Anatomic Location of Breast Cancer Micrometastasis in Sentinel Lymph Node Predicts Axillary Status

To the Editor:

We read with interest the paper by Viale et al,[1] and we would like to comment on the topic of sentinel node prediction of axillary status, based on data from a series we collected at our institution.

The assumption is that the great majority of patients with positive sentinel lymph node (SLN) are not expected to harbor additional metastases, after complete axillary lymph nodes dissection. Accordingly, Viale et al[1] tried to identify pathologic features able to predict the risk of additional non-SLN metastases, to avoid unnecessary surgery. They suggested that 3 features are strongly associated with non-SLN metastases, namely, the size of metastatic deposits, the number of SLN involved, and the peri-tumoral vascular invasion of primary tumor, the former being the most powerful predictor.

From January 2000 to December 2004, 540 patients with clinically negative lymph nodes and "small" (<3 cm) breast cancer underwent SLN biopsy at the Istituto Clinico Humanitas (Milan, Italy), according to previously described protocols.[2] Nodal metastases were found in 162 (30%) patients who underwent complete axillary dissection. SLN and non-SLN were examined on formalin-fixed, paraffin-embedded sections, as also reported by Viale et al,[1] without the aid of cytokeratin immunostaining. Clinicopathologic features of these patients were recorded and data reported as number and percentage, or mean and standard deviation, when appropriate; categorical data were compared with Fisher exact test.

Of 162 patients, SLN micrometastasis and metastasis were documented in 62 (38%) and 100 (61%) cases, respectively. The overall prevalence of additional non-SLN metastases was 32.7% (53 of 162 patients); patients with SLN metastasis had a significantly ($P < 0.0001$) higher proportion of additional metastases (43 of 100, 43%), as compared with patients with SLN micrometastasis (10 of 62, 16.1%). Interestingly, additional metastases from SLN micrometastasis were associated not only to the size of metastatic deposits, as shown by Viale et al,[1,3] but also to the anatomic site. Indeed, when SLN micrometastases were stratified according to their nodal site, the prevalence of additional metastasis was 3% for sinusal (1 of 31) and 29% (9 of 31) for intranodal location ($P = 0.026$); when SLN micrometastasis were stratified according to their size (up to 1 mm versus 1–2 mm), the prevalence of additional metastasis was 8% for those up to 1 mm (3 of 37) and 28% for those of 1 to 2 mm (7 of 25) ($P = 0.045$).

The association between the intranodal site of SLN micrometastasis and the axillary involvement has not been documented previously. According to our data, additional non-SLN metastases are significantly more frequent in patients with intranodal SLN micrometastasis as opposed to sinusal micrometastasis, being a new predictor for axillary status. Notably, analogous features have been reported in malignant melanoma: a worse outcome was signaled by Starz et al[4] in patients with intranodal SLN metastasis as opposed to capsular/subcapsular location. Common metastatic targets seem to be shared by malignant melanoma and breast carcinoma, and increasing evidence indicates that certain chemokines may play a specific role. Indeed, both tumors express the receptors CXCR4 and CCR7, which bind to cognate ligands CXCL12 and CCL21;[5] interestingly enough, these ligands are overexpressed in lymph nodes, lung, liver, and bone marrow which, in turn, are the commonest sites of breast cancer and malignant melanoma metastasis. "In vitro" experiments showed ligand–receptor interactions with generation of pseudopodia and invasive properties while neutralizing antibodies against ligand/receptor abrogated lymph node homing.[6] It is tempting to speculate that "in vivo" neoplastic cells, entering the subcapsular sinuses through afferent lymphatics, adhere to nodal parenchyma if specific ligands are expressed; if not, they can skip lymph node drainage and redirect to other targets. Studies on the chemokine profile of micrometastasis and clinical follow-up data are required to confirm this hypothesis.

Our results support the hypothesis that the size of micrometastasis is useful to predict the axillary status. This feature was previously investigated[3] and recently emphasized in the paper by Viale et al[1] where isolated tumor cells were also considered. Viale et al[1] suggested that patients with metastatic deposits to SLN can be stratified in 3 different risk groups, according to the size of metastatic deposits. We found that the risk of detecting additional metastasis in non-SLN is low but not negligible in micrometastasis up to 1 mm (8%), significantly greater for > 1 mm micrometastasis (28%), and fairly high in patients with SLN metastasis (43%). Our results are therefore in keeping with the suggestion that patients with positive SLN can be stratified into 3 different risk groups, namely, low (up to 1 mm), intermediate (1–2 mm), and high (>2 mm).

