April 14, 1999

To the Editor:

Laparoscopic techniques are thought to provide tremendous benefits to patients, including reduced postoperative pain, superior cosmetic results, and reduced hospitalization. However, the most important aspect favoring the laparoscopic approach may turn out to be the preservation of the patient's immune functions during and after surgery.[1] Conventional surgery is known to impair the systemic immune response. Postoperative changes in the systemic immune response are proportional to the degree of surgical trauma, and subsequent immune suppression may be implicated in the development of septic complications and tumor metastasis formation.[2]

Carbon dioxide (CO_2) is at present the most commonly used gas for abdominal insufflation, despite the serious drawback of causing respiratory acidosis due to transperitoneal absorption. West et al presented experimental data suggesting that these metabolic consequences of CO_2 can also benefit the patient. They proposed that cellular acidification induced by abdominal insufflation contributes to the blunting of the local inflammatory response during laparoscopic surgery, suggesting a partial scientific explanation for the observed scant inflammatory reaction to laparoscopic abdominal surgery.[3] This hypothesis has never been tested clinically. We therefore chose to compare CO_2 with helium insufflation. Helium is, in contrast to CO_2, metabolically inactive and is minimally absorbed across the peritoneum.[4]

Sixteen patients scheduled for elective laparoscopic cholecystectomy were included and randomly assigned to undergo laparoscopy using either CO_2 or Helium (prototype insufflator specially adapted for helium insufflation, kindly made available by Karl Storz, Endoscopy-America, Culver City, CA) for abdominal insufflation. There were no preoperative signs of acute cholecystitis or stones in the common bile duct. The surgical technique, the American method for laparoscopic cholecystectomy performed through four cannulas, has been published elsewhere.[5] None of the patients had other diseases or conditions causing immunosuppression, nor did they receive immunosuppressive therapy during the perioperative period. The postoperative acute phase response was assessed by measuring C-reactive protein (CRP). Postoperative immune function was assessed by measuring monocyte HLA-DR expression. All results are expressed as mean ± standard error of the mean, HLA-DR expression as percentage of preoperative value.

Laparoscopy using helium insufflation resulted in significantly higher levels of CRP one day after surgery when compared to CO_2 pneumoperitoneum (18.0 ± 3.5 vs 29.1 ± 3.8, $P < 0.05$, Mann-Whitney U Test). Helium insufflation resulted in a significant reduction of monocyte HLA-DR expression at 1 day (58% ± 7) and 2 days (56% ± 16) after surgery when compared with preoperative levels ($P < .05$, Wilcoxon Signed Ranks Test). No significant changes between pre- and postoperative values could be observed after CO_2 insufflation.

These results confirm the experimental data of West et al and suggests that CO_2 used for abdominal insufflation decreases the activation of the inflammatory response and preserves parameters reflecting immunocompetence. We therefore postulate that cellular acidification of cells of the peritoneum induced by abdominal CO_2 insufflation contributes to blunting of the local inflammatory response, thereby preserving postoperative immune functions.

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April 19, 1999

To the Editor:

I read with interest the excellent paper by Dr. Siewert and his colleagues and the comments by Drs. Brennan, Wanebo, and Demeester.[1] The 10-year long-term results of the very extensive German Gastric Cancer Study (GGCS) comparing limited (D1) and extended (D2) resection are of particular interest today because the conclusions of Dr. Siewert and colleagues are completely reversed from those by Bonenkamp and colleagues in their recently published Dutch randomized trial.[2]

Of 1182 patients with gastric cancer who underwent a resection with curative intent (UICC R0) in the GGCS, 379 had a D1 and 803 had a D2 resection. There was no difference in the postsurgical morbidity and mortality rates between patients with D1 and D2 lymph node dissection. In contrast, in the Dutch and MRC[3] randomized trial, D2 dissection was associated with a significant increase in postsurgical morbidity and mortality rates. As the authors of these trials note, however, pancreaticosplenectomy was largely responsible for this adverse effect on short-term outcome. Of particular interest therefore is the confirmation by the multiinstitutional GGCS of reports from specialized single-institution studies that D2 dissection is associated with low postoperative morbidity and mortality.[4–5] Postoperative mortality after D2 dissection is currently reported, even in the West, to be less than 2%.[6] Drs. Siewert and Brennan underlined that a surgeon's experience with lymph node dissection is the predominant factor for low morbidity and mortality associated with a D2 dissection.[1]

Whereas the effect of extended lymph node dissection on short-term outcome has been clear, the beneficial effect of this procedure on long-term survival is debatable. Superior stage-specific survival rates due to extended lymph node dissection have been reported

from Japan,[4] but there is a criticism that these favorable results are attributable largely to stage migration. This well-known phenomenon, in which D2 dissection providing more examined lymph nodes refines pathologic staging, confounds the objective comparison of D1 and D2 groups. Similarly, in the GGCS, a subgroup analysis showed that in patients with R0 stage II tumors, D2 dissection markedly improved the 10-year survival rate from 20% to 49% ($P < .0001$). The authors support that this survival difference reflects a real benefit of D2 dissection because they found that staging is reliable when more than 15 nodes are removed and examined.

