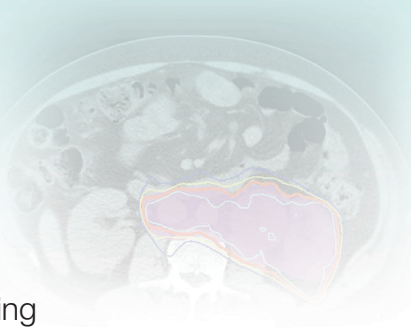
CHAPTER

39 Unknown Head and Neck Primary Site



William M. Mendenhall, Anthony A. Mancuso, and John W. Werning

INCIDENCE
Approximately 3% of head and neck squamous cell carcinomas metastasize to the neck from an unknown head and neck primary site.

BIOLOGIC CHARACTERISTICS
Biologic characteristics are similar to head and neck mucosal squamous cell carcinomas with known primary sites.

STAGING EVALUATION
Evaluation includes history and physical examination, computed tomography (CT) of the head and neck, chest radiography, direct laryngoscopy with ipsilateral tonsillectomy, and directed biopsies. Optional studies include chest CT and positron emission tomography (PET).

PRIMARY THERAPY AND RESULTS
Therapy consists of neck dissection to the involved neck or radiotherapy (RT) to the neck, oropharynx, and nasopharynx if RT is indicated for treatment of neck disease. The 5-year survival is approximately 50%.

ADJUVANT THERAPY
Concomitant cisplatin chemotherapy is administered for N2 and N3 neck disease and for close and positive margins or extracapsular extension following an initial neck dissection.

LOCALLY ADVANCED DISEASE
RT is administered to the oropharynx, nasopharynx, and both sides of the neck with concomitant chemotherapy followed by evaluation for a neck dissection.

PALLIATION
Moderate dose RT (30 Gy/10 fractions or 20 Gy/2 fractions with a 1-week interfraction interval) is administered to the involved neck.

In a small percentage of patients with squamous cell carcinoma metastatic to the cervical lymph nodes, the primary lesion cannot be found, even after an extensive evaluation. Patients with metastatic adenopathy in the upper neck have a good prognosis when treated aggressively, compared with those with metastatic lymph nodes in the level IV nodes or supraclavicular fossa.[1] The latter group is more likely to have a primary lesion located below the clavicles and the probability of cure is remote. Most patients have either squamous cell carcinoma or poorly differentiated carcinoma. Patients with adenocarcinoma almost always have a primary lesion below the clavicles, although if the nodes are located in the upper neck, one must exclude a salivary gland, thyroid, or parathyroid primary tumor.

This chapter addresses the management of patients presenting with squamous cell or poorly differentiated carcinoma in the upper or middle neck. Squamous cell carcinoma presenting in a parotid area lymph node is almost always metastatic from a cutaneous primary site and will not be addressed.[2]

DIAGNOSTIC EVALUATION

Patients should be evaluated with a thorough physical examination including careful evaluation of the head and neck by multiple examiners. A needle biopsy of the lymph node should be performed; fine-needle aspiration (FNA) is preferred to a biopsy because it is less traumatic, and there is a lower likelihood of seeding tumor cells along the needle track.[3-7] Evaluation of the neck node biopsy for Epstein-Barr virus (EBV) DNA, via polymerase chain reaction, may be useful in detecting a nasopharyngeal primary tumor in geographic areas where this malignancy is prevalent.[8] Similarly, evaluation of the biopsy for high-risk human papilloma virus (HR-HPV) may be useful for detecting an oropharyngeal carcinoma.[9] Most occult primary cancers that are detected in the United States are in the oropharynx so that, depending on the situation, testing in the biopsy for HR-HPV may be useful for determining the aggressiveness of the treatment plan.[10] HPV-positive oropharyngeal cancers have a better prognosis, and it may be possible to eliminate concomitant chemotherapy or use a lower RT dose. The necessity of adding a neck dissection may also be lower.

