Is Sentinel Node Biopsy A Better Predictor Of Survival Than Conventional Imaging For Patients With T1/T2 Squamous Cell Cancer Of The Oral Cavity And N0 Neck Disease?: Evidence Based Medicine

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Citation

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Abstract

Predicting the long-term survival of patients diagnosed with oral cavity squamous cell carcinoma who have clinically N0 neck disease is difficult. Traditionally, staging of the neck is performed by physical examination and more recently by the combination of physical exam and the use of conventional imaging studies such as computed axial tomography, ultrasonography or magnetic resonance imaging. These techniques have been shown to be unreliable in detecting very early occult metastatic disease. Sentinel node biopsy (lymphoscintigraphy) is being investigated as tool that would better predict occult neck malignancy in this population. The objective of this study is to document evidence-based information that supports the use of sentinel node biopsy over conventional imaging as a predictor of survival in oral cavity cancer patients with clinically N0 neck disease. An exhaustive literature search targeting evidence-based databases was performed on the topic. After review of the current literature, no sound evidence was discovered to support the use of lymphoscintigraphy over conventional imaging as a predictor of survival in patients with T1/T2 squamous cell carcinoma of the head and neck and N0 neck disease. While this intervention has been found to be reliable in the detection of occult disease, further investigation is needed in the form of randomized clinical trials to appropriately establish this technique as a reliable predictor of survival.

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Abstract of a course paper presented to Nova Southeastern University in partial fulfillment of the requirements for the degree of Doctor of Health Science

INTRODUCTION

Oral cavity lesions represent approximately thirty percent of head and neck malignancies (Shah, Zelefsky & O'Malley, 1999). Most of these malignancies (95%) are squamous cell in origin. In the United States, The American Cancer Society ([ACS], 2006) predicts 34, 360 new oral cavity cancer diagnoses for 2007 and estimates 7, 550 deaths from oral cavity cancer. Oral cavity cancer (and the sequelae of its treatment) presents significant quality of life changes for those afflicted. Early detection and treatment of oral cavity cancer has the potential to both improve quality of life and prolong survival for these patients. Predicting those patients who are at greatest risk for occult metastasis and who need early intervention is a difficult task for the treating clinician. Lymphoscintigraphy (sentinel node biopsy) is being investigated as a promising prognostic tool for these patients.

In squamous cell carcinoma of the head and neck, one of the important prognostic factors for disease specific survival is the presence of involved lymph nodes (Layland, Sessions & Lenox, 2005). Because of this, it is imperative that the presence of occult metastatic disease in clinically N0 necks (node negative) be identified and addressed during the initial evaluation and treatment of the patient. Most head and neck surgeons suggest that if there is a greater than 15% to 20% chance of lymph node metastasis in the neck, as determined by primary tumor pathological indicators, a neck dissection should be performed (Shah, Candela & Poddar, 1990).

Conventional head and neck imaging for metastatic disease

includes ultrasonography, computed axial tomography (CT) and magnetic resonance imaging (MRI). These techniques are not 100% effective in detecting histologically positive metastatic disease (Umeda, Nishimatsu, Teranobu & Shimada, 1998). Sentinel lymph node mapping has been proposed as a technique to increase the identification of occult metastatic disease. This technique has been extensively studied in breast cancer and melanoma but only recently investigated for oral cavity squamous cell carcinoma. The use of sentinel node biopsy in the management of the clinically N0 neck of patients with squamous cell carcinoma of the oral cavity is currently under investigation. Whether this intervention is superior to conventional imaging for detection of occult disease has profound implications for the treatment of oral cavity cancer patients. If occult disease can be detected more accurately with sentinel node biopsy than with conventional imaging without significantly increasing morbidity, the use of this technique could influence treatment planning for this population. Identification of those patients with true-negative neck disease would mean sparing them the possible neck dissection or external beam radiotherapy currently used to treat patients with suspected occult metastatic disease.

A review of the current literature seeking evidence-based data supporting the use of sentinel node biopsy over conventional imaging was done to identify supporting evidence for routine use of sentinel node biopsy in the patient TI/T2 oral cavity cancer patient with clinically staged N0 neck disease.