Despite the great effort of the authors to eliminate stage migration by including in their analysis patients with more than 15 removed and examined nodes, it appears very difficult to exclude this phenomenon, as Drs. Brennan and Wanebo emphasized in their comments.[1] In the Dutch trial, overall survival and risk of relapse were similar in two groups, whereas a marginally significant increase in D2 patients with stage IIIA was attributable to stage migration, according to Bonenkamp and his colleagues. Thus, the authors do not support D2 dissection. However, the D1 and D2 groups were not well balanced because pancreaticosplenectomy, which has a negative effect on short- and long-term outcome, was performed significantly more often in D2 than in D1 group.

Because the overall survival benefit of D2 dissection, if it exists, appears to be small, and stage migration blurs the distinction between the two procedures, it is extremely difficult to draw conclusions by the conventional comparison of D1 and D2 groups.[7] This problem prompted me to develop a simple new concept based on the fact that a curative resection for patients with pN2 disease (positive nodes in nodal stations 7 through 12, according to the Japanese Research Study for Gastric Cancer) is achievable only with an extended lymph node dissection. Fatal metastatic relapse arises from the positive N2 nodes left behind when a D1 dissection is performed. Therefore, the study of the frequency of the N2 disease among R0 patients and *particularly* of the long-term survival of these N2 patients after a D2 dissection (to be obtained if there are long-term survivors) can prove whether a D2 dissection provides a survival benefit.

Our prospective study was designed on the basis of this concern. The analysis of our findings showed that 25% of all D2 patients with a R0 resection had pN2 disease. For the subgroup of patients with node-positive disease, one of two patients had also an involvement of the N2-level nodes. The 5-year relapse-free survival rate for the subgroup with pN2 disease after curative D2 dissection in our study was 20%. This result reflects the survival benefit of D2 dissection.[6]

The findings of the German study prove that D2 dissection in experienced institutions is a safe procedure. Furthermore, our findings, evaluated with respect to a new concept, establish that D2 dissection provides a survival benefit in one of five patients with pN2 disease. This reflects the therapeutic value of D2 dissection, which is small, however, when is calculated for all R0 patients. Extended lymph node dissection remains the procedure of choice in specialized centers.

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July 6, 1999

Author's reply:

Dr. Roukos is right when he stresses the fact that the survival benefit of D2 lymphadenectomy is only demonstrable in a subgroup of patients with gastric cancer.

In the GGCS, this benefit was proven in the UICC tumor stage II. The Dutch trial makes benefit in the UICC tumor stage IIIA probable. Despite the different explanation of these results, it seems probable that there is a subgroup which should have a benefit.

Dr. Roukos published his own hypothesis in 1998. From the theoretical point of view, he is right that a subgroup of patients with lymph node involvement in the compartment 2 (not N2!) could have a benefit. He has interpreted his own data retrospectively in this way. Unfortunately, he has not included in his hypothesis the fact of microinvolvement of lymph nodes.[1] The problem is that every hypothesis needs a prospective evaluation, and this is not available so far.

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July 9, 1999

To the Editor:

We read the article by Rao et al[1] about the "introduction of appendiceal CT" with interest. Though the results are suggestive for the author's conclusion, that appendiceal computed tomography (CT) can be advocated in nearly all female and many male patients, the numbers and statistics quoted in this paper warrant some critical appraisal.

According to the authors, the negative appendectomy rate was statistically lowered from 20% of patients (98/493) in the pre-CT era to 7% (15/209). But in 1997, only 123 of 209 patients had an appendiceal CT before undergoing appendectomy, and in 117, it was interpreted as positive for appendicitis. Of these, 3% (n = 3) were found to have no pathologic signs for appendicitis. On the other hand, of 86 patients undergoing appendectomy without pre-operative CT scan during the same period, seven patients (8%) had a normal appendix. In our opinion, this number represents the true negative appendectomy rate that should be compared: 3% with CT versus 8% without CT during the observation period ($P = .07$, Pearson; $P = .1$, Fisher exact test), as opposed to the suggested 20% versus 7%.

