhibitor must be weighed against preventing the morbidity associated with adhesions, such as bowel obstructions, infertility, perforations, and death. Despite the recent discovery of unwanted side effects, COX-2 inhibitors remain one of the few approved antiangiogenic drugs. Unlike other angiogenesis inhibitors, however, COX-2 inhibitors are particularly suited for adhesion prevention because they are also pharmacologically effective against postoperative pain.

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REFERENCES

1. Garner SE, Fidan DD, Frankish RR, et al. Rofecoxib for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2005;1:CD003685.
2. Juni P, Nartey L, Reichenbach S, et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet*. 2004;363:2021–2029.
3. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med*. 2005;143:481–489.
4. Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med*. 2005;142:157–164.
5. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005;352:1081–1091.
6. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma preventions. *N Engl J Med*. 2005;17: 1071–1080.
7. Cahill RA, Sheehan KM, Scanlon RW. Effects of a selective cyclo-oxygenase 2 inhibitor on colonic anastomotic and skin wound integrity. *Br J Surg*. 2004;91:1613–1618.
8. Blomme EA, Chinn KS, Hardy MM, et al. Selective cyclooxygenase-2 inhibition does not affect the healing of cutaneous full-thickness incisional wounds in SKH-1 mice. *Br J Dermatol*. 2003;148:211–223.
9. Berger AC, Feldman Al, Gnant MF, et al. The angiogenesis inhibitor, endostatin, does not affect murine cutaneous wound healing. *J Surg Res*. 2000;91:26–31.
10. Lange-Asschenfeldt B, Velasco P, Streit M, et al. The angiogenesis inhibitor vasostatin does not impair wound healing at tumor-inhibiting doses. *J Invest Dermatol*. 2001;117:1036–1041.

Ischemic Preconditioning Impairs Liver Regeneration in Extended Reduced-Size Livers

To the Editor:

In the March 2005 issue of the *Annals of Surgery*, Eipel et al[1] have demonstrated, in an animal model, that ischemic pre-

conditioning (IPC) reduces the extent of liver regeneration after 70% partial hepatectomy (PHx), and reduces survival after 90% PHx. They concluded that, with a reduced liver mass, IPC may be dangerous. We would like to support their concerns on the effect of IPC on liver regeneration.

The mechanism of liver regeneration after PHx has a reparative/inflammatory basis,[2] and IPC has been shown to reduce inflammatory response.[3] We have evaluated the effect of isolated IPC-type stimulus (without further ischemia) on hepatic regenerative activity.

In our experimental group, 10 minutes of ischemia of right and caudate lobe of rat liver was followed by 10 minutes of reperfusion before 70% PHx by removal of median and left lobe (n = 6). The control group underwent 70% PHx only (n = 6). Bromodeoxyuridine index 24 hours after PHx showed reduced regenerative activity in the IPC group. Liver weight was higher in controls, but this was not statistically significant.

Our data support the findings of Eipel et al, with short periods of ischemia followed by reperfusion impairing liver regeneration after PHx, in a different but related model. Clinical applications of IPC should be restricted to patients with adequate functional mass until the mechanism relating IPC to liver regeneration has been clarified.

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REFERENCES

1. Eipel C, Glanemann M, Nuessler AK, et al. Ischemic preconditioning impairs liver regeneration in extended reduced-size livers. *Ann Surg*. 2005;241:477–484.
2. Michalopoulos GK, DeFrances MC. Liver regeneration. *Science*. 1997;276:60–66.
3. Teoh N, Field J, Sutton J, et al. Dual role of tumor necrosis factor-alpha in hepatic ischemia-reperfusion injury: studies in tumor necrosis factor-alpha gene knockout mice. *Hepatology*. 2004;39:412–421.

Reply:

We appreciate the insights provided by the results of Dr. Habib, demonstrating that liver regenerative capacity is deteriorated in animals undergoing ischemic preconditioning (IPC) of the liver prior to 70% hepatectomy without concomitant vascular clamping.[1] These data are in line with our previous report[2] on impaired proliferation of livers that underwent IPC and 70% hepatectomy under strict inflow occlusion.