After chest roentgenography, CT or magnetic resonance imaging (MRI) of the head and neck is obtained to detect an unknown primary lesion arising from the mucosa of the head and neck. We use CT initially and follow with MRI only in cases with equivocal findings in which MRI might yield additional useful information, such as a suspected primary site in the nasopharynx. A complete blood count is obtained to evaluate the patient for anemia, which may reduce the likelihood of local regional control after irradiation alone. A chest CT should be considered for patents with N3 neck disease, as well as those with N2b to N2c disease and bulky adenopathy in the low neck, to assess the lungs for pulmonary metastases.[11] The recommended diagnostic algorithm is depicted in Box 39-1.[12]

Preliminary evidence suggested that fluorodeoxyglucose (FDG) single-photon-emission computed tomography (SPECT) or PET scans may identify primary lesions that would not otherwise be identifiable.[13,14] Theoretically, tumor cells have a higher metabolic rate than normal tissues, and therefore, take up more FDG so that they appear "hot" on a PET or SPECT scan. If an FDG-SPECT or PET scan is obtained as part of the workup, it should be performed before panendoscopy so that any suspicious areas of increased uptake can be biopsied.

BOX 39-1 Diagnostic Algorithm

GENERAL

History
Physical examination
Careful examination of the neck and supraclavicular regions
Examination of oral cavity, pharynx, and larynx (indirect laryngoscopy with a flexible endoscope)

RADIOGRAPHIC STUDIES

Chest roentgenogram
Computed tomography (CT) or magnetic resonance imaging (MRI) scans of head and neck (special attention to nasopharynx, pharynx, and larynx)

LABORATORY STUDIES

Complete blood cell count
Blood chemistry profile

DIRECT ENDOSCOPY AND DIRECTED BIOPSIES

Nasopharynx, both tonsils, base of tongue, both pyriform sinuses, and any suspicious or abnormal mucosal areas
Ipsilateral tonsillectomy
Fine needle aspirate (FNA) or core-needle biopsy of the cervical node

From Mendenhall WM, Parsons JT, Mancuso AA, et al: Head and neck: management of the neck. In Perez CA, Brady LW, editors: Principles and practice of radiation oncology, ed 3, Philadelphia, 1998, J. B. Lippincott, pp 1135-1156.[12] [Table 44-20, p 1152]

TABLE 39-1 Detection of the Primary Site on FDG-SPECT

Patient Group	FDG-SPECT Negative*	FDG-SPECT Positive*
PEØ/RadØ	No data	1/5
PE+ or Rad+	2/6	6/15 (40.0%)
Total	2/6	7/20 (35.0%)

From Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2854, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; radø, radiological exam negative; rad+, radiological exam (CT or MR) suspicious, not definitely positive.
**Number of primaries detected/number of patients.*

TABLE 39-2 Detection of the Primary Site by FDG-PET or FDG-PET/CT

Patient Group	FDG-PET Negative*	FDG-PET Positive*
PEØ/RadØ	3/4	No data
PE+ or Rad+	8/12	3/5
Total	11/16 (68.8%)	3/5 (60%)

From Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2354, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; RadØ, radiological exam negative; Rad+, radiological exam (CT or MR) suspicious, not definitely positive.
**Number of primaries detected/number of patients.*

TABLE 39-3 Detection of a Primary Site versus Patient Group

Patient Group	Biopsy-Proven Primary Site/No. Pts (%)
PEØ/RadØ	21/72 (29.2%)
PEØ/Rad+	51/82 (62.2%)
PE+/RadØ	15/25 (60.0%)
PE+/Rad+	39/57 (68.4%)
Total	126/236 (53.4%)

From Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2354, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; RadØ, radiological exam negative; Rad+, radiological exam (CT or MR) suspicious, not definitely positive.