Concerning the 206 patients who *did* have an appendiceal CT but *did not* undergo appendectomy, it is unclear how many of these would have undergone appendectomy without prior CT scan. What were the inclusion criteria for CT scan of the appendix?

In our opinion, the perforation rate is calculated incorrectly. The true perforation rate should be perforated appendices of all operated appendices.[2] This calculation would lead to a different distribution: 87 of 493 (18%) in 1992 through 1995 versus 28 of 209 (13%) in 1997, not a statistically significant difference.

Even regarding the appendiceal perforation rate quoted in this paper, which was 87 of 395 (22%) with appendicitis in 1992 through 1995, and declined to 28 of 194 (14%) in 1997, some questions remain about the distribution of perforated appendices to the groups "CT scan prior to surgery (114/194)" and "no CT scan prior to surgery (79/194)." If the distribution of perforated appendices was equal in the two groups, the lower perforation rate in 1997 would be independent of appendiceal CT.

One important message of this article was that adult women could benefit the most from appendiceal CT. But the numbers given are somewhat puzzling: in Table 2, four of 19 (21%) adult women underwent negative appendectomy who did not undergo appendiceal CT prior to surgery in 1997. When this number is added to the six adult females (6/67, 9%) of all others with negative appendectomy rate, the total is ten of 86 patients (12%) with negative appendectomy of patients without prior appendiceal CT. But on the same page, the negative appendectomy rate was quoted to be 8% (7/86). Which of these numbers is the correct one is unclear, but whether the drop in negative appendectomy rate is truly due to the introduction of the appendiceal CT in this sub-population remains even more obscure.

Abdominal ultrasound, a potent diagnostic tool, was not mentioned in this article as an alternative method, but it has some potential benefits over CT. In studies including more than 1000 patients, specificity, sensivity, positive predictive value, and negative predictive value (a standard validation of a diagnostic tool, which was not given in this paper for the study group) of abdominal ultrasound was over 96%.[3,4] Similar or better results are reported regarding negative laparotomy and perforation rate, without the burden of radiographic exposure to the gonades (CT of the pelvis: skin dose of 36 mSv; organ dose for the uterus and ovaries, approximately 20 mSv[5]; mutation rate 1%/Sv).

To evaluate the diagnostic power of appendiceal CT, a prospective randomized trial comparing both methods should give the best and most accurate answer.

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August 7, 1999

To the Editor:

We read with interest the article by Rahusen et al[1] about the use of laparoscopic ultrasonography in the preoperative study of patients with colorectal liver metastases. In our opinion, the role of laparoscopic ultrasonography has been overemphasized in this study. In effect, the authors describe scantly or not at all the results and the methodology (technical features and imaging evaluation) of the preoperative imaging studies. The computed tomography (CT) results especially are very poor and somewhat surprising. We wonder how the authors were able to compute the true negatives of imaging studies, which are potentially infinite. There is a very large difference between the proportion of patients considered to be candidates for surgical resection on the basis of the previous imaging studies and the proportion of patients eligible after laparoscopic ultrasonography (29/47 [61%]).

An important flaw in this series is that the technique of preoperative abdominal CT scan (although only partially described) is clearly suboptimal. Accurate technique is critical to improve detection of liver metastases with CT. The authors studied the liver with 10-mm collimation. This collimation is definitely insufficient for an adequate study of the liver metastases, and the disappointing results of CT are thus not surprising. Most authors agree that helical CT of the liver should be performed with 5-mm collimation.[2,3]

Moreover, the authors do not describe the dose and the rate of contrast material. Again, this point is essential to obtain high-

quality diagnostic studies. In our institution, preoperative staging of patients with colorectal liver metastases is performed with helical CT. Details of the technique and results have been reported previously.[4] Briefly, scanning protocol includes 5-mm collimation and 1.5 pitch and subsequent reconstruction at 5-mm intervals. Either ionic or nonionic contrast material (170 mL) is injected at a rate of 3 mL per second and acquisition starts at 60 to 70 seconds.

Between October 1995 and December 1998, 119 patients with suspected liver metastases from colorectal cancer were operated on in our hospital. Preoperative staging was performed in all patients with helical CT. In all cases, an experienced hepatic surgeon performed the intraoperative ultrasound. Helical CT findings were correlated with pathologic findings on a lesion-by-lesion basis. Results of intraoperative ultrasound, liver palpation, and histologic study disclosed 288 metastatic lesions. Helical CT correctly detected 246 metastatic lesions. The overall detection rate for helical CT was 85.4% and the positive predictive value was 96%. The false-positive rate was 3.9% (10/256). In 11 patients (9%), surgical resection was not performed due to undetected extrahepatic disease (n = 5), no tumor (n = 2), more metastases than previously detected (n = 2), and location near vessels (n = 2).

