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Sentinel Node Biopsy in Head and Neck Cancer: Preliminary Results of a Multicenter Trial

Gary L. Ross, MD, David S. Soutar, ChM, D. Gordon MacDonald, FRCPath, Taimur Shoaib, FRCSEd, Ivan Camilleri, FRCS(plast), Andrew G. Roberton, PhD, Jens A. Sorensen, PhD, Jorn Thomsen, MD, Peter Grupe, MD, Julio Alvarez, MBBS, L. Barbier, MD, J. Santamaria, MD, Tito Poli, MD, Olindo Massarelli, MD, Enrico Sesenna, ChM, Adorján F. Kovács, PhD, Frank Grünwald, MD, Luigi Barzan, MD, Sandro Sulfaro, MD, and Franco Alberti, MD

Background: The aim was to determine the reliability and reproducibility of sentinel node biopsy (SNB) as a staging tool in head and neck squamous cell carcinoma (HNSCC) for T1/2 clinically N0 patients by means of a standardized technique.

Methods: Between June 1998 and June 2002, 227 SNB procedures have been performed in HNSCC cases at six centers. One hundred thirty-four T1/2 tumors of the oral cavity/oropharynx in clinically N0 patients were investigated with preoperative lymphoscintigraphy (LSG), intraoperative use of blue dye/gamma probe, and pathological evaluation with step serial sectioning and immunohistochemistry, with a follow-up of at least 12 months. In 79 cases SNB alone was used to stage the neck carcinoma, and in 55 cases SNB was used in combination with an elective neck dissection (END).

Results: In 125/134 cases (93%) a sentinel node was identified. Of 59 positive nodes, 57 were identified with the intraoperative gamma probe and 44 with blue dye. Upstaging of disease occurred in 42/125 cases (34%): with hematoxylin–eosin in 32/125 (26%) and with additional pathological staging in 10/93 (11%). The sensitivity of the technique with a mean follow-up of 24 months was 42/45 (93%). The identification of SNB for floor of mouth (FOM) tumors was 37/43 (86%), compared with 88/91 (97%) for other tumors. The sensitivity for FOM tumors was 12/15 (80%), compared with 30/30 (100%) for other tumor groups.

Conclusion: SNB can be successfully applied to early T1/2 tumors of the oral cavity/oropharynx in a standardized fashion by centers worldwide. For the majority of these tumors the SNB technique can be used alone as a staging tool.

Key Words: Cervical metastases—Elective neck dissection—Head and neck—Neoplasms—Sentinel node biopsy.

When approaching a case of head and neck squamous cell carcinoma (HNSCC), one of the most crucial management decisions, for staging, treatment, and prognosis, is determining the absence or presence of nodal metastasis.[1–3]

Staging of HNSCC, via the TNM classification, is both clinical and pathological.[3] Traditionally, for clinical staging, clinical palpation has been the mainstay of determining the presence of nodal metastasis. More recently, because of the relative unreliability of clinical palpation,[4–6] centers have turned to imaging techniques to locate the presence of nodal disease.[7–15] However, even these have been shown to be unreliable in the identification of early nodal disease.[16–20]

For pathological staging, hematoxylin and eosin (H&E) has traditionally been used to detect metastasis. More recently, additional pathological techniques such as step serial sectioning and immunohistochemistry have been described.[16–27]

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From the Plastic Surgery Unit, Canniesburn Hospital (GLR, DSS, TS, IC), Bearsden, Glasgow, UK; Department of Oral Pathology, Glasgow Royal Infirmary (DGM), Glasgow, UK; Beatson Oncology Centre (AGR), Glasgow, UK; Departments of Plastic and Reconstructive Surgery (JAS, JT) and Nuclear Medicine (PG), Odense University Hospital, Odense, Denmark; Servicio de C. Maxilofacial, Hospital de Cruces (JA, LB, JS), Cruces, Spain; Sezione di Chirurgia Maxillo-Faciale, Dipartmento di Scienze Otorino-Odonto-Oftalmologiche e Cervico Facciali (TP, OM, ES), University Hospital of Parma, Parma, Italy; Clinic for Maxillofacial Plastic Surgery (AFK) and Department of Nuclear Medicine (FG), Johann Wolfgang Goethe University Medical School, Frankfurt am Main, Germany; and Operative Units of Otolaryngology (LB), Department of Pathology (SS), and Department of Nuclear Medicine (FA), Azienda Ospedaliera "S. Maria degli Angeli," Pordenone, Italy.

