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Sentinel node biopsy in relation to survival in floor of the mouth carcinoma☆

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Abstract. Promising results have been obtained with sentinel node biopsy (SNB) in early oral carcinoma, but the floor of the mouth remains a site at risk of misdiagnosis. A retrospective and prospective study was designed to test the safety of SNB by comparing survival among patients with early stage carcinoma of the floor of the mouth (FOM) undergoing SNB, to a control group managed traditionally by a combination of clinical observation and elective neck dissection (END). A total of 63 patients with early stage carcinoma of the FOM were treated between 1991 and 2005. In the control group, 26 patients were managed with END and nine by close observation. In the test group, 28 patients were managed prospectively with SNB. Regional recurrence occurred in 23% (8/35) of control patients and 25% (7/28) of test patients. Approximately 25% of patients were successfully treated by salvage surgery. Disease-specific survival was 65.5% for control patients and 85% for SNB patients; the difference was not statistically significant. The use of SNB in the management of cancers of the FOM did not adversely affect survival and prevented 69.5% of patients undergoing unnecessary neck dissections, while clinical progress was better in the SNB group than in controls.

Keywords: head and neck neoplasms; sentinel node biopsy; N0 neck; floor of the mouth.

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The assessment of metastatic disease in early stage oral and oropharyngeal tumours has not changed significantly over the last three decades and with it the debate as to the optimum treatment of the N0 neck. On the basis of evidence available so far, it has not been possible to decide between elective neck dissection (END) and observation, as overall survival as well as disease-free survival are similar using both of these approaches.[1,2] Some authors champion elective neck dissection,[3] others a 'wait and see' policy.[4] Various retrospective studies have been published, but there is no consensus in the resulting recommendations.

The challenge is to identify patients with occult cervical metastasis at the time of presentation. Current radiological techniques are not sufficiently sensitive to detect small tumour deposits, and at present the standard of care adopted worldwide is END.

If it were to be accepted that there is little or no difference in survival between the 'wait and see' approach and END, then there would be no intellectual reason not

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to promote a conservative approach that cautiously tries to limit the number of ENDs performed by using the technique of sentinel node biopsy (SNB). The latter is the most recent innovation in the identification of micrometastatic disease arising from primary carcinoma of the oral cavity and oropharynx. This minimally invasive technique has improved functional outcomes compared to selective neck dissection.[5]

SNB is an accepted technique for the management of breast carcinoma and melanoma. Its application to carcinoma of the head and neck is, however, still under research and needs to be validated. Large multi-institutional clinical studies have been conducted at Canniesburn Hospital (UK)[6] and by the American College of Surgeons Oncology Group (ACOSOG),[7] with two others still to be reported (the Sentinel Node European Trial and the Danish Head and Neck Cancer Group trial (DAHANCA 22)).

SNB is an operator-sensitive technique and the floor of the mouth (FOM) is an anatomical area for which there is a high risk of false-negative results. This is attributed to radiation 'shine-through'. In this situation, the first echelon nodes lie in such close proximity to the primary tumour that the radiation from the colloid injected around the primary lesion obscures the radiation signal emitted from first-order lymph nodes.[8–10] Consequently, the rate of false-negatives reported in other series for tumours in the FOM is relatively high.[6,7,10] The objective of the present study was to target our patients with squamous cell carcinoma of the FOM and establish whether the SNB technique is safe at this site and produces comparable outcomes to those in historical controls. In particular, the results would indicate whether SNB has an adverse effect on outcomes in this specific at-risk population.

Materials and methods

The two study cohorts, one a retrospective group and the other consisting of patients managed prospectively, were selected from the records of the maxillofacial department. Before commencing the study, local research ethics committee approval was obtained.

In the period 1991–2000, a total of 200 consecutive patients with histologically confirmed T1–T2 N0 M0 squamous cell carcinoma of the oral cavity received definitive curative treatment. The primary carcinoma was located in the FOM in 35 of these patients and they represent the historical control group for the present study. These patients were treated by wide local excision and either clinical observation of the neck ($n = 9$) or elective neck dissection ($n = 26$).

