
DIAGNOSTIC EVALUATION OF SQUAMOUS CELL CARCINOMA METASTATIC TO CERVICAL LYMPH NODES FROM AN UNKNOWN HEAD AND NECK PRIMARY SITE

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Abstract: *Background.* The purpose of this study was to evaluate the efficacy of the modern diagnostic evaluation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site.

Methods. One hundred thirty patients were evaluated between June 1983 and June 1997. All underwent head and neck examinations, head and neck computed tomography (CT), and/or magnetic resonance imaging (MRI) scans, panendoscopies, and biopsies of head and neck mucosal sites. Twenty-four patients underwent 2-[fluorine-18]-2-deoxy-D-glucose (FDG) single photon emission computed tomography (SPECT); 34 patients underwent tonsillectomy.

Results. The primary site was identified in 56 patients (43%); the likelihood was increased in patients with suggestive findings on physical examination and/or radiographic evaluation. Eighty-three percent of the lesions were located in the tonsillar fossa and base of tongue. Results of FDG-SPECT scans were positive in 20 patients (83%); the primary tumor was detected in 7 patients (35%). Twelve (35%) of 34 patients who underwent tonsillectomy had a primary tumor discovered in the tonsillar fossa. Multivariate

analysis of successful primary site detection revealed that suggestive findings on physical examination ($p = .0225$) and suggestive findings on CT and/or MRI ($p = .0013$) were significantly related to this end point.

Conclusion. The primary lesion will be detected in over 40% of patients with physical examination of the head and neck and CT and/or MRI followed by panendoscopy and biopsies. Limited data pertaining to FDG-SPECT suggest that this provides additional useful information in a small subset of patients. Tonsillectomy is useful for those with suggestive findings on physical examination and/or radiographic evaluation. © 1998 John Wiley & Sons, Inc. *Head Neck* 20: 739–744, 1998.

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Cervical adenopathy is a relatively common presenting complaint for patients with squamous cell carcinoma of the head and neck. The primary lesion will be discovered on history and physical examination in the majority of these patients.^{1,2} Martin and Morfit¹ described a series of 218 patients with cervical lymphadenopathy seen at Memorial Hospital (New York) between 1933 and

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1937; the primary tumor was discovered by the referring physician in 57 patients (26%), at the first evaluation in the admitting office at Memorial Hospital in 56 patients (26%), and within 1 to 2 weeks after multiple physical examinations in 34 patients (16%). Similarly, Jones et al,² from the University of Liverpool, reported a series of 267 patients with squamous cell carcinoma of the head and neck with cervical lymphadenopathy; the primary tumor was found on history and physical examination in 148 patients (55%).

The optimal diagnostic evaluation¹⁻⁵ and management⁶⁻⁹ for the remaining subset of patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site is controversial. In the managed care environment, decisions pertaining to these issues increasingly fall within the purview of the primary care physician. Martin and Morfit¹ recommended a fine needle aspiration (FNA) of the enlarged lymph nodes; they suggested that open biopsy, preferably excisional, be performed only after multiple unsuccessful attempts to locate the primary site on physical examination and two or more negative FNAs. Thereafter, most clinicians recommended panendoscopy with directed biopsies of various head and neck mucosal sites.^{2-5,9,10}

In recent years, use of computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck before panendoscopy has been advocated.^{4,11} There is relatively little information regarding the yield of these diagnostic procedures in determining the primary site, and several questions remain: (1) How useful is CT and/or MRI of the head and neck? (2) What is the role of metabolic studies such as a 2-[fluorine-18]-2-deoxy-D-glucose (FDG) single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging?¹¹ (3) What is the yield of panendoscopy with directed biopsies following a modern radiographic workup? (4) Should routine ipsilateral tonsillectomy be performed?^{4,12,13} (5) Where are the primary lesions located?

