Positive Sentinel Lymph Nodes are a Negative Prognostic Factor for Survival in T1-2 Oral/Oropharyngeal Cancer— A Long-Term Study on 103 Patients

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Background: To evaluate prognostic value of sentinel node biopsy (SNB) in oral/oropharyngeal squamous cell cancer (OOSCC) concerning overall/disease-free survival.

Methods: One hundred three consecutive patients with T1-2N0 OOSCC were consecutively recruited for SNB as single invasive staging method for the neck. Two hundred seventy-three sentinel nodes (SNs) were removed (mean, 2.65 per patient). Nine patients had 10 positive SNs (upstaging rate, 8.7%) found in levels I to III, leading to a therapeutic neck dissection.

Results: Mean observation time of all patients was 6.7 years; mean survival time of patients with negative or positive SNs was 6.9 and 3.7 years, respectively. There has been no false-negative result of SNB to date becoming manifest in ipsilateral node metastasis during follow-up. Five-year overall/disease-free survival of all patients was 82%/72%, respectively. The same parameters for the patients with negative SNs were 85%/74%, for those with positive SNs 38%/47%, respectively (statistically significant). There has been a higher statistical risk for locoregional recurrence for patients with positive SNs. Rates of metachronous second primary tumors developing during follow-up were 10.6% (negative SNs) and 44.4% (positive SNs).

Conclusion: SNB was a valuable diagnostic method in patients with T1-2N0 OOSCC avoiding elective neck dissections. Patients with positive SNs had statistically significantly higher rates of locoregional recurrences, second primary tumors, tumor-related deaths, and a worse overall/disease-free survival. To date, no therapeutic consequences in case of a positive SN beyond execution of modified radical neck dissection (to remove other positive nodes) and closer attention during follow-up can be concluded from this study.

Sentinel node biopsy (SNB) in squamous cell cancers of the head and neck is an interesting technique which promises a reduction of elective neck dissections.[1] In stage I and II cutaneous melanoma

patients, the prognostic impact of a positive sentinel node (SN) is proven with respect to the likelihood of recurrence[2] and with respect to the benefit of immediate lymphadenectomy.[3] In breast cancer, data are inconclusive to date with respect to the significance of micrometastatic disease in SNs for locoregional control and the requirement for further treatment; however, SNB is a recommended staging method that leads to a recommended level I and II axillary

dissection in patients with incidentally detected micrometastatic disease in the SN.[4]

In head and neck cancer, standardization of the technique and the therapeutic consequences of SNB is not yet carried out. In the Department of Oral and Cranio-Maxillofacial Plastic Surgery, in cooperation with the Department of Nuclear Medicine at Frankfurt University, SNB has been conducted since March 2000 as single invasive staging method for the neck in patients with oral and oropharyngeal squamous cell cancer clinically staged as T1-3N0.[5–7] The resulting long-term follow-up of 103 patients with T1-2N0 cancer (a cohort well comparable with the international literature[1]) made it possible to look at a potential prognostic value of SNB in oral and oropharyngeal cancer concerning overall and disease-free survival.

PATIENTS AND METHODS

A total of 103 consecutive patients with T1-2N0 squamous cell cancer of the oral cavity were recruited for SNB. Initial staging examination included physical examination, chest radiography, sonography of the neck, computed tomography (CT) of the neck and upper thorax, and positron emission tomography (PET) of the trunk (whole-body scan, from the skull base to the pelvis). The morphologic method of CT and the functional method of PET have been used complementarily for staging of the neck. The common criteria for suspect neck lymph nodes by CT are: diameter >1 cm, marginal enhancement after intravenous administration of contrast medium, central necrosis, spherical form, nonsharp or undefinable contour, and unusual number.

PET studies were performed with a dedicated high-resolution full-ring PET scanner (Siemens/CTI ECAT EXACT HR 47, software version 7.2, Knoxville, TN). All patients fasted overnight, were controlled for blood glucose levels, and received [^{18}F]FDG activities between 278 and 433 MBq (7.5 to 11.7 mCi, depending on body weight) intravenously 1 hour before acquisition. Depending on the number of bed positions (5 to 6, 16 cm each), acquisition time ranged from 50 to 60 minutes, including segmented "hot" transmission. Imaging included emission tomograms with and without transmission correction in three planes.