Additionally, as a standard preoperative work-up, colonoscopy and CT of the chest and pelvis were performed in these patients to rule out disseminated disease. In the series by Rahusen and co-workers,[1] six (13%) patients were operated on and discarded for resection after intraoperative ultrasonography. Of course we agree that intraoperative ultrasonography of the liver by an experienced surgeon is the gold standard, and that any preoperative study must be compared with it. Bimanual surgical palpation and intraoperative ultrasound disclosed 42 additional metastatic lesions. One hundred and eight patients were submitted to liver resection; therefore, the resectability rate, taking the group as a whole, was 91%. Selection criteria for liver resection were medical fitness for major surgery and no signs of disseminated disease on preoperative imaging. We had no predefined criteria of resectability with regard to the number or size of the tumors, or to locoregional invasion, provided that resection could be complete and macroscopically curative. Postoperative mortality was 4.2% (5 patients). The median survival calculated from the time of liver resection was 44 months. The actuarial survival rate at 1, 2, 3, and 4 years was 88%, 74%, 57%, and 48%, respectively. In the majority of our patients (5/11 [5%]), peritoneal carcinomatosis was the reason they were not candidates for surgical resection after laparotomy. Of course, diagnostic laparoscopy could be very helpful in ruling out these patients, but minilaparotomy is another option to be considered.

The majority of patients with colorectal liver metastases have had previous abdominal surgery for resection of the primary tumor. In this condition, intraperitoneal adhesions occur frequently, and probably for this reason, the median time to accomplish the laparoscopy procedure was 70 minutes. This is a long time, and having to undergo two surgical procedures, laparoscopy and liver resection, certainly increases the patient's anxiety and discomfort.

In this paper, the resectability rate was very low (23/47 [48%]). The authors compare their results with a similar study from the literature,[5] but those data are rather old (1991) and the technique and results of the imaging studies have changed substantially during the intervening years. Our resectability rate of 91%, considering the entire group, is probably more realistic. More recent studies from the Memorial Sloan-Kettering Cancer Center in New York[6] showed data similar to our results (329/416 patients resected [79%]). Another reason for the low resectability rate of the authors could be very restrictive indications for resection. But considering that there is no other effective therapy for colorectal liver metastases, we believe that surgical resection should be considered the standard therapy whenever possible.

In conclusion, we believe that in this article, the role of laparoscopic ultrasonography (if any) is overemphasized, probably because the potential utility of the preoperative helical CT is underestimated.

In our experience, adequate selection of patient candidates for surgery can be done, in most cases, with a high-quality preoperative study of the liver with helical CT. The main reason for discrepancy with surgical findings is peritoneal metastases (11–18% of the patients) and these lesions can be ruled out with a minilaparotomy just before resection, or alternatively, with a diagnostic laparoscopy.

Moreover, this diagnostic approach is cost-effective because preoperative staging is performed on an outpatient basis, with low cost and a noninvasive technique. We consider that in this era of cost-containment in medicine, diagnostic strategies should be designed to consider both the accuracy and the cost as well as the patient's comfort.

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November 2, 1999

Authors' Reply:

We have read with great interest the comments by Drs. Figueras and Valls on our article in *Annals* and we gratefully take this opportunity to respond.

Drs. Figueras and Valls are concerned that the value of diagnostic laparoscopy (DL) and laparoscopic ultrasonography (LUS)

in the staging of colorectal liver metastases has been overemphasized. Let us begin by saying that we did not in any way emphasize the importance of DL and LUS. What we did emphasize, however, is that often a discrepancy exists between preoperative imaging and perioperative findings, with the intraoperative ultrasound being the reference standard for all imaging techniques used. As we concluded in our paper, "Advances in preoperative imaging, such as spiral CT or contrast-enhanced MRI, will hopefully exclude patients at an earlier stage, thereby decreasing the number of patients who will need to be evaluated for resection by more invasive techniques such as DL and LUS or exploration with IOUS."[1]

Our study was performed between 1992 and 1997, using conventional contrast-enhanced CT, which was the standard procedure at that time in many institutions around the world.