Limited data pertaining to the usefulness of FDG-SPECT and FDG-PET scans suggest these procedures may identify the primary site in a relatively small subset of patients.[15-17] The FDG-SPECT scan was the sole procedure that correctly identified the occult primary site in only 1 of 26 patients (4%) at our institution (Table 39-1).[10] Similarly, FDG-PET was the only means of detecting a primary site in none of 21 patients at the University of Florida (Table 39-2).[10] Currently, FDG-PET-CT scans are not routinely obtained at our institution as part of the diagnostic evaluation of these patients. When obtained, they may be useful in detecting distant metastases in patients with advanced neck disease and for evaluating suspicious cervical lymph nodes in areas that would otherwise not receive definitive RT, as opposed to a moderate dose employed for suspected subclinical disease.

Direct laryngoscopy with fiberoptic endoscopic visualization under general anesthesia is performed with directed biopsies of the nasopharynx, tonsils, base of tongue, and pyriform sinuses, and of any abnormalities noted on CT or MRI or suspicious mucosal lesions observed during endoscopy. A subset of patients will have the primary tumor site discovered at direct laryngoscopy. The likelihood of discovering the primary site is related to whether or not a suspected (but not definite) primary site is discovered on physical examination or radiographic evaluation (Table 39-3).[10] Most suspected primary sites are detected by pretreatment radiographic workup as opposed to physical examination.

An ipsilateral[10,15,18] tonsillectomy should be performed in patients who have not had a prior tonsillectomy and who have adequate lymphoid tissue remaining in the tonsillar fossa. Although some authors recommend a bilateral tonsillectomy,[19] the likelihood of finding the primary site in the contralateral tonsil for patients with ipsilateral neck nodes is probably quite low. Lapeyre et al[18] reported 87 patients who were evaluated between 1969 and 1992 and underwent a unilateral tonsillectomy; 26% of patients were found to have a tonsillar cancer. Seventy-nine of 236 patients who were evaluated as the University of Florida underwent a tonsillectomy at the time of direct laryngoscopy; the primary site was detected in the tonsil in 35 patients (44%).[10] The likelihood of detecting the primary site was related to whether there were suspicious findings on physical examination or radiographic evaluation (Table 39-4).[10]

Fifty-eight primary head and neck cancers were found in 126 of 236 patients (53%) in the University of Florida series.[10] The most common primary sites were tonsillar fossa (59 patients, 45%) and base of tongue (58 patients, 44%).[10] The reason for the decreased likelihood of detecting cancers in other sites may be that they are found on physical examination with fiberoptic endoscopy and on radiographic evaluation.[7,20,21] In contrast, it is still difficult to discern a small primary cancer hidden in the lymphoid tissue of the tonsillar fossa or tongue base.

PRIMARY THERAPY AND RESULTS

Treatment Techniques and Algorithm

Treatment options range from treatment of the involved neck alone with a neck dissection or RT to irradiation of the suspected primary site and both sides of the neck followed by evaluation for a planned neck dissection.[22-24] Although treatment of the potential mucosal primary site and contralateral neck appears to reduce the risk of a local regional recurrence, the impact on survival is modest at best. Therefore, patients with a single positive node without extracapsular extension may be treated with a neck dissection alone and followed closely, provided that the neck was not violated with an open procedure prior to surgery.[25-27]

If RT is indicated to treat the involved neck, we usually irradiate the nasopharynx and oropharynx, as well as both sides of the neck (Figure 39-1, *A*).[1] Although it may be tempting to irradiate the involved neck alone or combined with RT to the ipsilateral mucosal sites deemed to be at risk, the base of tongue is a midline structure that probably harbors the undetected primary site as often as the tonsillar fossa, so it has been our policy to treat the entire oropharynx.[28] Failure to do so is likely associated with an increased risk of a local regional recurrence and further RT would be complicated by the initial treatment.[29] It is not necessary to irradiate the oral cavity unless the patient has submandibular (level I) adenopathy, in which case we either do a neck dissection and observe the patient or irradiate the oral cavity and oropharynx. At one