Address correspondence and reprint requests to: Gary Ross, MD, 14 Northern Grove, Didsbury, Manchester, M202WL, UK; Fax: 44-1612916381; E-mail: gary.ross@canniesburn.org.

For HNSCC, although all patients are staged clinically with or without imaging, the dilemma is whether all patients should be staged pathologically.

Patients staged as clinically N+ traditionally have been staged pathologically, in the form of a therapeutic neck dissection (TND). The evidence suggests that over 70% of these clinically N+ patients will subsequently have pathological disease.[5] For clinically N0 patients the dilemma remains.

It is generally considered that pathological staging of the N0 patient is performed when the risk of metastasis is >15% to 20% on the basis of histopathological parameters of the primary tumor.[28,29] Previous incidences of metastasis, however, relied solely on routine H&E staining rather than additional step serial sectioning and immunohistochemistry. For the clinically N0 patient the advent of sentinel node biopsy (SNB) allows the use of these techniques to pathologically stage the neck with minimal node sampling.[16,17]

We have used either SNB alone or SNB-assisted elective neck dissection (END) to pathologically stage a homogeneous group of clinically N0 patients with T1/2 tumors of the oral cavity/oropharynx.

PATIENTS AND METHODS

Between June 1998 and November 2002, 227 SNB procedures were performed in six centers. Local ethical committee approval and informed consent were obtained prior to the SNB procedure in all cases. One hundred thirty-four cases involved management of T1/2 tumors of the oral cavity/oropharynx in clinically N0 patients, as previously described,[16–17] with preoperative lymphoscintigraphy (LSG), intraoperative use of blue dye/gamma probe, and pathological evaluation with step serial sectioning and immunohistochemistry, with a follow-up of at least 12 months.

All patients were classified as clinically N0 by either clinical palpation or radiological imaging techniques such as positron emission tomography or computed tomography. Preoperative LSG was performed in all cases within 24 hours prior to surgery. An injection of radiocolloid (either nanocoll or albures) was given in order to completely surround the tumor. Following acquisition of the LSG image, a unilateral or bilateral SNB procedure was planned. SNB alone or SNB-assisted END was performed within 24 hours. We suggested that all centers handle at least 10 cases of SNB-assisted END with an accuracy rate of over 90% among consecutive cases before commencing SNB alone.[30] In 55 cases SNB-assisted END was performed as either part of the learning curve for the SNB-alone procedure or in patients where an END was planned for both treatment and access to vessels for free-flap anastomosis. In 79 cases SNB alone was carried out as a staging tool.

All cases involved intraoperative use of blue dye and intraoperative use of a gamma probe detector. Radioactive nodes were excised and radioactivity within the node was confirmed ex-vivo. Sentinel nodes were labeled according to their color and radioactivity and their anatomical neck level.[31]

The sentinel nodes were fixed in 10% neutral buffered formalin and after fixation were bisected through their longest axis. If the thickness of the halves was more than approximately 2.5 mm, the slices were further trimmed to provide additional 2.5-mm-thick blocks. One H&E-stained section was prepared from each histological block and examined for possible metastasis. The full pathological protocol was used to examine nodes that appeared negative following examination with H&E, and these nodes were step-serial sectioned at 150-μm levels. One section from each level within the block was stained with H&E and examined. If the node still appeared free from tumor, immunocytochemistry for cytokeratin (AE1/3) was undertaken. Cytokeratin positivity was compared to the adjacent H&E section to confirm that it represented viable tumor cells.

In the SNB-alone group, if a patient was upstaged with routine H&E staining, step sectioning, or immunohistochemistry, a TND in the form of a modified radical neck dissection (MRND)[31] was undertaken with preservation of the accessory nerve, sternocleidomastoid muscle, and internal jugular vein. Pathological evaluation of the MRND was with H&E only. Patients staged negative were followed up in clinic every 3 months.

In the SNB-assisted END group, sentinel nodes were examined with routine H&E staining, step serial sectioning, or immunohistochemistry, and the remaining END specimen was examined with H&E only.

