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Practical aspects of sentinel node biopsy in oral cavity cancer: All nodes that emit a signal are important

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Abstract

Background and Objectives

Sentinel node biopsy (SNB) is a safe and effective way to examine an N0 neck in early-stage oral cavity cancer (OCC). In this study we evaluated the variables of SNB detection, surgery, and outcome.

Material and Methods

Ninety-two patients with N0 OCC examined with SNB were included. Number and brightness of nodes detected on preoperative imaging and during surgery were analyzed and compared with histological findings. Patients with recurrent disease were evaluated separately and the effect of smoking and alcohol consumption was analyzed.

Results

Eighteen patients had at least malignant cells in the sentinel lymph node (SLN); 18 patients had recurrent disease and nine patients died from the cancer. The negative predictive value of SNB was 95%. Six patients did not have metastases in the node with the strongest signal, but metastases were found in an SLN with a weaker signal. Smoking and alcohol consumption did not affect disease-specific or overall survival.

Conclusion and Significance

SNB has been confirmed to be safe and effective in early stage N0 OCC. However, it is important to carefully harvest up to four hottest SLNs that emit a signal. Treatment of patients with only isolated tumor cells (ITC) in the SLN appears to be necessary.

Key words

Head and neck cancer / oral cavity cancer / sentinel node biopsy / individual tumor cells

Introduction

Head and neck carcinoma is the seventh most common cancer globally, with about 600 000 new cases annually. Early stage head and neck squamous cell carcinoma (HNSCC) has a relatively good prognosis when treated properly. The cornerstone of treatment is adequate surgery of the primary tumor. Treatment of the neck in early stage carcinoma has long been a divisive issue, but D'Cruz et al. [1] have shown that watchful waiting is not enough and that the neck must be treated actively also in early stage oral cavity cancer (OCC). Opinions on optimal treatment of the neck still vary.

Sentinel node biopsy (SNB) has been used for years in the management of breast cancer and melanoma. The literature shows that SNB is a useful technique also when treating patients with stage N0 HNSCC [2]. When managing HNSCC, SNB makes staging of the neck more accurate [3].

If sentinel lymph nodes are free of cancer, it is unlikely that any distal node would be involved. It is possible to avoid extensive neck dissection if sentinel lymph nodes are free of disease. Thus the treatment of stage N0 patients can be more selective [2].

The purpose of this study was to evaluate the practical variables of the sentinel node protocol in N0 oral cavity T1-2 cancer. Specifically, we sought to clarify the correspondence between SPECT imaging intensity before the operation and gamma detector readings during surgery, and to determine the role of multiple positive lymph nodes in sentinel node detection.

Material and methods

In this retrospective study we analyzed patients with N0 OCC (ICD10: C00-C06) at Turku University Hospital from 2011 to 2016. Follow-up time was at least 3 years. Only patients treated with SNB were included. All patient information was collected from electronic medical records. The TNM classification was updated according to the 8th edition of the AJCC/UICC classification (2017). This study was approved by the institutional Research Ethics Board of Turku University Hospital (record number: T06/006/2019).

Sentinel node detection followed the standard procedure: 1 day before surgery, 37MBq of technetium-labeled nanocolloid was injected at four submucosal sites around the tumor and images were taken with SPECT-CT. For this study we evaluated the number and brightness of sentinel lymph nodes (SLN) found on preoperative imaging with those found with a gamma probe at surgery the next day. These characteristics were compared with the pathological status of the sentinel nodes. Histopathological analyses were performed according to the international protocol [4]. SPECT-CT images and gamma probe readings were analyzed and compared from patients with malignant diagnoses from SNB. Delay to re-treatment was also analyzed. All patients with recurrent disease were analyzed and the effect of smoking and alcohol consumption was investigated.

The association between SNB positivity and Disease Specific Survival (DSS) and Overall Survival (OS), smoking and DSS + OS, and alcohol consumption and DSS + OS was assessed with a Chi-squared test or Fisher´s exact. Statistical analyses were done with SAS for Windows, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Of the 92 patients who met the inclusion criteria, 51 were female and 41 male, with a mean age of 68 years (range 30–94) (Table 1). The most common site of cancer was the tongue (67 patients, 73%).

