CORRESPONDENCE

Impact of Tumor Size on the Clinical Outcomes of Patients with Robson Stage I Renal Cell Carcinoma

I read the report by Kinouchi et al.,[1] in which they concluded that the tumor grading of renal cell carcinoma was not predictive of the survival of Robson Stage I patients. This does not mean that the three-grading system is worthless; the authors simply showed that the grading system of the Japanese General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma[2] is not useful in the study of Robson Stage I renal cell carcinoma. The Japanese Rule[2] states that renal cell carcinoma should be classified according to the quantitatively dominant grade. Kinouchi et al.[1] omitted this explanation from their article. This "dominant rule" is obviously distinct from the other grading systems, according to which renal tumor grading is decided by the highest grade.[3,4] I am afraid that their report might mislead international readers. The Japanese General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma[2] was made in 1992. Its classification is different from "modern classification"[5–7] and even from the classification criteria of the Armed Forces Institute of Pathology.[3] Kinouchi et al.[1] nicely demonstrated the limitation of the Japanese Rule.[2] I would like to announce that it is time for the Japanese to throw away their old-fashioned Rule.[2] The recently published protocol of the Cancer Committee of the College of American Pathologists[8] has greater possibilities.

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First of all, it appears that Dr. Kanomata has misunderstood the grading system of the Japanese General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma, which consists of a 3-stage system (i.e., Grades 1, 2, and 3). Apparently, Dr. Kanomata has misunderstood that in the Japanese General Rule, renal cell carcinoma should be classified according to the quantitatively dominant grade; however, the Japanese General Rule does not observe the grading system Dr. Kanomata described. For example, if tumors contain heterogenous grading patterns, the Japanese General Rule recommends describing the grading as G1>G2 when the major area contains G1 tumor and the minor area contains G2 tumor. If half of the tumor tissue samples contain G1 tumor and another half G2 tumor, the Japanese General Rule recommends describing the grading as G1=G2.

Second, we indicated in our article that higher grade determines the grading system, which is reasonable for predicting the patient's prognosis, as Dr. Kanomata mentioned.

Finally, we recommend that the Japanese General Rule determine the grading system according to the higher grade used.

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Intrapleural Administration of Interleukin-2 for the Treatment of Patients with Malignant Pleural Mesothelioma

A Phase II Study

We read with interest the article by Astoul et al.[1] regarding the administration of interleukin-2 (IL-2) for the treatment of patients with malignant mesothelioma. Although this appeared to be a well-designed and adequately conducted Phase II study, which included 22 patients who all received their planned therapy, we are concerned about the statistical analysis and interpretation of the results. Specifically, the authors compared the survival rate of responders to therapy with that of nonresponders, remarking that "... the median survival time of responders differed significantly from that of nonresponders: 28 months (SE: 12.12) and 8 months (SE: 5.07), respectively ($P < 0.01$)" and concluded that "these results confirm that IL-2 given intrapleurally has antitumor activity." A considerable amount has been written, however, about the pitfalls of analyses comparing responders to nonresponders (see, for example, Anderson et al.,[2] Weiss et al.,[3] and Green et al.[4]). The main problem with this analysis is that patients have to live long enough to achieve a response; this "guarantee time" therefore biases the comparison in favor of the responders. Response status might also simply be a marker of patients with a better pretreatment prognosis who would have lived longer even had they not received therapy. Andersen et al.[2] discuss modifications of analyses based on response status that are less prone to bias, such as landmark analysis; however, none of these techniques can reliably be used to draw causal inferences regarding the effectiveness of treatment from Phase II data. Reviewers, authors, and editors must be aware of these important statistical issues as they generate medical literature.

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We appreciate the comments of Dr. Karrison and Dr. Vogelzang regarding our article on intrapleural interleukin-2 (IL-2) therapy for patients with malignant pleural mesothelioma, and we thank them for their interest in reading our article.[1]

When we statistically compared the survival rate of responders to therapy with that of nonresponders in a descriptive fashion, it was to point out our interest in performing "second-look" thoracoscopy on patients treated intrapleurally to assess their responses and we develop this point later. We are aware of the pitfalls of such analysis, although the survival of our patients was long enough to achieve a response based on an evaluation performed 36 days after the beginning of treatment (all eligible patients were assessable for response) and consequently all patients had "guarantee time."