This is an astonishing, but not imperceptible, interpretation that IPC, which has been shown to provide beneficial anti-inflammatory effects,[3] might interfere with the hepatic regenerative capacity, as this proliferative response might initially be dependent on inflammatory environment, inevitably inherent to the surgical trauma upon liver resection. In line with this, a recently published review based on a Medline search by Banga et al using the key words "ischemic preconditioning," "ischemia-reperfusion injury," "transplantation," and "hepatic resection" concludes that IPC reduces the severity of ischemic reperfusion injury in several animal models and in recent human trials.[4] However, there remains still the question to be answered why the liver benefits from IPC in patients with adequate functional liver mass, but not upon extended-reduced size.

Stress protein heme oxygenase-1 (HO-1) confers the protection against a variety of oxidant-induced cell and tissue injuries and has been reported to be significantly up-regulated in the human liver within minutes upon IPC.[5] Most recently, it has additionally been shown that cobalt-protoporphyrin-induced HO-1 overexpression improved regeneration of livers upon 70% hepatectomy and temporary inflow occlusion.[6] At first sight, this is in obvious contrast to what we just learned from animals[1,2] and human studies[7] opposing the application of IPC in extended liver resection. However, these conflicting results might be attributed to the fact that ischemic preconditioning, induced by vascular clamping, is not fully mimicked by pharmacologic upregulation of HO-1 and comprises several other seemingly proliferation-impeding events. In line with this view, it has been shown that IPC lowered transcription levels of immediate early genes, namely, *c-fos* and *c-jun*,[8,9] known to be critical elements in the process of cell proliferation.[10] There is ample evidence that cells fail to respond to proliferative signals after the blockade of Fos, the protein product of *c-fos*.[8] STAT-3 and MAP-kinase cascade, being activated by the binding of cytokines such as TNF and IL-6, control the intracellular signal transduction pathways involved in hepatic regeneration.[11] For example, upon nuclear shuttling, STAT 3 binds to the promoter of immediate early genes and activates MAPK pathway, which in turn triggers the production of DNA synthesis proteins, such as PCNA.[11] While IPC-induced repression of the early response gene *c-fos* turns out to increase ischemic tolerance of the brain[12] and to protect the liver against ischemia-reperfusion injury,[8,9] we like to hypothesize that the reduced presence of immediate early genes levels emerges as regenerative brake and thus as deleterious event the more the liver mass is reduced.

In case future research will confirm this view, it is imperative that interventions to enhance ischemic resistance of the liver prior to extended resection should focus on procedures that do not interfere with the immediate early genes as key players in the signal transduction pathway for regeneration.

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REFERENCES

1. Habib MM, Habib MM, Selden C, et al. Ischemic preconditioning impairs liver regeneration in extended reduced-size livers. *Ann Surg*. In press.
2. Eipel C, Glanemann M, Nuessler AK, et al. Ischemic preconditioning impairs liver regeneration in extended reduced-size livers. *Ann Surg*. 2005;241:477–484.
3. Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. *J Pathol*. 2000; 190:255–266.

4. Banga NR, Homer-Vanniasinkam S, Graham A, et al. Ischaemic preconditioning in transplantation and major resection of the liver. *Br J Surg*. 2005;92:528–538.
5. Patel A, van de Poll MC, Greve JW, et al. Early stress protein gene expression in a human model of ischemic preconditioning. *Transplantation*. 2004;78:1479–1487.
6. Glanemann M, Schirmeier A, Lippert S, et al. Cobalt-protoporphyrin induced heme oxygenase overexpression and its impact on liver regeneration. *Transplant Proc*. 2005;37:3223–3225.
7. Clavien PA, Selzner M, Rudiger HA, et al. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann Surg*. 2003;238:843–850.
8. Ishii S, Abe T, Saito T, et al. Effects of preconditioning on ischemia/reperfusion injury of hepatocytes determined by immediate early gene transcription. *J Hepatobiliary Pancreat Surg*. 2001;8:461–468.
9. Xiao JS, Cai FG, Niu Y, et al. Preconditioning effects on expression of proto-oncogenes c-fos and c-jun after hepatic ischemia/reperfusion in rats. *Hepatobiliary Pancreat Dis Int*. 2005;4:197–202.
10. Schlossberg H, Zhang Y, Dudus L, et al. Expression of c-fos and c-jun during hepatocellular remodeling following ischemia/reperfusion in mouse liver. *Hepatology*. 1996;23:1546–1555.
11. Michalopoulos GK, DeFrances MC. Liver regeneration. *Science*. 1997;276:60–66.
12. Barone FC, White RF, Spera PA, et al. Ischemic preconditioning and brain tolerance: temporal histological and functional outcomes, protein synthesis requirement, and interleukin-1 receptor antagonist and early gene expression. *Stroke*. 1998;29:1937–1950.

