Abstract: Background. Sentinel lymph node sampling may be studied profitably in series of patients with 1 tumor type, such as breast carcinoma, in 1 anatomic locale. The present work analyzes the efficacy of sentinel node sampling in a pathologically diverse group of lesions from an anatomically diverse region such as the head and neck; however, there are risks conflating the findings in different tumors with radically different behaviors, in the process producing muddled data. This report reviews the head and neck experience with sentinel sampling and concludes that certain tumor types that have a known propensity for aggressive behavior are the best candidates for trials employing sentinel node sampling; candidates include many cutaneous melanomas of the head and neck, oropharyngeal squamous carcinomas, and selected thyroid carcinomas. Despite the growing popularity of sentinel node sampling in a variety of regions of the body, however, at this juncture this technique remains an investigational procedure, pending demonstration of a tangible improvement in patient outcome through its use. It is recommended that studies of the efficacy of this technique strive, whenever possible, to segregate results of different tumor types in different head and neck locales from one another so as to produce more focused findings for discrete types of malignancies, and not group together tumor types that may in reality exhibit different biological behaviors. ©2006 Wiley Periodicals, Inc. Head Neck 28: 1122–1131, 2006

Keywords: sentinel node; biopsy; metastasis; head and neck; carcinoma

A central tenet of cancer staging has long been the belief that the future behavior of a malignancy can be predicted by knowledge of the extent of spread of that tumor at the time of initial presentation and diagnosis. Although diagnostic imaging modalities have grown increasingly sophisticated during the past decade, it still often falls to the attending surgeon to undertake some form of regional lymph node dissection so as to provide lymphoid tissue to the pathologist for microscopic study to assess for the presence or absence of metastatic deposits within those regional lymph nodes.

Sentinel lymph node sampling, with identification of the initial draining node(s) in the regional lymphatic chain by the use of dye or isotope or some combination thereof, has become the de facto standard of care for many patients both with cutaneous malignant melanomas and with breast carci-
nomas at many centers in the world. At the same time, investigations are under way to explore the expansion of sentinel node sampling to a variety of other tumor types, including those tumors arising in the head and neck region. The central value of sentinel node sampling, of course, is in crafting approaches to patients without clinical evidence of regional lymph node metastases who nevertheless are suspected to be at some significant risk of harboring nodal metastases.

For the purposes of the present discussion, the authors have diverged from the usual exploration of the utility of sentinel node sampling in the head and neck region as a whole. Instead, this report will examine the use of sentinel node sampling in discrete anatomic areas within the head and neck and, where appropriate, with regard to discrete histologic subtypes of tumors.

**CUTANEOUS MALIGNANCIES**

Cutaneous basal cell carcinomas have a decidedly limited capacity for any form of metastasis (to say nothing of metastasis to regional lymph nodes in particular), and accordingly there does not appear to be a strong rationale for the routine use of sentinel node sampling in these patients.

Cutaneous squamous carcinomas, by contrast, do metastasize to regional nodes; in the head and neck area in particular, estimates of the rate of spread of cutaneous squamous carcinomas to regional nodes range to as many as 16% of patients. The sheer number of cutaneous squamous carcinomas diagnosed each year (as many as 250,000 patients annually in the United States) makes it impractical to undertake sentinel node sampling in the case of each patient. Moreover, many squamous carcinomas of the skin are superficial lesions which are cured by topical therapy, cryotherapy, Mohs microsurgical excision, or simple excision. For sentinel node sampling to be a valuable adjunct to the care of patients with squamous carcinomas of the skin of the head and neck, some means of identifying those patients with clinically negative regional nodal chains who nevertheless are at some significant risk of the development of metastases would seem to be an essential step.

One guide to identifying more aggressive squamous carcinomas is traditional light microscopy, as cancers with a spindled/pleomorphic morphology and those with a small cell/desmoplastic morphology are both associated with a greater incidence of metastasis than are the more conventional types of squamous carcinomas. The incidence of such unfavorable histologic variants is not great, however, and so this still leaves a majority of squamous carcinomas of the skin yet to be segregated into high-risk and low-risk types. The depth of invasion of the lesion is more predictive than size for occult metastasis. Sentinel lymph node sampling may profitably be employed in those head and neck cutaneous squamous carcinoma patients either whose histologic patterns are suggestive of a more aggressive course, or in whom large lesion size at presentation similarly portends a worse prognosis.

The decision to undertake directed sentinel node sampling in the case of a cutaneous head and neck squamous carcinoma may actually sidestep a problem with undirected node dissection, that is, although these tumors most often spread to the first level of cervical lymph nodes, they are also capable of spreading to parotid area nodes in a sizable number of patients who develop metastases. These patients require parotidectomy and neck dissection.

