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Sentinel Lymph Node Biopsy in Head and Neck Cancers

Background

Tumor metastasis is one of the most important predictive factors in most solid tumors. In head and neck squamous cell carcinoma (HNSCC) survival is strongly affected by regional lymph node metastases, most commonly in the cervical chain [1, 2]. The treatment of metastatic disease can include surgery (neck dissection) or radiation [3, 4]. There are two arguments for treating metastatic lymph node disease surgically. First, this procedure is done for staging [5]. The number, size, location, and invasive characteristics of positive nodes all have impact on prognosis and are used to determine the post-operative treatment regimen [5]. The second argument for neck dissection is that it improves locoregional control of tumor, though not necessarily long-term survival [6, 7]. Thus, in head and neck cancer, neck dissection is said to serve two purposes: improved staging and potential therapeutic advantages [8].

Treatment of the clinically node positive (cN+) neck with surgery and/or radiation is the standard of care. The real area of controversy is the elective treatment of the clinically negative neck (cN0). The overall risk of occult metastases or neck recurrence in the cN0 neck with lower stage tumors is significant, estimated at between 10 and 30%, depending on tumor characteristics [9, 10]. Authors have argued extensively both for and against elective selective neck dissection in these cN0 patients [1, 8, 9, 11]. With the increased utilization of selective neck dissections, morbidity is even lower, with the most common post-operative complaints being from nerve damage, particularly the spinal accessory nerve [8, 12-15].

The strongest arguments for treatment of the cN0 neck revolve around the poor outcome for recurrence in the neck, the low morbidity of the selective procedures, and improved locoregional control [8]. However, other authors have argued for "watchful waiting", which entails careful monitoring of the neck for the appearance of clinical metastases. This clinical monitoring relies on clinical examination and radiological surveys such as CT scans, MRI, and ultrasound. In scans, the only variables that correlate with the presence of carcinoma are the size and the shape of the lymph nodes, where nodes >1 cm and nodes that are round instead of oval are suspicious [16-18]. Very advanced metastatic disease may show central necrosis. Newer monitoring has been described using CT scans paired with PET scanning which appears to improve the detection rate for metastases and improves the lower limits of the size of detectable metastases [18].

Despite advances in our understanding of which patients will benefit from neck dissection, advances in lowering the morbidity of treating the neck, and advances of detection of metastatic disease, treatment of the cN0 neck remains a controversial issue. Performance of elective neck dissection or neck irradiation in the cN0 neck is over-treatment for the majority of patients, but undetected and untreated neck metastases are associated with an unacceptably high failure rates. For these reasons, the sentinel lymph node procedure has been inviting for the treatment of the cN0 neck.

Sentinel Lymph Node Procedures

Many tumors are treated with primary surgery for tumor control and lymphadenectomy of the draining lymph nodes, which are evident by the routes of common metastases (Figure 1). The sentinel lymph node (SLN) procedure is really a “super-selective” nodal dissection. Head and neck surgeons have dramatically decreased the amount of tissue removed in nodal neck dissections, in converting from radical to selective neck dissections [7]. In breast carcinoma and melanoma treatment, where a lymphadenectomy used to be routine, the sentinel lymph node procedure is now commonly used as a selective procedure that has a lower morbidity [19]. This procedure was first popularized in the 1977 by Cabanas for staging of penile carcinoma [20], but was first described in parotid tumors in 1960 by Gould [21]. The procedure has now been attempted in nearly every type of tumor, and reported with varying success rates [22].