Only patients with nonsuspicious CT and having no uptake in the neck region at all were considered nodal negative (N0) and enrolled for SNB. Prerequisite also included patient operability (general condition, local resectability).

After staging examinations, the patients should receive one cycle of transfemoral superselective intra-arterial high-dose chemotherapy of the primary cancer region (150 mg/m^2 cisplatin and systemic neutralization with sodium thiosulfate) 3 to 4 weeks before surgery, except patients with Dacron prostheses of the carotid arteries, atherosclerotic occlusions of the carotid arteries, and serum creatinine >2 mg/dL, who should immediately be operated on.

At the day of operation, SN scintigraphy was performed before surgery. Informed consent was obtained from each patient. The Ethics Committee of the Medical Faculty of the University of Frankfurt in accordance with the Declaration of Helsinki (Edinburgh, October 2000) approved SNB without mandatory neck dissection in case of tumor negativity.

Between 15 and 51 MBq of technetium ^{99m}Tc-labeled albumin microcolloids (volume of <0.1 mL; Nanocoll; Amersham Sorin Srl, Saluggia Vercelli, Italy) with a mean size of 30 nm were injected intramucodermally in two to eight depots circumferentially around the primary tumor with a fine needle. The injection was performed by the nuclear medicine radiologist in the presence of the surgeon. The lymphatic drainage was monitored at the gamma camera visually, and static scans (in anterior and lateral views plus additional anterior view with the head tilted back) were obtained every 15 minutes up to 1 hour after injection (10 to 20 kilocounts/image, analogous imaging, Searle Pho/Gamma LFOV Basic; Scintillation Camera Systems, Des Plaines, IL).

SNs were marked on the skin surface under scintigraphic guidance of a ^{57}Co-labeled pen and controlled with the gamma probe. The operation was performed in the presence of the nuclear medicine radiologist approximately 2 to 3 hours after tracer administration. Intraoperatively, the SNs were reached via one to three minimally invasive neck approaches and removed from the respective levels. Magnifying glasses were mandatory. A sterile latex-covered handheld gamma probe (SI Gamma Finder; Silicon Instruments, Berlin, Germany) with a diameter of 10 mm was used to detect radioactivity. After removal, radioactivity was determined ex vivo. Inactive nodes found in the immediate vicinity were also removed. After lymphadenectomy, the primary tumor was resected in the same session. In case of a positive histology of an SN or an inactive node, modified radical neck dissection was added 1 week later.

Definitive pathologic assessment of SNs involved fixing the nodes in 10% neutral buffered formalin, initial routine histologic examination, additional step serial sections at approximately 150-μm intervals

TABLE 1. *Demographic, tumor-, and treatment-related patient data*[a]

Characteristic	Overall *n* (%)	Patients with negative sentinel nodes	Patients with positive sentinel nodes
Patients, *n* (%)	103 (100)	94 (91.3)	9 (8.7)
Sex, *n* (%)			
Male	60 (58.3)	55 (58.5)	5 (55.6)
Female	43 (41.7)	39 (41.5)	4 (44.4)
Age (y), median (range)	62.0 ± 11.6 (24–90)	62.5 ± 11.1 (24–90)	60.4 ± 16.3 (30–83)
Preoperative intra-arterial chemotherapy, *n* (%)			
Yes	55 (53.4)	50 (53.2)	5 (55.6)
No	48 (46.6)	44 (46.8)	4 (44.4)
Postoperative radiation, *n* (%)			
Yes	14 (13.6)	13 (13.8)	1 (11.1)
No	89 (86.4)	81 (86.2)	8 (88.9)
Primary tumor site, *n*			
Anterior floor of mouth	29	27	2
Lateral floor of mouth	10	10	0
Lateral tongue	25	21	4
Sublingual plane	9	8	1
Retromolar trigone, soft palate, oropharynx	15	14	1
Lip	9	9	0
Cheek mucosa	3	2	1
Mandibular gingival	2	2	0
Maxillary gingival	1	1	0
T classification, *n* (%)			
T1	45 (43.7)	41 (43.6)	4 (44.4)
T2	58 (56.3)	53 (56.4)	5 (55.6)

[a] There were no statistically significant differences between the groups.

through the block with hematoxylin and eosin (H&E) staining, and immunocytochemistry that used the multicytokeratin antibody AE1/3. All immunocytochemistry positivity has been compared with the H&E serial section.

