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To the Editor:

We read with interest the article by Urbach, Kennedy, and Cohen.[1] Clearly, the number of patients with drainage after colorectal anastomosis was low in the four articles analyzed. As expressed in their conclusions, however, we would like to add two more large, well-designed randomized controlled trials[2,3] focusing on drainage after colorectal anastomoses, which were not available when the authors did their meta-analysis. These should give further credibility to their conclusions.

When the 809 patients in these two trials are added to the 414 patients in the four other studies, one notes that they become responsible for at least 50% of the weight. Realizing that summarizing all the information in these six trials into a single odds ratio may lead to oversimplification,[4] the overall (Peto) odds ratio for mortality drops from 1.38 to 0.98, clearly supporting the idea that drainage after elective colorectal anastomoses do not affect mortality. Additionally, the odds ratio for radiologic fistula remains practically the same (1.01 to 0.92), but that for wound complications drops from 1.70 to 1.20, weakening slightly the risk of deleterious effects of drainage on wound complications. The risk for respiratory complications also remains the same, but the risk of clinical fistula increased from 1.47 to 1.80 (with a nearly statistically significant OR (IC = 0.94–3.46), reinforcing the idea that drainage may actually *increase* the rate of (clinical) leakage.

Our conclusions remain: neither pelvic nor abdominal drainage is needed after anastomosis in elective, uncomplicated, colorectal surgery.

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October 18, 1999

Authors' Reply:

We agree with the opinions expressed by Dr. Fingerhut and his colleagues. These large randomized controlled trials unfortunately had not been published when we performed our meta-analysis. It is reassuring that these trials are consistent with earlier observations that routine prophylactic drainage of colon and rectal anastomoses is unlikely to be associated with improved outcomes, such as a lower incidence of anastomotic leakage. As Dr. Fingerhut points out, adding the large number of patients evaluated by Merad and colleagues[1,2] to the patients from prior trials significantly increases the statistical power of a pooled analysis to rule out a beneficial effect of drainage.

However, a note of caution is warranted. Because anastomotic leakage is an infrequent outcome, an extremely large sample size is required to rule out relatively small effects that may nevertheless be considered to be clinically important. Even the large study on pelvic anastomoses by Merad and colleagues[2] only had sufficient power to rule out a reduction in the risk of anastomotic leakage from 20% to 10% (a 50% relative risk reduction). Purists may argue that smaller reductions in relative risk may still be important to surgeons and their patients, and that existing data do not rule out smaller effects with sufficient power.

Clearly, large multicenter trials of surgical procedures are enormously expensive, time-consuming, and difficult to perform. Drs. Fingerhut and Merad are to be applauded for their valuable contributions to this clinical problem. Still, additional trials comparing routine prophylactic drainage to no drainage for pelvic anastomoses are warranted, if we are to know for certain that this practice truly offers no benefit to patients.

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September 4, 1999

To the Editor:

We were interested to read the paper by Chakravarti et al,[1] which recommends adjuvant chemoradiation for all patients undergoing local excision for T2 rectal cancers, and for T1 tumors with high-risk pathologic features. We were surprised, however, that the discussion included no mention of transanal endoscopic microsurgery (TEM), which has made the York-Mason and Kraske approaches virtually obsolete in the management of early rectal cancer.

The main advantages of TEM include:

- A transanal approach avoiding the well-known complications of the transsphincteric or posterior rectal approaches
- A clear stereoscopic view of the lesion
- The ability to excise a lesion up to 20 cm from the anal margin
- Precise dissection with good local clearance
- An intact specimen for proper pathologic assessment

Transanal endoscopic microsurgery is now a well-established technique in the local management of early rectal cancer.[2,3]

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Author's Reply:

Mr. Daniels and Mr. Simson are quite correct to suggest that transanal endoscopic microsurgery (TEM) is an elegant and handy technique for local excision of rectal tumors. The equipment would be nice to have, and might make the occasional posterior proctotomy or transsphincteric approach unnecessary.

Nevertheless, the equipment is expensive. Furthermore, when meticulously done, the traditional approaches provide excellent results with rare "well-known complications." This technique is most applicable for large lesions or for tumors located rather high in the rectum. Because the real need for this apparatus is infrequent, many have decided that it is not worth the investment.

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June 23, 1999

To the Editor:

The article "Subareolar versus peritumoral injection for location of the sentinel lymph node" by Klimberg et al[1] demonstrated that subareolar injection of technetium-99 sulfur colloid usually identified the same sentinel node(s) as did peritumoral blue dye. Based on concordance of radioactivity and blue color, the authors suggest that subareolar injection of technetium is as accurate as peritumoral blue dye injection.