REVIEW OF LITERATURE

A comprehensive assessment of the literature with emphasis on evidence-based information was conducted. The initial investigation began with an OVID Medline Search. An advanced search using the keywords lymphoscintigraphy, oral squamous cell carcinoma and conventional imaging was performed. Limits of human studies and English language were applied. Next, a manual review of the articles retrieved to ascertain the applicability of the articles was done. Further limits were placed, limiting the studies to randomized controlled trials, meta-analysis and cohort studies. Additionally, a search using the terms sentinel node biopsy, because this term is frequently used interchangeably with lymphoscintigraphy, was performed.

The Cochrane Register of Controlled Trials was searched for any systematic reviews that may have been performed related to oral cavity cancer and the use of sentinel node biopsy and conventional imaging, and none were found. Other sources including Clinical Evidence, Bandolier, ACP Pier, Clinical Evidence, The Agency for Healthcare Research and Quality (AHRQ) and the Center for Evidence Based Medicine were searched utilizing the same keywords and limits. Again, after identifying appropriate articles for review, a manual review of the references of those articles for possible additional sources of information was performed.

Review of the selected articles show that lymphoscintigraphy has promise as a better predictor of occult lymph node metastasis in patients with clinically N0 neck disease than conventional imaging. There are studies which show that lymphoscintigraphy has a small risk of missing disease, thus it is not 100% accurate (Ross, Soutar, Shoaib, Camilleri, MacDonald Robertson, Bessent & Gray, 2002). The identification of positive metastatic lymph nodes in the clinically N0 neck identifies patients who are at risk of regional recurrence and thus are candidates for neck dissection. Early identification of these patients allows the surgeon to perform an appropriate neck dissection, thus giving the patient an increased chance of long-term survival. The studies note significant elements of morbidity associated with lymphoscintigraphy that are not associated with conventional imaging. These morbidities include adverse reaction to isosulfan blue dye and/or the radioactive tracer, additional costs of the procedure and additional operative time. Consideration of costs and morbidity need to be addressed prior to adopting lymphoscintigraphy as a standard of practice in the treatment of T1/T2 oral squamous cell carcinoma patients with a clinically N0 neck.

The one prospective study identified involved forty consecutive patients diagnosed with T1/T2 N0 squamous cell carcinoma of the oral cavity. This study was designed to compare the efficacy rates of palpation, ultrasonography, magnetic resonance imaging (MRI) and lymphoscintigraphy in the detection of occult metastatic disease in that specific population (Thomsen, Sørensen, Grupe, Karstoft & Krogdahl, 2004). The group identified 40 patients, 17 female and 23 male, ages 32 through 90 years of age with T1/T2 N0 squamous cell carcinoma of the oral cavity. The cohort was comprised of 24 T1 and 16 T2 primary oral cancer patients. The investigation began with two examiners staging the neck disease of the participants by palpation. Consensus was required for the patient to be considered N0. The participants were then imaged using MRI with gadolinium contrast. Five

of the forty participants did not undergo MRI due to claustrophobia. The MRI scans of the remaining thirty five were reviewed by one experienced radiologist using specific criteria. Nodes 11 millimeters (mm.) in size in Level II and ten mm. in the remaining levels were considered positive. Other criteria for inclusion as a suspicious node included irregular enhancement of the nodes and matted nodes or conglomerates of two or more nodes. One ultrasonographer performed all of the evaluations. The lymphoscintigraphy images were all read by one nuclear radiologist, and the lymph nodes were pathologically reviewed by one pathologist. All of the nodes identified as positive by lymphoscintigraphy were removed surgically utilizing a modified neck dissection technique. Patients were followed for recurrence of disease for three years at regular intervals.

The investigators found 14 of the 40 patients had metastatic disease, one with bilateral disease. Lymphoscintigraphy correctly identified 11 of the 14 neck positive patients. Three of the patients later developed recurrent disease in the neck. Eighty necks (bilateral) of the forty participants were evaluated by ultrasonography and lymphoscintigraphy, with fifteen of these necks found to have metastatic disease.

Sensitivity and specificity were determined for the all of the techniques. Ultrasonography was found to have a sensitivity of 87% (13/15) and specificity of 85% (55/65). Accuracy was determined to be 85% (68/80). Positive and negative predictive values were determined to be 57% (13/23) and 96% (55/57) respectively.

Magnetic resonance imaging identified nine of seventy necks with suspicious nodes. The sensitivity for MRI was determined to be 36% (5/14) and specificity was found to be 93% (52/56). Accuracy was calculated at 81% (57/70), with positive predictive value (PPV) at 56% (5/9) and negative predictive value (NPV) at 85% (52/61).