In conclusion, we not only confirmed that the size of micrometastasis in SLN breast cancer is a powerful predictor axillary status, but we also propose that the intranodal location of metastatic deposits should be taken into account as a new predictor of axillary status; whether the intranodal/sinusal location of SLN node micrometastasis actually reflects a chemokine-pattern driving phenomenon remains to be established.

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Reply:

Di Tommaso and colleagues confirm that size of axillary sentinel lymph node micrometastasis is correlated significantly with the risk of additional non-sentinel lymph node metastases in breast carcinoma patients, in agreement with our previous findings.[1] Furthermore, the authors emphasize that intranodal location of micrometastases may also predict the likelihood of additional metastases. This finding is strikingly similar to what was already shown by Dewar et al[2] for melanoma metastases. It would be interesting to assess, however, whether size and location of sentinel lymph node metastases are correlated features. If nodal sinus metastases are significantly smaller than parenchymal metastases, the relative predictive power of size and location of sentinel lymph node micrometastases should be addressed.

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Complicated Diverticulitis

It Is Not Yet Time to Rethink the Rules!

To the Editor:

Should we change the rules? No, of course not, at least not the rule that any published paper, but particularly the ones in high impact journals, should provide transparent data. The recent report by Chapman et al[1] on complicated diverticulitis unfortunately abandoned that policy. Despite a concentrated effort to recalculate the numbers quoted in the paper, it is impossible to truly reconstruct their origin, not to speak of their meaning. The authors looked at 337 patient with what they called complicated diverticulitis and grouped them into 6 different categories. Not only is the definition of complicated diverticulitis very fuzzy when it comes to phlegmon and perforation (as any form of diverticulitis consists at least of a microperforation and some degree of phlegmon), but in what ever way the figures are grouped back and forth, the total number of patients cannot be achieved, which means that there must be some (not disclosed) overlap between the various groups. In addition, the treatments administered to the patients have to be second-guessed from in-between the lines as well as the commentary. There is no mention about the role and duration of conservative management, no mention about the surgical attitude and the indications for surgery, no mention about whether the patients were operated during the index hospitalization or electively during a subsequent admission (as revealed in the commentary for at least 32 patients), no mention about CT-guided abscess drainage, no mention of which 67% of the patients underwent a CT and why the other 33% did not. The reader might be inclined to speculate that the patients with diffuse peritonitis were the ones not to require a CT, but again 51 of 337 only accounts for 15% of the patients. Hence, all we know is that virtually all patients (98%, 331 of 337) underwent surgery, which is substantially more than most other series on complicated diverticulitis, including our own,[2] where we reported a stage-dependent chance to avoid resective surgery between 38% and 68% for the subgroup of patients with an abscess.

One of Chapman and colleagues' key statements[1] p̄rovoking and, due to the lack of convincing evidence, disturbing at the same time ī̄s that a history of diverticulitis does not predispose to and predict subsequent complications, and that prophylactic resective surgery (to the present time still a common recommendation for selected patients) is therefore not indicated. As the authors' series with a close to 100% resection rate obviously lacks nonoperative follow-up data, their statement is based on indirect, retrospective evidence. But it remains questionable whether the just 17 of 337 patients (5%) with fatal outcome but negative prior diverticulitis history are sufficient to make such a general statement for the whole group, as the presence of other comorbidities (eg, immunosuppression) was superimposed and might have blurred the picture. More importantly, however, a closer look at Figure 3 indicates that roughly 48 patients (estimate extracted from the graph) with perforation had a previous diverticulitis history, which translates in 32% to 94% depending on whether the denominator consists of all 150 patients with perforation or just the 51 patients with peritonitis. Furthermore, approximately 45 of 75 patients (60%) with a phlegmon, approximately 60 of 99 patients with an abscess (61%), approximately 31 of 45 patients (69%) with a fistula, and approximately 39 of 76 patients (51%) with a stricture had a positive diverticulitis history. Hence, a high number of patients with complicated diverticulitis had a history of prior episodes. This means that elective surgery potentially could have saved a significant group of patients the relevant num-

ber of postoperative complications under nonelective conditions (41%) and the high number of necessary ostomies, which ranged from 27% in fistula/bleeding/phlegmon, to 30% in obstruction, 42% in abscess, and 78% in perforation and of which at least 20% if not more will be permanent. Shifting the focus away from just the fortunately relatively few fatalities, the paper should have been used to underscore rather than dissuade the potential benefit of an elective prophylactic resection. Yes, at this point, it is time to rethink this paper's data and conclusion, but in the absence of harder data on the natural course not (yet?) the rules of the ASCRS practice parameters.[3]

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Reply:

We are pleased to see that our goal of stimulating discussion on practice standards for diverticulitis has been achieved with Dr. Kaiser's letter on our paper "Complicated diverticulitis: is it time to rethink the rules!" However, on reading his first sentence, it is evident that Dr. Kaiser has missed the point. "Rethink," as defined by in *Merriam-Webster's Collegiate Dictionary*,[1] means "to think about again: reconsider." This is precisely what we meant when we included this in our title.