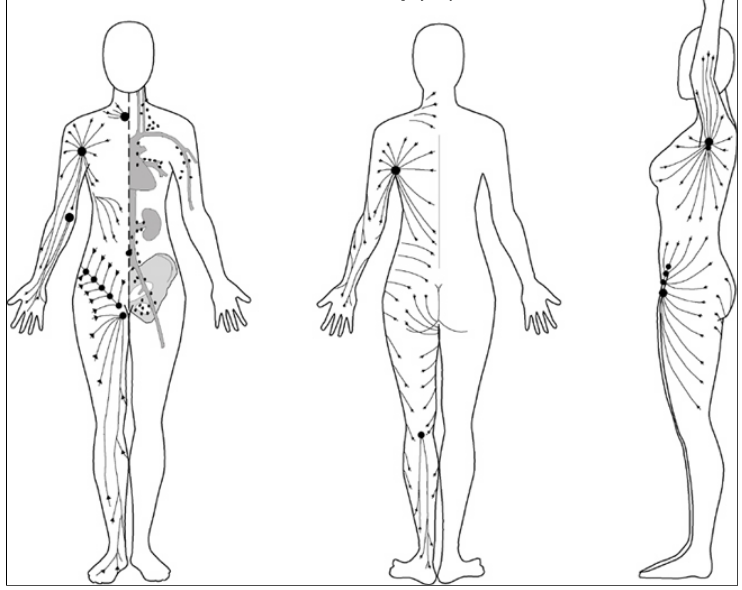


FIGURE 1: Skin draining lymph nodes

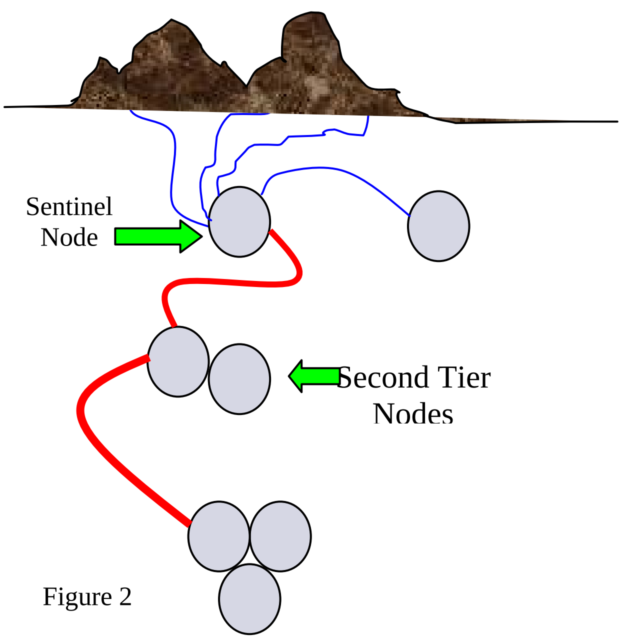
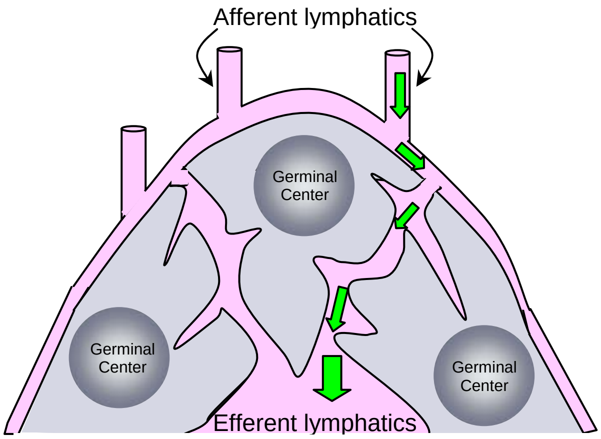


Figure 2

The theory behind the use of the SLN procedure is the assumption that lymphatic drainage from a particular anatomic site is predictable and hierarchical in nature. In other words, lymph from a certain anatomical site drains to predictable lymph node basins. It follows that tumor cells from a tumor in that location will gain access to the lymphatics and will become deposited in the same consistent regional lymph node basins (Figure 2). The lymph nodes in this basin are thought to be connected in series, meaning that the lymph flows into the first node in the chain (the sentinel lymph node, SLN), and then sequentially flows into the next lymph nodes in the chain (second tier nodes). The examination of this very first lymph node for metastases is therefore theoretically predictive of the status of all remaining lymph nodes.

The procedures utilized for identification of the SLN have involved two types of models: blue dye and radioactive injectable substances [23]. In both models, the substance is injected in the peritumoral tissues, where the lymphatics are preserved and are thought to be draining the tumor region. Both substances have particle sizes that



enable them to enter into the afferent lymphatics of the lymph node, and become trapped within the lymph node parenchyma (Figure 3). This enables the detection of the lymph node with the highest signal, either radioactivity measured by a gamma probe, or visually as the blue node. The size of the radiocolloid particles is different in the various radiocolloid preparations that are commercially available, and smaller particles pass through to the second tier nodes more easily and rapidly [24]. Many investigators have supported the use of both detection methods simultaneously, for increased specificity and sensitivity [23].

Methods to measure the success of the SLN procedure are variable. In early studies, patients were consented for an investigational trial and the SLN procedure followed by a typical lymph node dissection. The detection rate of at least one or more sentinel node(s) is the first variable that is measured; some patients will not have an SLN that is detectable using the methods described above. Most studies report high (>90-95%) detection rates for most tumor types [25]. The predictive power of the SLN should also be measured. In other words, how well does the SLN predict the status of the entire regional lymph node basin? The endpoints of the effect of SLN on survival and regional recurrence can only be assessed in randomized trial assessing the SLN procedure alone vs. the full lymph node dissection.   In breast cancer and in melanoma, the risk of regional recurrence in SLN alone is low (usually <5%) [26-28].   The SLN is often the only positive node in the majority of the patients [29], and because of this, some studies have questioned the necessity of the completion procedure in patients with a positive SLN [30, 31]. Importantly, morbidity is reduced when a complete lymph node dissection is not performed [19]. Despite all of the literature that suggests the SLN procedure is safe, beneficial, and decreases morbidity, there are investigators and clinicians who do not believe that it should be the standard of care and that it was prematurely adopted [19, 22, 25, 32-35].

From the pathologist’s perspective, handling of the sentinel node is important because it requires special care. One concern that pathologists may have is the safety of handling the radioactive sentinel lymph node. Some departments require quarantine of the tissues for a period of time, which makes intraoperative margin assessment by frozen section impossible. The literature on the safety of handling these specimens demonstrates that there is negligible risk to the person doing gross examination, except in the unlikely scenario of very high specimen volume handled all by one person [36]. Therefore, it is probably not necessarily to delay processing or to store the specimens in any special type of container. It is recommended to have radiation safety training for all individuals who come into contact with these specimens, from transport staff to the person performing the gross examination. There is essentially no risk in the histology laboratory or for other downstream processes.