The accuracy of sentinel lymphadenectomy for breast cancer—namely, the false-negative rate—can only be directly established by a concomitant axillary dissection for all patients, regardless of sentinel node status. Any comparison of modified techniques with those of proven accuracy should be held to rigorous standards. Because routine axillary dissection was not performed in this study, the accuracy of the new technique in predicting axillary metastases is thus unknown.

Indirect evidence for the accuracy of sentinel lymphadenectomy includes a similar percentage of positive sentinel nodes when compared to other authors who did validation studies including routine axillary dissection. Klimberg et al have reported that only 13.5% of T1 lesions had positive sentinel nodes, a rate well below the yield of other large studies.[2,3] This may partially reflect the lack of detailed pathologic analysis, but false-negative sentinel nodes may not have been included.

Additional indirect evidence of sentinel node accuracy not provided by this study is a low axillary recurrence rate with significant follow-up in patients with negative sentinel nodes.

I applaud the authors for their innovative approach, but the data presented do not allow acceptance at this time of the reliability of subareolar technetium injection. Without concomitant axillary dissection, accuracy is assumed rather than proven.

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July 26, 1999

Author's Reply:

In our study on subareolar versus peritumoral injection for location of the sentinel lymph node, we demonstrated that subareolar injection was as accurate as the established blue dye peritumoral technique and that the blue node was always hot. I agree with Dr. Guenther that a better study would be to then proceed

with an axillary lymph node dissection. However, our study is like comparing sentinel lymph node with a level I–II axillary lymph node dissection because a level I–III dissection would be the gold standard. If one reviews the data comparing level I and II dissections with level I–III, the false-negative rate ranges from 0.4% to 10%. Should we then compare the sentinel lymph node to a level I–III dissection?

The purpose of the article paper was to demonstrate that the location of the tumor is not as important as the drainage of the breast—which it did. This is further supported by the review of the literature that practically any method gives a high concordance rate with a level I and II axillary lymph node dissection.

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To the Editor:

We read with great interest the article by Chu et al, "Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection?"[1]

This paper addresses a topic that is being debated frequently by surgeons who have implemented the sentinel node (SN) procedure in breast cancer patients and who no longer perform an axillary lymph node dissection (ALND) when the SN is negative for metastatic involvement. The question frequently put forward is whether an ALND is necessary when the SN contains no more than a micrometastasis, defined by Chu and coworkers as a metastatic deposit <2 mm in diameter. Before one questions the prognostic significance of a micrometastasis in the SN in relation to the incidence of non-SN axillary metastases, however, one has to clearly define which is an SN and which is a non-SN.

In the paper by Chu et al, SNs are defined as nodes that can be radioactive only, blue only, or both. We find this definition not to be in accordance with the concept that the blue dye and the radioactive tracer will identify the same lymphatic drainage route that is followed by metastatic tumor cells. The fact that nodes that are blue only and/or radioactive only can both be designated as SNs, when both techniques are applied simultaneously in the same patient, is disturbing to us, as we reported earlier.[2,3] The blue dye and the radioactive tracer are expected to follow the same lymphatic drainage route and thus end up in the same node, which is the SN.[4]

By the criteria used by Chu et al, an average of 1.8 "SNs" were resected. More than one SN appeared to be positive, up to 5 per patient, but it is not clear in how many patients this was the case.

Furthermore, the size of the sentinel node metastasis was also determined in patients with more than one positive (sentinel?) node and related to the incidence of non-SN metastatic involvement.

We find it unlikely that non-SN metastatic involvement in the axilla can be predicted on the basis of more than one positive node removed with the sentinel node procedure. If more than one SN is positive, it is unclear which one should be used as the "reference" node for correlation with non-SN metastatic involvement. From dynamic lymphoscintigraphic images, we know that there may be more than one first-echelon node in the same patient. However, with increasing tumor load of the first echelon node(s), metastatic cells subsequently progress to second-echelon nodes by alternative routing. The same sequence of events is thought to occur for both the radioactive tracer and the blue dye.[5,6]

Therefore, when more than one positive node are called SNs, the additional node may actually be a second-echelon node, especially when additional, less radioactive nodes, are also defined as SNs, which was the case in this study.[1] This distinction may not be of importance when the sole purpose of the SN procedure is to establish node negativity in the axilla. When a study is designed to establish a relationship between SN tumor load and non-SN metastatic involvement, however, the distinction between first- and second-echelon nodes becomes an issue in our view. We therefore propose that SN tumor load can only be correctly correlated with non-SN metastatic involvement, in those patients with one positive SN.

Another point for discussion is the method used by Chu et al to determine the size of the SN metastasis. Not all metastases with a certain diameter have the same size, for the simple reason that metastases do not appear as perfect circles on a histology slide. This means that not all microscopic deposits with a diameter of 2 mm are equal in size. If tumor load in the sentinel node is to be correlated with non-SN metastasis, more objective and exact measurements are required.