A most interesting point made by Drs. Figueras and Valls is that the quality of preoperative imaging determines the resectability rate of the patients with colorectal liver metastases. In our view, the resectability rate does not necessarily reflect the quality of preoperative imaging, and other factors may play a more important role. Ultimately, the criteria used for resectability determine which patients will undergo resection upon exploration. Drs. Figueras and Valls stated that they had no predefined criteria of resectability with regard to the number or size of the tumors, provided that resection could be complete and macroscopically curative. In addition, locoregional invasion did not necessarily exclude their patients for resection. Therefore, their resectability rate is expected to be higher than ours. As Jarnagin et al[2] pointed out, the increase in resectability rate, when looking at several subsequent studies, is a reflection of both the use of improved imaging and a more aggressive surgical approach. Whether or not the latter is warranted is a matter of debate. Although it is true that surgical resection is the only possibility for cure, the proportion of patients who undergo resection for more than three colorectal liver metastases and benefit from an actuarial 5-year survival is less than 10% of all resected patients.[3]

We have therefore adhered to the stricter criteria for resection.[1] Of all unresected patients, however, 63% were not candidates for resection on the basis of factors *other* than the number of metastases. Furthermore, it must be stressed that we had a low threshold for evaluating patients by means of DL and LUS, in order not to deny them the possibility of resection. It might just be that, when preoperative imaging "correctly" suggests resectability in over 90% of patients, some patients may have been denied the benefit of an exploration and ultimately surgery.

Our study has indeed shown that both the sensitivity and the specificity of the preoperative imaging modalities used can be greatly improved upon. For instance, it appeared that six of 50 patients did not have metastatic disease to the liver after all, which also contributed to a decrease in our resection rate. We now also use spiral CT in the routine evaluation of patients with possibly resectable liver metastases. However, the "state of the art" in imaging is changing at a very rapid pace, and it will be hard for any institution to keep up with the latest developments, let alone make a choice from all available technologies for routine use in their patients. For this reason, the introduction of a new imaging technique for the purpose of staging liver tumors in our institution was made only after a careful assessment of all factors with regards to the most (cost-) effective imaging modality. Computed tomography with arterial portography appeared to be a sensitive method, but is invasive and has the disadvantage of a high false-positive rate. Magnetic resonance imaging technology has gone through many promising stages of development that have succeeded each other rapidly, but in the final analysis, it has proven to be more expensive with few advantages over state-of-the-art spiral CT.[4] Moreover, patients at our institution are now also staged with spiral CT and 5-mm collimation (and have been since 1997).

Because extrahepatic intraabdominal tumor recurrence is difficult to exclude with CT scanning, we have also looked at the possible value of positron emission tomography (PET) in the staging process.[5] The results of a pilot study were very promising, and a prospective randomized multicenter trial using both spiral CT and fluorodeoxyglucose-PET in patients with colorectal liver metastases is about to begin.

For all these reasons, we believe that the use of DL and LUS will continue to have a place in the assessment of patients with colorectal liver metastases, until the accuracy of combined imaging modalities is proven to be sufficient through prospective randomized clinical studies.

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October 20, 1999

To the Editor:

The rising z scores cited in the article by Peitzman et al (*Ann Surg* 1999;230:87–94) as a measurement of institutional trauma care improvement have been rising for trauma centers systemwide. The fundamentals of healthcare in the latter part of the 1990s differ greatly from when the TRISS coefficients were calculated in the mid-1980s in the seminal Major Trauma Outcome Study (MTOS). This article, I believe, incorrectly references z and w scores that are flawed by outdated coefficients.

z Scores represent standard deviations from the mean and can be translated into a probability. A z score of 6 (the article reported values as high as 9.44) translates to a *P* value equal to 10^{-9}. These

are astronomical numbers, and all that needs to be said is that a sample is statistically significant or not. Anything else can be misleading because there is an implication that these are "true" linear numbers. This was implied by placing these numbers on a graph, as in the article's Figure 4.

To test the present validity of the TRISS methodology, I requested z score component data from the Pennsylvania Trauma System Foundation for 42,897 randomly chosen trauma patients who were admitted during 1998 or 1999 with penetrating or blunt injuries (burns were excluded). Theoretically, in such a population, the cumulative predicted outcomes and actual outcomes should yield a mean z score of 0 with a standard deviation ±1.96. Anything in that range would have been statistically insignificant. However, the actual z score from this population was an unbelievable 27. Separated by injury type, penetrating and blunt injuries had z scores of 5 and 26. The w scores were likewise higher than the model predicted.

Care must be taken in using and interpreting these numbers. I suggest that the underlying TRISS coefficients should be updated and, perhaps, normalized on a regional basis. Otherwise, readers could be misled.