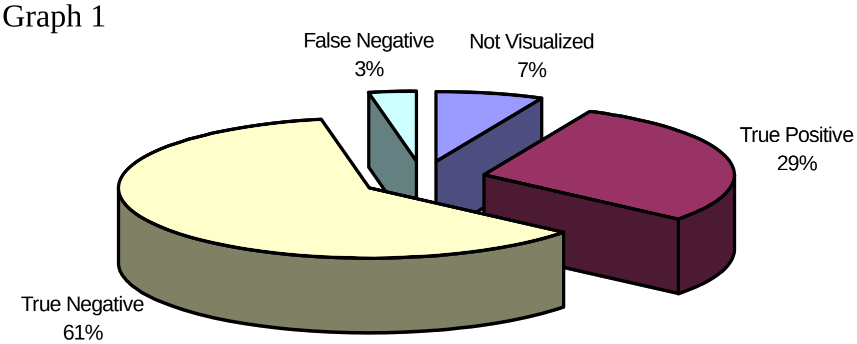
The role for intra-operative assessment is unclear. In breast cancer and melanoma, grossly positive nodes are usually easily diagnosed intra-operatively by frozen section or imprint cytology [37]. The false negative rate for micrometastases, however, is high [38]. The gross and histological handling of sentinel lymph nodes is far from standardized [39]. It is clear from the vast literature on this subject that the more sections that are examined and the finer the detail at which they are examined (i.e., immunohistochemistry), the more micrometastases will be picked up [27, 40]. And, it is also clear that missed micro-metastases are responsible for a significant number of failures of the SLN procedure with recurrence in the lymph node basin [27, 28]. The important role for IHC in detection of micro-metastases has been clearly established, but again, no standardized approach has been adopted.

Sentinel Lymph Nodes in Head and Neck Cancers

In the head and neck, we are in the initial phases of investigation of the SLN procedure for treatment of the neck. Multiple small series have been published that have shown the feasibility of the procedure and initial results were considered to be promising. Initial studies determined that the SLN was not effective in patients with clinically positive necks and may not detect grossly positive lymph nodes. This is most likely due to utilization of alternate lymphatic channels when metastases replacing lymph nodes and tumor plugs in the lymphatic channels block lymphatic flow [41, 42]. Obviously, in this situation, the blue dye or radio-colloid will not flow through these lymphatic channels either. Therefore, it has become clear that the SLN in head and neck cancer will be most useful in clinically N0 necks and in patients with relatively small primary tumors (T1 or T2).

Clearly, the SLN procedure in HNSCC is feasible. Seventeen studies of SLN procedures in HNSCC have been summarized in Table 1 and Graph 1. An analysis of all of the data presented in those studies shows that the sensitivity in picking up at least one sentinel lymph node in HNSCC of various sites, by various detection methods, is approximately 93%. Almost all studies found more than 1 SLN per neck examined, with an overall average of 1.6 nodes SLNs per neck. The SLN harbored metastases in a mean of 29% of patients. The false negative rate of the SLN in these procedures showed a mean of 3.2%, with a range of 0-10%.

Graph 1



Several studies have highlighted the fact that experience in performing the SLN procedure is critical [43]. One author has recommended that at least 10 SLN with completion neck dissection before attempting the SLN procedure without subsequent neck dissection [41, 44]. Other authors have argued that the SLN procedure should only be performed as part of clinical trials, since it is far too premature for it to become an acceptable option for routine therapy [45].

Pathologic analysis of sentinel lymph nodes in head and neck cancer is variable in the reported studies, from those studies that examine one routine H&E from the nodes, to those that utilize step sections through the node, to studies that utilize a combination of step sections and immunohistochemistry. The studies that have utilized step sections and IHC to detect metastatic disease show an increased number of micro-metastases or isolated tumor cells that are detected only on these additional studies [46, 47]. In breast cancer, the definition of isolated tumor cells is a cluster that measures <.2 mm. Though the significance of micrometastatic disease is not entirely understood, it does appear to portend a worse prognosis [48-50].

In head and neck cancer, the incidence of micrometastases is relatively high, with up to 10% of patients with metastasis having small tumor foci (identified with standard pathologic analysis). The incidence increases when additional levels and immunohistochemistry are added to the workup. We do not fully understand the clinical importance of micrometastatic disease in HNSCC but is likely to have significant prognostic implications [44].

Problems in SLN for head and neck cancers

The most significant arguments against using SLN for head and neck cancer have arisen from the anatomical variation and the inconsistent drainage basins in the head and neck. The presence of "skip metastases" and aberrant drainage patterns has been regularly described in the literature [51]. This has led to some concern that the nodal hierarchy may not be consistent and that the "sentinel" nodes may be falsely negative, resulting in the skip patterns have been seen infrequently [52].