Patients in whom a sentinel node was positive by additional pathology with no further evidence of disease in the neck dissection specimen were staged as pN1mi.[3,16,32] Patients in whom a sentinel node was unable to be identified were treated by standard individual unit protocols and were excluded from the study. The primary endpoint of the study was the presence of nodal disease in those patients undergoing a neck dissection. In those patients undergoing SNB alone, the endpoint was follow-up for a minimum period of 12 months.

RESULTS

Two hundred twenty-seven patients underwent SNB either alone or in combination with ENB at six centers

between June 1998 and November 2002; 134 patients undergoing SNB as a staging tool for clinically N0 patients with early-stage T1/2 disease in the oral cavity/oropharynx were considered suitable for this study. Patients were included only if excision was performed to the primary, all three elements of the triple diagnostic SNB technique were used in identifying sentinel nodes, full detailed pathological evaluation of all sentinel nodes was performed, and the follow-up was at least 12 months. Seventy-nine patients had SNB alone to stage the clinically N0 neck, and 55 had SNB-assisted END with full pathological workup of the sentinel node/s (Fig. 1). There were a higher number of FOM tumors in the SNB-alone group (30/79 vs. 12/55) and a larger number of cT1 tumors in the SNB-alone group (48/79 vs. 27/55) than in the SNB-assisted END group (see Table 1).

SNB was successful in identifying a sentinel node in 125/134 patients (93%). In 9/134 patients, 6 floor-of-mouth (FOM), 1 anterior tongue (AT), 1 lower alveolus, and 1 retro-molar-trigone (RMT) tumor, a sentinel node was not identified (identification rate, 93%). The identification rate for FOM tumors was 37/43 (86%), compared with 88/91 (97%) for other tumor groups ($P < .05$). The identification rate within the SNB-alone group was 72/79 (91%), compared with 53/55 (96%) in the SNB-assisted END group (Table 1).

Twenty patients (72; 28%) in the SNB-alone and 22/53 (42%) in the SNB-assisted END group were upstaged. When both groups were considered together, 42/125 patients (34%) with T1/2 HNSCC of the oral cavity/oropharynx were upstaged with SNB; 14/70 (20%) T1 patients versus 28/55 (51%) T2 patients were upstaged ($P < .05$) (Table 2). Table 3 details the upstaging of all tumor sites and the nodal distributions of all positive and negative sentinel nodes. Of 59 positive sentinel nodes, 12 were harvested from level 1, 31 from level 2, 14 from level 3, and 2 from level 4. There was no difference between the numbers of positive nodes and the numbers of negative nodes between neck levels.

TABLE 1.

	SNB alone	SNB assisted END	Combined results
Anterior tongue	24/25	24/25	48/50
FOM	25/30	12/12	37/42
Posterior tongue	5/5	4/4	9/9
RMT	6/6	5/6	11/12
Buccal	3/3	2/2	5/5
Lower alveolus	3/4	3/3	6/7
Hard palate	2/2	1/1	3/3
Soft palate	1/1	1/1	2/2
Lip	1/1	1/1	2/2
Tonsil	1/1		1/1
Upper alveolus	1/1		1/1
cT1	43/48	27/27	70/75
cT2	29/31	26/28	55/59
Identification rate overall	72/79 (91%)	53/55 (96%)	125 /134 (93%)

SNB, sentinel node biopsy; END, elective neck dissection; FOM, floor of mouth; RMT, retro-molar-trigone.

Of 59 positive sentinel nodes, 57 were identified with use of the intraoperative gamma probe and 44 with blue dye ($P < .05$) (Table 4). In only one patient was a positive blue node harvested when there was no positive hot node harvested. In 33/42 patients at least one positive hot and blue node was harvested.

Upstaging of disease occurred in 32/125 patients with H&E staining only (26%) and in 10/93 with additional pathological staging (11%), yielding a total upstaging of 42/125 (34%). Three hundred forty-eight sentinel nodes