The Site of the Tumor, Not the Type of Operation, Determines the Worse Prognosis of the Low Rectal Cancer

To the Editor:

I read with interest the paper by Marr et al,[1] stating that patients undergoing abdominoperineal excision (APR) have a higher local recurrence rate than patients undergoing an anterior resection (AR), and I appreciated the accuracy of their analysis of the surgical specimen.

As an oncologic surgeon involved in rectal resections for many years, I wonder why 2 operations so similar, except for a wider margin of transection at the distal level for the APR, yield different oncologic outcomes.

I question whether the results of the authors' report, coherently with their findings, could have a different explanation. I suspect that difference in local recurrence rate between APR and AR simply reflects the fact we are dealing with different tumors.

Main factors that favor the adoption of an APR instead of an AR are the distal site of the tumor (tumor of middle or low rectum vs. more proximal tumors) and the presence of a bulky mass and/or a narrow (male) pelvis. For these conditions, sometimes discovered during operation, the surgeon may convert a planned AR to an APR, but almost never does the opposite occur.

The rectum is by definition 15 cm long, and it is conceivable that the mean distance from anal verge is different in patients undergoing APR and AR.

It is well known that tumors of the distal rectum have a poorer prognosis than proximal ones,[2,3] even because the lymphatic spread to the iliac and obturator nodes (which are almost never removed by the European surgeons) is more common in these distal tumors,[4,5] and this could account for a high recurrence rate.

As a matter of fact, some years ago (in the premesorectal excision era), when we reviewed our experience on 350 tumors of the middle to low rectum, we found at the multivariate analysis a higher risk of recurrence (2.6 times) with AR compared with APR.[6] We also reviewed the literature comparing the two procedures for cancer of the middle and low rectum (11 authors, 1400 patients): in no study was there an excess of risk of local recurrence for APR, but three papers reported a statistically significant increase of risk for the AR.[6]

Furthermore, a very recent nationwide revision of the long-term outcome after standardization of rectal surgery (November 1993 to December 1999) did not find any difference in local recurrence rate after the two operations by multivariate analysis on 3174 patients.[7]

The role of a bulky tumor mass or of a narrow pelvis in determining the occurence of local recurrence is difficult to assess in quantitative terms. However, in this study, the author attempted to carefully measure the volume of resection and reported that total area of surgically removed tissue outside the muscular propria, as well as the linear dimensions of transverse slices of tissue containing tumor, were smaller in the APR specimen than in the AR group.

This means, in my view, that tumors were bigger in AP compared with AR and/or the volume of resection was by force smaller because in these distal tumors, treated by APR, bony structures limited wider margins of transection. In keeping with this observation is the finding of a lower left lateral measurement in males: since the surgeon stays on the left side of the patient, it is easier to displace the rectum to the left (with the left hand) while resecting the right attachments (with the right hand). When the pelvis is narrow (male pelvis, distal tumors) or the tumor is bulky, or both, this finally results in a smaller margin of transection on the left.

In conclusion, I accept the findings of Marr et al,[1] but I think they did not demonstrate a different curative potential of the two operations; rather, the worse prognosis of patients undergoing APR versus the AR did not reflect a lower radicality of the surgical procedure but a more unfavorable biology and anatomic location of tumors treated by APR.

