to 60 mg/m^2 and demonstrates a significant improvement in 10- year disease-free survival and overall survival when epirubicin is used at a dose of 100 mg/m^2 in combination with fluorouracil and cyclophosphamide (FEC100) versus the lower FEC50 dose. It is not scientifically valid to compare the results of two different clinical studies, particularly because the tumor types were different and the chemotherapy regimens varied due to the wide dose range of anthracycline doses. In Hequet's study,[5] one case of CHF in 141 patients has been observed in the overall population regardless of the anthracycline dose. In our study, two CHF cases possibly related to epirubicin have been observed in 150 node-positive breast cancer patients. Among our FASG 05 breast cancer patients, 96% had also received locoregional irradiation following chemotherapy to prevent local recurrence per protocol. The two patients who developed CHF had received left chest wall and nodal irradiation and, thus, irradiation may have been a contributing factor in development of late cardiac sequelae in these women. It should be noted that the percentages given in Dr Ventura's letter are not correct. To our knowledge, Habeshaw's study[6] was a comparison between two different doses of epirubicin and not a comparison between doxorubicin and epirubicin. Finally, the FASG cannot speak about the cost of doxorubicin and epirubicin as it differs a lot between countries. Irrespective of cost, based on our extensive clinical experience over the past 15 years, we have observed meaningful clinical differences between these anthracyclines; thus, epirubicin remains our clinical standard.

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Do PET and SNB Reduce the Rate of Elective Neck Dissection? A Hypothesis Still in Need of Validation

To the Editor: In their recent article, Kovács et al[1] report their experience utilizing positron emission tomography (PET), computed tomography (CT), and sentinel node biopsy (SNB) in a prospective cohort of patients with resectable T1-3 squamous cell carcinoma of the oral cavity and oropharynx. This experience represents an important addition to the literature regarding the use of PET in the management of such patients. The authors conclude that a strategy utilizing PET and SNB considerably reduces the number of extensive neck dissections performed when compared with a treatment strategy that relies on only CT. However, the data presented do not necessarily support this conclusion.

For the identification of cervical lymph node metastasis, the authors state that CT "had a clear advantage" regarding sensitivity and that PET "had a clear advantage" regarding specificity. However, because these differences were not statistically significant, it is inappropriate to conclude that either PET or CT is better. In addition, administration of high-dose intra-arterial cisplatin after imaging and before SNB or neck dissection could have sterilized microscopic disease and thus artifactually increased the observed false-positive rates for both CT and PET.

The authors claim that a strategy using SNB for patients who are cN0 by PET will reduce the number of neck dissections required. They begin with the a priori assumption that an ipsilateral level I-V modified radical neck dissection (MRND) is indicated for all patients with suspected cervical lymph node metastasis. Thus, if PET reveals evidence for cervical metastasis, a modified radical neck dissection is performed. If PET reveals no evidence for cervical metastasis, a modified radical neck dissection is performed only if SNB is positive.

The authors state that this strategy markedly reduced the number of neck dissections performed when compared with a CT-based strategy. First, they state in the abstract that 96 of 124 neck sides would have required a neck dissection (either selective or modified radical) on the basis of a CT approach, but only 41 of 124 neck sides actually required dissection with the PET + SNB approach. This statement generates confusion because the CT-based approach assumes that selective neck dissection is performed for all cN0 patients, whereas the PET-based approach assumes that SNB is performed for all cN0 patients. Thus, the authors are comparing two different treatment paradigms, not two different imaging tests.

The real comparison should be the difference in neck dissection rates for a PET + SNB approach versus a CT + SNB approach. With the PET-based approach, 41 neck dissections were performed. The number of neck dissections that would have been performed with a CT + SNB approach is theoretically derived from the observed sensitivity and specificity of CT and is approximately 45, but may be as high as 49. Thus, addition of PET spared only four to eight neck sides from dissection.

Finally, it should be emphasized that the "unnecessary" neck dissections with the CT + SNB strategy are attributed to an excess in false-positive CT results as compared with PET results. However, all of these excess CT false-positive cases were evaluated with only SNB, a technique that may underestimate the true likelihood of cervical metastasis when compared with the gold standard of level I-V neck dissection.[2] Thus, the reported CT false-positive rate may be artifactually elevated. If the false-positive rate of CT is truly lower than reported in this study, then the number of "unnecessary" neck dissections would decrease, further narrowing the difference between CT- and PET-based approaches.

