

Further Axillary Metastases Associated With Isolated Tumor Cells in Sentinel Lymph Nodes of Breast Cancer Patients

To the Editor:

Isolated tumor cells (ITCs) are defined as very low volume nodal (or systemic) involvement and are not considered metastases for staging purposes.¹ When found in the sentinel lymph nodes (SLNs) of breast cancer, no systemic or regional treatment has been suggested for this finding alone.² In contrast to this consensus statement, recently published data from the European Institute of Oncology (EIO)³ suggest that further nodal involvement beyond the SLNs may be encountered in up to 15% of the cases if the SLN contains only ITC, and on this basis the authors mandate axillary treatment even in the event of SLN ITCs.

By reviewing and meta-analyzing data on further nodal involvement associated with SLN micrometastasis and ITCs, we found a similar proportion of second echelon lymph node metastasis for the whole group⁴ and around 10% for SLN metastases detected by cytokeratin immunohistochemistry (IHC) alone. However, we were unable to separate the data according to SLN metastasis size because the definitions of ITC varied, and several authors reported results only in relation to the method of detection of the SLN involvement: IHC versus hematoxylin and eosin staining. ITCs are differently interpreted by pathologists,⁵ and this category of SLN involvement seems suboptimally reproducible.⁶ This is why the EIO data are important and of high impact, as they were generated in a single institution, with a systematic approach to SLNs involving complete step sectioning of the lymph nodes.

However, before making a general recommendation on the basis of their data, I would like to draw attention to one specific methodologic issue that weakens

their strong data on ITCs. The histopathologic workup of SLNs is based on frozen sections and hematoxylin and eosin staining of the SLNs, and IHC is used only in doubtful cases. The EIO has rejected the routine use of IHC (consistently with several current recommendations) on the basis of only a few cases. Although I agree that the role of IHC decreases as the distance between levels of step sectioning decreases,⁷ IHC still increases the rate of detecting ITCs as it is more sensitive. Detecting ITCs is a statistically random event⁸ and should not be considered the aim of SLN histology.⁹ Considering that both frozen sections (with their generally lower quality than paraffin embedded material) and the lack of routinely performing IHC allow more single cells or small clusters to remain undetected, I suggest that a number of ITCs have remained undetected at the levels sectioned. Therefore, ITC may be more frequent and be associated with a somewhat lower rate of non-SLN involvement in departments where complete step sectioning of the SLNs and IHC are used in conjunction.⁵

Despite this minor criticism, I congratulate the authors for the very important message of their paper, ie, metastasis size is a continuous variable, and the category of micrometastasis is not homogeneous as concerns the risks of further nodal involvement.

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REFERENCES

1. Sobin LH, Wittekind C, eds. *UICC TNM Classification of Malignant Tumours*, 6th ed. New York: John Wiley and Sons, 2002.
2. Schwartz GF, Giuliano AE, Veronesi U, et al. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19–22, 2001, Philadelphia, Pennsylvania. *Cancer*. 2002;94:2542–2551.
3. Viale G, Maiorano E, Pruneri G, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. *Ann Surg*. 2005;241:319–325.
4. Cserni G, Gregori D, Merletti F, et al. Nonsentinel node metastases associated with micrometastatic sentinel nodes in breast cancer:

metaanalysis of 25 studies. *Br J Surg*. 2004;91:1245–1252.

5. Cserni G, Amendoeira I, Apostolikas N, et al. Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in breast cancer: results of a questionnaire-based survey by the European Working Group for Breast Screening Pathology. *J Clin Pathol*. 2004;57:695–701.
6. Cserni G, Bianchi S, Boecker W, et al. Improving the reproducibility of diagnosing micrometastases and isolated tumor cells. *Cancer*. 2005;103:358–367.
7. Cserni G. Complete sectioning of axillary sentinel nodes in patients with breast cancer: analysis of two different step sectioning and immunohistochemistry protocols in 246 patients. *J Clin Pathol*. 2002;55:926–931.
8. Weaver DL. Sentinel lymph nodes and breast carcinoma: which micrometastases are clinically significant? *Am J Surg Pathol*. 2003;27:842–845.
9. Cserni G. Sentinel node biopsy in breast cancer and its implications for histopathological examination. *Histopathology*. 2005;46:697–706.