Gamma camera images were taken preoperatively, with 0–6 sentinel lymph nodes detected (mean 2.16). During surgery, a gamma probe detected 0–6 SLNs (mean 2.43), with a mean count of 882 per second in the first SLN (range 72–17 375) and 296 in the second (range 12–2 600). As expected, the image brightness and the count number of the gamma probe correlated well, except for patient #8.

Elective neck dissection (ND) was performed in six patients as part of the primary surgery, as we were only implementing the SNB protocol at our institute. In addition to these six patients, in one case the tumor reached the midline and SNB was performed to control the contralateral side of the neck, and in one case no nodes were detected on imaging or with a gamma probe, therefore neck dissection was performed as part of the primary surgery. All these patients were SNB-negative and their ND was clean.

Altogether 18 patients (20%) had at least isolated tumor cells (ITC) in the histopathological analyses of the sentinel nodes. These patients and the harvested lymph nodes are listed in Table 2. Out of 24 positive lymph nodes, six had ITC, six were micrometastases (size >0.2 mm but <2 mm) and 12 were macrometastases (>2 mm). Most of these positive SLNs were located at level 1B (10, of which one was on the contralateral side of the neck) and the rest at level 1A (one), 2A (six), 2B (two), and level 3 (five). At imaging 0–5 (mean 2.0) SLNs were visualized, and perioperatively 0–5 (mean 2.5) were detected with the gamma probe. Six patients had no metastases in the SLN with the strongest signal, but metastases were still detected in a node with a weaker signal.

Eight SNB-positive patients received definitive oncological treatment (no surgery but (chemo)radiation with curative intent) after primary surgery. One patient underwent ND combined with oncological treatment. One patient was treated with ND only and three patients were treated with additional resection of the primary site and ND. Three patients had additional resection, ND and combined oncological treatment. Two patients did not get any further treatment due to problems with co-morbidity; both then developed recurrent disease, one undergoing local resection, ND and chemoradiation therapy (CRT) but the other still not receiving further treatment. The mean number of harvested lymph nodes at ND was 18 (range 7–49). Five SNB-positive patients had additional

metastasis found at ND. The mean time interval from primary surgery to additional treatment was 38 days (range 5–77), time to surgery being on average 27 days and to oncological treatment 57 days. The mean follow-up time was 4.2 years (51 months).

In the SNB-positive group, three patients had local, two had regional and three had distant recurrent disease. One patient had multiple recurrences. Twelve patients were alive with no evidence of disease. Six patients died of cancer. Of the SNB-negative group, five patients had local recurrent disease and five had regional recurrent disease, giving a negative predictive value of 95% for SNB. The false negative rate was 7%. Two patients had recurrent disease more than once. Five patients in this group died of cancer. The overall recurrence rate in this study was 20% (18/92). The mean time from first treatment to recurrent disease was 18 months. More detailed information on patients with recurrent disease is given in Table 3. Five SNB-negative and one SNB-positive patient had a second primary cancer, from which two of them died.

SNB positivity or negativity did not affect DSS (p=0.35) or OS (p=0.16). Smoking or alcohol consumption did not affect DSS or OS. Smoking status for 10 patients and alcohol consumption for 32 patients was not available. Statistical analyses were carried out with or without this information, which did not affect the overall results as statistical significance was not reached in either model.

Discussion

An N0 neck has to be managed, even in early OCC [1]. The National Comprehensive Cancer Network guidelines list the options for N0 neck management as elective ND, SNB, or radiotherapy [5]. In clinical practice, sentinel lymph node biopsy has an established role in the management of early N0 OCC due to the good overall survival, good negative predictive value and low morbidity [6]. It should of course be remembered that unlike ND, SNB is not actually a treatment but a diagnostic test that should be followed with therapeutic treatment if the SNB is positive [6].

In this retrospective cohort we show that with careful preparation, good clinical quality can be achieved already upon implementation of the SNB technique. In review articles on SNB, the acceptable false negative rate varies from 5% to 14% [7–9]. The negative predictive value has been reported to vary between 88% and 97% [10–12]. In this series we reached a false negative rate of 7% and negative predictive value of 95%. If we limit the disease progression time to 2 years consistent with the guidelines by Garrel et al., the false negative rate drops to 3% [8].

