In Reply: We appreciate the interest by van Akkooi et al in our study[1] and the opportunity to respond to their correspondence by addressing the questions raised. Among our large cohort of patients who had at least one histologically positive sentinel lymph node (SLN), we used multiple measures of SLN microscopic tumor burden to comprehensively assess in both univariate and multivariate models patients who may be at low as well as high risk of having non-SLN involvement in their complete therapeutic lymph node dissection (cTLND) specimen. SLN tumor burden was assessed by the diameter of the largest SLN metastatic focus, SLN tumor square area, the number of SLN metastatic foci, the microanatomic location of SLN metastasis (subcapsular, intramedullary, or both), and the presence or absence of microscopic extracapsular extension. Tumor square area was calculated as the sum of the cross-sectional products of all SLN deposits. While all aforementioned measures of tumor burden were included in the multivariate analysis and found to be independent predictors of non-SLN involvement, the largest metastatic focus was chosen for our working model based on the potential for easy widespread applicability and its association with the highest odds ratio among the various measures of tumor burden examined.

We agree with van Akkooi et al that tumor square area is challenging to accurately measure (as has been noted by others)[2]; these data were presented as part of a comprehensive analysis of predicting non-SLN involvement using multiple measures of tumor burden. In fact, we used recursive partitioning methodologies to identify multiple cutoff points for each measure of SLN microscopic tumor burden. While van Akkooi et al have employed single cutoff point univariate approaches (eg, ≤ 0.1 or ≤ 0.2 mm) to interrogate this important clinical issue, our analysis provides a comprehensive range of SLN tumor burden thresholds that facilitate identification of patients not only with low-risk of harboring non-SLN involvement but also those patients at significant risk of non-SLN involvement (ie, up to 50%), and provides the melanoma community with data to further elucidate the significant heterogeneity of non-SLN involvement among patients harboring SLN metastases. While these lower cutoff points may be potentially useful in helping to define those patients at lowest risk for harboring non-SLN metastases, it is also potentially limiting; the multivariate modeling we report comprehensively addresses these important questions.

van Akkooi et al provide a table that summarizes, albeit in a distilled format, the results of select studies in which SLN microscopic tumor burden was assessed in melanoma patients to determine its association with risk of non-SLN involvement in the cTLND specimen and alternatively, in some studies, survival. However, the extremely limited annotation of the data in the table and, in particular, its inclusion of survival end points that were not at all a theme of our manuscript, prohibit comment; the table is at significant risk of misinterpretation and is therefore not appropriate to discuss further in this forum.

A decision to not perform cTLND at this time should be made cautiously. Predictions regarding non-SLN involvement are based almost exclusively on routine evaluation of the cTLND specimen and may therefore underestimate the incidence of clinically relevant microscopic non-SLN disease. Before elimination of cTLND can be advocated in patients with limited melanoma micrometastasis, prospective clinical trials designed to assess the long-term safety of omitting formal cTLND with respect to survival and locoregional control in low-risk groups are needed. The ongoing Multicenter Selective Lymphadenectomy Trial II,[3] which compares cTLND with close observation with sonography and clinical examination for patients with a positive SLN, should provide valuable information about which patients might be spared a cTLND.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Tumor Biology and Prognosis of Gastrointestinal Carcinoids

Dear Editor: Yao et al[1] have published an interesting article on neuroendocrine tumors (NETs) in the United States. However, some caveats are warranted concerning the conclusions drawn by the authors. The survival data published by Yao et al[1] reflects overall survival and not carcinoid-related survival. Carcinoid patients are known to have a high risk for second neoplasms. For example, patients with rectal carcinoid disease suffer from synchronous or metachronous second malignancies in up to 22% of cases.[2]

Important to note, the risk of lymph node metastases of rectal carcinoids is not inferior to the metastatic risk of rectal adenocarcinoma of the same size.[3-4] The prognosis of patients with metastatic rectal carcinoid disease is not better than the prognosis of patients suffering from metastatic rectal adenocarcinoma.[2-5] Five-year-survival of rectal carcinoid patients with distant metastases is 15% to 30%.[2-6] For nodal-positive rectal carcinoid disease (without distant metastases at the time of diagnosis), 5-year-survival amounts to 54% to 73%.[3,5] In contrast, nodal-negative rectal carcinoids that are smaller than 1 cm and do not show angioinvasion or infiltration of the muscularis propria have an excellent 5-year-survival of 98.9% to 100%.[3-7] As Yao et al[1] did not observe a statistically significant difference in survival duration among patients with local and regional NETs over time, confounding factors have to be taken into account.