METHODS

Between June 1983 and June 1997, 130 patients with squamous cell carcinoma metastatic to the cervical lymph nodes from an unknown head and neck primary site were evaluated at the University of Florida College of Medicine. One hundred twelve patients (86%) were men and 18 patients (14%) were women. The mean age was 58.7 years

(range, 33 to 84 years). Patients were not eligible for the study if they exhibited one or more of the following: (1) tumor in the supraclavicular or low internal jugular lymph nodes, (2) primary tumor diagnosed before referral, (3) primary site detected on physical examination at the University of Florida, (4) inadequate diagnostic evaluation, (5) histology other than squamous cell carcinoma, (6) cervical adenopathy secondary to a previously diagnosed primary cancer, (7) prior treatment.

Patients with low neck presentations were not included because of the high likelihood that the primary tumor was located below the clavicles. An adequate diagnostic evaluation was defined as history and physical examination including a comprehensive head and neck examination, CT and/or MRI of the head and neck, chest radiograph, and panendoscopy with directed mucosal biopsies. Biopsy of the neck mass (153 procedures) was performed in 124 patients: FNA, 83 patients; core needle biopsy, 10 patients; incisional biopsy, 11 patients; excisional biopsy, 47 patients; neck dissection, 2 patients. The first biopsy procedure was an incisional biopsy in 8 patients and excisional biopsy in 27 patients; essentially all were performed before referral to the University of Florida. Six patients did not undergo a neck biopsy. Distribution according to the 1983 American Joint Committee on Cancer (AJCC) neck stage¹⁴ was as follows: N_{EXC}, 10 patients (8%); N1, 19 patients (15%); N2A, 26 patients (20%); N2B, 30 patients (23%); N3A, 29 patients (22%); N3B, 16 patients (12%). No patient had evidence of distant metastases at diagnosis.

Patients with head and neck cancer who are referred to the University of Florida are routinely presented at a weekly head and neck tumor conference attended by otolaryngologists, radiation oncologists, plastic surgeons, diagnostic radiologists, pathologists, and dental oncologists. The pathologic slides and radiographic studies are reviewed, and the patients undergo one or more head and neck examinations (in addition to the one[s] performed by the initial attending physician).

Patients were stratified into two groups based on the findings of head and neck examination: no apparent primary site, 98 patients (75%); and suspected primary site, 32 patients (25%). If there was a discrepancy in the attending physicians' impressions before, compared with after, review of the radiographic studies, the former were scored because they were not biased by the radiographic findings. Patients who underwent CT

and/or MRI scans before referral had the studies repeated if they were thought by the attending diagnostic radiologist to be suboptimal. One hundred twenty-nine patients (99%) underwent one or more CT scans of the head and neck, whereas 18 patients (14%) underwent MRI scans, reflecting the institutional bias that the former is more useful in the evaluation of the unknown primary site. Twenty-four patients (18%) underwent FDG-SPECT scans; all were performed at the University of Florida during the latter years of the study. Radiographic studies were scored as either "no primary site apparent" or "suggestive of a primary tumor."

Patients who underwent an adequate panendoscopy with directed biopsies before referral did not undergo repeat endoscopy. However, if panendoscopy was thought to be suboptimal or if a suspect site was not biopsied at the initial procedure, it was repeated one or more times. The numbers of panendoscopies and/or direct laryngoscopies performed were: one, 90 patients (69%); two, 38 patients (29%); and three, 2 patients (2%). Tonsillectomy was performed at the time of panendoscopy in 34 patients (26%). The decision to perform tonsillectomy varied with the following variables: the attending physician, the degree of suspicion that the primary site was in the tonsillar fossa, likelihood that a positive biopsy could be obtained without performing a tonsillectomy, and presence of enough tonsillar tissue to warrant tonsillectomy.

A multivariate analysis of variance using the

method of least squares to fit general linear models was performed for the end point of successful primary site identification.^{15,16} The following variables were included in the analysis: suggestive findings on physical examination, suggestive findings on CT and/or MRI scan, suggestive findings on FDG-SPECT scan, number of panendoscopies and/or direct laryngoscopies (1 versus ≥ 2), and tonsillectomy (performed or not performed). A modified chi-square test or Fisher's exact test was used to determine the statistical difference between proportions.^{17,18}