In summary, this article supports the hypothesis that excellent outcomes can be achieved using SNB to evaluate the clinically negative neck. However, there appears to be no clinically or statistically significant difference between PET and CT when integrated with SNB in the staging of patients with head and neck cancer.

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In Reply: I very much appreciate the criticism of Smith et al. They are absolutely right in stating that the title of our article is the summary of our single-center experience, which needs further validation. We ended our text with the expression of our hope that "the benefit for the patients is evident if the results were lasting and could be affirmed by other working groups." [1]

However, our experience of a comparison of positron emission tomography (PET) and computed tomography (CT) with regard to neck staging is much older dating back to 1994, and results were published in 1998 and 2000.[2,3] The specificity of PET proved to be higher, and we started staging the neck in oral and oropharyngeal cancer patients as described in our more recent publication. Decision making for the neck using PET is extremely simple as compared to CT, not to speak of the detection of second primaries and distant metastases in a large portion of patients without additional examinations (panendoscopy, abdominothoracic CT).

All other considerations of Smith et al ignore the main support (and concurrent greatest weakness) of our study: the observation time without neck relapses (to date, 33 months; desirable end point, 60 months). In avoiding elective neck dissections and pathohistological work-up, we have to rely on time, which may or may not approve our results. If there will be a rate of neck recurrences $>$ 10% in sentinel node biopsy (SNB) -negative patients, we have to re-evaluate the method. If SNB is correctly staging the neck and no neck metastases will become clinically evident in these patients in the future, all apprehensions of Smith et al with regard to the relevance of the different treatment methods of the neck will be dispelled.

In the last paragraph of their letter, the major concern of Smith et al becomes manifest. It does not seem so much to be the method of SNB but the estimation of CT in comparison to PET. We surely know that PET is a cost-intensive method, which is not as widely used as the more conventional CT. Therefore, the CT + SNB approach claimed by the colleagues was already executed. The initiators of the first multicenter trial on SNB (Plastic Surgery Unit, Canniesburn Hospital, Glasgow, United Kingdom) decided that patients should be "classified as clinically N0 by either clinical palpation or radiological imaging techniques such as positron emission tomography or computed tomography."[4] In 72 patients staged by SNB alone, 20 positive sentinel nodes were detected (28%), and in 53 patients examined by SNB assisted elective neck dissection, the rate has been 41% (22 of 53 patients). Other relevant studies ($>$ 10 patients) on SNB in cancer of the head and neck[5-13] similarly relied on elective neck dissections as reference, staged the neck using CT or ultrasound, and had rates of positive sentinel nodes between 10% and 61%, with a median of 27%. All had an excellent small rate of false-negative SNB results in comparison with pathohistology. We, therefore, willingly acknowledge the possibility of using CT as prerequisite for SNB, but with the consequence of higher rates of positive sentinel nodes, and, consequently, a higher rate of consecutive neck dissections. This rate, however, will still have the chance to be lower due to SNB as compared to conventional surgical treatment of the neck. As far as we know, conventional treatment of oral and oropharyngeal cancer patients in most centers of the world always comprises a neck dissection of some type.

The speculation that intra-arterial local chemotherapy might have "sterilized microscopic disease" in the neck nodes

would be, of course, a fantastic point in favor of that method but is not proven at all. Our own investigations to date concerning this problem demonstrated only small plasma concentrations of cisplatin,[14] and will be continued because of the relevance of this issue. According to our state of knowledge, it is the selection by PET that has to be the reason for the low rate of positive sentinel nodes in our sample.

To conclude, the main goal pursued with our article was to demonstrate the possibility of reducing the rate of elective neck dissections in oral and oropharyngeal cancer patients by combination of imaging techniques and SNB. The emphasis lies on the use of SNB. If other groups are able to demonstrate this using CT and SNB, we will be happy. However, we believe that PET is the optimal method of selection for SNB, and it is our task as members of a university hospital to investigate the best possible method.

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The author indicated no potential conflicts of interest.

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