Our objective, with what is in essence a surgical cohort study of patients hospitalized for complicated diverticulitis, was to compare morbidity and mortality in 2 tertiary care centers with classic studies reported 30 to 40 years ago. We found, as we expected, that mortality rates in the modern day are not nearly as high as had been reported in these studies, which provide the basis for current treatment guidelines. Data on diverticular disease have clearly not kept pace with the advances in surgical management of the disease. With improvement of perioperative and operative management of complicated diverticulitis, we, along with others who have reported similar results,[2–4] question the validity of the 2 episode/elective resection tenant with the avowed goal of preventing the high morbidity and mortality (>10%) quoted in data from the 1960s, 1970s, and 1980s. This guideline seems to have been based on the theory that diverticulitis is a progressive disease, one in which one or two "warning" episodes of acute resolving diverticulitis often lead to a subsequent complication with attached significant mortality. Our paper, plus the others mentioned above, given that they are retrospective studies and are not true natural history studies, indicate that in most cases diverticulitis is not progressive nor does it have a predictable pattern. We therefore may be operating on many patients who will never develop complicated diverticulitis and, subjecting them to a 2% to 4% mortality rate, which is higher than mortality from all of the complications in this study except for perforation, (mortality rate for perforation was 12%, abscess 3.9%, obstruction 2.6%, and all other complications 0%) and a colostomy rate of around 15% with anastomotic leaks and the like. In addition, we are doing nothing to prevent complicated diverticulitis in the more than 50% who develop complicated diverticulitis as an initial event. Prophylactic resection, therefore, under current guidelines, may come too late for many patients in preventing complicated diverticulitis, and may be unnecessary in other patients. Careful reading of our paper does not reveal any such statement "that prophylactic resective surgery . . . is therefore not indicated," as Dr. Kaiser states. To the contrary, both in the abstract and in the conclusion, we state that new prospective data are needed to potentially redefine target groups for prophylactic resection. We are calling for *reevaluation*, not change, on the basis of this and other retrospective data.

Dr. Kaiser is correct in that the numbers, as he outlines them, do not add up and we were remiss in not stating this more clearly. On thorough review of the original data, we found that 7 patients were not specifically diagnosed with complicated diverticulitis, and we must apologize for that error. However, this error does not, in any way, change the outcome in the 330-patient cohort; in fact, it strengthens our point. Dr. Kaiser

TABLE 1. Breakdown of the Numbers and Percentages Regarding Presentation of Complicated Diverticulitis

Form of Complicated Diverticulitis	Total No. of Complications	1 Complication Only	% of Complications Presenting Alone for Each CD
Perforation	151	91	60.3
Obstruction	79	44	55.7
Abscess	103	38	36.9
Fistula	45	23	51.1
Phlegmon	75	14	18.6
Hemorrhage	15	10	66.7

	1 Complication [No. of Complications (% of Group)]	2 Complications [No. of Complications (% of Group)]	≥3 Complications [No. of Complications (% of Group)]
Perforation	91 (60.3)	39 (25.8)	21 (13.9)
Obstruction	79 (55.7)	24 (30.4)	11 (13.9)
Abscess	38 (36.9)	43 (41.7)	22 (21.4)
Fistula	23 (51.1)	17 (37.8)	5 (11.1)
Phlegmon	14 (18.6)	43 (57.4)	18 (24.0)
Hemorrhage	10 (66.7)	4 (26.7)	1 (6.6)
Overall	220 (66.7)	85 (25.7)	25 (7.6)

The majority of patients presented with one form of complicated diverticulitis, but 25.7% had more than one complication of diverticular disease and 7.6% had 3 or more.

had a problem with the numbers, not because of these 7 patients, but because many patients had more than one complication (Table 1). This was done on the advice of our statistician, since who can say whether the abscess or the fistula in any 1 patient is the more serious complication? The inclusion of phlegmon is defined in the Materials and Methods section as "a symptomatic inflammatory mass not associated directly with pus." The question regarding the inclusion of phlegmon was also answered in the Discussion section in response to Dr. Fry's comments. This is the definition that was used in the classic papers to which our more recent data were compared. Since "phlegmon" was used in these studies, we felt it necessary to include this category to have a comparable data set, even though we would not use this term today.[5–8] Other information which Dr. Kaiser seeks, such as the role and duration of conservative management, the surgical attitude and indications for surgery, the timing of the operation, CT scanning for staging (many patients who perforated had free air on plain abdominal films and did not have CT), and the CT-guided abscess drainage issue, was beyond the scope and intent of this study, and for our purposes, irrelevant. Careful reading of the last paragraph of the paper delineates areas of controversy, which we cannot address in the narrow focus of this work.

