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To the Editor:

We are writing to respond to the editorial by Brennan[1] appearing in *Annals of Surgery* in the same issue as our paper on the survival of patients staged by FDG-PET before resection of hepatic metastases from colorectal cancer.[2]

Dr. Brennan levels two main criticisms at our work. The first is that we claimed priority for the finding that about 25% of patients who undergo FDG-PET after conventional staging with CT are discovered to have more extensive disease than originally suspected. In fact, the introduction of our paper reviews, in some detail, the prior studies that established this fact, including one from Dr. Brennan's own institution.[3] The meta-analysis[4] cited in the editorial was published after our paper was in press.

The second criticism is that we reportedly claimed that FDG-PET increases the survival rate of patients with colorectal cancer metastases to the liver. In fact, we were quite careful to state the following in our discussion: "...use of FDG-PET is not improving survival by itself, but is allowing surgical techniques to be applied with greater likelihood of benefit to patients. The result is better survival of patients who do receive surgery because the target population for surgery has changed, rather than because FDG-PET and surgery produce longer survival times for the same sort of patients represented in previously published studies." Therefore, neither criticism is justified on careful reading of our paper.

Concern was also expressed regarding use of the terms "overall survival" and "resectability rates." The term "overall survival" was used to contrast with "disease-free survival" in the resected patients. The paper is clear that the survival referred to was that in the patients who underwent resection. Regarding operability and resectability rates, these terms were used in conformity with commonly accepted definitions in the surgical literature. Again, it is clear in the test and figures that "resectability rate" referred to the frequency of resection in patients who came to laparotomy after FDG-PET.

I believe that Dr. Brennan missed the opportunity to set the course in this important area. An editorial is by definition the opinion of the journal and its editor, although today an editor often selects a surrogate to represent him or her in a specialized area. The editorialist has at least three responsibilities to the journal's readers. The first is to inform why the article was considered sufficiently meritorious and interesting to be selected for publication (and for editorial comment) and in what way it affects the field. The second is to discuss the shortcomings of the research, and the third is to outline questions unanswered and work yet to be done. This editorial falls short in each of these areas. Instead, it tells us that all three papers on the subject of PET scanning published in the March 2001 issue of *Annals of Surgery*[1,5,6] have little merit and that randomized controlled trials should have been performed.

Randomized controlled trials are, of course, the gold standard toward which we should aim. However, they are costly and often lengthy. As a result, selectivity is required in deciding which questions are of sufficient promise and merit to warrant study via this process. Nonrandomized, single-institution studies of an emerging technology like FDG-PET, such as our own study and that published by the editorialist's own institution,[3] often provide the rationale for a randomized trial. Therefore, they may have a very important role in this respect alone.

We have carefully considered whether a randomized trial could be done to confirm the findings of our study and we have presented our data as the basis for the planning of a multi-center study by the American College of Surgeons Oncology Group (ACOSOG). The data were judged by the ACOSOG hepatobiliary organ site committee to be so convincing that a Phase II study, rather than a randomized Phase III trial, was recommended. There was a consensus that sufficient equipoise would not exist in the surgical community and among patients to have a control group in a multi-center trial of the use of FDG-PET in metastatic colorectal cancer. In effect, it was predicted that a randomized, controlled trial would fail because of lack of accrual.

Furthermore, it was felt that a Phase II trial would be sufficiently conclusive as to the value of FDG-PET if it showed that FDG-PET detected new disease after conventional staging, particularly if this new disease would not have been discovered at laparotomy. This trial is now being put forward through the auspices of the ACOSOG. For these same reasons, two currently open ACOSOG studies of the utility of FDG-PET in lung and esophageal cancer, respectively, are also both Phase II trials.

Dr. Brennan laments the lack of randomized controlled trials of FDG-PET in cancer, but doesn't provide the journal's readers with any insight regarding how he believes these could be accomplished.