Reply:

We wish to thank Dr. Cserni for his interest in, and appreciation of, our paper. We definitely agree that extensive use of immunohistochemistry is likely to increase the detection rate of minimal involvement of axillary lymph nodes.

This, however, does not necessarily mean, as speculated by Dr. Cserni, that a lower rate of nonsentinel lymph node involvement would be expected. Indeed, it should be considered that nonsentinel axillary lymph nodes in our, as well as in other groups' studies, have been less extensively examined, with one to few sections cut per lymph node. Should all the nonsentinel lymph nodes be more thoroughly examined by serial sectioning and immunohistochemistry, then the rate of detection of additional metastases to these lymph nodes would also increase. As a consequence, the actual risk of additional nonsentinel lymph node metastases in case of minimal involvement of the sentinel lymph nodes may well remain similar to the one reported in our paper, or even increase.

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Geometry and Biomechanics of the Esophagogastric Junction: Implications for Antireflux Surgery

To the Editor:

With interest we read the article by Pandolfino et al.¹ The authors have to be congratulated for this outstanding work, which represents an important contribution to improve our understanding of mechanisms underlying gastroesophageal reflux disease.² Based on their findings, fundoplication works by creation of a “high pressure” junctional canal between the esophagus and the proximal stomach with decreased distensibility thus impairing reflux into the esophagus also during periods of transient lower esophageal sphincter (LES) relaxations. It remains to be questioned if gastric wrap-induced repair and stabilization of junctional geometry would also impair diaphragmatic excursion and peristalsis-induced longitudinal movement of the junctional mucosa out of the pressure zone into the acidic environment of the proximal stomach? Such a biomechanic effect would contribute to healing and repair of reflux-induced morphologic changes (carditis, columnar lined esophagus).³

Most importantly, the findings of Pandolfino et al¹ may also have important clinical implications for laparoscopic treatment of another motility disorder involving the LES: achalasia.⁴⁻⁷ Achalasia is characterized by impaired swallow-induced distensibility of the LES and aperistalsis of the esophagus. Surgical treatment aims to restore distensibility of the junctional canal by Heller-type myotomy of the LES.^{4,5} Experimental and clinical experience with transmurular dissection of the esophagogastric junction for treatment of severe forms of achalasia has also been reported.^{6,7}

Discrepancy still exists whether Heller myotomy should be conducted with or without an antireflux procedure.⁸ During laparoscopic myotomy, hiatal attachments between the esophagogastric junction and the crural diaphragm are dissected.^{4,5} It is well accepted that LES

performance follows a close structure-function relationship.¹ LES characteristics (ie, manometric pressure, length, and swallow-induced relaxation) depend on intrinsic LES function and extrinsic contribution, including hiatal attachments, the crura of the diaphragm, intra-abdominal pressure, and the acute angle of His.¹ Surgical treatment of achalasia affects intrinsic and extrinsic contributors of LES integrity. Going in line with this notion, Richards et al⁴ recently found that esophageal acid exposure is increased after myotomy without fundoplication, when compared with myotomy with Dor fundoplication. Taken together, the findings by Pandolfino et al¹ and the results of recent studies⁴⁻⁷ are in strong favor of myotomy with fundoplication for surgical treatment of achalasia. Finally, the above considerations indicate that antireflux surgery works by acting on extrinsic contributors of LES function.¹

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REFERENCES

- Pandolfino JE, Curry J, Shi G, et al. Restoration of normal distensive characteristics of the esophagogastric junction after fundoplication. *Ann Surg.* 2005;242:43-48.
- Wykypiel H, Gadenstätter M, Granderath FA, et al. Pathophysiology of gastroesophageal reflux disease (GERD) with respect to reflux induced carcinogenesis. *Eur Surg.* 2002;34:296-302.
- Chandrasoma P. Controversies of the cardiac mucosa and Barrett's oesophagus. *Histopathology.* 2005;46:361-373.
- Richards WO, Torquati A, Holzman MD, et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. *Ann Surg.* 2004;240:405-412.
- Cacchione RN, Tran DN, Rhoden DH. Laparoscopic Heller myotomy for achalasia. *Am J Surg.* 2005;190:191-195.
- Cosentini E, Riegler M, Koperek O, et al. Transgastric stapled esophagofundostomy (TSE) and partial fundoplication: a technical illustration of a new concept for surgical treatment of achalasia. *Eur Surg.* 2204;36:89-94.
- Caporale A, Cosenza UM, Galati G, et al. Oesophagocardioplasty for residual dysphagia