RESULTS

The relationship between biopsy-proven cancer from a head and neck primary site and findings on physical examination and radiographic evaluation, prior to surgical endoscopy, is shown in Table 1. Fifty-eight primary lesions were found in 56 patients (43%); the likelihood of successfully detecting the primary site was higher for patients with suggestive findings on physical examination and/or radiographic workup. The likelihood of successfully detecting the primary site was similar in patients taken back for a second or third panendoscopy (16 of 40, or 40%) compared with those who underwent one panendoscopy (40 of 90, 44%). The primary sites included tonsillar fossa, 25 (43%); base of tongue, 23 (39%); pyriform sinus, 5 (9%); posterior pharyngeal wall, 2 (3%); lateral pharyngeal wall, 1 (2%); vallecula, 1 (2%); and lingual surface of the suprahyoid epiglottis, 1 (2%). The two patients who had synchronous pri-

Table 1. Biopsy-proven primary site versus physical and radiographic findings and number of panendoscopies.

Patient group	No. of patients with biopsy-proven primary site/no. patients evaluated*			Total no. patients (%)
	No. of panendoscopies			
	1	2	3	
PE⌀/Rad⌀	6/34 (18%)	0/7	1/1	7/42 (17%)
PE⌀/Rad⊕	19/34 (56%)	9/21 (43%)	1/1	29†/56 (52%)
PE⊕/RAD⌀	4/6	1/3	No data	5/9 (56%)
PE⊕/RAD⊕	11/16 (69%)	4/7	No data	15‡/23 (65%)
Total	40/90 (44%)	14/38 (37%)	2/2	56/130 (43%)

*Significance levels: 7/42 versus 34/65, $p = .00023$; 7/42 versus 15/23, $p = .00012$; 34/65 versus 15/23, $p = .20413$.

†One of 29 patients had a positive 2-[fluorine-18]-2-deoxy-D-glucose (FDG) single photon emission computed tomography (SPECT) scan and a negative computed tomography (CT) of the head and neck; the remaining 28 patients had a positive CT and/or magnetic resonance imaging (MRI) scan.

‡Two of 15 patients had a positive FDG-SPECT scan and a negative CT of the head and neck; the remaining 13 patients had a positive CT and/or MRI scan.

Key: PE \emptyset = no suggestive findings on physical examination; PE \oplus = suggestive of a primary site but not definitely positive; RAD \emptyset = no suggestive findings on radiographic studies; RAD \oplus = radiographic studies suggestive of primary site.

mary tumors had lesions of the base of tongue and pyriform sinus, and base of tongue and tonsillar fossa, respectively.

The relationship between successful detection of the primary site and findings on FDG-SPECT scan is depicted in Table 2. Twenty (83%) of 24 patients had positive scans; the primary tumor was discovered in 7 (35%) of 20 patients. Six (86%) of the 7 patients had suggestive findings on physical examination and/or CT or MRI scans; 1 patient had a negative head and neck examination and radiographic workup (other than the positive FDG-SPECT scan). Four patients had suggestive findings on physical examination and/or CT/MRI and a negative FDG-SPECT scan; the primary tumor was discovered in 2 of 4 patients.

The relationship between biopsy-proven tumor in the tonsillar fossa and findings on physical examination and radiographic workup is shown in Table 3 for the subset of patients who underwent a tonsillectomy. Twelve of 34 patients (35%) had a primary tumor in the tonsillar fossa; the incidence was higher for those with suggestive findings in the tonsil before direct laryngoscopy.

Multivariate analysis of successful detection of the primary site revealed that suggestive findings on physical examination ($p = .0225$) and suggestive findings on CT and/or MRI of the head and neck ($p = .0013$) were significantly related to this end point. Positive FDG-SPECT scan ($p = .2733$), number of panendoscopies ($p = .3413$), and whether or not a tonsillectomy was performed ($p = .8248$) were not significantly predictive of primary site detection.

DISCUSSION

Cervical adenopathy secondary to metastatic squamous cell carcinoma from an unknown head

Table 2. Biopsy-proven primary site versus 2-[fluorine-18]-2-deoxy-D-glucose (FDG) single photon emission computed tomography (SPECT) findings (no. of patients with biopsy-proven primary site/no. of patients having FDG-SPECT study).