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To the Editor:

This letter is written to comment on and clarify certain statements made in an editorial regarding various aspects of our recently published article entitled "Decision Analysis for the Cost-Effective Management of Recurrent Colorectal Cancer" by Park et al.[1]

The editorial's author, Dr. Brennan, in discussing baseline results of our cost-effective analysis, stated that "...it appears that the cost increase (incurred by an imaging strategy of CT+PET vs. CT alone) is $429 but the increase in life expectancy (LE) is 9 days! That certainly would be hard to justify when one considers a delay of 9 days is a common event in obtaining approval for a test or an operation under managed care." We would certainly agree with his comment if the 9-day increase in LE meant, as he thought, that each patient would live 9 days longer than without the new imaging strategy. In fact, what is meant by this result is that across the relevant patient population partaking of this new strategy (~6,000), on average, there would be an increase of LE per patient of 9 days (i.e., one patient may live an additional 5 years, one 3 years, one 2 months, etc.). Or alternatively, 6,000 patients × 9 days/patient = 54,000 days or 148 years of available increased LE distributed over the *entire* patient group. What is being looked for preliminarily in this type of analysis is not merely the absolute value of the average increase/decrease in LE per patient, but rather whether it is an increase or decrease and how much more or less, in the case of a LE increase, it will cost additionally per patient to compare it to other medical technology assessment scenarios. This is not unlike a portfolio manager asking if his investors sustained an overall profit or loss in their equity portfolio, which would in and of itself carry some meaning separate from the *amount* of profit or loss that he/she would want to know next.

The above point relates directly to the concept of incremental cost-effectiveness ratio (ICER), which the author misunderstood to reflect "no benefit" in the analysis, and found that "...minor differences in the projected estimates compound to make major differences in the outcome." First, the ICER is a ratio tool used to examine whether we are spending more money on the new technology to increase LE for the patient population (a second choice, of course, to spending less) and how much more.[2] By definition, the ICER is obtained by dividing the difference in cost for the compared technologies by the difference achieved in LE. In the ideal case of spending less and gaining more LE for patients, there is no argument to implementing the new technology because we have a "win/win" situation. In the scenario where we must spend more to achieve the increase in LE, our savvy "portfolio manager" would be asking how *much* more, and would righteously raise the point that his healthcare industry estimates say that the going acceptable ceiling for ICERs in new medical technologies is currently $50,000 per 1 year LE increase.[3,4] With that in mind, our baseline results revealed an ICER of $16,437/yr, which the Dr. Brennan said showed "no benefit." In fact, our ICER shows that the increased cost incurred with the proposed new technology strategy is well within the acceptable national ceiling, and so considered a benefit. But to convince our "portfolio manager," we went a step further to be able to state at what cost/new scan (baseline results used $2000/FDG PET scan) we could spend *less* overall and keep our increased LE. This threshold occurs at a cost of $1,171/scan; which leads us to the next criticism by the Dr. Brennan.

What was perceived as the compounding of minor differences in projected estimates to make major differences in outcome is actually just the opposite. It is the selective investigation of individual variables singly to discover which affect outcome (ICER) the most if economic, technical, and other factors change over time (e.g., the cost of an FDG PET scan dropping to $1,171, or the sensitivity of CT for the whole body increasing significantly). What the Dr. Brennan misunderstood was that showing how the ICER outcome ranges as pertinent factors are systematically varied (sensitivity analysis)[5,6] is an established method of demonstrating robustness to an outcome; it is exactly the opposite of his implication that if there are major differences, it is an unreliable outcome showing no benefit.

Without understanding sensitivity analysis, misunderstandings are certain to follow. Dr. Brennan points out that "...a CT scan is not just a CT scan in the year 2000." It is for this very reason that sensitivity analysis becomes valuable. Through the analysis, we can directly measure the effect of diagnostically different CT scans on the competing strategies. Not only are we able to see if this variable has an effect on the cost effectiveness of a given strategy, but we can also answer the question of how good (at what value) does the variable (CT scan) have to be so that the baseline strategy becomes favorable. Furthermore, by performing sensitivity analysis on all variables used to construct the decision tree, we are able to validate the structure and function of the decision tree model based on its ability to demonstrate predictable outcomes. As an example, let us look at our value for the sensitivity of a CT scan (0.757). Because it is impossible to say that this value is 100% correct, we use sensitivity analysis to vary this variable within its given range of values to see how it affects the results (ICER). In our analysis we found that at a CT sensitivity value of 0.879, the results become unfavorable for the CT+PET strategy. This is what would be predicted because as the diagnostic value of the CT scan becomes better than PET, an additional PET scan might not be necessary. This lends confidence in the results because it allows us to understand how bad our estimate of 0.757 has to get before the ICER becomes unfavorable.