The importance of the first echelon and brightness of SLNs in SPECT-CT has been discussed, and it is known that sentinel nodes are not necessarily dependent on each other [13]. This is highlighted in our study, as 6/18 (33%) of the patients with a positive SNB did not have malignancy in the node with the most abundant tracer uptake (Table 2). In one case, only the fourth node was diagnostic (patient #11, Table 2). It has been suggested that when staging neck, it is sufficient to harvest three or four hottest SLNs and in case of more than 4 SLNs a critical discussion with the pathologist is recommended [6,14]. Although different anatomical subsites have typical metastatic areas in the neck, lymphatic drainage pathways can be unpredictable and variable [15]. This requires patience in the operating theatre to locate every node seen on SPECT-CT or emitting a probe signal. It can sometimes be difficult to detect the nodes in the submandibular area due to "shine-through", even if the primary tumor is resected first. In this case, if the node appears in e.g., the anterior part of level 1B on SPECT-CT, one can dissect all the fat-lymphatic tissue between the submandibular gland and anterior belly of the digastric muscle and detect the correct node ex vivo.

The importance of micrometastases or ITC in the SLN is unclear and debated [16,17]. Number and type (ITC/micro/macro) metastases seem to predict the number of non-SLN metastases [18]. It is also known that even patients with micrometastases have shorter disease-specific survival than patients with pN0 disease [19]. In this series, five patients only had ITC in the SNB and all of them received neck treatment afterwards. Nonetheless, two of them suffered recurrent disease, suggesting that ITC cannot be ignored.

Previous studies have shown that smoking has a negative effect on the overall survival of OCC patients [20]. In our study, smoking did not affect OS or DSS. However, our study population had only early-stage cancers, while previous studies have included cancers of all stages. Also, almost half of our study group were never-smokers, suggesting a different etiology for their cancer. The role of alcohol consumption in the mortality of head and neck cancer is also known. In our study cohort there was no connection between OS and alcohol consumption, which is consistent with the results of a prospective study by Beynon et al. [20].

Conclusion

For staging early N0 oral cavity cancer, sentinel node biopsy is a safe and effective approach with low morbidity. For accurate diagnoses it is important to carefully harvest up to four hottest SLNs as metastases can be detected in any of them. Furthermore, the treatment of isolated tumor cells should also be considered.

Methodical considerations / limitations

The strength of this study is that it analyzes a real-life patient population over a period of 6 years treated with SNB in a tertiary care academic center with careful follow-up. The limitations arise from the retrospective nature of the study, causing missing data regarding e.g., smoking status.

Disclosures

The authors have no conflicts of interest to declare.

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	N (%)
Male	41 (45%)
Female	51 (55%)
Age, yrs	Mean 68 (min 30 max 94)
Previous smoking	49 (53%)
Site of cancer	
Tongue	67 (73%)
Gingiva	7 (8%)
Floor of mouth	5 (5%)
Other	13 (14%)
T class	
T1	59 (64%)
T2	29 (32%)
T3	4 (4%)
Recurrence	18 (20%)
Local	8 (3 SLN positive, 5 SLN negative)
Regional	7 (2 SLN positive, 5 SLN negative)
Distant	3 (SLN positive)
2nd primary disease	6 (7%)
SLN positive	1
SLN negative	5
Dead from disease	12 (13%)
SLN positive	7
SLN negative	5