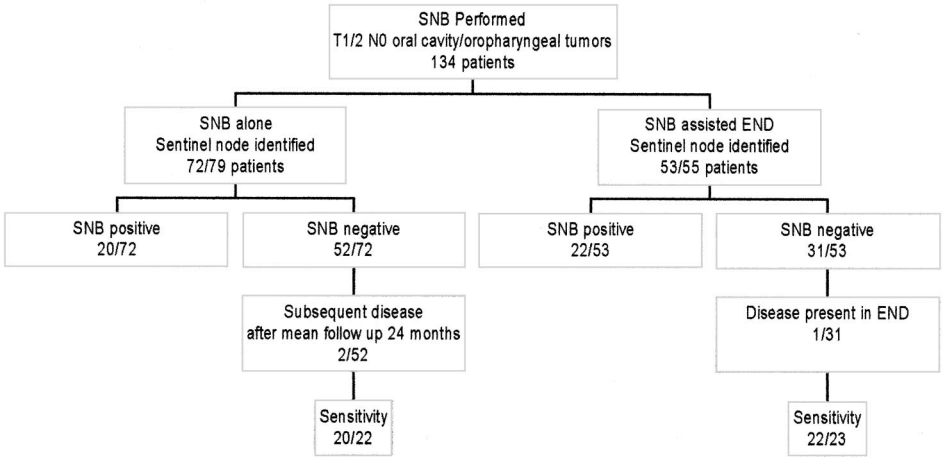

FIG. 1. The use of sentinal node biopsy to stage the clinically N0 neck in T1/2 N0 oral cavity/oropharyngeal tumors.

TABLE 2.

	SNB alone	SNB assisted END	Combined results
Anterior tongue	8/24	8/24	16/48
FOM	4/25[a]	8/12[a]	12/27[a]
Posterior tongue	2/5	3/4	5/9
RMT	4/6	2/5	6/11
Buccal	0/3	1/2	1/5
Lower alveolus	1/3	0/3	1/6
Hard Palate	1/2	0/1	1/3
Soft Palate	0/1	0/1	0/2
Lip	0/1	0/1	0/2
Tonsil	0/1		0/1
Upper Alveolus	0/1		0/1
cT1	5/43[a]	9/27	14/70[a]
cT2	15/29	13/26[a]	13/26[a]
Overall upstaging with SNB	20/72 (28%)	22/53 (42%)	42/125 (34%)

[a] In the SNB alone group two cT1 FOM tumors were staged SNB−ve but developed disease during follow-up. In the SNB assisted END group one cT2 FOM tumor was staged SNB−ve but had disease in the END specimen.

SNB, sentinel node biopsy; END, elective neck dissection; FOM, floor of mouth; RMT, retro-molar-trigone.

were harvested from 125 patients, an average of 2.8 per patient; 59/348 (17%) of sentinel nodes were positive. Out of these 59, 42 were positive on initial H&E staining, 7 on serial sectioning, and 10 on immunohistochemistry; 17/298 nodes (6%) were upstaged with additional pathology.

Of the 20 patients staged SNB-positive in the SNB-alone group, 19 underwent subsequent TND. One patient staged SNB-positive was deemed unsuitable for general anesthesia for a TND and was followed-up in clinic. The 52 patients staged SNB-negative in the SNB-alone group were also followed-up in clinic. After a mean follow-up of 24 months, two patients developed subsequent disease. The sensitivity of SNB alone as a staging tool was 20/22 (91%).

Twenty-two patients undergoing SNB-assisted END were upstaged with use of SNB. There was one patient in whom disease was present in the END when the sentinel node was negative. The sensitivity of SNB-assisted END as a staging tool was 22/23 (96%). No patients have developed subsequent nodal recurrence.

All three patients in whom the sentinel node did not reflect the rest of the nodal basin had FOM tumors. The overall sensitivity of the technique was 42/45 (93%). However, for FOM tumors the sensitivity was 12/15 (80%), compared with 30/30 (100%) for other tumor groups ($P < .05$). A comparison of FOM tumors with other tumor sites is shown in Table 5.

In total 41 patients underwent neck dissection when sentinel node(s) were found to be positive; 25 nonsentinel nodes from 14 patients contained metastasis. Fourteen of 41 patients (34%) had further disease in the neck dissection specimen, noted on routine H&E staining; 25/832 (3%) of nodes, excluding sentinel nodes, were found to be positive on examination of the neck dissection specimen with H&E only. These included 7/179 (4%) from level 1, 8/227 (4%) from level 2, 7/204 (3%) from level 3, 3/141 (2%) from level 4, and 0/81 from level 5. In 5/14 patients, 2 FOM, 2 AT, and 1 RMT tumor in a level one node was located in the neck dissection specimen when the positive sentinel node was located in a lower level.