In light of the demonstrated successes with the application of sentinel lymph node sampling in the care of patients with cutaneous malignant melanomas elsewhere in the body, it should seem reasonable to expect similar results in the head and neck area; indeed, this appears to be the case. As head and neck melanomas may, like squamous carcinomas, spread to both cervical nodes as well as to parotid area nodes, sentinel node sampling may avoid the necessity of performing both an elective neck dissection and parotidectomy (and thus limit potential damage to the facial nerve, as is risked in parotidectomy); this may be particularly important in melanomas arising in the vicinity of the ear, face, and anterior scalp. Many investigators have reported satisfactory preliminary results with sentinel node sampling in this context, others, however, have found the combination of a widespread distribution of potential sentinel nodes with the difficulty, at times, of identifying sentinel nodes within the parotid gland (in light of the propensity of salivary gland tissue to exhibit high background concentrations of radionuclide) to limit, to some extent, the reliability of sentinel node sampling in this context. This may be an instance in which preoperative lymphoscintigraphy may aid in refining the approach to sentinel node identification, particularly in the vicinity of the parotid. A summary of the results obtained in these studies is shown in Table 1.
On balance, the potential value of sentinel node sampling in head and neck cutaneous melanomas appears to relate in particular to those tumors with a thickness that exceeds 1 millimeter (mm) (Breslow depth).

Although uncommon, cutaneous Merkel cell tumors (cutaneous neuroendocrine carcinomas) are found in the head and neck region. These tumors are notorious for their propensity to metastasize to regional nodes, and so this has been an appealing area for investigation of the utility of sentinel node sampling. Preliminary results have been encouraging, and so Merkel cell tumors appear to be a type of tumor—like invasive breast carcinoma or many forms of cutaneous melanoma—that may well come to be routinely staged by sentinel node sampling.

Other, rarer forms of cutaneous malignancy, such as cutaneous adnexal eccrine carcinomas or cutaneous adenocarcinomas, have occasioned less comment in large clinical trials, and, as such, it is difficult to make sweeping recommendations for these tumor types. Perhaps the best suggestion that can be made at this juncture is to observe that tumors in this group which are both large and known to follow an aggressive course (eg, cutaneous malignant acrospiroma) may benefit from sentinel node sampling.

### Table 1. Sensitivity and percent of false-negative cases in sentinel lymph node biopsy studies on cutaneous melanomas of the head and neck.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of cases</th>
<th>Sensitivity (%)</th>
<th>False-negative cases (%)</th>
</tr>
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<tbody>
<tr>
<td>Bostick et al</td>
<td>1997</td>
<td>117</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>Wagner et al</td>
<td>2000</td>
<td>70</td>
<td>99</td>
<td>2</td>
</tr>
<tr>
<td>Rasgon</td>
<td>2001</td>
<td>27</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>Eicher et al</td>
<td>2002</td>
<td>43</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>Schmalbach et al</td>
<td>2003</td>
<td>80</td>
<td>94</td>
<td>4.5</td>
</tr>
<tr>
<td>Carlson et al</td>
<td>2005</td>
<td>132</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

### ORAL CAVITY AND PHARYNGEAL MALIGNANCIES

Oral cavity and pharyngeal malignancies are, in the main, squamous carcinomas, which will be treated in the present work. The clinically positive neck presents little dilemma, as these patients are candidates for neck dissections. But what about the clinical N0 patients? Sentinel node sampling has, to date, won a great deal of early approval, but most investigators continue to stress the preliminary nature of their findings and note in the strongest terms that long-term studies are essential before adopting this approach as the standard of care for clinical N0 necks. The results of these works are summarized in Table 2. A recent meta-analysis concluded that sentinel node biopsy procedure in oral and oropharyngeal squamous cell carcinomas has a high degree of sensitivity and is both reliable and reproducible. Potential problems that have been identified include the potential for skip metastases to confound attempts at predicting treatment plans on the basis of the appearances of the sentinel node(s), and technical difficulties in learning the techniques and applying them consistently (including potential for spillage of radionuclide and high background radionuclide concentration in salivary gland tissue). At this point, it is probably most accurate to note that many centers are aggressively pursuing the question of the utility of sentinel node sampling in oral and oropharyngeal carcinomas as a means of reducing the incidence of (presumably unnecessary) modified radical neck dissections, but are not yet ready to make blanket recommendations about the routine use of this technique in this setting.