TABLE 39-4 Detection of the Primary Site on Tonsillectomy

Patient Group	No. of Patients with Pathologically Proven Site in Tonsillar Fossa/ No. Patients Having Tonsillectomy
PEØ/RADØ*	9/22 (41.1%)
PE+ and/or RAD+*	26/57 (45.6%)
Total	35/79 (44.3%)

From CianchettiM, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2354, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; RadØ, radiological exam negative; Rad+, radiological exam (CT or MR) suspicious, not definitely positive.
**Radiographic evaluation = CT or MRI with or without FDG-SPECT or FDG-PET or FDG-PET/CT.*

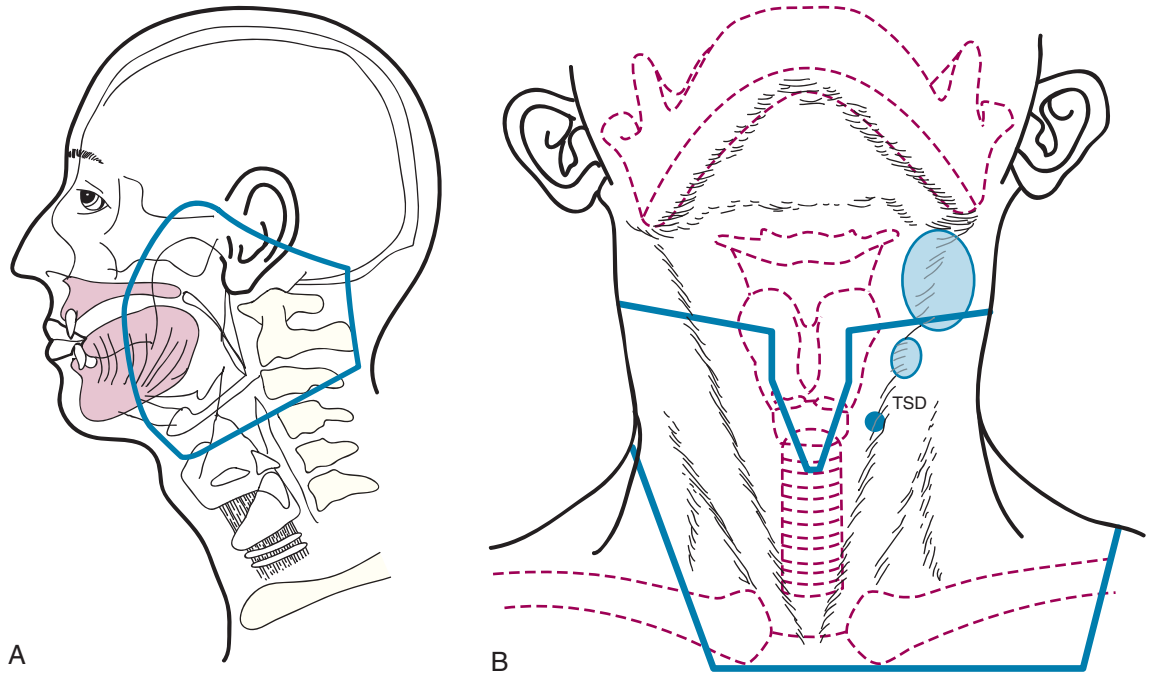


Figure 39-1 **A,** Radiation treatment technique for carcinoma from an unknown primary site. Superiorly, the portal treats the nasopharynx and the jugular (level II) and spinal accessory (level V) lymph nodes to the base of skull. The posterior border is behind the spinous process of C2. The inferior border is at the thyroid notch. Antero-inferiorly, the skin and subcutaneous tissues of the submentum are shielded, except in the case of advanced neck disease. The anterior tongue margin is set so as to obtain a 2-cm margin on the base of tongue and tonsillar fossa, as well as the nasopharynx. One portal reduction is shown (reduce off spinal cord). **B,** Fields for bilateral lower neck radiotherapy. The larynx shield should be carefully designed. Because the internal jugular vein lymph nodes (level III) lie adjacent to the posterolateral margin of the thyroid cartilage, the shield cannot cover the entire thyroid cartilage without producing a low-dose area in these nodes. A common error in the treatment of the lower neck is to extend the low neck portal laterally out to the shoulders, encompassing lateral supraclavicular lymph nodes that are at negligible risk while partially shielding the high-risk midjugular lymph nodes with a large rectangular laryngeal block. The inferior extent of the shield is at the cricoid cartilage or first or second tracheal ring; the shield must be tapered because the nodes tend to lie closer to the midline as the lower neck is approached. Lateral borders of the low-neck portals are set to cover only the lymph nodes in the root of the neck when the risk of low-neck disease on that side is small (i.e., stage N0 or N1 disease). If there are clinically positive lymph nodes in the lower neck or if major disease is present in the upper neck, the lateral border of the low-neck field is widened on that side to cover the entire supraclavicular region out to the junction of the trapezius muscle with the clavicle. *TSD,* Target-to-skin distance.