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November 11, 1999

Author Reply:

The Major Trauma Outcome Study (MTOS) and TRISS methodology provided a major advance in objective measurement of trauma center care. The initial objective of MTOS was to develop national norms for trauma care so that hospitals or EMS systems could compare their outcomes with national norms based on the management of injuries of similar severity. Since its development, TRISS has been the method commonly used to derive norms to assess outcomes and quality of trauma care. TRISS is not without shortcomings, however, and other authors have suggested the development of regional standards.[1,2] Although such regional norms facilitate comparison of care for a limited geographic area, comparison between broader regions remains an essential goal in the assessment of trauma systems. As recently presented by us, the need to update the coefficients of TRISS is real.[3]

Dr. Landry's analysis of a statewide z score is predictably high because the z score depends in part on sample size. As suggested, the w statistic is a more meaningful indication of the clinical significance of unexpected outcomes.[4,5] Despite the limitations of TRISS, the progressive rise in z scores and w statistics support a positive change in trauma patient outcome as our system matured.

More importantly, the purpose of the paper was to describe in detail the process of the maturation of a trauma center, linking change in process to outcome. Major organizational changes, the addition of personnel, the commitment of more physical plant, and expansion of educational programs resulted in growth in the volume of patients and more rapid evaluation and treatment of these patients. As a result of these changes in the process of patient care, patient outcome significantly improved. This observation was confirmed by a decrease in unexpected deaths, a decrease in mortality

for injured patients with ISS >15, and a remarkable decrease in complications, along with the changes in z scores and w statistics. Thus, the hypothesis and conclusion of the paper were supported by extensive data. As the trauma center matured, the process of delivering patient care became more efficient. The result was improved survival, fewer complications, and shorter length of stay.

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October 28, 1999

To the Editor:

In their careful analysis, Khuri et al[1] found no association between hospital procedural volume and 30-day mortality with eight common operations in the VA Health System. Their findings contrast sharply with consistently strong volume/outcome associations described in the private sector over the past two decades. In explaining the discrepancy, the authors suggest that volume/outcome relationships described in previous studies, based predominantly on administrative data, could be attributable to inadequate case-mix adjustment.

Their own prospective clinical data, however, suggest that case-mix adjustment in volume/outcome analysis may not be important after all. As in most previous studies, the authors found no systematic differences in patient age, illness severity, or other risk factors between high- and low-volume providers in the VA. Under these conditions, adjusted and unadjusted analysis of volume/outcome relationships will produce the same results.

Instead, the lack of an association between hospital procedural volume and mortality in the VA may reflect structural and organizational factors unique to the VA system. Compared to low-volume hospitals in the private sector, low-volume VA hospitals may "overperform" because their staffs often include high-volume surgeons from university affiliates. Conversely, high-volume VA hospitals may "underperform" relative to their private sector counterparts; for example, VA hospitals lack market incentives that encourage surgeons to develop clinical niches and specialized expertise. In addition, surgical residents may be providing a relatively large proportion of care in VA hospitals.

The work by Dr. Khuri and the NSQIP suggests that there may be little to gain from regionalizing surgery within the VA. For the

remaining 98% of patients undergoing high-risk surgery in the private sector, however, policies concentrating selected procedures in high-volume centers could potentially save thousands of lives each year.[2]

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December 14, 1999

Authors' Reply:

Thank you for the opportunity to respond to Dr. Birkmeyer's letter. Although in our study, illness severity tends to be similar in high- and low-volume Veterans Affairs Medical Centers, we believe that the use of outcomes unadjusted for severity of illness differences in studying volume/outcome relationships may be dismissed by discerning readers. We therefore used the National VA Surgical Quality Improvement Program data, which has rich clinical data on preoperative risk factors, to provide better severity-of-illness adjustment than can be accomplished with administrative data. We do not, however, attribute our findings of no volume/outcome relationship in eight operations of intermediate complexity to the differences between the use of administrative and primary data sets. One of the limitations of our study, which was noted in the Discussion, is that VA surgical services tend to be at the low to medium end of the volume spectrum, which may account for why we do not observe the volume/outcome relationship observed in many other studies.

Dr. Birkmeyer's hypothesis that low-volume VA surgical services may tend to "overperform" compared to low-volume private sector hospitals, and that high-volume VA hospitals (which are more comparable to medium-volume private sector hospitals) "underperform" compared to high-volume private sector hospitals is speculative. We have no data to support such conclusions. The intent of our study was to demonstrate empirically that extrapolation of the results of existing volume/outcome studies done in the private sector should not be used as a justification for closing down a VA surgical service based on volume alone. Managerial decisions to enhance or diminish VA surgical services should be based on direct observation of the quality of care, rather than on a putative volume/outcome relationship that we were unable to demonstrate empirically in the VA. Conversely, we did not mean to imply that the results of our empirical study of the VA should be generalized to the private sector.