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REFERENCES

1. Marr R, Birbeck K, Gavircan J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Ann Surg*. 2005;242:74–82.
2. Gilchrist RK, David VC. A consideration of pathological factors influencing five year survival in radical resection of the large bowel and rectum for carcinoma. *Ann Surg*. 1947;126:421–438.
3. Freedman LS, Macaskill P, Smith AN. Multivariate analysis of prognostic factors for operable rectal cancer. *Lancet*. 1984;8405:733–736.
4. Sauer I, Bacon HE. A new approach for the excision of the carcinoma of the lower portion of the rectum and anal canal. *Surg Gynecol Obstet*. 1952;95:229–242.
5. Suzuki K, Muto T, Sawada T. Prevention of local recurrence by extended lymphadenectomy for rectal cancer. *Surg Today*. 1995;25:795–801.
6. Bozzetti F, Mariani L, Doci R, et al. Cancer of the low and middle rectum: local and distant recurrences, and survival in 350 radically resected patients. *J Surg Oncol*. 1996;62:207–213.

7. Wibe A, Eriksen MT, Syse A, et al. Effect of hospital caseload on long-term outcome after standardization of rectal cancer surgery at the national level. *Br J Surg*. 2005;92:217–224.

Reply:

We thank the authors for their interest and kind comments on our paper.[1]

We believe that several reasons can explain the poorer survival seen when patients undergo an APR. First, the tumor is incompletely resected being found at the circumferential resection margin (CRM) up to 3 times more frequently in APR than in AR, as shown in Table 1. Incomplete resection has been confirmed as an adverse prognostic factor in multiple studies over the last 20 years,[1,6–11] strongly suggesting that this is an important factor. Second, the frequency of perforation of APRs is up to 4 times higher in APR than AR (as shown in Table 2), and lastly the quality of resection of APRs as judged by the surgical plane of resection is poorer.[4]

"I wonder why two operations so similar, except for a wider margin of transection at the distal level for the APR, yield different oncologic outcomes." We would question the validity of this statement for the evidence of a wider surgical margin of excision in APRs than AR. While APR is considered a more radical operation, we must contradict this view. We have recently shown in an international randomized trial that the quality of surgery in APRs is generally poor, with one third of cases having the resection margin in the lumen, submucosa, or sphincters rather than on the surface of the sphincters or wider using a complete levator excision.[4] The mesorectal excision is also performed less well in APRs than in anterior resections.

We would agree with them that the distance from the anal verge is different between AR and APR; however, the studies quoted by them as showing a biologically more aggressive lesion have not taken into account the high CRM involvement rate, the perforation rate, and the quality of surgery in this area.

We know that some authors have reported very low local recurrence rates in low rectal cancer,[13] suggesting that it is possible to change the outcome in these patients. Our suggestion is that a change in operative technique would yield great benefits.

The authors present new evidence from before the era of total mesorectal excision. The authors do not report their CRM-positive rates from this study. In recently reported multisite studies from a number of European countries of over 4000 patients (Dutch TME study, n = 1530 patients;[11] Norwegian low rectal cancer, n = 2136 patients;[3] MRC CLASICC study, n = 400 patients[2]), the local recurrence rates are higher in APR than AR.

The Norwegian paper quoted[14] reports no difference in local recurrence but does show a significant difference in survival between AR and APR with a higher hazard ratio of 1.4 for risk of death with APR. The same group report elsewhere in 2136 patients a local recurrence rate in APs 15% versus ARs 10% and poorer survival APs 55% versus ARs 68%.[3] In the recent study,[14] both an involved CRM and perforation have an impact on local recurrence (HR, 1.5 and 2.4) and survival (HR, 1.4 for both); thus, whatever is changing the significance of local recurrence between these two reported series, it does not change the importance of the higher rates of CRM involvement and perforation we find in APR. The importance of the quality of surgery is strongly emphasized in this quoted paper,[14] with high volume centers achieving better outcomes.