Of the 31 patients staged SNB-negative in the SNB-assisted END group, 1 developed local recurrence, 2 had a second HNSCC primary, and three died of unrelated causes; 28 patients remain in follow-up. Of the 52 patients staged SNB-negative in the SNB-only group, two have developed nodal recurrence, one had local recurrence, three had a second HNSCC primary, one had a distant metastasis, and two died of unrelated causes. The remaining 43 SNB-negative patients remain in follow-up (mean, 19 months; range, 12–33 months).

DISCUSSION

This is the first multicenter trial to determine whether SNB may be used to stage the clinically N0 neck in early T1/2 tumors of the oral cavity/oropharynx. We have used SNB alone and SNB-assisted END as staging tools to determine which technique is best suited to stage the clinically N0 neck for different tumor sites, with use of a standardized technique within a number of centers. Although these are preliminary trial results, we have already found important differences. The identification rate for FOM tumors (37/42; 86%) was less than that for other tumor groups (88/92; 96%). The sensitivity for FOM tumors was 12/15 (80%), compared with 30/30 (100%) for other tumor groups ($P < .05$). FOM tumors were the only group in which the sentinel node did not reflect the staging of the rest of the nodal basin. It would seem that the close proximity of the FOM to the draining nodal basin leads to difficulty in both identifying and harvesting the sentinel node. Even with use of techniques such as software masking and lead shields, as previously described, this remains a challenge.[16,17,30,36,39]

The identification of and sensitivity for FOM tumors were worse in the SNB-alone group than in the SNB-assisted END group. It would seem that the smaller access incision used for the SNB-alone procedure might hamper the harvesting of the sentinel node in FOM tumors, where a more-detailed examination could be more appropriate. For all other tumor sites this study

TABLE 3.

	No. of pts upstaged	No. of necks upstaged	Level 1	Level 2	Level 3	Level 4	Level 5	No. of nodes upstaged
Anterior tongue	16/48	17/54	4/24	9/88	6/38	2/10	0/2	21/162
Floor of mouth	12/37	13/47	2/14	9/51	5/28		0/1	16/94
Posterior tongue	5/9	5/9	1/1	7/16	3/15	0/1		11/33
Retromolar trigone	6/11	6/11	4/7	4/14				8/21
Buccal	1/5	1/5	0/4	1/2		0/1	0/1	1/8
Lower alveolus	1/6	1/7	1/6	0/2	0/4			1/12
Hard palate	1/3	1/4	0/3	1/3				1/6
Lip	0/2	0/3	0/3	0/1				0/4
Tonsil	0/1	0/1		0/2				0/2
Soft palate	0/2	0/2	0/1	0/2			0/1	0/4
Upper alveolus	0/1	0/1	0/1	0/1				0/2
Total	42/125 (34%)	44/144 (31%)	12/64 (19%)	31/182 (17%)	14/85 (16%)	2/12 (17%)	0/5	59/348 (17%)

TABLE 4.

	Hot and blue	Hot only	Blue only	Total
Positive	42	15	2	59
Negative	149	110	30	289

shows that SNB alone has similar identification rates and sensitivities in comparison with SNB-assisted END, suggesting that SNB alone can be used to accurately stage these tumors.

The use of SNB to stage the neck has been described previously.[16,17,33–49] The majority of studies, however, have compared the pathology of the sentinel node against the pathology of the neck dissection with routine H&E staining. This study uses the additional pathological techniques previously described to determine the influence on staging of early T1/2 tumors of the oral cavity/oropharynx. The chance of finding a metastasis in a sentinel node has been shown to be 59/348 (17%). If an END had been carried out without SNB, with the use of H&E staining only, the number of nodes found with metastasis would have been 67/1180 (6%). SNB allows additional pathological sampling of a small number of neck nodes: 2.8 per patient in our series. With concentration on the sentinel node(s), the additional pathological techniques are less time-consuming than those required to assess a full-neck dissection. Further studies are required to determine the ideal amount of pathological sampling of the sentinel node.