Interestingly, the argument of inconsistent drainage patterns is used to argue against SLN, but it could just as easily be used to support the use of SLN. Since the SLN procedure allows the surgeon to map and identify unusual drainage sites, it may allow for more extensive dissection in high risk areas that would not usually be sampled in a routine selective neck dissection [44, 53, 54]. Studies in other organ systems have shown that there is increased pick-up of positive nodes when the SLN procedure is used as opposed to lymph node dissection [55]. In some ways, the argument for using SLN in the head and neck may become that it will allow directed specialized study of high-risk nodes in patients who are otherwise at lower risk for occult metastases. This is a similar argument that has been used for SLN in colon cancer, where the lymph nodes are removed anyway, but the procedure will allow the pathologist to examine certain nodes in greater detail [56-58].

Another area of concern in the use of SLN in HNSCC is the fact that radiated tissues are not suitable for the procedure since the drainage flow patterns are greatly altered or even destroyed by the radiation induced tissue damage. In today's era of treating HNSCC, primary radiation is becoming a main-stay of treatment for some cancers, and this will certainly affect the applicability of SLN procedures [9, 59]. It appears that prior chemotherapy may also increase the risk of false negative SLN [58, 60]. Interestingly, however, the SLN procedure has been also proposed to be helpful in identifying unusual patterns of lymphatics in post-radiation patients that are being treated by salvage surgery [61].

The recurrence of carcinoma in the neck with the need for salvage surgery has a poor prognosis [8, 62]. Therefore, some authors have expressed concern that false negatives in SLN would be unacceptable. This argument may be counteracted, however, by the fact that using immunohistochemistry can up-stage lymph nodes significantly, with one study suggesting detection of metastases in 2/24 patients with H&E increased to 14/24 patients with IHC [63]. Therefore, patients may actually be staged more accurately by use of the SLN procedure when a specific protocol including IHC is used for examining the pathology specimens [44, 64].

Finally, several studies have highlighted the fact that floor of mouth cancers have produced significantly high false negative rates in using the SLN procedure. The authors have postulated that the primary tumor signal masks the signal of the SLN [24].

Recommendations for practice

SLN procedure for HNSCC will more than likely come into use in some centers, but is unlikely to become the standard of care within the next five years. Although initial results are promising, there are still some unresolved problems with the procedure, including the issues with certain sub-sites, previously treated patients, and most authors are suggesting caution before making the SLN standard of care [64]. Some authors have described enhanced procedures that combine the use of SLN localization with the results of pre-procedure PET scanning or combine SLN with fine needle aspiration [65, 66]

For the pathologist, the question will become how to properly analyze the SLN for HNSCC. From all of the literature in breast cancer and melanoma on handling SLNs, it is clear that specialized assessment for SLNs is needed. The most appropriate handling will include specialized fresh assessment, grossing, multiple histological sections, and immuhistochemistry.

The first question is whether the SLN should be assessed in the intra-operative setting and how. In the breast and melanoma literature, the intra-operative assessment of the SLN has been shown to be fraught with error using either touch/imprint cytology or frozen sections [38, 67, 68]. The low sensitivity and high specificity are thought to be because of sampling errors, particularly for micrometastases, and also because the morphology of breast and melanoma cells can be subtle. In HNSCC, sensitivity and specificity is likely to be somewhat higher, since the morphology of metastatic SCC is usually not subtle [69]. The risks of inadequate sampling of micro-metastatic lesions will still remain high.