The authors state that the tumors are bigger in APR. We agree and in our recent study differed by 0.4 cm.[4] This is a further reason for carefully considering the management of these patients and considering downstaging them with preoperative therapy and wider surgical planes. We would suggest that the narrow pelvis can contribute to the poor quality of surgery of APRs that we have recently reported. A change in operative approach to performing the dissection with the patient prone as performed by Holm at the Karolinska Hospital Stockholm, Sweden avoids the difficulty of deep pelvic operating. This approach is also used by other surgeons and, we believe, should be adopted more frequently.

Tumors of the rectum do have a slightly different biology to those of the right colon. They have a higher rate of p53 mutations, loss of heterozygosity and overexpression, a higher frequency of DNA aneuploidy, and a lower rate of microsatellite instability. However, we are unaware that any studies have contrasted the molecular biology of low rectal cancers to those of the mid and upper rectum. This must remain in the realm of speculation until proven. The lymphatic drainage from distal rectal cancers is different from mid and upper rectal cancers, and it is true that lateral lymph node dissection is not routinely practiced in the West; however, the frequency of lateral lymph node metastases is relatively low compared with the reported rates of CRM involvement and perforation in low rectal cancer. Lateral lymph node spread may contribute to the worse outcome, but its relative contribution will be easier to dissect if the former are minimized by improved surgery and multimodality therapy.

Thus, we think that there is a rapidly accruing body of evidence from Leeds,[1] the United Kingdom,[2,5] Holland,[4] and Norway[3,12] that suggests we urgently need to review the performance of the standard APR. This may lead to the same level of improvement of outcome in low rectal cancer that has been seen by the worldwide adoption of total mesorectal excision.

TABLE 1. Frequency of CRM Involvement in Rectal Cancer by Operation Type

	APR (%)	AR (%)
Marr et al[1]	36.5	22.3
MRC CLASICC trial[2]	22	10
Norwegian audit[3]	12	5
Dutch RT/TME trial[4]	29	12.2
Mercury study rectal cancers <6 cm[5]	33	13

TABLE 2. Frequency of Perforation in Rectal Cancer by Operation Type

	APR (%)	AR (%)
Mercury study rectal cancers <6 cm[5]	13.7	—
Norwegian audit[12]	16	4
Dutch RT/TME trial[4]	13.7	2.5

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REFERENCES

1. Marr R, Birbeck K, Garvican J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Ann Surg*. 2005;242:74–82.
2. Guillou P, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet*. 2005;365:1718–1726.
3. Wibe A, Syse A, Andersen E, et al. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. *Dis Colon Rectum*. 2004;47:48–58.
4. Nagtegaal ID, van de Velde CJH, Marijnen van Krieken JHJM, et al. Low rectal cancer; a call for a change of approach in abdominoperineal resection. *J Clin Oncol*. 2005;23:9257–9264.
5. Daniels I, the MERCURY Study Group. Magnetic resonance imaging of low rectal cancers: a multi-centre, multi-disciplinary European study of 285 tumours located within 6 cm of anal verge. *Colorectal Dis*. 2004;6(suppl 2):1.
6. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma is caused by inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet*. 1986;8514:996–999.
7. Ng IO, Luk IS, Yuen ST, et al. Surgical lateral clearance in resected rectal carcinomas: a multivariate analysis of clinicopathological features. *Cancer*. 1993;71:1972–1976.
8. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet*. 1994;344:707–711.
9. de Haas-Koch DF, Baeten CGMI, Jager JJ, et al. Prognostic significance of radial margins of clearance in rectal carcinoma. *Br J Surg*. 1996;83:781–785.
10. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg*. 2002;89:327–334.
11. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimetre but two millimetres is the limit. *Am J Surg Pathol*. 2002;26:350–357.
12. Eriksen MT, Wibe A, Syse A, et al. Inadvertent perforation during rectal cancer resection in Norway. *Br J Surg*. 2004;91:210–216.
13. Dehni N, McFadden N, McNamara DA, et al. Oncologic results following abdominoperineal resection for adenocarcinoma of the low rectum. *Dis Colon Rectum*. 2003;46:867–874.
14. Wibe A, Eriksen MT, Syse A, et al. Effect of hospital caseload on long-term outcome after standardization of rectal cancer surgery at the national level. *Br J Surg*. 2005;92:217–224.