### Table 2. Summary of results of sentinel lymph node biopsy studies in oral and pharyngeal squamous cell carcinomas.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of cases</th>
<th>Sensitivity (%)</th>
<th>False-negative cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionna et al</td>
<td>2002</td>
<td>41</td>
<td>95</td>
<td>0</td>
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<tr>
<td>Pastore et al</td>
<td>2002</td>
<td>20</td>
<td>95</td>
<td>0</td>
</tr>
<tr>
<td>Hyde et al</td>
<td>2003</td>
<td>19</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>Kohno et al</td>
<td>2003</td>
<td>8</td>
<td>100</td>
<td>12.5</td>
</tr>
<tr>
<td>Kontio et al</td>
<td>2004</td>
<td>15</td>
<td>100</td>
<td>6.6</td>
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<tr>
<td>Ross et al</td>
<td>2004</td>
<td>132</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>Gallegos-Hernandez et al</td>
<td>2005</td>
<td>48</td>
<td>100</td>
<td>8.3</td>
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<tr>
<td>Kovacs et al</td>
<td>2005</td>
<td>39</td>
<td>95</td>
<td>0</td>
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<tr>
<td>Nieuwenhuis et al</td>
<td>2005</td>
<td>22</td>
<td>89</td>
<td>5</td>
</tr>
</tbody>
</table>
LARYNGEAL MALIGNANCIES

As is the case with oral cavity squamous carcinomas, clinical N0 patients with squamous carcinomas of the larynx have been the subject of a great deal of scrutiny by researchers interested in the potential applicability of sentinel node sampling in this context.15,37,42,43,63 Here too, preliminary enthusiasm for the efficacy of sentinel node biopsy has been tempered by strong cautions that any long-term advantages of this procedure remain to be demonstrated; as such, laryngeal squamous carcinomas and sentinel node sampling continue to enjoy an experimental relationship, as calls for standard sentinel node sampling in patients with tumors of the larynx have not yet been heard.126 Moreover, the more difficult access of laryngeal carcinomas to the preoperative injection of blue dye or radiocolloid could be a factor that might limit its generalized use.

THYROID GLAND MALIGNANCIES

 Although thyroid cancer is sometimes considered in the literature as a single monolithic entity, in truth the thyroid gland may give rise to a variety of individual tumor types of differing degrees of aggressiveness.12,30,45,127,128 Minimally invasive follicular carcinomas (low-grade follicular carcinomas) of the thyroid do not often metastasize, and so (as with the low-grade salivary gland tumors) this may be a tumor type for which sentinel node sampling might not be routinely applicable. On the other hand, widely invasive follicular carcinomas, papillary carcinoma, medullary carcinoma, and anaplastic carcinoma of the thyroid all have a very real likelihood of spread to regional nodes, and so these pathologic types of tumors may benefit from studies of potential applications of sentinel node sampling. Sentinel lymph node biopsy has been carried out on thyroid cancer patients using a vital dye technique, a radiotracer technique, and a combination of both techniques. In the current literature the average rate of sentinel node identification is 91% (range, 66% to 100%), and, when identified, the sentinel node accurately predicts the disease status of the neck in most patients (range, 80% to 100%). Limitations to carrying out the sentinel node biopsy on thyroid cancer patients include staining of parathyroid glands, identification of lymph nodes draining into the mediastinum, and the “shine-through” effect. Sentinel lymph node biopsy is technically feasible, but for a disease in which nodal metastases are of debatable prognostic value, and elective neck dissection is not routinely indicated (except in medullary carcinoma), the clinical value of sentinel lymph node biopsy in the management of patients with differentiated thyroid cancer appears less than promising.47–49

It remains to be seen whether sentinel node sampling will prove useful in this arena, as large studies comparing sentinel node sampling results with results of formal regional node dissection in patients with thyroid malignancies have yet to be carried out.

Sentinel node sampling may have some application in the care of patients with parathyroid carcinomas, but studies to establish this have yet to be carried out.

TECHNICAL MATTERS

Two technical matters not considered above should be touched upon before concluding: one surgical and the other pathologic. The surgical matter relates to the means used to actually identify the sentinel node(s) themselves. Some surgeons rely on the intraoperative use of both blue dye (isosulfan blue dye in the United States, patient blue dye [Patent Blue-V] in Europe) as well as radiotracer (in the United States, technetium Tc 99m sulfur colloid; in Europe, technetium Tc 99m-labeled human serum albumin) to identify the sentinel nodes; others rely on blue dye alone. Visual detection of the blue dye–stained lymph nodes, with or without detection of the technetium tagged nodes by way of a hand held gamma counter, guides the attending surgeon in the selection of nodal tissue for sentinel node sampling. In several studies of sentinel node sampling, other investigators have employed preoperative lymphoscintigraphy with marking of the skin overlying the “hot spots” identified.56 Novel methods for sentinel lymph node detection are currently under investigation, as are the use of MR lymphangiography and carbon dye labeling.71 These methods appear to provide temporal and anatomic localization of the sentinel node with a single investigation. Moreover, carbon dye is a sensitive and persistent visual marker of MR-targeted sentinel lymph nodes.