following multiple pneumatic dilatations for achalasia. *Br J Surg.* 2004;91:995-996.

- Clemente G. Fundoplication after myotomy for achalasia: to do or not to do? *Ann Surg.* 2005; 241:1029.

Reply:

We thank the authors for their appreciation of our study¹ demonstrating the efficacy of fundoplication in restoring the normal distensive characteristics of the esophagogastric junction (EGJ). The fundoplication surgical procedure anatomically remodels the EGJ region by wrapping the fundus externally around the hiatus and suturing the 2 walls together, resulting in an enhanced stiffness of this region when compared with gastroesophageal reflux disease patients. The authors of this correspondence raise the question of whether axial mobility of the intrinsic sphincter is impaired after fundoplication and what biomechanical ramifications this may have on EGJ morphology postsurgery.

In this context, a related paper from our research group,² comparing the mechanics of antegrade bolus emptying in normal subjects and postfundoplication patients, showed that fundoplication can be associated with an inability of the distal esophagus to generate sufficient active muscle tone for complete esophageal emptying. One source of the reduced muscle tone may be that reflux disease is associated with a deficient tonic capability in the distal esophagus. However, another potential cause is the limited axial mobility of the sphincter postfundoplication. The normal esophageal emptying process is associated with the oral excursion of the intrinsic sphincter during formation of the phrenic ampulla. This temporary herniation of the intrinsic sphincter over the distal esophageal bolus cavity places it in an optimal position to generate rapid increases in cavity muscle tone, which in turn will facilitate transhiatal flow. We hypothesized that, in the normal swallow, the inhibition of intrinsic sphincter tone initiated soon after the swallow is restored after repositioning of the sphincter oral over the ampulla, and that this reconstituted sustained sphincteric muscle squeeze is a major contributor to the sudden increase in tone. This rapid increase in tone causes a rapid increase in the driving pressure and forces open

the hiatal canal. Hence, we concluded that the lack of rapid increase in cavity muscle tone post fundoplication reflects, in part, the restricted axial motion of the intrinsic sphincter by the surgical procedure.³ Although our analysis was focused on antegrade opening, our data do support that movement of the squamocolumnar junction is restricted post-fundoplication. Thus, it is possible, as the authors suggest, that fundoplication may also limit axial mobility of the squamocolumnar junction and/or junctional mucosa into the acidic gastric compartment.

In terms of the last comment regarding the need for fundoplication in patients undergoing myotomy, we agree with the authors and strongly favor this approach. An effective myotomy will obliterate the intrinsic lower esophageal sphincter and does have the potential to alter the integrity of the extrinsic sphincter. This scenario provides the appropriate “2 hits” for acid reflux to occur and may potentially increase gastroesophageal reflux disease severity.

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REFERENCES

1. Pandolfino JE, Curry J, Shi G, et al. Restoration of normal distensibility characteristics of the esophagogastric junction after fundoplication. *Ann Surg.* 2005;242:43–48.
2. Ghosh SK, Kahrilas PJ, Zaki T, et al. The mechanical basis of impaired esophageal emptying postfundoplication. *Am J Physiol Gastrointest Liver Physiol.* 2005;289:G21–G35.
3. Kahrilas PJ, Lin S, Spiess AE, et al. Impact of fundoplication on bolus transit across esophagogastric junction. *Am J Physiol Gastrointest Liver Physiol.* 1998;275:G1386–G1393.

Can Journals Help the Improvement of Meta-Analyses Quality in Plastic Surgery?