We have used a different technique for measuring the size of SN metastases. The size of the metastasis in the SN was determined by digital surface area measurements under the microscope and expressed in square millimeters. We arbitrarily defined micrometastases as those with a surface area ≤ 1 mm^2, which may be considerable smaller than those defined as ≤ 2 mm in diameter. At least six sections were done of each SN with micrometastatic deposits.

In our patients, all SN procedures were done using both radioactive tracer and blue dye. Nodes were designated as SNs when preoperative lymphoscintigraphy showed focal accumulations in the axilla and when the resected nodes were radioactive, with a residual radioactive count in the axilla less than 10% of the hottest node resected (ex vivo count), before the SN procedure was terminated. The blue dye served to facilitate recognition of the radioactive nodes in the axilla.

Of the 77 patients with a positive SN procedure, only 28% with one positive SN had additional axillary metastases, whereas 65% with more than one positive SN had additional axillary metastases upon ALND. We further examined the correlation between tumor load of the SN and the incidence of non-SN metastases only in the group of patients with one positive SN. We found that 16% (4/25) with metastasis <1 mm^2 had non-SN metastasis, regardless of mode of histologic detection and regardless of primary tumor size.

Therefore, the preliminary analysis of our data suggests that, with stricter criteria for the SN that is to be used as the reference node in which the measurement is done, and with more objective measurements of the metastatic size, the involvement of non-SN axillary nodes in patients with micrometastases to the SN is greater than the 6% found by Chu et al (T1 and T2 tumors).

In at least three studies,[7–9] SNs were occasionally found to be negative for metastatic tumor cells, while nodes that were neither radioactive nor blue were grossly involved with tumor metastases. It is thought that the grossly involved nodes are unable to retain either radioactive tracer or blue dye. This phenomena may explain

in part the existence of micrometastases in the SN with non-SN being positive upon ALND.

The incidence of non-SN metastasis in patients with micrometastasis in the SN should be investigated in larger series of patients.

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Authors' Reply:

We greatly appreciate the insightful comments and questions of Drs. Rahusen, Meijer, and van Diest, who raise the important issue of identifying the true sentinel node (SN). The SN is the first node(s) to receive lymphatic drainage from a primary tumor and therefore the most likely lymph node to contain tumor metastasis. The goal of the surgeon in performing sentinel lymphadenectomy (SLND) is to identify this node consistently and accurately. Although many institutions have performed SLND with very high SN detection rates and very low false-negative rates, it is not possible to prove that a blue-stained or radioactive ("hot") lymph node is the true SN unless examination of all nodes in the drainage basin shows that this is the only node containing tumor cells. Our group previously reported an exhaustive analysis of all non-SNs from patients who underwent SLND with blue dye only and had tumor-free SNs.[1] Immunohistochemical staining of 1,087 non-SNs identified only one positive node not detected by hematoxylin and eosin staining.

Although our current study included patients who underwent intraoperative mapping using both blue dye and radioisotope, we have since abandoned the routine use of radioisotope because in our hands it did not improve the results and did add to the cost and complexity of SLND. Moreover, the kinetics of radioisotope and even the type of isotope have not been well determined, and thus the definition of a hot SN varies greatly from surgeon to surgeon.[2] Based on our proven accuracy rates for identifying the SN, we believe that if the radioisotope and the dye fail to identify exactly the same node(s),[3,4] the blue rather than the hot node should be considered the true SN. However, we remind Drs. Rahusen, Meijer, and van Diest that only 10 node-positive patients in our study underwent SLND using radioisotope in addition to blue dye, and all patients had a single positive SN which was *both* hot and blue.

If more than one SN contains metastatic disease, then a second node excised as an SN may well be a second-echelon node due to the alteration or progression of lymphatic flow that Drs. Rahusen, Meijer, and van Diest have suggested. However, even if this node is a second-echelon node, it is receiving lymphatic flow directly from the primary tumor site and therefore is functioning as an SN. If more than one SN is involved with tumor, then it is reasonable to assume an increased risk of non-SN involvement.

Drs. Rahusen, Meijer, and van Diest state that their incidence of non-SN metastasis was 28% among patients with single positive SN and 65% among patients with more than one positive SN. These rates are quite similar to the 29% and 51%, respectively, reported in our study. However, their definition of "micrometastasis" specified tumor deposits much smaller than those defined in our study, and they reported a much higher incidence of non-SN involvement in patients with SN micrometastasis (16% *vs.* 7%). This discrepancy is disturbing and underlies the need for further study to understand the progression of lymphatic metastases. If non-SN tumor burden is higher in patients with SN micrometastases than SN macrometastases, the SN identified during SLND may not be the "true" SN. We firmly believe that surgeons must scrutinize their results with SLND and determine the accuracy of this technique in their hands.

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