Obviously, the authors' statement that "NETs generally have a better prognosis than adenocarcinomas at the same site"[1]

does not hold true for metastatic rectal carcinoids and metastatic rectal adenocarcinomas.[3-4]

As pointed out by Yao et al,[1] analysis of data obtained from the Surveillance, Epidemiology, and End Results (SEER) registries likely underestimates the total number of patients with NETs. As only patients with (supposedly) malignant NETs are included in the SEER registries, many small benign-appearing NETs (ie, appendiceal tumors) likely are excluded from the SEER registries. Important to note, the distinction between benign and malignant behavior is often not possible for NETs at the time of diagnosis. The normal appearance of regional lymph nodes on radiological imaging does not exclude metastatic spread.[8] Thus, a 6-mm–sized, well-differentiated carcinoid of the rectum with normal-appearing regional lymph nodes (on imaging) may be considered a benign-appearing rectal carcinoid. If lymph node dissection is performed and lymph node involvement is found histologically, the 6-mm–sized, well-differentiated rectal carcinoid (with preoperatively normal appearing lymph nodes on imaging) is postoperatively reclassified as a malignant carcinoid.[8] Therefore, the quality of the data on carcinoids of the SEER registries would be much improved if all NETs were registered. The currently available SEER data on carcinoids appears to be biased.

The prevalence of rectal carcinoids in adults (mean/median age, 48.8 to 54 years) undergoing screening endoscopy is known to be 0.05% to 0.07%.[9-11] In 2006, 57.1% of US men and women age 50 years or older reported they had received at least one examination with flexible sigmoidoscopy or colonoscopy.[12] When considering that about 55 million US citizens have been scoped and on the basis of a prevalence rate of 0.05% to 0.07%, one would expect some 27,500 to 38,500 rectal carcinoids to have been diagnosed by screening endoscopy in the United States. Coincident with the implementation of colorectal cancer screening, overall 5-year-survival of patients with rectal carcinoid disease has increased steadily in the United States.[5] Therefore, we should no longer regard rectal carcinoids that are detected by screening endoscopy as incidentally identified lesions. The early detection of colorectal carcinoids is one of the aims of endoscopic screening of the colorectum. The observed shift to more localized tumor stages at the time of diagnosis of NETs argues for the effectiveness of endoscopic screening.

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In Reply: In the accompanying correspondence, Dr Scherübl made several observations regarding our article.[1] A number of these points warrant our attention.

Dr Scherübl correctly notes that our survival analyses reflect overall survival and not disease-specific survival. While the Surveillance, Epidemiology, and End Results (SEER) program database provides data on cause of death based on International Classification of Diseases (ICD), we chose to perform overall survival analyses for several reasons. First, accurate assessment of cause of death is needed for disease-specific survival analyses. While it is possible to reliably ascertain the cause of death by meticulous review of medical records in a small retrospective case series, this is not possible with population-based registries. In the case of neuroendocrine tumors (NETs), this is further complicated by the lack of specific ICD-9 codes for the majority of NETs.

Until now, ICD-9-CM, the official system of assigning codes to diagnoses and procedures associated with medical resource utilization in the United States, only contained discrete codes for islet cell carcinoma (157.4) and hormonal syndrome due to carcinoid tumors (carcinoid syndrome, 259.2). Other NETs such as small bowel or rectal carcinoids were coded as carcinomas of respective primary sites. Thus, it would have been impossible to distinguish a rectal carcinoid from a rectal adenocarcinoma based on ICD-9-CM codes. While it is possible to tease out the NET diagnoses from the SEER database using International Classification of Diseases for Oncology, third edition, codes, it cannot be used to determine cause of death.

ICD-9-CM codes are also the means by which we communicate diagnoses between health care providers and third party payors. As we enter the age of targeted therapy for NETs and develop effective antineoplastic therapy beyond symptom control,[2-4] we will also need NET-specific ICD-9-CM codes to offer our patients appropriate therapy. To this end, we approached the Center for Disease Control and the Centers for Medicare and Medicaid Services in 2007 and applied for a disease-specific set of ICD-9-CM codes for NETs, which came into effect on October 1, 2008 (Table 1). It is hoped that these new codes, in time, would also provide the