On Statistical Reanalysis, the EORTC Trial Is a Positive Trial for Adjuvant Chemoradiation in Pancreatic Cancer

To the Editor:

Klinkenbijl et al have previously reported the results of the European Organization for Research and Treatment of Cancer (EORTC) Trial # 40891 in *Annals of Surgery*.[1] This trial was the second prospective randomized multicenter trial designed to evaluate the potential benefit of adjuvant chemoradiation (vs. observation) for patients with resected pancreatic cancers. The first trial was initiated in the United States by the Gastrointestinal Tumor Study Group (GITSG) in 1974, which was slow to accrue and was terminated early following an analysis of the first 43 patients that demonstrated a statistically significant survival advantage to adjuvant chemoradiation and maintenance chemotherapy in patients with resected adenocarcinoma of the pancreas.[2,3] The EORTC trial was a larger-powered study designed to validate the result of the smaller GITSG trial, and adjuvant therapy was similar save for the fact that the GITSG study used maintenance chemotherapy while the EORTC trial did not.

Unlike the GITSG trial, the EORTC trial did not find a statistically significant benefit to adjuvant chemoradiation. One of several criticisms of this trial was that it allowed enrollment of nonpancreatic periampullary adenocarcinomas, which are well known to have better survival outcomes when compared with adenocarcinomas of the pancreatic head. To address these prepublication critiques, Klinkenbijl et al reported statistical analyses of not only survival in all eligible patients, but also for the subgroups of pancreatic head cancers and periampullary cancers separately. When pancreatic head cancers were analyzed as a subgroup, survival curves demonstrated consistent separation of the observation and treatment arms over time, indicative of a potential benefit to adjuvant chemoradiation (Figure 1). However, this difference did not reach statistical significance when tested with a two-sided log-rank test ($P = 0.099$).

In retrospect, given the positive findings of the GITSG trial, which involved a similar treatment arm, a closer examination of the statistical design used in the EORTC trial is warranted. On reanalysis with more appropriate statistical methods, there is a statistically significant benefit to adjuvant chemoradiation for patients with pancreatic head cancers. The justification for such a reanalysis is rooted

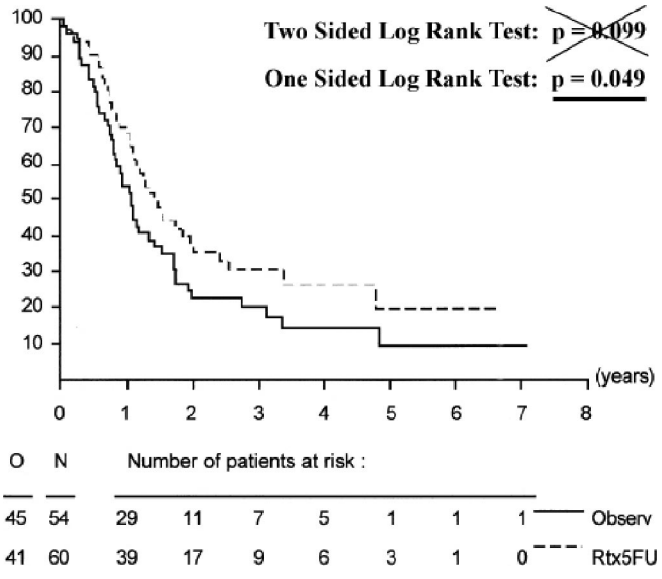

FIGURE 1.

in the fact that the authors of the EORTC trial chose to use a two-sided log-rank test for statistical analysis at the 0.05 level of significance. However, there were no indications to use such a statistical design when this trial was conceived, and a one-sided log-rank test would have been most appropriate. A two-sided statistical design is only appropriate when there are data to suggest that the experimental therapy arm (adjuvant chemoradiotherapy) could be better or worse than the control arm.[4] A one-sided log-rank test is appropriate for trials in which the experimental arm is being tested for improvement (not detriment) over the control arm (ie, when there is no reason to believe that the outcome of patients in the experimental arm would be significantly worse than the control arm).[4]