Patient group	FDG-SPECTØ	FDG-SPECT⊕
PEØ/RADØ	No data	1/5*
PE⊕ and/or RAD⊕	2/4	6†/15* (40%)
Total	2/4	7/20 (35%)

* $p = .4058$.

†Two of 6 patients had a positive FDG-SPECT, a negative head and neck CT, and suggestive findings on physical examination.

Key: FDG-SPECTØ = no evidence of a primary site; FDG-SPECT⊕ = findings suggestive of a primary site; PEØ/RADØ = no evidence of a primary site on physical examination or radiographic studies; PE⊕ and/or RAD⊕ = findings suggestive of a primary site on physical examination, radiographic studies (CT and/or magnetic resonance imaging), or both.

Table 3. Biopsy-proven primary site in the tonsillar fossa after tonsillectomy versus physical and radiographic findings.

Patient group	No. of patients with biopsy-proven primary site in tonsillar fossa/no. patients having tonsillectomy
PEØ/RADØ	1/10 (10%)
PE⊕ and/or RAD⊕	11/24 (46%)
Total	12/34 (35%)

Key: PEØ/RADØ = no evidence of a primary site on physical examination or radiographic studies; PE⊕ and/or RAD⊕ = findings suggestive of a primary site on physical examination, radiographic studies (computed tomography and/or magnetic resonance imaging), or both.

and neck squamous cell carcinoma is relatively uncommon. There are few data pertaining to the likelihood of successful detection of the primary site, particularly since the availability of CT and MRI scans. Following is a discussion of our data and the pertinent literature relative to this entity.

CT and/or MRI of the Head and Neck. Muraki et al¹⁹ reported a series of 12 patients with squamous cell carcinoma from an unknown head and neck primary site who were evaluated at the University of Utah. The primary site was successfully identified in four patients (33%). Computed tomography and/or MRI correctly identified the primary site in 28 (50%) of 56 patients evaluated at the University of Florida who had no suggestive findings on physical examinations. Because MRI was obtained in a small subset of patients either before referral or in the case of equivocal findings on CT, it is not possible to compare the efficacy of MRI versus CT as the primary imaging modality.

Metabolic Imaging Studies. Although a relatively small subset of our patients underwent FDG-SPECT as part of the diagnostic evaluation, there are almost no other published data. It appears that FDG-SPECT identifies a small subset of primary lesions that are not apparent on physical examination and/or radiographic evaluation with CT and/or MRI. However, the majority of patients tested had positive FDG-SPECT scans, and most who had the primary site detected also had suggestive findings on physical examination and/or CT or MRI scans. Based on the limited data available, the value of FDG-SPECT is very modest.

Valdes Olmos et al²⁰ reported nine patients with head and neck cancer from an unknown primary site who underwent thallium-201 SPECT scans in addition to CT and/or MRI of the head

and neck. The thallium-201 SPECT scans were positive in six patients and negative in three patients; the primary site was successfully detected in five of six patients with positive scans. The authors suggested that thallium-201 SPECT imaging was a useful adjunct to CT and/or MRI in the detection of the unknown primary site.

Surgical Endoscopy. It is difficult to determine the yield of surgical endoscopy (ie, direct laryngoscopy, panendoscopy) following physical examination of the head and neck but without CT or MRI of the head and neck. Jones et al² described 267 patients with neck nodes containing squamous cell carcinoma who were evaluated at the University of Liverpool between 1963 and approximately 1992. The primary lesion was detected by history in 7 patients (3%); physical examination, 141 patients (53%); radiography, 10 patients (4%); and panendoscopy, 44 patients (16%); it appeared "later" in 22 patients (8%), was found postmortem in 7 patients (3%), and was never found in 36 patients (13%). Although not clearly stated, CT and/or MRI of the head and neck was not routinely obtained, and 9 of 10 patients who had the primary lesion detected radiographically had lung cancer. Additionally, 29 patients (11%) had supraclavicular adenopathy, and 25 patients (9%) had received previous treatment. Despite this, 44 of 109 patients (40%) who had no evidence of a primary tumor after history and physical examination had the primary tumor detected on panendoscopy. However, the most common sites were nasopharynx (41%) and hypopharynx (25%); most cancers in these locations are currently detected on head and neck examination with fiberoptic endoscopes. Additionally, 5 patients (11%) had primary cancers discovered in the lung, probably due to inclusion of patients with involvement of low neck lymph nodes.