***A,** From Mendenhall WM, Mancuso AA, Amdur RJ, et al: Squamous cell carcinoma metastatic to the neck from an unknown head and neck primary site. Am J Otolaryngol 22(4):261-267, 2001. **B,** From Million RR, Cassisi NJ, Mancuso AA, et al: Management of the neck for squamous cell carcinoma. In Million RR, Cassisi NJ, editors: Management of head and neck cancer: A multidisciplinary approach, ed 2, Philadelphia, 1994, J. B. Lippincott Company, pp 75-142.*

time, it was our policy to irradiate the larynx and hypopharynx, but because the likelihood of a primary tumor in these sites is low, and because the morbidity of irradiating these areas is significant, we modified our technique in approximately 1997.[28] It could be argued that the nasopharynx should also be eliminated from the primary treatment volumes. However, the incidence of positive retropharyngeal nodes is relatively high in patients presenting with advanced neck disease[30] so that the volumes must include the skull base (jugular foramen and retropharyngeal nodes) and at least part of the nasopharynx. It is our belief that a modest increase in the size of the treatment volumes to adequately irradiate the nasopharynx does not significantly increase morbidity.

Patients are treated with parallel-opposed fields at 1.8 Gy per fraction to a midline dose of 64.8 Gy with reduction off the spinal cord at 45-Gy tumor dose (see Figure 39-1, *B*).[31] The lower neck is treated through a separate en face anterior field. Treatment is administered with cobalt-60, 4-MV x-rays, or 6-MV x-rays. Dosimetry is obtained at the level of the central axis (which usually corresponds to the oropharynx) and the nasopharynx. The dose to the nasopharynx is usually 3 Gy to 5 Gy lower than the central axis. Currently, the majority of radiation oncologists obtain a multilevel three-dimensional dosimetric analysis to evaluate the dose delivered to the clinical target volume (CTV), planning target volume (PTV), and organs at risk (OARs). Patients with ipsilateral nodes may be treated with intensity-modulated radiotherapy (IMRT) to reduce the dose to the contralateral parotid (≤26 Gy mean dose) to reduce the likelihood of long-term xerostomia. Patients with bilateral-positive nodes are better treated with parallel-opposed fields to reduce the risk of a marginal miss.[32] Patients with advanced, fixed adenopathy undergo a boost to the involved part of the neck using anteroposterior wedged beams to a total dose in the range of 70 Gy to 75 Gy. Concomitant chemotherapy should be considered for patients with N2 and N3 neck disease. Our preference is to use weekly cisplatin (30 mg/m^2) or cisplatin 100 mg/m^2 every 3 weeks for two cycles.[33]