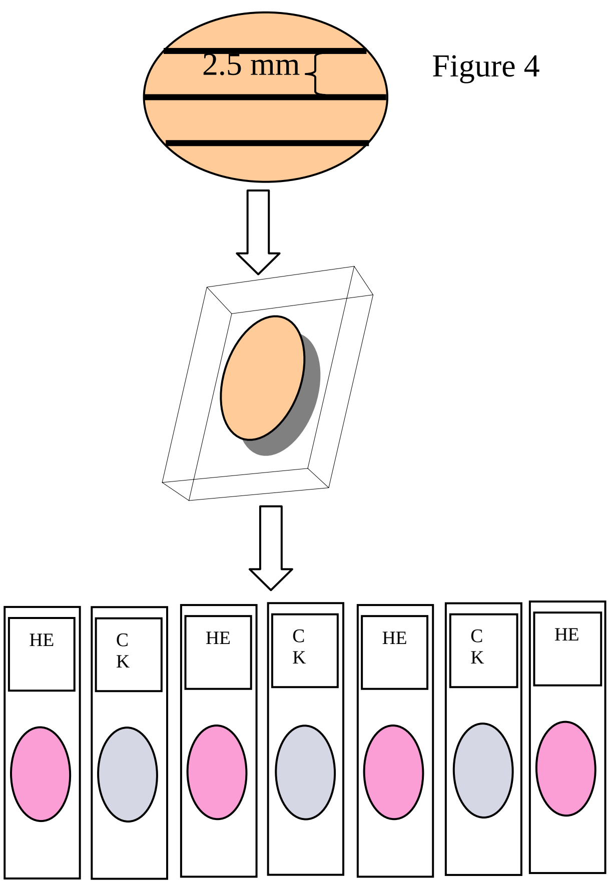


Figure 4

Grossing and histology of the SLN should also be standardized, at least within each institution. Ideally, the pathologist will visualize of as much as the node as possible (Figure 4). Serially sectioning larger SLNs at cassette-appropriate intervals (i.e., 2.5 mm thickness slices) and submission of the entire node are important. If the node is positive on initial H&E section, no further workup is necessary. If the initial H&E is negative, additional H&E sections (step sections) and intervening immunohistochemical staining will optimize detection of micrometastases. In many practices with turnaround time concerns, however, waiting to review the initial section before obtaining additional levels and immunohistochemical stains could result in a significant delays, and therefore up front SLN protocols may be implemented. The optimal number of slides to be examined and the number of IHC stains has not been determined, though it is clear from the literature that the more sections the pathologists sees, smaller and smaller tumor deposit will not escape detection. If SLN becomes an acceptable alternative to elective selective neck dissection in HNSCC, discussions between pathologists, surgeons, oncologists and radiation oncologists and close interactions between these physicians will become critical. All of our clinician colleagues should be aware of the false negative rate of intraoperative assessment (frozen section and cytology), because there will be a need for a completion neck dissection as a second procedure in these intraoperative false negative cases.

Despite the initial promising results in these studies of SLN in HNSCC, it still remains to be seen with larger clinical trials and randomized studies, whether the SLN procedure will serve the purpose of adequately staging patients and with no negative effects on long-term survival [70-72]. Furthermore, standardization of the approach and protocols, and determination of the optimal pathologic workup should precede widespread implantation of the SLN procedure in head and neck surgery practices.

Table 1: Studies of SLN in head and neck cancers. The detection methods utilized radiocolloid (RC) with or without the addition of blue dye (Dye). The number of patients with an identifiable SLN is given, as is the average number of SLNs detected per patient. The number of SLNs that were positive, of the total number detected in the study and the number of patients who had a negative SLN and another positive node in the neck dissection are both listed. The type of pathologic analysis, when described, is listed.

Author	Year	Method	Number	Identification of an SLN in the patients	Avg # of nodes	Positive SLN in pt	SLN-(pN+)	Pathology
Koch [73]	1998	RC	5	3/5	2.3	2/3	0/3	
Shoaib [74]	2001	Dye/RC	40	36/40	2.2	16/36	1/36	One H&E
Alex [75]	2001	RC	15	14/15	3.1	1/14	0/14	
Taylor [76]	2001	RC	11	9/11	2.0	4/9	0/9	One H&E
Werner [77]	2001	RC	48	48/48	NA	10/48	5/48	NA
Ross^ [64]	2002	RC	316	301/316	NA	76/301	8/301	Variable
Pitman [42]	2002	RC	20	19/20	2.9	2/19	1/19	
Ionna [53]	2002	Dye/RC	41	39/41	1.1	4/39	0/39	
Civantos [66]	2003	RC	18	18/18	NA	10/18	2/18	One H&E & IHC
Asthana# [78]	2003	Dye	32	30/32	NA	8/32	2/32	H&E
Kontio [47]	2004	Dye/RC	15	14/15	3.1	3/14	1/14	One H&E & IHC
Ross [44]	2004	Dye/RC	57	43/48	2.4	15/43	1/43*	Steps & IHC
Ross^ [79]	2004	Dye/RC	134	125/134	2.8	59/125	3/55**	Steps & IHC
Hoft [80]	2004	RC	50	46/50	3.2	12/46	0/36	Steps & IHC
Alex [24]	2004	RC	20	20/20	NA	3/20	0/20	NA
Niewuenhuis [81]	2005	RC	27	22/27	1.1	8/22	1/22	Steps & IHC
Payoux [82]	2005	RC	37	36/37	1.8	6/36	1/36	2 H&E
Total			886	823/886 (93%)	1.6	239/823 (29%)	26/823 (3.2%)	

*=no neck dissection performed, but patient recurred in the neck
#=Patient sample included both clinically N0 and clinically N+ necks
**=neck dissection only performed in subset (55/134) patients
^=Multiple centers participated
NA=Not available
H&E=Hematoxylin and eosin; Steps=step sections; IHC=immunohistochemistry stains