Sentinel node biopsy was able to detect positive nodes in 12 necks. The statistics for sentinel node biopsy reveal a sensitivity of 80% (12/15), specificity of 100% (65/65), accuracy rate of 96% (77/80), PPV of 100% (12/12) and NPV of 96% (65/68).

The group concluded that staging by palpation was inadequate. Ultrasound alone was determined to predict too many false positive nodes, and the technique was considered too operator dependent. MRI was found to be less predictive than anticipated, possibly due to the sizing criteria used for identification of suspicious nodes. The researchers also concluded that their observations were consistent with other investigators regarding sentinel node biopsy. Several investigators have stated that SNB has lowered the sensitivity, specificity, accuracy, PPV and NPV for MRI, CT and Pet scans (Civantos, Gomez, Duque, Pedroso, Goodwin, Weed, et al., 2003), (Hamakawa, Takemura, Sumida, Kayahara, Tanioka, and Sogawa, 2002) and (Stoeckli, Steinert, Pfaltz & Schmid, 2002). The authors support the use of sentinel node biopsy combined with ultrasonography to increase the detection of occult nodal metastatic disease in patients with T1/T2 N0 squamous cell carcinoma of the oral cavity.

One meta-analysis addressing the use of sentinel node biopsy for squamous cell cancer of the oral cavity and oral pharynx was found (Paleri, Rees, Arullendran, Shoaib & Krishman, (2005). This meta-analysis examined the sensitivity of sentinel node biopsy (SNB) versus elective neck dissection (END) for detection of metastatic disease. No comparison to conventional imaging was performed. Seventeen prospective studies and three retrospective studies investigating the use of sentinel node identification of occult disease in patients with oral cavity squamous cell carcinoma and N0 necks were also identified and reviewed.

Paleri, et al. (2005), performed a systematic review and diagnostic meta-analysis of all published data regarding sentinel node biopsies in head and neck cancer through December 2003. This group followed guidelines previously recommended by Devillé et al. for the appropriate evaluation of pooled data. These guidelines include formulating an effective search strategy, identification of criteria to be included in the study, assessment of the quality of methodology, performance of data extraction, analysis of pooled data and reporting of methods used to determine heterogeneity and publication bias.

This group identified articles through the use of the key words sentinel node biopsy (SNB) in head and neck squamous cell carcinoma. Their search included reviews of Medline, Embase, Zetoc and conference proceedings. They also contacted regional and international experts in the field for additional information. Finally, a manual review of the references of identified articles was performed. Inclusion criteria identified prior to the review included the following: positive histological diagnosis of mucosal squamous cell carcinoma (SCC), sentinel node identification was to have been performed by any of the standard techniques, surgical harvest of the sentinel node must be done, standard

histopathological assessment must have been performed to assess nodal involvement, neck dissection must be performed regardless of histopathology of the identified sentinel node, patients were to be over the age of sixteen and the data in the article must be sufficient to determine sensitivity and specificity. During the review of the Methods and Materials sections, two of the investigators were blinded to the origin of the article and year of publication. Both investigators reviewed the articles independently for inclusion criteria. Those articles identified as fulfilling the inclusion criteria were then accepted for quality assessment and data extraction. The authors developed quality assessment criteria and subjected all articles to this ordinal scale. The validity of the studies for inclusion was determined by Cochrane recommended guidelines for validity on diagnostic studies. Data extracted from the reviews included demographic and tumor information, technique details, quality assessment scores and numbers of true-positives, true- negatives, false-positive and false-negatives. Information was classified as indeterminate if no sentinel nodes were identified in the cohort. Many of the studies revealed sensitivities of 100%, and because of this, the reviewers utilized the Clopper-Pearson method to pool the sensitivity results. Confidence intervals were generated by using a random-effects logistic regression model. Specificity of 100% (no false-positives), was reported in all studies because a finding of one sentinel node qualified the patient as having regional disease. The authors could not utilize summary receiver operating characteristic curves (ROC) due to the lack of false-positive cases in the studies reviewed.

In the meta-analysis, a total of 153 abstracts were reviewed, and 43 full text articles were identified for further review. Finally, nineteen articles satisfied all criteria for inclusion. Two of the articles included lacked good descriptions of the sentinel node detection technique and histological assessment of the sentinel node was not well described in nine of the studies.