Lastly, the Dr. Brennan raises the important point that "...CT scanning is so widely disparate that no one institution can be compared to another, let alone form the basis of a retrospective evaluation of added benefit." Yet he goes on to make an excellent suggestion of proposing a randomized trial led by surgeons to prospectively evaluate new technology where "...high quality CT scanning, carefully defined with rigid parameters, could be compared in a randomized fashion to patients who undergo the same CT scan with the addition of a PET scan." We agree, that in order to conduct a comparative study, parameters must be *carefully defined*, which is the format we followed in constructing our model. Because technology is so complex, there are real limitations to establishing and choosing study parameter starting points and definitions that can facilitate both clinical and theoretical investigations. We agree that every possible variation of sophisticated technology cannot be studied or modeled, and unfortunately certain rigid definitional constraints must be established if collecting study data are to be accomplished at all.

We hope this response helps to clarify certain real issues and misunderstandings for readers that were raised in the editorial. In the original manuscript we had much more detailed explanations of all of the findings but were asked to significantly truncate the manuscript for cost-effectiveness of a different sort! It is difficult

to convey all the subtleties of decision analysis, and we hope the above responses are helpful.

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From the Editor:

The readership should appreciate that I thought Dr. Strasberg's manuscript to be comprehensive, thoughtful, and well written. He did comment in the discussion "a subtle but important point is that FDG-PET is not improving survival by itself." My issue was that it was impossible for a diagnostic test per se to directly influence survival.

As judged by others, surgeons have been strongly criticized for their descriptive attempts at surgical research. I believe it is fair to say that we have some experience with the difficulties of randomized trials, but have continued to try to perform them. I do applaud Dr. Strasberg's attempts to convince the American College of Surgeons Oncology Group to perform a randomized Phase III trial, and am personally disappointed that they concluded, "that the data were so convincing that a Phase II study, rather than a randomized Phase III trial, was recommended." The literature is replete with promising phase II studies, subsequently disproved by randomized trials.

It was my intent to provide encouragement for surgeons in general to take a leadership role in the validation of tests that we use. It appears, however, that I have unnecessarily and unintentionally provoked Dr. Strasberg.

Mr. Park, Ms. Schwimmer and Dr. Gambhir write to try to clarify issues that I failed to understand in their manuscript. As I pointed out, I did find the manuscript difficult to read, and other readers can make their own judgment. I still favor clarity over prolixity.

I have read and reread the explanation. Unfortunately, I still have a problem. If the overall increase in life expectancy is an average of 9 days, but some patients may live 5 years, then must not other patients live less than the average 9 days? I can only leave the readers to decide whether the manuscript and the added explanation is clear enough to allow us to accept the author's conclusions. It is encouraging that Dr. Gambhir and his colleagues support the concept of a randomized trial.

If we take Dr. Strasberg's definition of an editorial, it seems that we fulfilled all of his requirements, and if we allow that an editorial should provoke vigorous debate, it may have been valuable.

Let there be no mistake, we need manuscripts that examine critically the value of technological advances measured in terms of patient care benefit.

Our problem is to prove to other than ourselves that we have established such benefit.

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To the Editor:

Dr. Huang et al.[1] should be congratulated for their evaluation of the quality of life (QOL) in pancreaticoduodenectomy survivors. For this study, they used a QOL tool developed at our institution looking at the overall physical, psychological, and social domains. In addition to these QOL domains, we feel that the spiritual domain is an important component of the tool.[2] The overall QOL scores were high, and compared favorably to patients who underwent a laparoscopic cholecystectomy and healthy controls. In subgroup analysis, they show the chronic pancreatitis and pancreatic adenocarcinoma patients may rate their QOL lower than other groups, especially related to such outcomes as abdominal pain, thirst, foul stools, and diabetes. Therefore surgeons may need to focus their efforts on these QOL concerns.