References

1. Smith, G.I., et al., *Management of the neck in patients with T1 and T2 cancer in the mouth.* British Journal of Oral & Maxillofacial Surgery, 2004. **42**(6): p. 494-500.
2. Mastronikolis, N.S., et al., *The management of squamous cell carcinoma of the neck. The Birmingham UK experience.* European Journal of Surgical Oncology, 2005. **31**(5): p. 461-6.
3. Moore, M.G. and N. Bhattacharyya, *Effectiveness of chemotherapy and radiotherapy in sterilizing cervical nodal disease in squamous cell carcinoma of the head and neck.* Laryngoscope, 2005. **115**(4): p. 570-3.
4. Hosal, A.S., et al., *Selective neck dissection in the management of the clinically node-negative neck.* Laryngoscope, 2000. **110**(12): p. 2037-40.
5. Jose, J., A.P. Coatesworth, and K. MacLennan, *Cervical metastases in upper aerodigestive tract squamous cell carcinoma: histopathologic analysis and reporting.* Head & Neck, 2003. **25**(3): p. 194-7.
6. Clark, J., et al., *Outcome of treatment for advanced cervical metastatic squamous cell carcinoma.* Head & Neck, 2005. **27**(2): p. 87-94.
7. Mira, E., et al., *Efficacy of selective lymph node dissection in clinically negative neck.* Otolaryngology Head & Neck Surgery, 2002. **127**(4): p. 279-83.
8. Duvvuri, U., et al., *Elective neck dissection and survival in patients with squamous cell carcinoma of the oral cavity and oropharynx.* Laryngoscope, 2004. **114**(12): p. 2228-34.
9. Andry, G., M. Hamoir, and C.R. Leemans, *The evolving role of surgery in the management of head and neck tumors.* Current Opinion in Oncology, 2005. **17**(3): p. 241-8.
10. Sparano, A., et al., *Multivariate predictors of occult neck metastasis in early oral tongue cancer.* Otolaryngology Head & Neck Surgery, 2004. **131**(4): p. 472-6.
11. Sarno, A., et al., *Does unnecessary elective neck treatment affect the prognosis of N0 laryngeal cancer patients?* Acta Oto Laryngologica, 2004. **124**(8): p. 980-5.
12. van Wilgen, C.P., et al., *Shoulder and neck morbidity in quality of life after surgery for head and neck cancer.* Head & Neck, 2004. **26**(10): p. 839-44.
13. El Ghani, F., et al., *Shoulder function and patient well-being after various types of neck dissections.* Clinical Otolaryngology & Allied Sciences, 2002. **27**(5): p. 403-8.
14. Cappiello, J., et al., *Shoulder disability after different selective neck dissections (levels II-IV versus levels II-V): a comparative study.* Laryngoscope, 2005. **115**(2): p. 259-63.
15. Genden, E.M., et al., *Complications of neck dissection.* Acta Oto Laryngologica, 2003. **123**(7): p. 795-801.
16. Kovacs, A.F., et al., *Positron emission tomography in combination with sentinel node biopsy reduces the rate of elective neck dissections in the treatment of oral and oropharyngeal cancer.* Journal of Clinical Oncology, 2004. **22**(19): p. 3973-80.
17. Ojiri, H., et al., *Lymph nodes of patients with regional metastases from head and neck squamous cell carcinoma as a predictor of pathologic outcome: size changes*

at CT before and after radiation therapy.[see comment]. Ajnr: American Journal of Neuroradiology, 2002. **23**(10): p. 1627-31.
18. Schwartz, D.L., et al., *FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma.* International Journal of Radiation Oncology, Biology, Physics, 2005. **61**(1): p. 129-36.
19. Lee, K.K., et al., *Sentinel lymph node biopsy.* Clinics in Dermatology, 2004. **22**(3): p. 234-9.
20. Cabanas, R.M., *An approach for the treatment of penile carcinoma.* Cancer, 1977. **39**(2): p. 456-66.
21. Gould, E.A., et al., *Observations on a "sentinel node" in cancer of the parotid.* Cancer, 1960. **13**: p. 77-8.
22. Schulze, T., A. Bembenek, and P.M. Schlag, *Sentinel lymph node biopsy progress in surgical treatment of cancer.* Langenbecks Archives of Surgery, 2004. **389**(6): p. 532-50.
23. Radovanovic, Z., et al., *Blue dye versus combined blue dye-radioactive tracer technique in detection of sentinel lymph node in breast cancer.* European Journal of Surgical Oncology, 2004. **30**(9): p. 913-7.
24. Alex, J.C., *The application of sentinel node radiolocalization to solid tumors of the head and neck: a 10-year experience.* Laryngoscope, 2004. **114**(1): p. 2-19.
25. Singh-Ranger, G. and K. Mokbel, *The sentinel node biopsy is a new standard of care for patients with early breast cancer.* International Journal of Fertility & Womens Medicine, 2004. **49**(5): p. 225-7.
26. Morton, D.L., et al., *Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial.* Annals of Surgery, 2005. **242**(3): p. 302-11.
27. Li, L.X., et al., *Pathologic review of negative sentinel lymph nodes in melanoma patients with regional recurrence: a clinicopathologic study of 1152 patients undergoing sentinel lymph node biopsy.* American Journal of Surgical Pathology, 2003. **27**(9): p. 1197-202.
28. Jeruss, J.S., et al., *Axillary recurrence after sentinel node biopsy.* Annals of Surgical Oncology, 2005. **12**(1): p. 34-40.
29. Cox, C., et al., *The clinical relevance of positive sentinel nodes only versus positive nonsentinel lymph nodes in breast cancer patients.* American Journal of Surgery, 2003. **186**(4): p. 333-6.
30. Pu, L.L., et al., *Prevalence of additional positive lymph nodes in complete lymphadenectomy specimens after positive sentinel lymphadenectomy findings for early-stage melanoma of the head and neck.[see comment]*. Plastic & Reconstructive Surgery, 2003. **112**(1): p. 43-9.
31. Mack, L.A. and J.G. McKinnon, *Controversies in the management of metastatic melanoma to regional lymphatic basins.* Journal of Surgical Oncology, 2004. **86**(4): p. 189-99.
32. Kell, M.R. and M.J. Kerin, *Sentinel lymph node biopsy.* Bmj, 2004. **328**(7452): p. 1330-1.
33. Gipponi, M., et al., *New fields of application of the sentinel lymph node biopsy in the pathologic staging of solid neoplasms: review of literature and surgical perspectives.* Journal of Surgical Oncology, 2004. **85**(3): p. 171-9.