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December 14, 1999

To the Editor:

Dr. Moore's article on the costs of endovascular versus transabdominal abdominal aortic aneurysm (AAA) repair[1] deserves comment. A significant reduction in cost was reported with endovascular AAA repair, with the ratio of endovascular/transabdominal repair being 0.62. These conclusions are in absolute divergence to other recent studies, shown in Table 1.[2–4] In these three studies, relative costs were directly proportional to the cost of the endograft device. The hospital costs for open and endovascular AAA repair were equivalent when the device cost was $5,000,[2] but the cost of endovascular repair was significantly greater than that of open repair when the device cost was $8,000[3] or $10,400.[4]

How can such disparate results be reconciled? The paper from Dr. Moore's group did not provide actual costs that could be compared to these studies, nor the specific methodology by which the costs were estimated. Interestingly, the ratio of endovascular to open costs reported (0.62) is quite similar to the ratio from the studies in Table 1 (0.62–0.76) if the endograft device cost is *excluded*. Perhaps the cost data in Dr. Moore's study did not include current device cost; as the initial institution trialing the EVT/Ancure endograft, UCLA may not have been charged for the device. Other explanations could include a much higher than average per-day bed cost at his institution, which would increase the open cost well above the $12,500 range seen in the studies cited in Table 1.

With the current commercially available endograft devices in the United States (AneuRx-MedtronicAVE and Ancure-Guidant) costing approximately $10,000, endovascular AAA repair is significantly more costly than open repair.[4,5] At many institutions, moreover, Medicare reimbursement may not be sufficient to cover the cost of endovascular repair.[4]

As these devices become more widely used in the United States, it seems critical that the economic implications be clearly understood. Many hospitals are facing an uphill battle to remain financially solvent. Hospital administrators who expect endovascular AAA repair to improve their bottom line will likely be disappointed. With current device pricing, it is doubtful that many institutions will find endovascular AAA repair to be associated with the lower costs and higher profit margins reported by Dr. Moore.

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Table 1. COMPARATIVE MEAN HOSPITAL COSTS FOR OPEN AND ENDOVASCULAR AAA REPAIR*

Author	N (open/endo)	Open	Endo Cost		Endo/Open Ratio	
			+ Device	− Device	+ Device	− Device
Seiwert[2]	16/16	$12,714	$12,905	$7,905	1.02	0.62
Patel[3]	N/A	$12,381	$16,189	$8,187	1.31	0.66
Sternbergh[4]	49/131	$12,546	$19,985	$9,585	1.59	0.76

* Excludes professional fees.

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January 24, 2000

Author Reply:

Dr. Sternbergh has raised some interesting points in his letter, and I appreciate the opportunity to respond. First, with respect to the reporting of actual numerical cost, I was able to get the actual cost figures from our hospital accounting office with the understanding that I would use comparative ratios in order to preserve the confidentiality of hospital data. With respect to the inclusion of device cost in our calculation, it is true that the first few implants were done with the device provided by the company at no cost. Very quickly, however, the company received permission from the FDA to recover "costs" by charging our institution for each individual device used. This averaged approximately $6000 per device, and that cost was included in the overall cost calculation for patients receiving the endovascular implant. Because that figure is less than the $10,000 currently being charged, Dr. Sternbergh is partially correct in his assumption that there was a cost reduction during the study phase. Because there was an important reduction in resource utilization, however, in the endovascular aneurysm group when compared with patients undergoing open repair (e.g., median ICU stay, 0 vs. 2 days; median hospital stay, 2 vs. 7 days; blood replacement, 0.4 vs. 1.6 units), the device costs were more than offset by resource cost savings.

Resource cost reduction in our institution was made possible by a clinical pathway protocol. We decided from the inception of the program that patients undergoing endovascular repair did not need to go to an ICU, and barring any complications could be discharged from the hospital the day after operation, with subsequent follow-up accomplished in an outpatient setting. Other institutions, however, had a reflex reaction that all patients, including those undergoing endovascular repair for AAA, needed to be followed, at least initially, in an ICU. In addition, until a comfort level was achieved with the procedure, endovascular patients were kept in the hospital several days for observation. This practice clearly drove up the cost and eliminated any cost benefit derived from the endovascular repair.

There is one final important point not raised by Dr. Sternbergh: the cost of following endovascular patients versus those undergoing open repair. Because there is a new complication of endoleak in some cases of endovascular repair, periodic CT scanning must be done and repeated through the years of follow-up. This will clearly drive up the long-term care costs, and thus, the overall cost of patient management. Furthermore, if additional secondary procedures need to be carried out in patients with endoleak, that cost must be added to the overall cost management of patients undergoing endovascular repair. Thus, to Dr. Sternbergh's comment that hospital administrators are bound to be disappointed may also be added the fact that third-party payers are also likely to be disappointed as they look at the overall cost management of patients with AAA.