We also agree that response status might simply be a marker of patients with a better pretreatment prognosis. However, except for three patients with Stage IA disease, the others had advanced cancer and represented homogenous cohort, and only one patient presented a fibrosarcomatous type that suggested a poor prognosis.[2] Taking into account the total protocol dose delivered, the toxicity experienced, and the patient population, we do not think that survival was associated with some basic underlying factor.

The landmark method compares a group of patients who have responded by a landmark time with another group that has failed to respond. It is quite different from a comparison of people who respond to therapy with those who do not respond to therapy.[3]

We did not suggest that longer survival for responders was due to intrapleural IL-2 therapy; this was not the aim of our Phase II study. Our last sentence stresses the need for Phase III comparative studies. However, based on computed tomography (CT) scan and "second-look" thoracoscopy, we think that the evaluation of antitumoral response was suitable. It is the first time, to our knowledge, that such an evaluation was performed after intrapleural treatment. Yasumoto et al. reported antitumoral responses in patients with malignant pleural effusions due to lung carcinoma treated with intrapleural IL-2.[4] However, those antitumoral responses were based on CT scan and pleural fluid as well as the disappearance of malignant cells, which is questionable.

In our Phase II study, it was noteworthy that the patients we considered to be responders (even thoracoscopy was not easy after intrapleural therapy) were those with prolonged survival. However, it is our opinion that the 43% 24-month and 31% 36-month survival rates of patients with Stage II malignant pleural mesothelioma (which is usually associated with poor prognosis) must be confirmed by comparative randomized Phase III studies to establish that the longer survival of responders was due to the treatment.

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Expression of p53 Protein and Resistance to Preoperative Chemotherapy in Locally Advanced Gastric Carcinoma

Cascinu et al. investigated the association between p53 status and response to preoperative chemotherapy in locally advanced gastric carcinoma.[1] Their study was based on determining the true extent of the tumor so that the p53 status could be analyzed cor-

rectly. In their study, tumor extent was evaluated with 2 completely different methods: laparotomy in 53% (16 of 30) of patients and computed tomography (CT) scan of the abdomen in 47% (14 of 30) of patients. The authors did not include any detailed information regarding the true disease stage of the patients prior to the administration of chemotherapy; they stated only that all patients had locally advanced disease.

As we all are aware, evaluation of response to chemotherapy is difficult in patients with locally advanced gastric carcinoma. The primary tumor site usually involves an ill-defined mass rather than an easily measurable lesion. Although upper gastrointestinal barium examination may determine the size of gastric lesions, it is ineffective in determining the depth of gastric wall involvement. Imaging modalities that can detect tumor invasion through the gastric wall into perigastric structures play a major role in staging.[2] CT, one of the most frequently used modalities, can detect only enlarged lymph nodes and predict direct invasion of adjacent structures by gastric carcinoma. However, due to its limited spatial resolution, CT cannot detect the depth of a tumor spread within the gastric wall and also is incapable of distinguishing fat plane obliteration caused by tumor invasion, inflammation, or cachexia. It is well known that normal size lymph nodes may contain tumor. This also explains the limited ability of CT to detect lymph node metastases.[2] In a study performed by McFee and Aust,[3] CT was shown to have a sensitivity of 67% and a specificity of 61% for detecting lymphadenopathy in patients with gastric carcinoma and it also failed to show pancreatic invasion, with a sensitivity of 27%.