Patients with large T2 primary tumors and/or positive neck histology were scheduled to undergo postoperative radiotherapy. All patients were followed up in a strict regimen every month in the first year after treatment, every second month in the second year, and so on. All local and regional recurrences were noted as ending of the disease-free interval; deaths were noted for the overall survival calculation.[8] A false-negative result of SNB was defined as regional recurrence in the examined neck side during follow-up without the occurrence of second primary tumors in the upper aerodigestive tract. Second primary tumors of the head and neck were defined as having more than a 3-cm distance to the site of the first primary tumor. Peripheric second primary tumors and distant metastases were distinguished according to the results of analysis of biopsy samples or the radiologic report.

Data for the 103 study patients (March 2000 to December 2007) including pre- and postoperative treatment are listed in Table 1. There was no statistically significant difference between the groups, especially concerning pre- and postoperative treatment (Table 1).

RESULTS

Planar lymphoscintigraphy was successful in all but two patients (98%), who showed no uptake in the neck. These two patients had uneventful follow-up. Table 2 lists the results of the collection of SNs. Eleven nodes in neck level I detected in lymphoscintigraphy in nine patients could not be found during surgery; however, in all these patients, other SNs were removed, and therefore, patients were followed up routinely. Two hundred seventy-three SNs were removed, making a surgical detection rate of 96.1% and a mean of 2.65 nodes per patient. Nine patients had 10 positive SNs making an upstaging rate of 8.7%. The mean of SNs was 2.67 nodes per patient in the group with negative, and 2.4 in the group with positive SNs. Positive nodes were found in levels I to III.

The mean observation and survival time of all patients was 6.7 years; the mean survival time of patients with negative or positive SNs was 6.9 and 3.7 years, respectively. Eleven (11.7%) of 94 patients died in the group of patients with negative SNs, with

TABLE 2. *Results of sentinal node biopsy*

Characteristic	n	No. of patients with negative sentinel nodes	No. of patients with positive sentinel nodes
No. of patients	103	94	9
Sentinel level (n)			
I	63	55	8 (4 positive)
II	117	106	11 (5 positive)
III	65	63	2 (1 positive)
IV	18	17	1
V	5	5	0
VI	5	5	0
Sum	273	251	22

TABLE 3. *Data for patients with positive sentinel nodes*

Patient	T stage	Primary tumor site	Neck level	Largest diameter of lymph node (mm)	Largest diameter of metastasis (mm)	No. of additional positive nodes in modified radical neck dissection	Recurrence/second primary tumor
1	2	Cheek mucosa	Ib	12	2	0	Local
2	1	Floor of mouth	Ib	10	4	0	
3	1	Oral tongue	IIa	10	3	1	Second primary (SCC maxillary sinus)
4	2	Oropharynx	IIa	17	10	0	Second primary (lymphoma)
5	2	Oral tongue	IIa	14	0.5	0	
6	1	Floor of mouth	III	15	5	0	Contralateral late neck metastasis
7	2	Oral tongue	IIa	15	7	0	
8	1	Sublingual plane	IIa	15	3	0	Second primary (submandibular gland)
9	2	Oral tongue	Ib	12	1.6	0	Second primary (SCC hypopharynx)
9	2	Oral tongue	Ib	10	3	0	
Mean/median				13/13	4.6/3.5		

SCC, squamous cell carcinoma.

7 (63.6%) of these of non-tumor-related causes. There have been eight local recurrences (8.5%), seven of which could be operated on successfully, and two neck metastases (2.1%; one related to a second primary tumor in the hypopharynx, and one in the contralateral neck that could be removed). Therefore, there has been no false-negative result of SNB to date. One patient died as a result of local recurrence, and three patients died as a result of second primary tumors of the hypopharynx, colon, and prostate. Accidental findings in SNs of this group have been metastases of thyroid cancer (twice; patients treated nonsurgically) and follicles of the thyroid gland (twice). These patients are fine to date.