34. Schwartz, G.F., *Clinical practice guidelines for the use of axillary sentinel lymph node biopsy in carcinoma of the breast: current update.* Breast Journal, 2004. **10**(2): p. 85-8.
35. Thomas, J.M. and M.A. Clark, *Sentinel lymph node biopsy: not yet standard of care for melanoma.[see comment][comment]*. Bmj, 2004. **329**(7458): p. 170-1.
36. Hunt, J.L., Z.W. Baloch, and V.A. LiVolsi, *Sentinel lymph node evaluation for tumor metastasis.* Seminars in Diagnostic Pathology, 2002. **19**(4): p. 263-77.
37. Wada, N., et al., *Evaluation of intraoperative frozen section diagnosis of sentinel lymph nodes in breast cancer.* Japanese Journal of Clinical Oncology, 2004. **34**(3): p. 113-7.
38. Schrenk, P., et al., *Intraoperative frozen section examination of the sentinel lymph node in breast cancer.* Rozhledy, 2005: p. 217-22.
39. Viale, G., et al., *Histopathologic examination of axillary sentinel lymph nodes in breast carcinoma patients.* Journal of Surgical Oncology, 2004. **85**(3): p. 123-8.
40. Cohen, C., et al., *Immunohistochemical evaluation of sentinel lymph nodes in breast carcinoma patients.* Applied Immunohistochemistry & Molecular Morphology, 2002. **10**(4): p. 296-303.
41. Ross, G.L., et al., *The First International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer and adoption of a multicenter trial protocol.* Annals of Surgical Oncology, 2002. **9**(4): p. 406-10.
42. Pitman, K.T., et al., *Sentinel lymph node biopsy in head and neck squamous cell carcinoma.* Laryngoscope, 2002. **112**(12): p. 2101-13.
43. Posther, K.E., et al., *Sentinel node skills verification and surgeon performance: data from a multicenter clinical trial for early-stage breast cancer.* Annals of Surgery, 2005. **242**(4): p. 593-9.
44. Ross, G.L., et al., *Improved staging of cervical metastases in clinically node-negative patients with head and neck squamous cell carcinoma.* Annals of Surgical Oncology, 2004. **11**(2): p. 213-8.
45. Rigual, N.R. and S.M. Wiseman, *Neck dissection: current concepts and future directions.* Surgical Oncology Clinics of North America, 2004. **13**(1): p. 151-66.
46. Stoeckli, S.J., et al., *Histopathological features of occult metastasis detected by sentinel lymph node biopsy in oral and oropharyngeal squamous cell carcinoma.* Laryngoscope, 2002. **112**(1): p. 111-5.
47. Kontio, R., et al., *Sentinel lymph node biopsy in oral cavity squamous cell carcinoma without clinically evident metastasis.* Head & Neck, 2004. **26**(1): p. 16-21.
48. Rivera, M., et al., *Controversies in surgical pathology: minimal involvement of sentinel lymph node in breast carcinoma: prevailing concepts and challenging problems.* International Journal of Surgical Pathology, 2004. **12**(4): p. 301-6.
49. Calhoun, K.E., et al., *Nonsentinel node metastases in breast cancer patients with isolated tumor cells in the sentinel node: implications for completion axillary node dissection.* American Journal of Surgery, 2005. **190**(4): p. 588-91.
50. Kuijt, G.P., et al., *The prognostic significance of axillary lymph-node micrometastases in breast cancer patients.* European Journal of Surgical Oncology, 2005. **31**(5): p. 500-5.

