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EDITORIAL – THORACIC ONCOLOGY

Sentinel Node Biopsy in High-Risk pT1 Esophageal Cancer: A Long-Awaited Study

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I read with enthusiasm the article by Frederiks et al.[1] in this issue entitled "Feasibility and safety of tailored lymphadenectomy using sentinel node navigated surgery in high-risk T1 esophageal adenocarcinoma patients." This is a truly exciting and important study in which the authors performed sentinel node (SN) biopsy following endoscopic resection of high-risk pT1 esophageal adenocarcinomas.

The authors defined "high-risk" as either pT1a with poor differentiation and/or lymphovascular invasion (LVI), or pT1b with submucosal invasion > 500 µm, and/or poor differentiation, and/or LVI. They used a hybrid tracer, technetium-99m (^{99m}Tc) nanocolloid combined with indocyanine green (ICG) to detect SNs. A total of ten patients underwent SN biopsy, seven of whom had had a pT1b cancer resected, endoscopically. Two of the seven pT1b patients were found to have a positive sentinel lymph node (29%). Both elected to undergo close endoscopic surveillance rather than completion esophagectomy.[1]

The concept of the sentinel node (SN), i.e., the initial lymph node to which a primary tumor drains, was introduced as an anatomical construct decades ago. However, in 1992, Morton et al.[2] described its use in patients with melanoma using isosulfan blue dye to identify the regional lymphatic basin, often not the basin closest to the tumor. Guiliano et al.[3] popularized the SN concept in breast cancer in 1994, demonstrating its potential to reduce the extent of lymphadenectomy and to direct the pathologist to the most important lymph nodes for additional levels and analysis.

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While SN biopsy has gradually gained acceptance in treatment algorithms for other cancers (e.g., colorectal), it has, up until now, never achieved mainstream status in the treatment of esophageal cancer. Writing about the feasibility of the SN concept in esophageal cancer in 2005,[4] Udugawa stated that "The theory is elegant, but there are many questions to be answered and technical hurdles to overcome before its application is widely accepted."

Colloid particles between 4 and 100 nm in size are needed to translocate from the interstitial injection site to lymphatic channels, and to be retained in the SN. The type of radiocolloid available for clinical use is strongly dependent on a country's legislation. Kitagawa et al. first described the technique in patients with esophageal squamous cell cancer in 2000,[5] using ^{99m}Tc-tin fluoride colloid, a colloid with a particle size of 100 nm. A colloid of this size is retained in the SN for a longer period of time, allowing for injection 24 h prior to surgery and preoperative lymphoscintigraphy. However, these early studies were plagued with lower radioisotope counts in metastatic lymph nodes (due to the large size of the colloid), and a high incidence of skip metastases.

Lamb et al.[6] then published their landmark study in patients with esophageal adenocarcinoma in 2005. They endoscopically injected ^{99m}TC-albumin nanocolloid, a smaller particle size than the ^{99m}Tc-tin colloid used in Japan, with a median transit time to SNs of 10 min, and a half-time for washout of activity in the node(s) between 4 and 8 h. It therefore made both logistical and economic sense to inject all 57 patients directly before surgery. They reported a 96% accuracy rate in identifying the SN in patients with advanced esophageal or junctional adenocarcinoma. They also found that tumor cells in patients with adenocarcinoma followed a predictable linear drainage pattern to "first tier" nodal stations, with over 90% detected within 3 cm of the primary tumor.

We set up our own trial in Adelaide, with the aim of using the technique to justify our unit's predisposition to a conservative lymphadenectomy in patients with esophageal cancer.[6] We enrolled 31 consecutive patients between 2008 and 2011, and using ^{99m}Tc-antimony trisulfide colloid (with a particle size of 10 ± 3 nm) immediately before esophagectomy, we identified a SN in 29 of 31 patients (success rate, 94%).[7] In 28 of 29 patients, the SN accurately predicted the status of non-sentinel nodes (accuracy, 96%). Similar to Lamb et al.'s study,[5] 14% of our patients were upstaged following serial sections and immunohistochemistry on negative SNs.[7]

However, we did not adopt SN biopsy into routine management of patients with esophageal cancer for two reasons. First, and most important, the technique did not limit the extent of surgery in the same way as was seen in melanoma and breast cancer. The radioactive tracer technique did not lend itself to reliable results in vivo, due to the proximity of SNs to the primary tumor. An ex vivo dissection was needed to avoid the shine-through effect. Blue dye had complicated Lamb et al.'s study[5] when used in their initial 20 patients (along with radioactive colloid) due to extensive staining of adjacent tissues that obscured the operative field. Second, endoscopic resection techniques were not as advanced as they are currently, with interventional endoscopists capable of resecting increasingly large pT1 tumors.[8]

However, with this landmark study,[1] new hope is on the horizon. The authors hit the nail on the head with a hybrid tracer: ^{99m}Tc-nanocolloid with indocyanine green (ICG). ICG is a water-soluble anionic amphiphilic tricarbocyanine probe with a small 1.2 nm diameter.[9] It migrates quickly in the lymphatic system and, with a near-infrared fluorescence device, can improve visualization of SNs. Jimenez–Lillo et al. published a recent meta-analysis that included six studies (for a total of 65 patients) that revealed a high detection rate of SNs of 89%.[10] However, while ICG showed a high sensitivity (84%) for LN metastases, it had a low specificity (15%), supporting its use as a hybrid tracer.