Three (33.3%) of nine patients died in the group with positive SNs, one (33.3%) of causes unrelated to tumor; two patients died as a result of second primary tumors. There has been one local recurrence (11.1%) and one contralateral neck metastasis (11.1%); both could be treated surgically. Planned postoperative radiation was only carried out in one patient with positive SNs; five patients refused, and three patients were in bad general condition.

Table 3 examines the positive nodes in detail. Median diameter of positive nodes was 13 mm. All metastases but one (patient 5) have been detected by

H&E staining. Median diameter of metastases was 3.5 mm. There have been three micrometastases (≤2 mm). One neck dissection specimen (from patient 3) yielded another nodal metastasis; all other specimens were free of disease. None of the positive nodes had extracapsular spread of the tumor.

Figures 1 and 2 show the overall and disease-free survival of both groups. Five-year overall and disease-free survival of all patients were 82% and 72%, respectively. The same parameters for the patients with negative SNs were 85% and 74%, and for those with positive SNs 38% and 47%, respectively. Statistical differences between the curves were significant (overall survival: $P < 0.002$, $\chi^2 = 9.6$; disease-free survival: $P < 0.001$, $\chi^2 = 11.2$, log rank test).

Looking at the occurrence of locoregional recurrences (Fig. 3), there has been a statistically borderline higher risk with respect to positive SNs ($P = 0.058$, $\chi^2 = 3.6$, log rank test). With regard to metachronous second primary tumors developing during follow-up, the rate was 10.6% (10 of 94 patients) in the group with negative SNs, and in the group with positive nodes, the rate was 44.4% (4 of 9 patients; Table 3). No distant metastases could be detected by CT and PET for the patients with recurrences or second primary tumors.
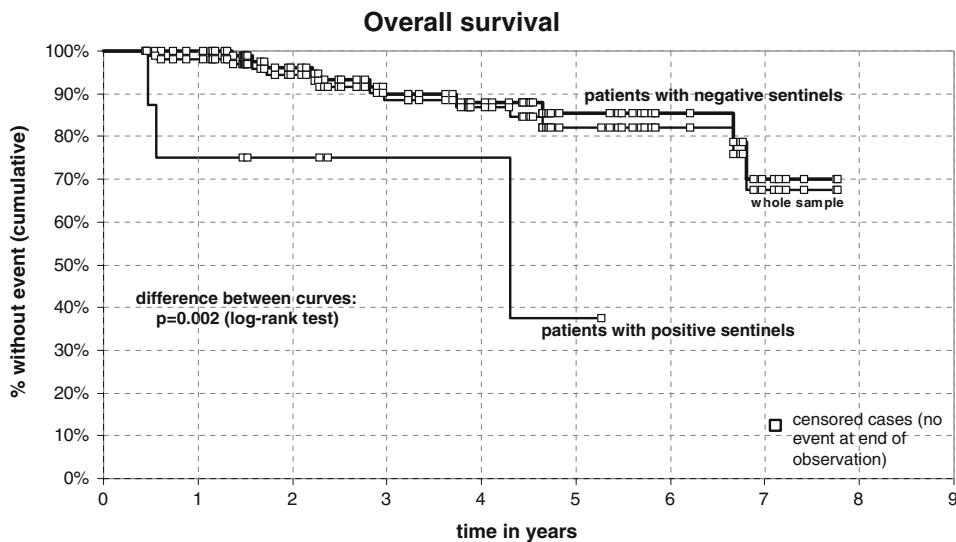
Overall survival

group	cases	died	alive	%	mean survival time (censored cases accounted for)	25%	50%	75%	1 y.	2 y.	3 y.	5 y.
patients with negative sentinels	94	11	83	88%	6.9 (SE 0.2, CI 95% 6.4-7.4)			7 y.	100%	96%	90%	85%
patients with positive sentinels	9	3	6	67%	3.7 (SE 0.7, CI 95% 2.3-5.1)		4 y.	1 y.	75%	75%	75%	38%
Total	103	14	89	86%	6.7 (SE 0.2, CI 95% 6.2-7.2)			7 y.	98%	94%	89%	82%