The selection of mucosal sites for biopsy at panendoscopy in the present series was biased by the radiographic evaluation. Therefore, the anticipated yield of panendoscopy without CT and/or MRI is probably close to the 24% observed in the subset of patients with no suggestive findings on radiographic evaluation.

Tonsillectomy. Righi and Sofferman¹² described a series of six patients with unknown primary squamous cell carcinoma of the head and neck and a negative head and neck CT scan in whom a subclinical tonsillar cancer was detected only after tonsillectomy. Lapeyre and colleagues¹³ re-

ported a series of 87 patients with squamous cell carcinoma of the head and neck from an unknown primary site who were evaluated at the Centre Alexis Vautrin (Nancy, France) between 1969 and 1992. The authors did not state whether evaluation routinely included CT and/or MRI of the head and neck. All patients underwent a tonsillectomy at the time of direct laryngoscopy; subclinical cancer was found in the tonsillar fossa in 23 patients (26%). In the present series, 34 patients underwent a tonsillectomy, which revealed cancer in 12 patients (35%). However, 24 of 34 patients had suggestive findings on physical examination and/or radiographic evaluation. One of 10 patients (10%) with a negative head and neck examination and a negative radiographic evaluation had the primary tumor detected. Therefore, it appears that tonsillectomy is useful primarily in the subset of patients in whom the primary tumor is thought to be located in the tonsillar fossa.

Location of the Primary Lesions. The primary cancer was detected above the clavicles in 152 patients evaluated at Memorial Hospital, as follows: tonsil, 35 patients (23%); nasopharynx, 33 patients (22%); base of tongue, 29 patients (19%); and supraglottic larynx, 22 patients (14%).^{1,5} Jones et al² reported that the most common sites for the occult primary tumor were the oropharynx, hypopharynx, larynx, and nasopharynx. However, most of the primary tumors detected in both series were diagnosed on history and physical examination and were not really "unknown primaries." Forty-four primary tumors were discovered at panendoscopy in the University of Liverpool series; the sites included nasopharynx, 18 (41%); hypopharynx, 11 (25%); oropharynx, 8 (18%); oral cavity, 2 (5%); and bronchus, 5 (11%).

The primary lesions detected in the present series were located in the base of tongue or tonsil in over 80% of cases. The probable reason for the lower incidence of occult tumor detected in the nasopharynx, hypopharynx, and supraglottic larynx is that these tumors are more easily detected on physical examination with fiberoptic endoscopes and on radiographic evaluation; thus, the vast majority of these tumors are apparent before panendoscopy is performed (and are excluded from the present series).²¹ In contrast, an occult submucosal primary cancer of the tonsillar fossa or base of tongue may be indistinguishable from lymphoid tissue often found in these sites and, thus, much more difficult to detect.

CONCLUSION

Diagnostic evaluation of the unknown primary squamous cell carcinoma of the head and neck will detect the primary cancer in slightly less than half the patients. Computed tomography and/or MRI of the head and neck enhances the likelihood of successful detection of the primary site. However, the yield for CT and/or MRI depends on the use of optimal radiographic techniques. Computed tomography has been the preferred imaging modality at the University of Florida, with MRI being used to supplement CT to investigate equivocal findings. The additional benefits of FDG-SPECT and/or tonsillectomy are uncertain. Based on our limited data, FDG-SPECT is of very modest value and should not be a routine part of the diagnostic workup. Panendoscopy with directed biopsies should follow the radiographic evaluation; the most likely primary sites are the tonsillar fossa and base of the tongue. Although unlikely to reveal the primary site, biopsies should also be performed of the nasopharynx and ipsilateral pyriform sinus. If there is sufficient tonsillar tissue, ipsilateral tonsillectomy should be performed, particularly if there are suggestive findings in the tonsil based on physical examination and/or radiographic evaluation. A second panendoscopy should be performed if a site or sites suspected of harboring the primary tumor are not adequately sampled on the initial endoscopic procedure.

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