The second objective of this paper was to determine how many patients who were hospitalized and surgically treated for complicated diverticulitis had antecedent episodes of acute resolving diverticulitis. Again, consistent with other studies,[2–4] this proved to be a minority of these patients (less than half, 45.4%, had a prior history of acute uncomplicated diverticulitis).

The literature supports our finding that perforated diverticulitis is not only associated with increased morbidity and mortality, but is commonly the initial presentation of diverticular disease in many patients.[5,8,9] Again, to clearly restate the data, 68.2% of all patients who perforated had no previous history of diverticulitis, 15 of the 17 patients who died of perforation had no prior history of acute diverticulitis; it is evident that perforation is by far the most disastrous form of complicated diverticulitis, and from our data the mortality from other forms of complicated diverticulitis today is very low. While Dr. Kaiser dismisses the importance of perforation in this picture, it is the very focus and heart of this study.

Therefore, yes, we are suggesting a reevaluation of prophylactic resection, and we are suggesting even more aggressive prophylaxis in such groups as very elderly patients who have a single episode, transplant patients, and other immunosuppressed patients, and patients on chemotherapy. Furthermore, we need prospective data, more clearly defining the natural history of diverticulitis, and comparing results in patients with 2 episodes treated nonoperatively and observed, with patients who undergo resection after 2 episodes. With such data in hand, we can then think about truly changing the rules rather than rethinking them.

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Positron Emission Tomography/Computed Tomography Influences on the Management of Resectable Pancreatic Cancer and Its Cost-Effectiveness

To the Editor:

I would like to commend Heinrich and colleagues on their very fine article on the influence of positron emission tomography/computed tomography (PET/CT) on the management of pancreatic cancer.[1]

However, I would like to raise several concerns regarding the reporting of the results of the paper, which I feel is biased in favor of the use of PET/CT. First, the authors suggest that the addition of PET/CT to the staging process is superior to contrast enhanced CT (ceCT) alone in the detection of distant metastasis as 5 patients missed by ceCT were detected via PET/CT. However, careful analysis of the study revealed that only 2 of these metastases were abdominal (1 hepatic and retroperitoneal nodes, 1 abdominal wall). The other metastases were in the lungs ($n = 2$) and cervical lymph nodes, which were not within the field of the abdominal ceCT. Hence, this raises the question of whether the addition of ceCT of the thorax (instead of abdomen alone) would be more cost-effective than PET/CT. Additionally, it is important to note that the abdominal wall metastasis was actually seen clearly on ceCT retrospectively, although it was missed initially. Second, the authors suggest that PET/CT can detect synchronous neoplasms (2 colorectal cancers in the study). Once again, this point is debatable as both cancers were actually demonstrated but missed on ceCT. These neoplasms would probably also have been detected intraoperatively if a complete and thorough laparotomy was performed during pancreatic resection.

Finally and most importantly, regarding the cost-effectiveness of PET/CT, the authors calculated the cost savings based on the assumption that the 5

patients with distant metastasis would have avoided the operative and hospitalization costs of a pancreatic resection. However, this is probably an overestimation. For example, the patient with intra-abdominal metastasis would probably not have undergone a pancreatic resection, even without a preoperative PET/CT, as the liver metastasis would have been detected during laparoscopy and the high costs and long hospitalization associated with pancreatic resection would than be avoided (diagnostic laparoscopy is probably more sensitive that PET/CT, and this is supported by the author's findings whereby 2 patients with small liver metastasis were missed by PET/CT but detected at laparoscopy).

Hence, although I agree with the authors that the addition of PET/CT to standard staging tests will probably have a positive impact on the accurate diagnosis[2] and staging of pancreatic carcinoma, the cost/benefit for the routine use of this modality remains unproven.

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Reply:

We thank Dr. Goh for his interest in our study and the valuable comments.[1] Dr. Goh questions the relevance of PET/CT abdominal findings since these lesions were possibly visible on ceCT or would have been found during surgical exploration. In addition, he challenges the conclusion that PET/CT was superior to ceCT in our series because of the larger field covered by PET/CT compared with abdominal ceCT. A further criticism concerned the overestimated cost-effectiveness of PET/CT.