So why the excitement over this study? It is simple. This study has the potential to revolutionize the approach to esophageal cancer treatment, particularly for patients with pT1 esophageal cancer. It is disheartening to perform an esophagectomy in a patient with pT1 cancer, only to find no residual cancer in the specimen, nor the lymph nodes.

What is the absolute risk of LN metastasis in pT1 cancer? The risk in pT1a cancer ranges from 0 to 6.9%[8,11] and, for upper third pT1b (sm1) cancer, it ranges from 0 to 23%.[12] A recent study from Germany examined mid-to-deep pT1b lesions resected endoscopically.[12] They found an overall rate of LN metastasis of 21.7% in pT1b (sm2) and 35.9% in pT1b (sm3) tumors. This means we are potentially subjecting the majority of patients with a pT1b tumor to an unnecessary, morbid procedure.

Frederiks et al.[1] indeed are the first investigators to evaluate an "esophageal preserving treatment algorithm" for patients with high-risk T1 esophageal adenocarcinoma. As they rightly point out, SN navigated surgery in patients with esophageal cancer can be challenging and there is room for improvement. Much work is ongoing with hybrid tracer development [e.g., superparamagnetic iron oxide nanoparticles (SPIONs)], and we await results from the PREFER registry (NCT03222635), which will hopefully identify the optimal patient subset for SN biopsy. The authors must be commended for a long-awaited study, and I look forward to longer-term results from this group.

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REFERENCES

1. Frederiks CN, Overwater A, Bergman JJGHM, et al. Feasibility and safety of tailored lymphadenectomy using sentinel node navigated surgery in high-risk T1 esophageal adenocarcinoma patients. *Ann Surg Oncol*. 2023. https://doi.org/10.1245/s10434-023-13317-6.
2. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127:392–9.
3. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg*. 1994;220:391–8.
4. Udagawa H. Sentinel node concept in esophageal surgery: an elegant strategy. *Ann Thorac Cardiovasc Surg*. 2005;11:1–3.
5. Lamb PJ, Griffin SM, Burt AD, Lloyd J, Karat D, Hayes N. Sentinel node biopsy to evaluate the metastatic dissemination of oesophageal adenocarcinoma. *Br J Surg*. 2005;92:60–7.
6. Thompson SK, Bartholomeusz D, Devitt PG, Lamb PJ, Ruszkiewicz AR, Jamieson GG. Feasibility study of sentinel lymph node biopsy in esophageal cancer with conservative lymphadenectomy. *Surg Endosc*. 2011;25:817–25.
7. Thompson SK, Bartholomeusz D, Jamieson GG. Sentinel lymph node biopsy in esophageal cancer: should it be standard of care? *J Gastrointest Surg*. 2011;15(10):1762–8.
8. Kamarajah SK, Phillips AW, Hanna GB, Low DE, Markar SR. Is local endoscopic resection a viable therapeutic option for early clinical stage T1a and T1b esophageal adenocarcinoma? A Propensity-matched analysis. *Ann Surg*. 2022;275(4):700–5.
9. Ekman M, Girnyi S, Marano L, et al. Near-infrared fluorescence image-guided surgery in esophageal and gastric cancer operations. *Surg Innov*. 2022;29(4):540–9.
10. Jimenez-Lillo J, Villegas-Tovar E, Momblan-Garcia D, et al. Performance of indocyanine-green imaging for sentinel lymph node mapping and lymph node metastasis in esophageal cancer: systematic review and meta-analysis. *Ann Surg Oncol*. 2021;28:4869–77.
11. Nieuwenhuis EA, van Munster SN, Meijer SL, et al. Analysis of metastases rates during follow-up after endoscopic resection of early "high-risk" esophageal adenocarcinoma. *Gastrointest Endosc*. 2022;96(2):237–47.

12. Manner H, Wetzka J, May A, et al. Early-stage adenocarcinoma of the esophagus with mid to deep submucosal invasion (pT1b sm2-3): the frequency of lymph-node metastasis depends on macroscopic and histological risk patterns. *Dis Esophagus*. 2017;30(3):1–11.