To the Editor:

We read with great interest the article by Dixon et al¹ in the March issue. We found that the article repre-

sented a very critical, in-depth contribution to the issue of creditability of meta-analyses and their application in everyday clinical practice. The authors evaluated a series of meta-analyses by applying the Overview Quality Assessment Questionnaire (OQAQ) and coined some criteria of their own. We performed an evaluation of the literature in the fields of the plastic, reconstructive, and cosmetic surgery, making use of two of those criteria.

Selection of the literature was performed in the same manner as the previous mentioned authors, by the use of the PubMed (MEDLINE) search engine, and the same criteria, except of the fact that we did not have publication date limitations. As factor A, we termed the hypothesis that at least one of the authors had already contributed to a meta-analysis in the past. As factor B, we named the assumption that at least one author was a member in a department of public health or epidemiology.

We managed to identify only seven relevant meta-analyses for our evaluation.^{2–8} From those articles, only three of seven qualified for criteria A or B. Interestingly enough, articles that satisfied assumption A were also positive for criterion B. These three articles^{6–8} were then appraised using the OQAQ, and all of them had minor methodologic flaws. However, some issues arise that are specific for the field of plastic surgery: meta-analyses in our discipline are scarce and difficult to conduct. Therefore, most of the authors are inevitably first timers. Furthermore, with the profusion of publications in scientific and biomedical journals, it is difficult for busy clinicians, educators, and investigators to keep abreast of new developments; more so, if they cannot be sure of the quality of the report itself. When scientific and biomedical journals publish an article of any type, in our case a meta-analysis, shouldn't they be the ones that make an appraisal first before publishing it? Would it be incorrect for one to grant a consideration to providing readers of a given meta-analyses with an OQAQ score printed at the beginning or the end of the article?

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REFERENCES

1. Dixon E, Hameed M, Sutherland F, et al. Evaluating meta-analyses in the general surgical literature: a critical appraisal. *Ann Surg.* 2005;241:450–459.
2. Kierner AC, Zelenka I, Gstoettner W. The sternocleidomastoid flap: its indications and limitations. *Laryngoscope.* 2001;111:2201–2204.
3. Koch BB, Perkins SW. Simultaneous rhytidectomy and full-face carbon dioxide laser resurfacing: a case series and meta-analysis. *Arch Facial Plast Surg.* 2002;4:227–233.
4. Pacini S, Ruggiero M, Morucci G, et al. Bio-alcamid: a novelty for reconstructive and cosmetic surgery. *Ital J Anat Embryol.* 2002; 107:209–214.
5. Ching S, Thoma A, McCabe RE, et al. Review of data describing outcomes that are used to assess changes in quality of life after reduction mammoplasty. *Plast Reconstr Surg.* 2003;111: 469–480; discussion 481–482.
6. Jones SA, Bain JR. Measuring outcomes in aesthetic surgery: a comprehensive review of the literature. *Plast Reconstr Surg.* 2001;108: 62–67.
7. Chadbourne EB, Zhang S, Gordon MJ, et al. Clinical outcomes in reduction mammoplasty: a systematic review and meta-analysis of published studies. *Mayo Clin Proc.* 2001;76:503–510.
8. Hoshaw SJ, Klein PJ, Clark BD, et al. Breast implants and cancer: causation, delayed detection, and survival. *Plast Reconstr Surg.* 2001; 107:1393–1407.

Reply:

Labanaris et al raise some interesting points in their letter. A meta-analysis based on multiple reasonably well-constructed clinical trials provides a “best evidence” summary of the data for clinical decision making. Although a meta-analysis of primarily observational studies, a limited number of clinical trials, or trials with significant methodological flaws, may only generate new hypotheses rather than being definitive in treatment recommendations.

Statistical software and ready access to identify articles by electronic databases make performing a meta-analysis easier. These steps are only part of the comprehensive methodology of meta-analysis. Our criteria to identify prior publications of a meta-analysis or including individuals with formal train-

ing in clinical epidemiology was as surrogates for the authors having a more comprehensive understanding of meta-analysis methodology.

The QUORUM guideline has helped

editors standardize the reporting of published meta-analysis. We encourage all editors and readers to become more familiar with techniques to appraise the quality of published articles.

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