The authors report that ten of the nineteen articles lacked notation of the number of nodes sampled from the neck dissection specimen. Twenty to fifty nodes were reported sampled in eight of the studies and one study reported sampling less than twenty nodes in each neck specimen. . It was noted that none of the studies were blinded, and no indication of bias avoidance was found in any article. All of the articles fulfilled three of the five identified validity criteria.

The diagnostic meta-analysis included 301 patient with oral cavity primary cancers and 46 with oropharyngeal primary tumors (Paleri et al., 2005). One study included twenty patients with oral and oropharyngeal primary tumors, bringing the total of patients included to 367. Articles including laryngeal and hypopharyngeal primaries were excluded on the basis of inability to properly inject the primary site for lymphoscintigraphy or blue-dye identification of metastatic disease. The technique for identifying sentinel nodes in two of the studies was injection of blue dye; the remaining seventeen used radioactive tracer identification.

The identification rate for sentinel nodes was found to be 97.7%, while the mean number of nodes removed per person was 1.6. The authors noted a wide variation in the amount of radioactive tracer used in the studies. The dosage used was not correlated to either the number or nodes removed or the identification rate.

The authors developed a forest plot to show the sensitivity of each study and its confidence interval (CI). They determined the results to be homogeneous enough to pool the data. Only one article noted no true-positive or false-positive cases, thus no sensitivity and specificity information was determined for that data. Pooled data included only the remaining eighteen studies. The authors report that no publication bias was noted in any of the studies.

A decision analysis tree was developed to compare the pooled SNB data and known data regarding elective neck dissection (END), looking at disease free survival rates.

After review of the data comparing the results of SNB to END and their role in predicting recurrence and mortality, the authors concluded that SNB was slightly (1%) less effective than END in these roles. This information provides basis for further study of SNB and its role in improving survival and reducing morbidity in patients with oral squamous cell carcinoma and clinically N0 neck disease.

One multi-center trial was identified (Ross, Soutar, MacDonald, Shoaib, Camilleri, Roberton, et al., 2004). The authors of this trial sought to determine the reliability and reproducibility of sentinel node biopsy as a staging tool in patients with head and neck squamous cell carcinoma, clinically staged T1/2 N0. The authors did not compare conventional imaging to sentinel node biopsy in this trial.

The study reports the result of 227 SNB performed at six centers from June 1998 through June 2002. The authors identified patients with 134 T1/T2 primary oral cavity/oropharyngeal tumors and clinically N0 neck disease. The patients underwent preoperative lymphoscintigraphy and intra-operative use of isosulfan blue-dye/ gamma probe identification of sentinel nodes. Pathological confirmation was performed using step serial sectioning and immunohistochemistry identification of disease. Follow-up of these patients was reported to be at least 12 months. The authors identified 79 cases where SNB alone was used to stage the neck and 55 cases where SNB was used in combination with elective neck dissection.

Results revealed a 93% (125/134 cases) rate of sentinel node identification. Fifty nine of the positive nodes were identified by intra-operative gamma probe and forty-four were identified by isosulfan blue dye. The authors concluded that SNB can be successfully utilized in T1/T2 oral cavity cancer patients to identify occult disease. This study did note the clinical methods of staging of the neck disease. Techniques identified were standard palpation (physical exam), positron emission tomography (PET), or computed tomography (CT). This information was not compared to SNB in the final report.

Three retrospective reviews of SNB in patients with oral cavity SCC were identified. These studies addressed the role of SNB in accurately identifying metastatic neck disease. Tao, Lefèvre, Callard, Périé, Bernaudin & St. Guily (2006), surmise that identification of atypical patterns of lymphatic drainage by lymphoscintigraphy could direct the treatment of patients undergoing neck dissection for oral cavity cancer; they did not address conventional imaging in their retrospective review. Sentinel node biopsy as an alternative technique in neck staging for oral cavity cancer was investigated by Shoaib, Soutar, MacDonald, Gray, and Ross (2005). They confirmed variability of lymph node drainage in head and neck oral cavity lesions. This variability is often not addressed in the standard neck dissection techniques for the specific oral cavity cancer sites. Sentinel node biopsy was determined to identify atypical drainage patterns, thus offering more specific identification of metastatic disease, possibly leading to decreased morbidity and increased long-term survival. This group also did not include conventional imaging in their investigation.

Minamikawa, Umeda, and Komori (2005) reviewed the role of SNB and the identification of “skip metastasis” in oral cavity SCC. No mention of conventional imaging was noted in their study. Their retrospective review concluded that SNB was useful as a technique for identification of metastatic disease and that further investigation of the technique is warranted to provide patients with a reliable technique to identify metastatic disease, thus possibly influencing long-term survival and the morbidity of extensive surgical resection.