On the positive side, however, is the fact that as more companies bring endovascular devices to market, competition is likely to drive down the cost of the device. Ultimately, the bottom line is the issue of patient satisfaction and the reduction in morbidity and mortality in the multicenter trials that have now been reported to the FDA. These findings clearly make a compelling argument for the use of endovascular repair in properly selected patients by experienced endovascular surgeons.

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January 21, 2000

To the Editor:

Klinkenbijl et al. have reported survival results for a Phase III trial of adjuvant chemoradiotherapy to patients with both pancre-

atic and periampullary cancer (*Ann Surg* 230:776–784). The results show a trend (P = .099) toward statistically significant improved survival for those with pancreatic adenocarcinoma assigned to the treatment regimen. However, they have not reported the comparison of those *actually treated* with adjuvant chemoradiotherapy against those who did not receive the therapy (there were 23 patients assigned to treatment who did not receive the therapy—I extrapolate from the text that there were 5 of the 50 patients with pancreatic cancer assigned to treatment but not treated, and 18 with periampullary cancer and not treated). It seems only fair to the readers (and to the therapy) to provide us with these comparison.

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To the Editor:

Klinkenbijl et al. in their article, "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* 230:776–784), conclude in both the Conclusions section of their abstract and in the Discussion section of the manuscript that "routine use of adjuvant chemoradiotherapy is not warranted as standard treatment in cancer of the head of the pancreas or periampullary region." Subset analysis of patients with pancreatic head adenocarcinoma and periampullary adenocarcinoma was performed because these diseases have different natural histories and patterns of treatment failure. For patients with adenocarcinoma of the pancreas, median survival was 17.1 months for the 60 patients who received adjuvant chemoradiation, and 12.6 months for the 54 patients who received surgery alone (RR = 0.7, 95% CI = 0.5–1.1, P = .099). On page 780 in the Results section of the manuscript, the authors acknowledge that follow-up duration and patient numbers were insufficient to draw conclusions about the potential benefit of postoperative adjuvant therapy for patients with adenocarcinoma of pancreatic origin. In fact, a trend in favor of adjuvant therapy was shown (RR = 0.7). Further, the confidence intervals (95% CI = 0.5–1.1) include clinically relevant values (e.g., RR = 0.5) indicating that the data do not exclude the possibility that a meaningful survival benefit may be associated with adjuvant chemoradiation.

The Conclusion section of the abstract and the final paragraph of the manuscript clearly convey to the reader that there is no indication for adjuvant 5-FU–based chemoradiation after pancreatectomy for patients with adenocarcinoma of the pancreas. This is not supported by data in the manuscript (as acknowledged by the authors in a much less visible part of the manuscript), is clearly misleading, and may negatively impact the care of patients with pancreatic cancer due to the wide readership of this journal.

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Author Reply:

Regarding Dr. Hoffman's comments, in the control arm, 103 patients were eligible (54 had pancreatic head cancer, 48 periampulllary cancer, unknown for one patient; Table 2, page 779). In the adjuvant treatment arm, 104 patients were eligible (60 had pancreatic head cancer and 44 periampullary cancer; Table 2). Ten of these 104 patients refused treatment, 11 met a contraindication to receive the treatment before its start, and no data were received for two other patients. In a total, 81 patients actually received the treatment.

Fifty of these 81 patients had pancreatic head cancer and 31 periampullary cancer (Treatment Data, page 778). In other words, in the adjuvant treatment arm, 10 of the 60 eligible patients with pancreatic head cancer did not receive treatment. Your question is therefore: can statistical comparison be provided between these 50 patients and the 54 patients with pancreatic head cancer randomized in the control arm? The answer is no. First, this is a subset analysis where 10 patients would be "removed" in one arm only. The nonadministration of the treatment can be related to the treatment itself or to the prognosis of the patients. Removing these patients from analysis will clearly introduce a bias in the comparison of the two arms. Finally, a "per treatment" analysis was not planned a priori and the study was not designed to answer that question.

Regarding Dr. Evans's letter, we do not think the paper is "misleading." It states that a larger difference between the two treatment arms was found in the group of the patients with cancer of the head of the pancreas than in the entire group of eligible patients randomized in the study. However, this difference is not significant and might be due to "chance," to lack of power (i.e., too-small sample size or follow-up) or due to the size of the real difference existing between the two therapy approaches. Indeed the 95% CI (RR = 0.5–1.1) is including the value 0.5, but it also contains values around 1. Based on this study, no firm conclusion can be drawn, so the adjuvant therapy can not be recommended as standard treatment.

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