The second group comprised 60 patients, again all with T1–T2 N0 M0 oral squamous cell carcinoma, who were part of a prospective sentinel node trial (2001–2005). Within this group, there were 28 patients with cancer of the FOM and they represent the test population.

The test group was treated in a similar way to the traditional treatment cohort, namely by wide local excision of the primary tumour, but at the time of surgery underwent SNB. In the event that the sentinel node was negative, the neck was simply observed; if it was positive, the patient went on to have a therapeutic neck dissection (i.e., as treatment rather than elective surgery). The technique of SNB used has been reported before[8–11]; in brief, 0.2 ml of a radionuclide marker (Nanocoll labelled with Tc-99, 40–50 MBq) is injected around the periphery of the tumour, 0.5–1 cm from the margins, and lymphatic mapping is performed by preoperative dynamic lymphoscintigraphy (LSG). All imaging was carried out within 24 h before surgery. We considered the first node on the lymphatic drainage pathway from the primary tumour to be the sentinel node. Prior to surgery, a hand-held gamma probe was used to identify the sentinel node by detecting the radiation with a Geiger counter, and the site was marked on the patient's skin. We used patent blue V dye and malleable lead blocks to assist location in the shine-through level I area. In the case of tumours within 2 cm of the midline, contralateral lymph nodes (as well as the ipsilateral ones) were considered for study.

The retrieved sentinel nodes were examined in detail by serial sectioning and dual-staining immunohistochemistry with haematoxylin and eosin (H&E) and cytokeratin.[6–11] Most of our sentinel node patients were recruited in a multi-institutional study,[10] and the protocol for the selection and evaluation of sentinel nodes was defined at that time. In brief, no frozen sections were allowed and formalin-fixed specimens were examined using H&E and cytokeratin staining, as described in detail in the report of the previous study.[10] The recruitment of that study started in 1998 and finished in 2002; at that time, a protocol was submitted to the European Organisation for Research and Treatment of Cancer (EORTC) culminating in the Sentinel Node European Trial, and the two studies had similar protocols: when the SN was positive for occult disease, neck dissection was undertaken within 3 weeks of the original surgery. Type III modified radical neck dissections were performed, as in the Canniesburn trial,[8] being carried out once a positive sentinel node had been confirmed. The neck dissection nodes were examined first by direct inspection and then further investigated by conventional H&E staining.

The use of immunocytochemistry for cytokeratin has allowed larger numbers of positive sentinel nodes to be detected.[10,12] On the other hand, the meaning of these findings has not yet been established for the head and neck.

The follow-up period was >5 years for both the test and historical control groups.

The statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The survival rate was calculated by Kaplan–Meier method and the log rank test was used to assess differences in survival between groups. A result was considered significant when the *P*-value was less than 0.05.

Results

The combined study group included 63 patients with carcinoma of the FOM who were treated with curative intent. The mean age of the combined traditional control and sentinel node patients was 61.21 years (range 41–87 years), with 89% of patients being men. The position of the tumour and stage distribution in each of the groups is shown in Table 1.

In the retrospective group ($n = 35$), occult metastasis was detected in 40% of cases (clinical observation 4/9; neck dissection 10/26). In the prospective sentinel node group ($n = 28$), occult disease was present in 39% of the patients (positive SNB 7/28; false-negatives 4/28).

Of the 28 SNB cases, the midline was affected in eight cases, which could correspond to 36 neck dissections. In these patients, no contralateral necks were involved; there were seven positive nodes and four false-negatives. Overall, this could mean the percentage of unnecessary neck dissections avoided by SNB in our series was 69.5%.

Patients in both groups received postoperative radiotherapy: traditional

Table 1. Midline affected by groups.

Treatment group	Midline	Lateral	T1	T2
Traditional	9	26	15	20
SNB	9	19	21	7

SNB, sentinel node biopsy.