We have recently used a similar tool to assess QOL related to patients with intestinal stomas. A mailed survey to 1,600 respondents resulted in 43% colostomy patients, 40% ileostomy patients, and 17% urinary diversion patients. In subgroup analysis of cancer versus noncancer patients with colostomies, cancer patients reported a better overall QOL for each domain except for spirituality, where both groups were similar. In addition, problem areas such as sexual function, dietary adaptations, travel, and body image were identified. Individual or group counseling was seen to be important for most colostomy patients. Therefore, as with Dr. Huang's study, groups of patients can be identified where early interventions can potentially improve QOL parameters. We are also examining outcomes for ileostomy and urinary diversion patients to identify problem areas.

Finally, we are looking at QOL as related to palliative procedures for cancer patients. For this effort, we are attempting to assess how surgical interventions can impact end of life care. Therefore, we are agree that studies such as those conducted at the John Hopkins Medical Center are extremely important in helping to define the role of surgery and improve QOL outcomes.

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To the Editor:

It has been shown that the prion strain causing bovine spongiform encephalopathy (BSE) in cattle has infected human beings while manifesting itself as a novel human prion disease, a variant of Creutzfeldt-Jacob Disease (CjD).[1] Recently, a number of reports have discussed the potential risk of transmitting CjD via infected surgical instruments.[1] Two papers[1,2] recommend that instruments used in treating patients with CjD should be destroyed by incineration because the prion has shown to be highly resistant to standard sterilization procedures.[3,4] However, due to the long incubation time (approximately 15 years),[3] there might be a risk that a number of patients who have not developed the disease yet will undergo an operation in the future. It has been shown that BSE can be transmitted via blood from one sheep to another in the latent phase.[6] Therefore, destroying instruments used with patients having CjD is not sufficient.

To the best of our knowledge, CjD has only been identified in the brain, the spinal cord, retina,[5] lymphatic tissue, and appendix.[3] Moreover, BSE has been identified in the blood of sheep.[6] However, future research might show that other forms of tissue may contain CjD.

Contaminated instruments have been suggested as a potential source for transmitting CjD.[1,2] A case-controlled study[7] showed that the risk of developing CjD increased after surgical procedures. The risk progressively increased with the number of surgical treatments, to a maximum of three procedures. However, another potential source for transmitting CjD needs to be considered. Catgut is still widely used in surgery, and BSE has been identified in cats.[8] A case of simultaneous occurrence of spongiform encephalopathy in a man and his cat has been reported.[9] The normal procedure for dealing with this complication is to sterilize catgut with gamma radiation. However, BSE is extremely resistant to high doses of ionizing and UV radiation (Advisory Committee on Dangerous Pathogens –SEAC 1998).[3] Until safe sterilization procedures has been developed, we are concerned about the continuous use of catgut in surgery.

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To the Editor:

We read with interest the article "Pain and Functional Impairment 1 year After Inguinal Herniorraphy ..." by Bay-Nielsen et al.[1] As Condon underlined in the editorial,[2] the 29% incidence of chronic pain 1 year after herniorraphy reported by the Danish group is unexpectedly higher than reported before in other series. I agree with Condon that a "self reporting especially of the severity of such a subjective matter of pain is confounded" by many factors. I agree with Bay-Nielsen and with Condon in considering a neuropathic origin of the pain in most of the cases. Bay-Nielsen says that "no documentation regarding the outcome of intentional severing of the nerves of the groin" was reported.

In 1999 we published the results of a prospective study on the prevention of posteriorraphy persistent pain by neurectomy of the iliohypogastric nerve in 180 anterior herniorraphies, with polypropilene plug and sutured mesh.[3] No patients complained of postoperative persistent pain. Regional hypo-anesthesia, never considered incapacitating, was present in 1% of patients after 2 years. In another series of 50 consecutive patients with bilateral groin hernias, we performed no neurectomy on one side and iliohypogastric neurectomy on the other side. There is a difference in early and late postoperative pain on the two sides, with statistically less pain on the neurectomy one (unpublished data).

In the same period we successfully treated two cases of persistent pain after anterior tension-free herniorraphy, performed in other hospitals, removing the iliohypogastric nerve entrapped into the mesh.

We consider the persistent pain after herniorraphy a major drawback of this minor but very common surgery. More consistent data should be acquired by performing further multicentric studies on neurectomy versus traditional technique.

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