Editorial

Sentinel Node Concept in Esophageal Surgery: an Elegant Strategy

Harushi Udagawa

Introduction

Japanese style radical operation for esophageal cancer with extended lymph node dissection has improved the prognosis of the disease.[1] However, because of its considerable morbidity and long-standing postoperative problems, a less invasive strategy has been sought for years, particularly for earlier stage patients. The application of the Sentinel Node (SN) concept to esophageal surgery is one of such strategies. The theory is elegant, but there are many questions to be answered and technical hurdles to overcome before its application is widely accepted. This paper overviews the results of several feasibility studies, and discusses the future prospects of the SN concept in esophageal surgery.

Sentinel Node Concept

The SN concept is based on the following two assumptions.
1: Lymphatic flow from a certain tumor in which tumor cell spread is consistent, and there is (are) always a specific node (nodes) that first receives the flow.
2: No tumor cell can pass through the first lymph node, and the first step of metastasis occurs within the node the tumor cell first reaches.
These specific nodes are called Sentinel Nodes (SN). The logical consequence is that if metastasis is absent in SN, no further lymph node dissection is necessary to cure the patient.

The SN concept is very similar to 'The Idea of Sequential Dissemination' expressed by Halsted[2] more than 100 years ago, and has been an implicit theoretical basis of surgical treatment of malignant tumors. Cabanas, a urologist used the term 'Sentinel Node' in 1977 in the field of penile cancer as a very reliable indicator of lymphatic tumor spread.[3] Since Morton reported modern lymphatic mapping in the field of melanoma[4] in 1992, the concept has been accepted gradually. Now the SN Navigation Surgery (SNNS) is widely accepted as a practical and reliable strategy for less invasive treatment of malignant melanoma and breast cancer. The most important point of Morton's success is that he limits the application of the concept to earlier stage diseases. With the technical break through that the SN became accessible intraoperatively with the single cell scintillation counter, many trials of wide application of the concept were initiated in many different organs. Among these organs, the esophagus is one of the least promising because of its wide and complex lymphatic spread. Kitagawa introduced the SN concept in the management of esophageal cancer[5] and the common desire of esophageal surgeons for less invasive treatment has helped promote study of the SN concept in this seemingly least suitable organ.

Feasibility Studies

Kitagawa was the first to report the results of a feasibility study of the SN concept application to esophageal cancer.[5] He reported a 14/16 identification rate, 13/14 accuracy, and 8/9 sensitivity. Yasuda in 2003 reported a 6/6 sensitivity in selected pT1/2 patients.[6] There was a workshop session on the SN concept in the 58th annual meeting of the Japan Esophageal Society[7] held in Tokyo in June 2004. Seven leading groups in the field in Japan presented their experiences in the workshop. We reported our experience with ^{99m}Tc-Tin and ^{99m}Tc-Phytate. We had performed 24 SN mapping for cT1N0 patients. Thirteen out of the 24 patients had lymph node metastasis, and only 9 of these 13 patients had 1 or more metastases in SN (sensitivity 69%). The negative predictive value was only 11/15 (73%).

Our result is the worst among the reports. But the values of sensitivity are in a wide range from 69% to 100%, and our values and those of Ohyama from Keio University (9/13 vs. 27/31) do not show statistical difference.

From Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan

Address reprint requests to Harushi Udagawa: Department of Gastroenterological Surgery, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan.

Validity of the Concept

The SN concept holds well but with statistical limitation. Anatomists or histologists may claim that there are many intra- and extranodal lymphatic shunts. However, the SN concept should be interpreted as a functional concept including such apparent contradiction. Therefore, as long as we have good tracer material as a surrogate of tumor cells, such anatomical and histological problems can be disregarded. If all the tumor cells have a very high ability to actively creep through a lymph node, we would have failed to cure a large number of patients with our radical operations. It is most probable that passing-through of tumor cells do occur, particularly when the tumor has a high tendency of lymphatic spread. Such tendency would vary among tumors. The proper exclusion of unsuitable tumors is of great importance.

The validity of the concept is affected by pN status. When a patient has a lymph node largely occupied by tumor cells, the lymph flow would be blocked and altered. In such circumstance, the detected SN is not the original one and it is very dangerous to modify operation with such information. This is the reason cN0 is considered a basic requirement in applying this concept to patients. However, can all the lymph nodes with altered lymph flow by relatively large metastasis be accurately detected preoperatively? Small but massive lymph node metastases are occasionally observed, and some of them are very difficult to identify in preoperative staging.

The depth of tumor to which the SN concept can be applied is another point of debate. Many investigators consider both cT1 and cT2 patients to be candidates, and some claim that cT2 patients should be excluded. The histological difference of the lymphatic system in each layer could have an effect on this matter. Because tracer injection is performed to the sm layer, at least the first step application should be started in the cT1 population.