Table 1. Study cohort information

Patient	ICD 10	Primary site	SLN	Level	Brightness	Gamma probe	PAD
1	C02.3	Tongue	1	2A	1	2830	0
			2	1B	2	1087	Micrometastasis
2	C06.0	Buccal mucosa	1	1B	-	337	0
			2	1B	-	285	0
			3	1B	-	185	Isolated tumor cells
3	C02.11	Tongue	1	1A	1	1680	Isolated tumor cells
			2	3	2	282	0
			3	3	3	113	0
4	C02.11	Tongue	1	2A	SPECT-CT not done*	155	Macrometastasis
5	C03.1	Mandibular gingiva	1	1B	1	195	Macrometastasis
6	C06.0	Buccal mucosa	1	1B	1	364	Micrometastasis
			2	1B	-	119	Micrometastasis
7	C02.3	Tongue	1	2B	1	120	Isolated tumor cells
			2	3	-	21	0
8	C02.11	Tongue	1	3	1	1057	Micrometastasis
			2	3	2	384	0
			3	2A	3	473	0
			4	1B	4	213	0
			5	3	-	9	0
9	C02.11	Tongue	1	2A	1	429	0
			2	1B	2	335	Isolated tumor cells
			3	2A	-	155	0
10	C02.2	Tongue	1	2A	1	189	Macrometastasis
			2	3	2	139	Macrometastasis
			3	3	-	89	Macrometastasis
11	C04.8	Floor of the mouth	1	6	1	345	0
			2	2B contralateral	2	253	0

#	Code	Site	SLN	Level	Order	Count	Pathology
			3	3	3	87	0
			4	1B	-	53	Isolated tumor cells
12	C02.9	Tongue	1	3	1	471	Macrometastasis
			2	3	2	116	0
			3	2A	3	116	0
13	C02.11	Tongue	1	4	1	338	0
			2	3	2	270	Micrometastasis
14	C02.11	Tongue	1	2B	1	769	Macrometastasis
			2	2A	2	420	Macrometastasis
			3	2A	3	359	0
			4	2A	-	299	Macrometastasis
15	C02.11	Tongue	1	3	1	371	0
			2	2A	2	61	Macrometastasis
16	C02.11	Tongue	1	1B contralateral	1	100	Isolated tumor cells
			2	2A	2	47	Micrometastasis
				1B	3	-	
				2A	4	-	
				3	4	-	
17	C06.2	Retromolar area	1	1B	-	72	Macrometastasis
			2	1B	-	12	0
18	C00.1	Lower lip	1	1B	1	-	Macrometastasis

Table 2. List of patients with positive SLN. SLNs are listed in order of brightness detected by SPECT-CT.
* SPECT-CT machine not working

Patient (#: patient ID in Table 2)	Primary site	SLNB histology +/-	Minimal surgical margin (mm)	Additional treatment after SNL operation	Time between primary operation and recurrent disease (months)	Location of recurrent disease	Last follow-up (months)	Status	Smoking
A (#5)	Mandibular gingiva	+	3	CRT	10	Neck	46	DOD	Yes
B (#7)	Tongue	+	0.5	Re-resection + ND + CRT	24	Lungs	39	DOD	Yes
C (#8)	Tongue	+	2.2	CRT	36	Tongue	88	NED	No
D (#9)	Tongue	+	0	Re-resection + ND	4	Tongue	55	NED	Yes
E (#12)	Tongue	+	1	-	9	Neck	26	DOD	Yes
F (#13)	Tongue	+	0.3	Re-resection + ND + CRT	9	Vertebral column	11	DOD	Yes
G (#17)	Retromolar area	+	0.15	-	15	Mandibular gingiva	16	DOD	No
H (#18)	Lower lip	+	<1	ND + CRT	3	Lungs	13	DOD	Yes
I	Mandibular gingiva	-	2	-	13	Mandibular gingiva	64	AWD	No
J	Tongue	-	3.5	-	9	Mandibular gingiva	18	DOD	No
K	Tongue	-	7	-	24	Neck	32	NED	No
L	Mandibular gingiva	-	0.9	-	9	Mandibular gingiva	35	NED	No

M	Tongue	-	5	-	32	Neck (contralateral side)	50	NED	No
N	Tongue	-	Only scar	-	37	Tongue	92	AWD	No
O	Buccal mucosa	-	5	-	32	Neck	44	DOD	Yes
P	Tongue	-	2	Re-resection	11	Neck	53	DOD	Yes
Q	Tongue	-	3	-	20	Tongue	58	NED	No
R	Tongue	-	Only scar	-	25	Neck	89	NED	Yes

Table 3. List of patients with recurrent cancer

AWD = alive with disease
NED = no evidence of disease
DOD = dead of disease
ND = neck dissection
CRT = chemoradiotherapy