Whereas some investigators have reported satisfactory results with blue dye and visual identification of sentinel nodes alone, others have found that the use of radiotracers yields a net increase in the rate of successful identification of sentinel nodes. Indeed, in light of the variable, even idiosyncratic, patterns of lymphatic drainage in the
head and neck region, this may be an area of the body in which the added power to identify sentinel nodes offered by radiotracers may be particularly beneficial. This invites consideration of this question: Should preoperative lymphoscintigraphy be employed, perhaps in conjunction with these other approaches, to most accurately identify the sentinel nodes?

One cosmetic problem is posed by the use of blue dye in exposed areas that are not subsequently excised, such as the face, and this is the risk of permanent tattooing of the skin.94

On the pathology side of the equation, it remains uncertain how best to handle the sentinel node tissue itself: Should it be studied by frozen section? By intraoperative cytology or fine-needle aspirate cytology? How about the use of intraoperative immunohistochemistry? Should it, instead, be fixed and then studied by way of several different levels and immunohistochemical staining for cytokeratin?40,129–134 The latter approach may be attracting some adherents, as a few investigators have opined that, in the grossly negative node, intraoperative frozen section does not often add much to the treatment planning and has a poor track record of identifying micrometastases.135–138 Nevertheless, many surgeons who are recent graduates of a variety of training programs that teach sentinel node sampling graduate having learned to undertake intraoperative frozen section examination of sentinel nodes as a matter of course, and so this issue is likely to remain open for discussion for the foreseeable future.

It is important to observe that the pathologic analysis of the intraoperative sentinel lymph node, which is expected to be the lymph node to which a cancer directly drains, may be an imperfect means of predicting the lymph node status of cancer patients in some instances for the following reasons54:

1. The intraoperative examination (frozen-section analysis) and the routine pathologic assessment of the sentinel lymph node can underestimate the true incidence of metastasis. False-negative sentinel lymph nodes may contain tiny deposits of microscopic metastatic disease but these may not be caught in the examined histologic slides; serial sections, immunohistochemical stains, and molecular marker assays (based on the reverse transcriptase-polymerase chain reaction technique) increase the detection rate of sentinel lymph node metastases and could be useful for better assessing the status of the lymph nodes. These sensitive and specific methods have been shown to upstage patients previously referred to as “lymph node-negative.”126

2. The possibility that tumor cells may escape the first draining lymph node and metastasize to other lymph nodes (skip metastases) is well documented in patients with head and neck cancers.139

3. Free soft tissue disease (defined as a metastatic carcinoma in the soft tissue of the neck with no evidence of a lymph node architecture) is well documented in the literature140–143 and obviously cannot be studied by sentinel lymph node biopsy. Soft tissue deposits have a high prevalence in neck dissection142 and have been found also in patients with clinically N0 necks.140,141,143

**FUTURE DIRECTIONS**

As noted at the outset, many centers have adopted sentinel node sampling as a de facto standard of care for many of their patients with breast carcinoma and cutaneous melanoma. However, some dissenting voices are beginning to question the blanket acceptance of sentinel node sampling for a variety of primary tumor types; many observers have noted that, whereas sentinel node sampling may be both technically feasible and a means of reducing the incidence of unnecessary formal regional node dissections, a clear association between sentinel node sampling and an improved long-term outcome has yet to be demonstrated in many instances.144,145 In addition, it has been noted that detection of micrometastases, which sentinel node sampling with exhaustive pathologic examination excels at, might not actually carry with it any true clinical import.137,146,147 Finally, applications of a great variety of molecular investigations to the study of sentinel node specimens are only just beginning to be explored, suggesting that the definitive story of sentinel node sampling and head and neck malignancies is yet to be written.148–151

**CONCLUSION**

Sentinel lymph node biopsy is feasible, but it is alone insufficient to stage the disease accurately. A negative sentinel lymph node biopsy does not definitively exclude the presence of positive basin lymph nodes, hence adds no further staging information. Sentinel lymph node biopsy in head and neck mucosal squamous cell carcinoma is still an
ongoing debate, and at this juncture this technique remains an investigational procedure. As such, it has not yet achieved the status of "standard of care" for the treatment of head and neck cancer patients. It is recommended that studies of the efficacy of sentinel lymph node biopsy strive, whenever possible, to segregate results of different tumor types in different head and neck locales from one another so as to produce more focused findings for discrete types of malignancies, and not group together tumor types that may in reality exhibit different biological behaviors.

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