Using 150-μm levels, we have upstaged 10/93 patients (11%) staged pathologically N0 on routine H&E staining. This seemed to be a reasonable compromise between sensitivity and cost-efficiency. It is unknown, as yet, what the ideal distance between levels should be in order to pick up the highest number of metastasis. We also do not know whether the three cases in which the sentinel node did not reflect the rest of the neck dissection specimen were due to inadequate pathological sectioning or inappropriate sentinel node harvesting. It is also unclear as yet whether there are any other metastases missed, as the mean follow-up at present is only 24 months. However, we would expect over 90% of recurrences to have already occurred within this follow-up period.[43]

The majority of nodes were harvested from levels I–III.[50] Many centers have adopted the supraomohyoid neck dissection to treat the clinically T1/2 N0 tumor of the oral cavity/oropharynx.[51] In this series 5/125 patients (4%) with disease in level 4 would have been missed had a supraomohyoid neck dissection been used to stage the clinically N0 neck. The authors have recommended an MRND[31] for sentinel node–positive disease. However, there were no patients in this series with disease in level 5; therefore, an anterolateral neck dissection (levels I–IV) may be sufficient in the treatment of this group of primary tumors.

There were bilateral sentinel nodes harvested from 19/125 patients (15%), of which 2/19 were positive (11%). The use of preoperative LSG enables one to determine this prior to surgery so that patients can consent to bilateral exploration, and SNB is proving a useful tool in staging the contralateral neck.

A number of units do not use blue dye in the identification of sentinel nodes within the head and neck. We have found that the gamma probe identified 57/59 nodes. The majority of these nodes were also identified by blue dye (42/57). In only one patient was a positive blue node harvested when there was no positive hot node harvested. Although the use of the intraoperative gamma probe is essential in identifying sentinel nodes, we have found the blue dye useful during surgery. For oral cavity/oropharyngeal tumors, blue dye does not seem to interfere with surgical margins, and we have had no reported side effects from the injection process.

Current accepted practice suggests that if the risk of metastasis of a tumor is $>$15% to 20%, then the clini-

TABLE 5.

	Identification rate for SNB alone	Sensitivity of SNB alone	Identification rate for SNB assisted END	Sensitivity of SNB assisted END	Identification rate for both techniques	Sensitivity for both techniques
FOM tumors	25/30 (83%)	4/6 (67%)	12/12 (100%)	8/9 (89%)	37/42 (88%)	12/15 (80%)
Other tumors	47/49 (96%)	16/16 (100%)	41/43 (95%)	14/14 (100%)	88/92 (96%)	30/30 (100%)
All tumors combined	72/79 (91%)	20/22 (91%)	53/55 (96%)	22/23 (96%)	125/134 (93%)	42/45 (93%)

SNB, sentinel node biopsy; END, elective neck dissection; FOM, floor of mouth.

cally N0 neck should be treated surgically.[28,29] This work would suggest that the incidence of metastasis for T1/2 oral cavity/oropharynx tumors is higher than 20%, and the question then remains what elective surgical treatment should be performed. Although radical neck dissection was once thought to be the treatment of choice for the N0 neck, more conservative neck dissections have more recently been popularised.[50] This study would suggest that an anterolateral neck dissection (levels I–IV) would be the most appropriate selective neck dissection for staging. However, bilateral metastasis would still be left untreated.

We also have to remember that the reason for treating the clinically N0 neck surgically is for pathological staging. Pathological staging of neck dissection specimens has traditionally been through routine H&E staining. This is due to the increased labor and cost required to apply additional pathological techniques to pathologically stage every node within a neck dissection specimen.[25–27]

SNB-assisted END not only allows LSG to determine which tumors may have bilateral drainage but also targets those nodes most likely to harbor metastasis. The additional pathological techniques employed on sentinel nodes only are less labor-intensive and more cost-effective than evaluating full-neck specimens. Thus, SNB-assisted END provides better treatment of the N0 neck and pathologically stages the N0 neck more appropriately. However, SNB-assisted END, like other forms of END, still overtreats the majority of clinically N0 patients with T1/2 tumors of the oral cavity/oropharynx.

SNB alone as a staging tool in HNSCC, on the other hand, is minimally invasive and yields minimal morbidity yet combines LSG and additional pathological techniques to stage the neck. It is even more cost-effective than SNB-assisted END in that for SNB-negative patients only the sentinel node(s) need to be examined pathologically. It would seem from the preliminary results of this trial that SNB alone can be used to stage the clinically N0 neck for the majority of T1/2 tumors of the oral cavity/oropharynx. FOM tumors, however, are more difficult, in both the identification and the harvesting of sentinel nodes.

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