Seventeen articles were identified that addressed SNB and oral cavity squamous cell carcinoma. Of these, eleven studies specifically included the use of clinical identification of suspicious lymphadenopathy by palpation, ultrasonography (US), computed axial tomography (CT), or magnetic resonance imaging (MRI). The remainder of the articles used palpation of the neck as the primary method of staging.

Rigual, Douglas, Lamonica, Wiseman, Cheney, Hicks and Loree (2005) studied 20 patients with T2N0 oral cavity malignancies. The neck staging in these patients consisted of physical exam (palpation) and CT imaging. All patients were evaluated by standard SNB techniques, and all patients underwent neck dissection. Sentinel nodes were identified in all 20 patients. Ten of the twenty patients enrolled were up-staged by SNB, indicating that conventional imaging failed in 50 % of the patients. This study found the sensitivity of SNB to be 83% and the specificity to be 100%. The occult regional metastatic rate was determined to be 60% in this cohort. The authors concluded that SNB was accurate and feasible in the accurate staging of patients with T2N0 SCC of the oral cavity.

In 2005, Payoux, Dekeister, Lopez, Lauwers, Esquerré, and Paoli reported their review of 30 previously untreated patients with T1-T4 SCC of the oral cavity or oropharynx with clinically N0 necks. The patients necks were staged by palpation and iodine contrast CT. These patients underwent sentinel node identification followed by neck dissection for a total of 30 patients and 37 necks. Pathological evaluation revealed seven patients (25%) with metastatic disease. The authors reported a sensitivity of 86%. These authors also recommended further prospective, randomized clinical trials.

The team of Stoeckli, Steinert, Pfaltz and Schmid (2001) evaluated 19 patients with histologically confirmed SCC of the oral cavity. Neck staging was performed by palpation and CT imaging studies. These patients also received neck dissections. This group reported a 32% incidence of occult

metastasis detected by SNB.

In 2005, a prospective study involving 20 patients with N0 squamous cell carcinoma of the head and neck was reported by Hart, Nasser, Trites, Taylor, Bullock, and Barnes. The neck staging included physical examination and CT imaging. Tumors were staged T1-T4. Resection of the primary tumor was followed by neck dissection. Review of the pathological neck dissections reveals metastatic disease in 4 of the 20 patients (20%). The histological results of the sentinel nodes were compared with the results of the neck dissection results, revealing a 100% negative predictive value. This means that in no instance was a sentinel node found to be negative and the corresponding neck dissection found to harbor disease. The authors found SNB to be a promising predictor of occult metastatic disease in the clinically N0 neck of patients with SCC of the oral cavity.

The use of sentinel node biopsy as an adjunct surgical tool in SCC of the oral cavity was investigated by Kovács, Landes, Hamscho, Risse, Berner, and Menzel, 2005. Thirty nine patients with oral and oropharyngeal SCC and N0 necks were evaluated by SNB. No elective neck dissection was performed after the biopsy. The neck staging prior to SNB included physical exam, CT of the head and neck and positron emission tomography (FDG-PET). Only those patients with FDG-PET negative scans were enrolled in the SNB study. This study included intra-arterial infusion of chemotherapy prior to SNB. Due to the addition of this treatment modality, the results of the study are not comparable to the studies investigating SNB followed by neck dissection. The authors in this convoluted investigation concluded that SNB instead of neck dissection may have a role staging of oral cavity SCC neck disease.

Civantos, Gomez, Duque, Pedroso, Goodwin, Weed, Arnold and Moffat (2003) were among the earliest to investigate the possibility of using SNB for stage the clinically N0 neck. They report a study involving 18 patients with oral cavity cancer staged T1-T3. The clinical neck staging was done using conventional physical examination, CT and PET imaging. The patients all underwent SNB followed by neck dissection. The authors reported that the PET scan evaluation in their study failed to identify significant replacement of nodes by tumor, and it also failed to reveal the presence of a second primary papillary carcinoma of the thyroid identified in the neck tissue specimen. The authors revealed that a total of ten true-positive nodes were identified by SNB. Seven true-negative findings were also confirmed. One false-negative sentinel node was identified in eleven true-positive necks, for a false-negative rate of 9.1% or a sensitivity of 80.9%. The small study size hampered true statistical determination of sensitivity. This study did report the presence of a false-negative node on SNB that was found to be pathologically positive on histological review. This node was completely replaced with tumor and the authors surmise that this contributed to the lack of normal lymphatic architecture to adequately take up radioactive material. This group also recommends further study before recommending SNB as routine staging for occult neck metastasis in the clinically negative neck.