The poor outcome in many patients with pancreatic cancer deemed resectable after standard staging is mostly due to missed metastases at the time of surgery.[2] These metastases are missed because either the imaging tools do not cover the area of metastasis (eg, thorax) or the lesions are overseen. In this context, PET/CT clearly add new information because it covers the entire body with low exposure to radiation and may detect misinterpreted or overseen findings due to additional functional information related to FDG uptake. Here, we also need to emphasize that our aim was not to compare PET/CT with ceCT, but rather to evaluate whether patients with pancreatic cancer evaluated through a standard staging protocol may benefit from an additional PET/CT. The results clearly indicated that patients do benefit from this new modality, since the oncologic management was changed in a significant number of patients based solely on additional PET/CT findings.

As pointed out in our manuscript, consensus on cost data related to PET/CT is currently not available. Therefore, we would agree with Dr. Groh that cost analysis should be interpreted with caution. We based our estimation on the actual cost of standard staging, PET/CT and surgery. When surgery is performed in patients judged unresectable during surgical exploration, a palliative "double bypass" is often offered due to expected prolonged survival under modern chemotherapy.[3] Because of similar complication rates, costs are unlikely to differ significantly from Whipple procedure, thus avoiding surgery by optimal preoperative staging is crucial to reduce cost. Based on our analysis, we found that routine PET/CT in patients with pancreatic cancer deemed resectable on conventional workup provides significant cost saving. As the next step, we are currently evaluating whether cePET/CT may replace all conventional imaging modalities.

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Immunologic Benefits of Spleen Transplantation in the Absence of Graft-Versus-Host Disease

To the Editor:

With interest we read the paper by Tzakis et al, recently published in your journal,[1] that summarizes the evolution and current status of clinical multivisceral transplantation. One of the conclusions of the authors is that a multivisceral graft seems to facilitate engraftment of organs, suggesting that this procedure offers a degree of immunologic advantage. As the authors state in their discussion, this advantage could be partly attributed to the inclusion of the spleen in the graft, and they referred to a previous study of ours relating to spleen transplantation.[2]

We would like to comment on some of the immunologic aspects of spleen transplantation, particularly with regard to its effect in inducing a state of donor-specific unresponsiveness, the lack of associated graft-versus-host-disease (GVHD), and the incidence of post-transplantation lymphoproliferative disease (PTLD) (as discussed in the panel discussions on pages 491–493).[1]

Following an extensive review of the literature of spleen transplantation, mainly in rodent models,[3] we and colleagues carried out spleen allotransplantation across minor-mismatch, MHC class 1 and MHC full-mismatch barriers in a preclinical miniature swine model.[4–6] Recipient pigs of MHC-mismatched grafts received induction therapy consisting of

a low dose of whole body irradiation (100 cGy on day −2), which is nonmyeloablative,[6] and thymic irradiation (700 cGy on day −1); maintenance immunosuppression consisted of cyclosporine monotherapy for 45 days only.

In all recipients of successful spleen grafts, multilineage chimerism was detected in the blood for periods up to 6 months,[6] and donor cells were identified in the bone marrow and thymus. In vitro assays, such as mixed leukocyte reactivity and cell-mediated lympholysis, indicated that donor-specific T-cell reactivity was suppressed while third-party responses were maintained intact.[6] In 2 recipients of spleen transplants, kidney transplantation was subsequently performed from a pig MHC-matched to the original spleen donor, without exogenous immunosuppression. Although these grafts eventually failed from uncertain cause (although not from classic rejection) after >4 and >7 months, respectively, this was in great contrast to kidney grafts in control asplenic nonimmunosuppressed recipients that were rejected within 4 and 15 days, respectively.[6]

A very mild, transient, and self-limiting form of cutaneous GVHD was observed in a minority of recipients, but no serious manifestations of this condition were seen even in pigs that demonstrated >50% donor T-cell chimerism.[4,6]

Although none of the patients with a spleen as part of their multivisceral transplant developed PTLD in the series reported by Tzakis et al,[1] we observed 2 cases in pigs with spleen transplants, but only when the levels of cyclosporine therapy had been excessively high.[7]

In conclusion, we agree with the authors of this paper in believing that a spleen allograft has immunologic benefits and has the potential to induce a state of unresponsiveness not only to itself but also to other donor-specific organs. Using the regimen we followed, even when the level of chimerism was high, GVHD was not a problem, and PTLD could be avoided by careful monitoring of immunosuppressive drug levels. We think that spleen transplantation has considerable potential as a means of inducing a state of tolerance to other donor-specific organs and is worthy of further investigation.

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