Sample size: n=103

FIG. 1. Overall survival of study patients with T1-2N0 squamous cell cancer of the oral cavity.
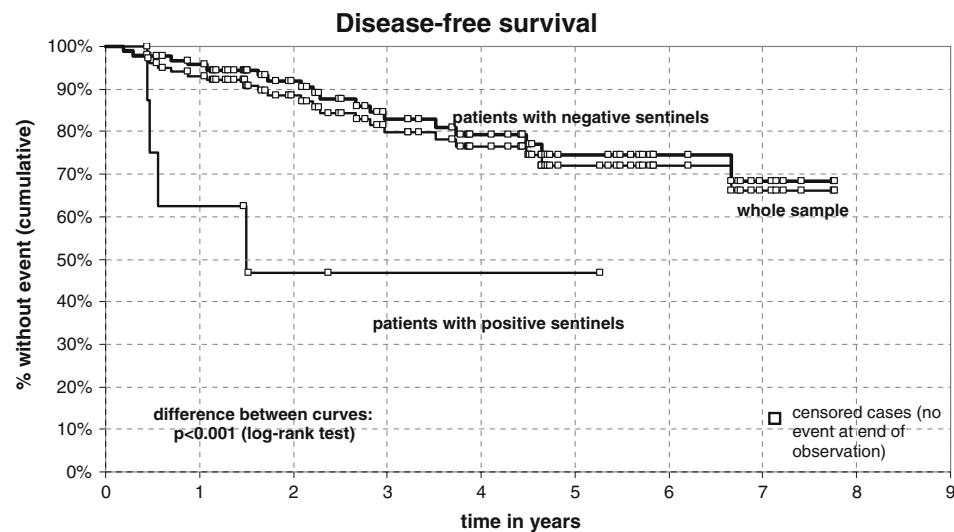
Disease-free survival

group	cases	recurrence or death	no recurrence, still alive	%	mean survival time (censored cases accounted for)	25%	50%	75%	1 y.	2 y.	3 y.	5 y.
patients with negative sentinels	94	18	76	81%	6.4 (SE 0.3, CI 95% 5.8-6.9)			5 y.	96%	92%	83%	74%
patients with positive sentinels	9	4	5	56%	2.9 (SE 0.8, CI 95% 1.3-4.5)		2 y.	0 y.	63%	47%	47%	47%
Total	103	22	81	79%	6.2 (SE 0.3, CI 95% 5.6-6.7)			4 y.	93%	88%	80%	72%

Sample size: n=103

FIG. 2. Disease-free survival of study patients with T1-2N0 squamous cell cancer of the oral cavity.
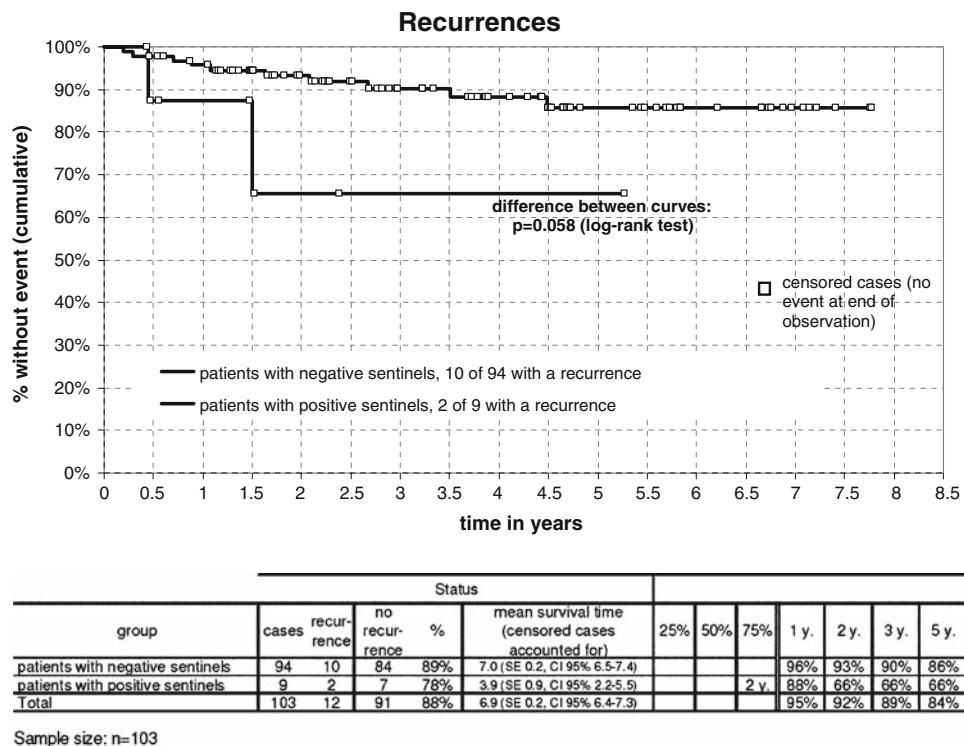
FIG. 3. Survival with respect to recurrences of study patients with T1-2N0 squamous cell cancer of the oral cavity.