Technical Problems

Beside the essential requirement of validity of the concept, there are many technical hurdles to overcome before the application of the concept to daily clinical practice. First is the tracer material. Dye injection is one of the main methods of SN visualization, but it has a major disadvantage. Dyes in ordinary use are water soluble and can easily pass through lymph nodes. This means that the secondary and tertiary echelon nodes are also stained sequentially, and functional evaluation of 'intra-nodal shunt' is impossible. Apart from this disadvantage, dye injection is not suitable for the esophagus because most lymph nodes connected to the esophagus are located deep in the mediastinum, and they cannot be examined at a glance with the spread of the dye with the esophagus in situ. The most suitable tracers of the existing candidates are ^{99m}Tc-labeled colloids. RI tracers remain problematic. Radio-active tracers are under very strict legal regulation. They have to be injected in authorized clinical settings, usually in the RI laboratory not in the endoscopy room or operating room. The smaller the colloid particle, the better it floats into the lymphatics, but too small a particle will pass through SN like a water soluble dye. Therefore, the standardization of particle size is very important but not easy for ordinary hospitals without an investigational section. There are several trials with new ideas. Among them are fluorescent beads[8] and ferumoxides.[9] The latter requires technological advance of the magnetometer but has the advantage that ferumoxides containing lymph nodes can be detected with MR imaging techniques. Such technological advance will strongly promote application of the SN concept.

Related to the tracer material, precise preoperative imaging will help the clinical use of the concept. Most RI tracers remain at the injection site, and form very strong illumination, which interferes with the detection of SN close to the injection site. Radiologists are working hard on this issue and the images they produce are becoming better. This problem might be solved with the introduction of new tracers.

Another technical problem involves pathological diagnosis. The conventional pathological diagnosis of lymph node metastasis made with H&E staining of the largest cross sectional slice of lymph nodes is far from complete. Immunohistochemical staining of cytokeratin is a great help to detect micrometastasis. PCR detection of RNA specific to cancer cells should be much more sensitive. However, such a special system would be another obstacle for wider application of the SN concept if application of the system were necessary in all cases.

Clinical Application and Future Prospect

If application of the SN concept can promote even limited safety, it is worth performing. From here, we could start by assuring the safety of curtailment of lymph node dissection with intraoperative SN biopsy in high risk patients or in patients who are unwilling to undergo the standard operation. Another possible application is to use the

SN mapping lymphoscintigram to determine the radiation field when chemoradiation is the patients' selection. However, they are both very limited uses of the concept.

What accuracy does real SNNS require? What percentage of failure is acceptable in exchange for successful less invasive surgery, or ideally, organ preserving treatment? In the field of breast cancer the sensitivity is estimated to be around 95%.[10] In esophageal cancer, as mentioned in the paragraph 'Validity of the concept', the figure is between 69% and 100%. If we can realize 95% sensitivity at any time, the SN concept will be widely accepted and will change the therapeutic strategy for at least cT1N0 tumors. Then how about overall accuracy of 95%? If cT1N0 patients are assumed to have 10% risk of lymph node metastasis, only 50% sensitivity can realize 95% overall accuracy. If the metastatic rate is 50% (as was our experience), 90% sensitivity is necessary. In both situations, metastases in 5 out of 100 cT1N0 patients are overlooked, but in the former, 5 patients are selected properly to undergo further radical treatment, and safe organ preservation can be achieved in 90 patients, and in the latter, 45 patients are selected properly to undergo further radical treatment, and safe organ preservation can be achieved in 50 patients. It is apparent that the latter has more impact than the former, but either can be accepted by a large proportion of patients. In this sense, the pioneering trial of Kagoshima University to start organ preservation treatment guided by SN biopsy to clinically m3 and sm1 tumors (ie, tumors invading only muscularis mucosae and/or superficial 1/3 of sm layer) is reasonable. However, it is clear that our goal is much wider application of the SN concept to minimize esophageal treatment, and whether we can assure constantly high sensitivity, not overall accuracy, is the crucial point.

Most esophageal surgeons consider the SN concept insufficiently reliable at present to accept wide application of SNNS in the field of esophageal surgery. Standardization of the technique, a multi-institutional feasibility study on a large number of subjects, and new tracers that can be used without strict legal regulations should contribute to the SN concept achieving 95% sensitivity and enable wide application for safe organ preservation treatment.

References

1. Udagawa H, Akiyama H. Surgical treatment of esophageal cancer: Tokyo experience of the three-field technique. *Dis Esophagus* 2001; **14**: 110–4.
2. Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Johns Hopkins Hosp Bull* 1894-1895; **4**: 297–323.
3. Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer* 1977; **39**: 456–66.
4. Morton DL, Wen D, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**: 392–9.
5. Kitagawa Y, Fujii H, Mukai M, et al. The role of the sentinel lymph node in gastrointestinal cancer. *Surg Clin North Am* 2000; **80**: 1799–809.
6. Yasuda S, Shimada H, Chino O, et al. Sentinel lymph node detection with Tc-99m tin colloids in patients with esophagogastric cancer. *Jpn J Clin Oncol* 2003; **33**: 68–72.
7. The 58th Annual Meeting of the Japan Esophageal Society. *Proceedings* 2004; 101–4. (in Japanese)
8. Hihara J, Ueno H, Toge T. A new tracer for sentinel node detection in esophageal and lung cancer–fluorescent microspheres. *Nippon Geka Gakkai Zasshi* 2003; **104**: 762–4. (in Japanese)
9. Nakagawa T, Minamiya Y, Katayose Y, et al. A novel method for sentinel lymph node mapping using magnetite in patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003; **126**: 563–7.
10. Mansel RE, Goyal A. European studies on breast lymphatic mapping. *Semin Oncol* 2004; **31**: 304–10.