Endoscopic ultrasound (EUS) is a highly accurate method for the assessment of gastrointestinal malignancies. It has become the standard imaging modality for local staging of gastric carcinoma.[4] The accuracy of EUS in determining the extent of primary tumor infiltration ranges from 67–97%.[5–11] EUS is superior to CT in its ability to show the layers of the gastrointestinal wall, but is not as accurate as CT in the assessment of regional lymph nodes (N2) or distant metastases.[2] The combined results in 326 patients in the assessment of tumor extent showed that the accuracy of EUS was remarkably superior to CT (EUS: range, 82–92%, and CT: range, 11–43%). The accuracy of lymph node assessment by EUS and CT were found to range from 74–87% and from 25–51%, respectively.[8,11,12] Conversely, laparotomy is a valuable method with which to detect occult intraabdominal metastatic disease. After subsequent laparotomy >25% of patients are reported to have been found to be understaged by CT scanning.[13] However, laparotomy may not define the tumor extent in the gastric wall, especially in patients with less advanced disease with N0 status, which may lead to difficulties in the evaluation of the stage.

CT and EUS are complementary rather than competitive. EUS is superior in locoregional staging and CT is preferred for the diagnosis of distant metastases. It is clear that EUS is an invaluable method in gastric staging and should be combined with CT scanning of the abdomen or with a more invasive method such as laparotomy in determining the true stage of disease. In the study by Cascinu et al.[1] the two different methods used for staging differ greatly in their sensitivity and specificity, which may result in the erroneous evaluation of disease stage as well as response rates. Consequently, this would affect response rates to preoperative chemotherapy and its association with p53 status.

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In their correspondence, Drs. Özgüroglu and Demir point out the major role of endoscopic ultrasound (EUS) in the staging of locally advanced gastric carcinoma. Given the lack of staging with EUS in our study, they question the reliability of our results regarding the predictive value of p53 expression for resistance to chemotherapy.[1]

In our opinion, the criticisms by Drs. Özgüroglu and Demir are only partially convincing. First, some problems still are encountered with EUS imaging.[2–4] Second, this examination may not be necessary for assessment of response to chemotherapy in the presence of unresectable disease with macroscopic locoregional tumor involvement defined by endoscopy plus biopsies and computed tomography (CT) scan.[5]

In some studies, EUS has displayed a tendency to overestimate tumor extent because of the coexistence of peritumoral inflammation, especially in the presence of ulcerated tumor. In addition, artifacts due to erroneous scanning (tangential) may simulate increased thickness of layers. EUS may have poor accuracy in determining surface extension of the tumor.[2–4] Overestimation of the lymph node status may be observed due to inflammatory hypertrophy of lymph nodes being a source of error for EUS. Similar to CT imaging, identification by EUS of metastases to lymph nodes with normal size and microinfiltration may be very difficult. In general, figures regarding EUS accuracy for the determination of lymph node status may be lower than reported by Özgüroglu and Demir, with a range of 50–87%.[2–4] Finally, recent data suggest that underestimation of lymph node status by EUS may be related to differences in the histologic subtype of gastric carcinoma, with a lower accuracy for the detection of lymph node metastasis from undifferentiated compared with differentiated tumors.[6,7]

The definition of locally advanced gastric carcinoma may comprise different presentations of the disease. Patients may have high risk but resectable gastric carcinoma or they may present with unresectable disease with large volume local spread.[5] In our opinion, staging with EUS particularly is indicated for the selection of high risk patients with small volume disease who are candidates for surgery and are eligible for studies of neoadjuvant chemotherapy.[3–5] In addition, recent experiences have suggested that staging with EUS may be predictive of the risk of postoperative recurrence after radical surgery for gastric carcinoma.[7]

In our series, patients underwent endoscopy with biopsies and CT scans that demonstrated unresectable disease with bulky regional involvement or clear signs of infiltration of the pancreas, aorta, omentum, esophagus, and liver. After chemotherapy, partial response was defined as evidence on both endoscopy and CT scan of a >50% reduction in the tumor or the complete disappearance but positive endoscopic biopsy at the site of the tumor. Complete response was defined as a negative CT scan together with normal endoscopic view with negative biopsies.

In the presence of conspicuous locoregional involvement, the imaging we adopted for defining tumor burden may be adequate.[4] In addition, the major criteria for evaluating response reduced the risk of erroneous evaluation of tumor shrinkage.[4] We believe the relation we found between p53 overexpression and resistance to chemotherapy to be reliable.

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