Given that the EORTC trial was designed in part to validate the GITSG study, the use of a two-sided log-rank test was inappropriate as there was no suggestion from the results of the GITSG trial that the survival of patients in the adjuvant chemoradiotherapy arm would be worse than the control arm of surgery alone; indeed, they implied a benefit. Further, in both the GITSG and the EORTC trials, chemoradiotherapy was safe and very well tolerated with no suggestions that it significantly contributed to grade 3, 4, or 5 toxicity. Therefore, a one-sided log-rank test should have been used to test for significance in the EORTC trial based on the fact that the previously published GITSG trial suggesting only a potential benefit from treatment and no suggestion of worsening/decreasing survival due to treatment and/or associated toxicity. If a one-sided log-rank test would have been used (as would have been appropriate), the 14% improvement in overall survival at 2 years (37% vs. 23%) favoring adjuvant chemoradiotherapy in patients with pancreatic head cancers would have reached statistical significance as illustrated in Figure 1 ($P = 0.049$).

Given the positive results of the GITSG and EORTC trials favoring adjuvant chemoradiotherapy, cooperative group protocols in the United States are conducting trials to refine adjuvant chemoradiotherapy.[5] By contrast, our European colleagues have concluded that the EORTC trial and the subsequent ESPAC-1 trial were negative trials for adjuvant chemoradiotherapy.[6] Consequently, present European cooperative group trials do not include radiation in any experimental adjuvant arm, which is reflective of this difference in opinion.[7] It is unfortunate that this approach is currently being taken because, with the reanalysis presented above, the results of the EORTC trial demonstrate a benefit to adjuvant chemoradiotherapy. Together with the results of the GITSG trial, there is strong phase III evidence that patients may benefit from adjuvant chemoradiotherapy. In contrast, the controversial results of the ESPAC-1 trial do not support a benefit, and with the presented reanalysis of the EORTC trial, the ESPAC-1 trial now stands alone in this respect. Numerous criticisms of the ESPAC-1 trial have undermined the validity of its results and have been summarized previously in the literature.[8–11]

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REFERENCES

1. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999;230:776–782.
2. Kalser MH, Ellenberg SS. Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985;120:899–903.
3. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer*. 1987; 59:2006–2010.
4. Green S, Benedetti J, Crowley J, eds. *Clinical Trials in Oncology* (*Interdisciplinary Statistics*). Boca Raton, FL: Chapman & Hall/CRC Press, 1997.
5. Radiation Therapy Oncology Group. RTOG 97-04. (accessible at http://rtog.org/members/protocols /97-04/97-04. pdf).
6. Neoptolemos JP, Stocken DD, Friess F, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200–1210.
7. ESPAC-3(v2) phase III adjuvant trial in pancreatic cancer comparing 5-FU and D-L-folinic acid vs gemcitibine. National Cancer Research Network Trials Portfolio (accessible at http://www.ncrn.org.uk/portfolio/data.asp?ID=669).
8. Choti MA. Adjuvant therapy for pancreatic cancer: the debate continues. *N Engl J Med*. 2004;350:1249–1251.
9. Morris SL, Beasley M, Leslie M. Chemotherapy for pancreatic cancer [Letter to the editor]. *N Engl J Med*. 2004;350:2713.
10. Crane CH, Ben-Josef E, Small W. Chemotherapy for pancreatic cancer [Letter to the editor]. *N Engl J Med*. 2004;350(26):2713–14.
11. Bydder S, Spry N. Chemotherapy for pancreatic cancer [Letter to the editor]. *N Engl J Med*. 2004;350:2714.

Reply:

The statisticians of the EORTC at the time did carefully design the statistical setup. In the light of the more recent confirmation of our study by the ESPAC data, it seems far fetched to go back to the very old GITSG trial with really very few patients to still try to prove that radiotherapy is effective. The meta-analysis of 2005 also clearly demonstrated no effect.

It is not any more relevant to argue against the recent data by taking data from the GITSG study performed in an ancient time of pancreatic surgery. We recently reanalyzed the data of our study with a follow-up of more than 10 years and found again no benefit of radiotherapy. We will publish these data soon.

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