Kontio, Leivo, Leppänen and Atula (2004) investigated the use of SNB in fifteen previously untreated oral cavity SCC patients with clinically N0 neck disease. Their primary tumors were staged T1 or T2. Neck disease was documented by physical examination, MRI or CT imaging. All received planned neck dissection after sentinel node identification. The results of the investigation revealed a 20% (three of fifteen patients) incidence of occult malignancy. One false-negative SLN was found in the group studied. This group also noted that not all reported studies of sentinel node identification utilized both injection of blue dye and radioactive material. More investigations utilizing standardized techniques are required before a definitive endorsement of SNB can be done.

Khafif, Schneebaum, Fliss, Lerman, Metser, Ben Yosef, Gil, Reider-Trejo, Genadi and Even-Sapir (2006) recently investigated the use of fused single photon emission computed tomography (SPECT) and low-dosed CT imaging compared to planar imaging in sentinel node mapping of patients with oral cavity squamous cell carcinoma. All patients (20) were newly diagnosed with SCC of the oral cavity and were evaluated with SNB followed by neck dissection. The N0 neck was staged by the use of physical exam, ultrasound imaging, CT or MR imaging. The day prior to surgery, the patients underwent lymphoscintigraphy utilizing planar imaging techniques. They were then evaluated using SPECT /CT study and the images were then fused. Standard sentinel node identification with a gamma probe was conducted intra-operatively. The use of blue dye was also incorporated in the study of the lymphatic drainage. Intra-operatively, all patients had identifiable nodes by lymphoscintigraphy. After histological examination of the neck dissection specimens, the overall accuracy of SNB was assessed at 95% and the sensitivity for detection of occult

metastatic disease was assessed as 87.5% or 7/8 patients. For oral tongue and floor of mouth patients the sensitivity was assessed as 100% (7/7 patients). One patient with a primary tumor in the retromolar trigone was found to have a nodal metastasis that was not detected on SNB. The added use of fused SPECT/CT images was found to improve pre-operative identification and localization of sentinel nodes prior to SNB in this cohort. These authors advocated further investigation of SNB and fused SPECT/CT in the identification of occult metastatic disease in patients with oral cavity SCC.

Also investigating the use of SPECT/CT in the pre-operative evaluation of the clinically N0 neck of oral cavity SCC patients are Lopez, Payoux, Gantet, Esquerré, Boutault and Paoli (2004). Their study included 10 oral cavity cancer patients with N0 staged necks. Neck disease was clinically staged by physical exam and CT imaging. Tumors were staged T1– T3. Prior to surgery, planar lymphoscintigraphy was performed, followed by SPECT/CT. The sensitivity of the planar imaging was assessed to be 100%, and all pre-operatively detected sentinel nodes were confirmed by sentinel node lymphoscintigraphy. The hand-held gamma probe detected 90% of the sentinel nodes. The study revealed only one false-negative result upon histologic evaluation. Ninety percent of the resected nodes had previously been detected by planar images. This study promotes the use of SPECT/CT imaging to aide in the detection of occult metastatic disease.

Gallegos-Hernandez, Hernandez-Hernandez, Flores-Diaz, Sierra-Santiesteban, Pichardo-Romero, Arisa-Ceballos, Minauro-Munoz and Alvarado-Cabrero (2005) present their non-randomized prospective study of 48 patients with oral cavity cancer and clinically staged N0 necks. The false-negative rate for their study was reported as 17.3%, with the possibility of false-negative results in patients with tumors greater than two centimeters. The authors recommend a dual approach of dye and lymphoscintigraphy with radio colloid as useful in identifying occult metastatic disease in oral cavity cancers.