51. Byers, R.M., et al., *Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue.* Head & Neck, 1997. **19**(1): p. 14-9.
52. Mamelle, G., *Selective neck dissection and sentinel node biopsy in head and neck squamous cell carcinomas.* Recent Results in Cancer Research, 2000. **157**: p. 193-200.
53. Ionna, F., et al., *Prognostic value of sentinel node in oral cancer.* Tumori, 2002. **88**(3): p. May-Jun.
54. Mozzillo, N., et al., *Therapeutic implications of sentinel lymph node biopsy in the staging of oral cancer.* Annals of Surgical Oncology, 2004. **11**(3 Suppl).
55. Doubrovsky, A., et al., *Sentinel node biopsy provides more accurate staging than elective lymph node dissection in patients with cutaneous melanoma.* Annals of Surgical Oncology, 2004. **11**(9): p. 829-36.
56. Bilchik, A.J., et al., *Molecular staging of early colon cancer on the basis of sentinel node analysis: a multicenter phase II trial.* Journal of Clinical Oncology, 2001. **19**(4): p. 1128-36.
57. Smith, F.M., et al., *Sentinel nodes are identifiable in formalin-fixed specimens after surgeon-performed ex vivo sentinel lymph node mapping in colorectal cancer.* Annals of Surgical Oncology, 2005. **12**(6): p. 504-9.
58. Kovacs, A.F., et al., *Sentinel node biopsy as staging tool in a multimodality treatment approach to cancer of the oral cavity and the oropharynx.* Otolaryngology Head & Neck Surgery, 2005. **132**(4): p. 570-6.
59. Bernardi, D., et al., *Treatment of head and neck cancer in elderly patients: state of the art and guidelines.* Critical Reviews in Oncology Hematology, 2005. **53**(1): p. 71-80.
60. Kovacs, A.F., et al., *Pattern of drainage in sentinel lymph nodes after intra-arterial chemotherapy for oral and oropharyngeal cancer.* Journal of Oral & Maxillofacial Surgery, 2005. **63**(2): p. 185-90.
61. Pitman, K.T., *Sentinel node localization in head and neck tumors.* Seminars in Nuclear Medicine, 2005. **35**(4): p. 253-6.
62. Smith, B.D., et al., *Do PET and SNB reduce the rate of elective neck dissection? A hypothesis still in need of validation.* Journal of Clinical Oncology, 2005. **23**(12): p. 2874-5.
63. Yoshida, K., et al., *Immunohistochemical detection of cervical lymph node micrometastases from T2N0 tongue cancer.* Acta Oto Laryngologica, 2005. **125**(6): p. 654-8.
64. Ross, G., et al., *The use of sentinel node biopsy to upstage the clinically N0 neck in head and neck cancer.* Archives of Otolaryngology Head & Neck Surgery, 2002. **128**(11): p. 1287-91.
65. Nieuwenhuis, E.J., et al., *Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node?* Head & Neck, 2002. **24**(3): p. 282-9.
66. Civantos, F.J., et al., *Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry.* Head & Neck, 2003. **25**(1): p. 1-9.

67. Khalifa, K., et al., *The accuracy of intraoperative frozen section analysis of the sentinel lymph nodes during breast cancer surgery.* International Journal of Fertility & Womens Medicine, 2004. **49**(5): p. 208-11.
68. Gipponi, M., et al., *Sentinel lymph node biopsy in patients with Stage I/II melanoma: Clinical experience and literature review.* Journal of Surgical Oncology, 2004. **85**(3): p. 133-40.
69. Tschopp, L., et al., *The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx.* Otolaryngology Head & Neck Surgery, 2005. **132**(1): p. 99-102.
70. Dulguerov, P., I. Leuchter, and W. Lehmann, *Sentinel lymph node radiolocalization in head and neck squamous carcinoma: curious methods.* Laryngoscope, 2001. **111**(10): p. 1866-7.
71. Loree, T.R., *Sentinel lymph node biopsy for early stage clinical n0 squamous cell carcinoma of the oral cavity.* Annals of Surgical Oncology, 2004. **11**(8): p. 725-6.
72. Shah, J.P., *Extent of surgical intervention in case of N0 neck in head and neck cancer patients.* European Archives of Oto Rhino Laryngology, 2004. **261**(6): p. 293-4.
73. Koch, W.M., et al., *Gamma probe-directed biopsy of the sentinel node in oral squamous cell carcinoma.* Archives of Otolaryngology Head & Neck Surgery, 1998. **124**(4): p. 455-9.
74. Shoaib, T., et al., *The accuracy of head and neck carcinoma sentinel lymph node biopsy in the clinically N0 neck.* Cancer, 2001. **91**(11): p. 2077-83.
75. Alex, J.C., et al., *Sentinel lymph node radiolocalization in head and neck squamous cell carcinoma.* Laryngoscope, 2000. **110**(2 Pt 1): p. 198-203.
76. Taylor, R.J., et al., *Sentinel node localization in oral cavity and oropharynx squamous cell cancer.* Archives of Otolaryngology Head & Neck Surgery, 2001. **127**(8): p. 970-4.
77. Werner, J.A., et al., *Number and location of radiolabeled, intraoperatively identified sentinel nodes in 48 head and neck cancer patients with clinically staged N0 and N1 neck.* European Archives of Oto Rhino Laryngology, 2002. **259**(2): p. 91-6.
78. Asthana, S., et al., *Intraoperative neck staging using sentinel node biopsy and imprint cytology in oral cancer.* Head & Neck, 2003. **25**(5): p. 368-72.
79. Ross, G.L., et al., *Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial.[see comment].* Annals of Surgical Oncology, 2004. **11**(7): p. 690-6.
80. Hoft, S., et al., *Sentinel lymph-node biopsy in head and neck cancer.[see comment].* British Journal of Cancer, 2004. **91**(1): p. 124-8.
81. Nieuwenhuis, E.J., et al., *Histopathologic validation of the sentinel node concept in oral and oropharyngeal squamous cell carcinoma.* Head & Neck, 2005. **27**(2): p. 150-8.
82. Payoux, P., et al., *Effectiveness of lymphoscintigraphic sentinel node detection for cervical staging of patients with squamous cell carcinoma of the head and neck.* Journal of Oral & Maxillofacial Surgery, 2005. **63**(8): p. 1091-5.