DISCUSSION

SNB in oral cancer patients was a remarkably safe and successful multidisciplinary diagnostic procedure. The rate of lymphoscintigraphic and surgical detection of SNs in the neck was high (98% and 96.1%, respectively); the sensitivity of the method was high expressed in the low rate of one additional positive node in nine neck dissection specimens. The value of SNB as diagnostic method could be further demonstrated by the small diameter of the detected metastases being below the threshold of CT and PET. After a mean observation time of 6.7 years, only three neck metastases (one related to a second primary tumor, two in the contralateral neck side) developed, demonstrating a high accuracy of SNB. The upstaging rate of SNB was approximately 9%, resulting in a reduced number of extensive neck dissections in oral cancer patients without locoregional hazard. This relatively low upstaging rate with no observed extracapsular spread surely has to be regarded as the result of the selection for SNB on the basis of CT and PET, which has been explained elsewhere.[6,9]

The prognostic value of SNB concerning survival, however, remains dubious. To our knowledge, no investigation concerning this problem was published in the international literature. Gallegos-Hernández et al.[10] performed SNB and parallel elective neck dissection and found a correlation between the number of detected nodes and the possibility of identifying patients with hidden metastases in non-sentinel nodes, i.e., the number of nodes being a "prognostic factor" for this possibility. Ionna et al.[11] used the term *prognostic* for the value of SNB to determine the neck levels to be dissected after SNB. The question whether a positive SN has a negative effect on overall or disease-free survival in oral cancer patients has not yet been discussed.

In this study, statistically significant differences could be verified for the incidence of local or regional recurrences as well as between the overall and disease-free survival rates of patients with negative or positive SNs. There was also a higher rate of second primary tumors in combination with a higher rate of tumor-related deaths in the group with positive SNs. Nothing could be said about the distant metastasis rate in both groups because no distant metastases could be found by the imaging techniques, and no autopsies were carried out in the patients who died. It is unlikely that distant metastases were mistaken for second primary tumors. All in all, the reason for the

worse survival of patients with positive SNs is hard to explain. Obviously, there is a summation of negative events, and it can only be stated as a fact that according to the findings in this cohort, positive sentinels are a negative prognostic factor in T1-2N0 oral/oropharyngeal cancer patients.

The role of single metastases, especially micrometastases, is still controversial. Statistically, no difference in regional control or survival could be proven between patients undergoing elective neck dissection for micrometastasis or those undergoing therapeutic neck dissection for N1 disease.[12,13]

The preoperative intra-arterial high-dose chemotherapy of the primary cancer region is an approach that is not widely used and may be blamed for several unwanted effects that might interfere with SNB, and that might therefore have an effect on the presented results. However, it could be demonstrated that it is neither responsible for the lower upstaging rate in the patients of this institution[7] nor for any interventional complications of SNB.[14]

It can be concluded that SNB was a valuable diagnostic method in patients with T1-2N0 oral/oropharyngeal cancer avoiding elective neck dissections. Patients with positive SNs had higher rates of locoregional recurrences, second primary tumors, and tumor-related deaths, as well as worse overall and disease-free survival. Therefore, patients with positive sentinels seem to deserve closer attention, although a specific reason for poorer outcome could not be found to date. Consequently, no special therapeutic efforts in case of a positive SN beyond the execution of a modified radical neck dissection (to remove other positive nodes) can yet be concluded. Further multi-institutional studies with larger sample sizes (like the American College of Surgeons Oncology Group Z0360 Validation Trial,[15] which, however, has a different end point) and even longer observation time are necessary to prove a causal connection between a positive SN and the mentioned prognoses that would justify further advanced therapeutic regimens.

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