After extensive review of the identified literature, there are no clear indications that sentinel node biopsy is a better predictor of survival in oral cavity cancer patients with clinically staged N0 neck disease than conventional imaging. The studies reviewed were a mixture of small, prospective trials and retrospective reviews with no large randomized-controlled clinical trials. The prospective trials were not uniform in their approach to investigation of sentinel node identification. Some utilized multiple oral cavity sites and others single sites. The techniques of sentinel node identification were not standardized. Clinical staging of the neck disease was not consistent. The one meta-analysis identified did not compare sentinel node identification and conventional imaging studies. The current literature suggests that sentinel node biopsy is a significant tool for use in the investigation of occult neck disease in the patient with oral cavity squamous cell carcinoma with clinically node negative neck disease. Investigation using randomized-controlled clinical trials comparing conventional imaging studies of CT, MRI and ultrasound will need to be conducted prior to definitively recommending the use of sentinel node biopsy over conventional imaging to predict occult metastatic disease in patients with clinically N0 neck disease.

METHODOLOGY AND PROCEDURES

METHODOLOGY

The search strategy for the clinical question began with an OVID Medline Search. This incorporated the use of the advanced search tab and the medical subject heading (MeSH) keywords lymphoscintigraphy and oral squamous cell carcinoma. The Boolean AND was used to combine these keywords. The limits of human studies and English language were applied. Further limits were placed on publication types, limiting the studies to clinical trials, randomized controlled trials, and meta-analysis. Additionally, the literature search was performed using the terms sentinel node biopsy, because this term is frequently used interchangeably with lymphoscintigraphy. A preliminary search revealed sixty-six articles, with twenty-two remaining after applying the limits. The selected articles were reviewed to ascertain the applicability of the articles to the clinical question. Only one article was identified that specifically compared conventional imaging techniques and sentinel node biopsy in patients with T1/T2 oral cavity squamous cell carcinoma an N0 neck disease.

The Cochrane Register of Controlled Trials was searched to identify any systematic reviews that may have been performed related to sentinel node biopsy and oral squamous cell carcinoma and conventional imaging. Additionally, the Pub Med data base was searched for articles using the keywords sentinel node biopsy, oral cavity cancer, squamous cell carcinoma of the oral cavity and lymphoscintigraphy. Limits placed on the search again included human studies,

English language, clinical trials, randomized controlled trials and meta-analysis.

Other sources including Clinical Evidence, Bandolier, ACP Pier, Clinical Evidence, The Agency for Healthcare Research and Quality (AHRQ) and the Center for Evidence Based Medicine were searched utilizing the same keywords and limits. Again, after identifying possible data for review, a manual review the references of those articles for possible additional sources of information was performed.

PROCEDURES

The comprehensive literature review was performed with an emphasis on evidence-based information pertaining to the predictive value of sentinel node biopsy in patients with T1/T2 oral cavity squamous cell carcinoma and clinically staged N0 neck disease. The search targeted the highest levels of clinical evidence, meta-analysis, randomized controlled clinical trials and clinical trials. One article was identified specifically investigating the predictive value of conventional imaging as compared to sentinel node biopsy in the target population.

Also identified were one meta-analysis, one multi-centered trial, seventeen prospective clinical trials and three retrospective clinical trials investigating sentinel node biopsy in the target population. All of this information was then carefully reviewed using criteria applicable to prognostic literature. The results of the studies were scrutinized for validity. Inclusion and exclusion criteria were noted as was the possibility of selection bias. Next, follow-up in each study was determined and compared. Prognostic factors pertinent to oral cavity cancer survival were noted and the studies were reviewed for proper adjustment for these factors. The outcomes of the studies were reviewed for objectivity and bias.

The information was reviewed for clinical applicability to commonly presenting (T1/T2) oral cavity cancer patients. The studies were evaluated for their similarity in demographics, severity and co-morbidities. Finally the results were reviewed for their applicability to patient care. The underlying question addressed was, “Is sentinel node biopsy a better predictor of survival in patients with T1/T2 oral cavity cancer with N0 neck disease when compared to conventional imaging studies?”

DISCUSSION

The use of sentinel node biopsy or lymphoscintigraphy in the patient with squamous cell carcinoma of the oral cavity was first described in 1996 by Alex and Krag (Alex & Krag, 1996). Since then, this technique has been used by many to identify possible occult metastatic disease in oral cavity cancer patients with clinically N0 neck disease. Detecting occult disease in the clinically N0 neck has significant implications in determining survival for those patients affected. Although primary tumor related factors (size, depth of invasion, site of primary) are taken into account when determining survival and treatment, the presence of occult metastasis is also significant in predicting survival.

It has been noted that in patients screened with physical examination and/or conventional methods of imaging, (CT and MRI), that there remains a 20-30% chance of occult metastasis. The standard of care used by many practitioners is to treat those patients with a 15 % to 20% or greater risk of occult disease as determined by the pathological parameters of the primary tumor. The treatment options available include neck dissection, external beam radiotherapy, combined surgery and radiotherapy and “watch and wait”. The associated morbidity with surgery and radiotherapy are weighed against the possibility of recurrent disease. Thus, many patients and their clinicians will chose active treatments which have significant morbidity. Using the technique of sentinel node biopsy to detect occult disease in these patients could potentially reduce the morbidity associated with treatments and be a better predictor of long-term survival than conventional imaging alone.

A search for evidence-based literature to support the use of sentinel node biopsy as a better predictor of survival than conventional imaging in this patient population yields only one prospective trial comparing the efficacy of conventional imaging to lymphoscintigraphy in staging N0 oral cavity cancers (Thomsen, Sørensen, Grupe, Karstoft, and Krogdahl, 2004). Also identified were one meta-analysis and one multi-center trial, and neither of these specifically addressing comparisons between the two. There are numerous prospective and several retrospective trials addressing sentinel node biopsy in the target population. The identified information was reviewed carefully using criteria appropriate for review of prognostic literature. Validity of all the results was compared and possible areas of bias were noted. The studies were evaluated as to their applicability to commonly presenting patient populations. The demographics, tumor specific information, and types of

imaging were also noted and reviewed. Many of the studies had small population sample sizes. Others used one or more primary tumor sites or included pharyngeal tumors in their studies. None of the studies consistently utilized one specific modality of imaging, and many used several methods to determine N0 status. The sentinel node biopsy techniques were not standard across the literature. Some investigators utilized isosulfan blue dye identification and radio-labeled colloids while others used only radio-labeled substances.

After comparison of the literature, no clear evidence-based information was located to support the use of sentinel node biopsy over conventional imaging when determining survival in T1/T2 oral cavity cancer patients with N0 necks. There is preliminary evidence supporting the use of sentinel node biopsy in this population, but further investigation including well developed randomized controlled trials will be needed. Because of the nature of the outcomes (recurrent or metastatic disease), randomized controlled trials may not be feasible in this population. Many patients would not be willing to be randomized to a "wait and see" arm, weighing the possibility of occult disease.

In their prospective trial, Thomsen and associates evaluated forty consecutive patients diagnosed with T1 or T2 oral cavity cancers and N0 necks. They evaluated the positive and negative predictive values of manual neck palpation, ultrasonography, magnetic resonance imaging and lymphoscintigraphy in the identification of occult metastatic disease. They concluded that lymphoscintigraphy combined with Doppler ultrasonography could improve the detection of occult disease in this patient population.

The one meta-analysis of the current literature compared the use of sentinel node biopsy to elective neck dissection (Paleri et al., 2005). The results slightly favored neck dissection (1%) over sentinel node biopsy in predicting survival. To date, only one study has been located addressing conventional imaging versus sentinel node biopsy. Until evidence-based studies can be devised to assess whether sentinel node biopsy can improve survival, no evidence-based recommendation for sentinel node biopsy over conventional imaging for detection of occult disease can be made.

CONCLUSION

The use of sentinel node biopsy for the detection of occult metastatic disease in patients with T1/T2 oral cavity squamous cell carcinoma is relatively recent. Large scale, randomized controlled trials have not been performed documenting the efficacy of this technique in predicting survival. Only one meta-analysis investigating the use of sentinel node biopsy versus elective neck dissection in determining occult disease has been performed. This analysis only slightly favored elective neck dissection over sentinel node biopsy for detection of occult neck disease. No controlled studies have been performed investigating the prognostic value of conventional imaging over sentinel node biopsy in terms of patient survival.

The review of the available literature reveals that sentinel node biopsy may be slightly better at predicting occult metastatic disease than conventional imaging. No properly conducted trials, utilizing standardized methods have been conducted to conclusively determine that sentinel node biopsy is a better predictor of survival than conventional imaging in oral cavity cancer patients with clinically N0 neck disease. The options for patients with clinically staged N0 neck disease include elective neck dissection and/or post operative external beam radiotherapy. Both of these interventions offer treatment for occult metastatic disease with significant morbidity. These associated morbidities range from cosmetic deformity, functional changes including xerostomia and decreased muscle function to osteoradionecrosis. It is because of these associated morbidities that further studies should be designed to definitively address the routine use of sentinel node biopsy for detection of occult metastatic disease in the oral cavity cancer patient with N0 neck disease.

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