Treatment of the neck depends on the extent and location of the adenopathy. Patients with N1 and early N2B neck disease located in the high-dose fields may be treated with irradiation alone if the nodes have resolved completely.[34-36] Similarly, if the patient has undergone an excisional biopsy of a single positive node, the neck may be treated with radiation alone with a 95% likelihood of neck control.[37] Patients undergo a CT scan of the neck 1 month after completing RT at our institution and the decision whether to proceed with neck dissection depends on the likelihood that viable tumor remains in the neck.[38-40] The criteria employed for determining whether a neck dissection should be performed are outlined in Table 39-5.[38,40] Because the likelihood of cure is low if a regional recurrence develops in a clinically positive neck after treatment with radiotherapy alone, we usually proceed with a modified neck dissection if the risk of residual disease exceeds 5%.[41] In practice, patients with N2-N3 neck disease and those with gross disease neck disease after an open neck biopsy often undergo a planned neck dissection after radiation therapy.[36,42]

The treatment algorithm is depicted in Figure 39-2.

Results

One hundred thirty-six patients were treated at the M. D. Anderson Hospital between 1968 and 1992 and had a median duration of follow-up of 8.7 years.[43] Both sides of the neck and potential head and neck mucosal primary sites were irradiated. A mucosal head and neck cancer developed in 14 patients (10%); 6 of the 14 cancers were located in unirradiated sites. Recurrent disease in the neck developed in 12 patients (9%). The 5-year cause-specific survival rate was 74%.

The incidence of subsequent mucosal primary lesions was compared by Erkal et al[44] for patients with a known primary site and a series of 126 patients treated for an unknown primary site at the University of Florida. The incidence for both groups was similar at 5 years, suggesting either that mucosal irradiation significantly reduced the risk of primary site failure or that patients with unknown primary sites have a much lower risk of a second primary head and neck cancer developing subsequently (Figure 39-3).[44] The 5-year absolute and cause-specific survival rates for the 126 patients with an unknown primary were 47% and 67%, respectively. The 5-year outcomes stratified by N-category are shown in Figures 39-4, *A-D*.[44]

Reddy and Marks[29] reported 52 patients treated to the neck alone (16 patients) or to the neck and potential head and neck primary sites (36 patients). Failure in the head and neck mucosa occurred in 44% of those who underwent treatment to the neck alone, compared with 8% in those who underwent irradiation of the head and neck mucosa ($p = 0.0005$). The 5-year survival rates were similar for the two treatment groups.

Grau et al[45] reported 273 patients treated with curative intent at five cancer centers in Denmark between 1975 and 1995 with surgery alone (23 patients), RT to the ipsilateral neck alone or combined with surgery (26 patients), and RT to the neck and head and neck mucosa alone or combined with

TABLE 39-5 Predictive Value of Postradiotherapy CT Findings at 4 Weeks in the Hemi-Neck Correlated to Neck Dissection Pathology (n = 193 Hemi-Necks)

	NPV		PPV	
Finding	**No./Total No.**	**%**	**No./Total No.**	**%**
Any lymph node >1.5 cm	85/118	72	24/75	32
Any focally abnormal lymph node*	49/57	86	49/136	36
Any lymph node with focal lucency	75/98	77	34/95	36
Any lymph node enhancement	111/147	76	21/46	46
Any lymph node with calcification	102/144	71	15/49	31
Two or more focally abnormal lymph nodes*	90/113	80	34/80	43
Any lymph node >1.5 cm and any focally abnormal lymph node	32/34	94	55/159	35

From Liauw SL, Mancuso AA, Amdur RJ, et al: Postradiotherapy neck dissection for lymph node-positive head and neck cancer: The use of computed tomography to manage the neck. J Clin Oncol 24:1421–1427, 2006.

CT, *computed tomography;* NPV, *negative predictive value;* PPV, *positive predictive value.*

**Focally abnormal lymph node = grades 3 to 4 focal lucency, focal enhancement, or focal calcification.*

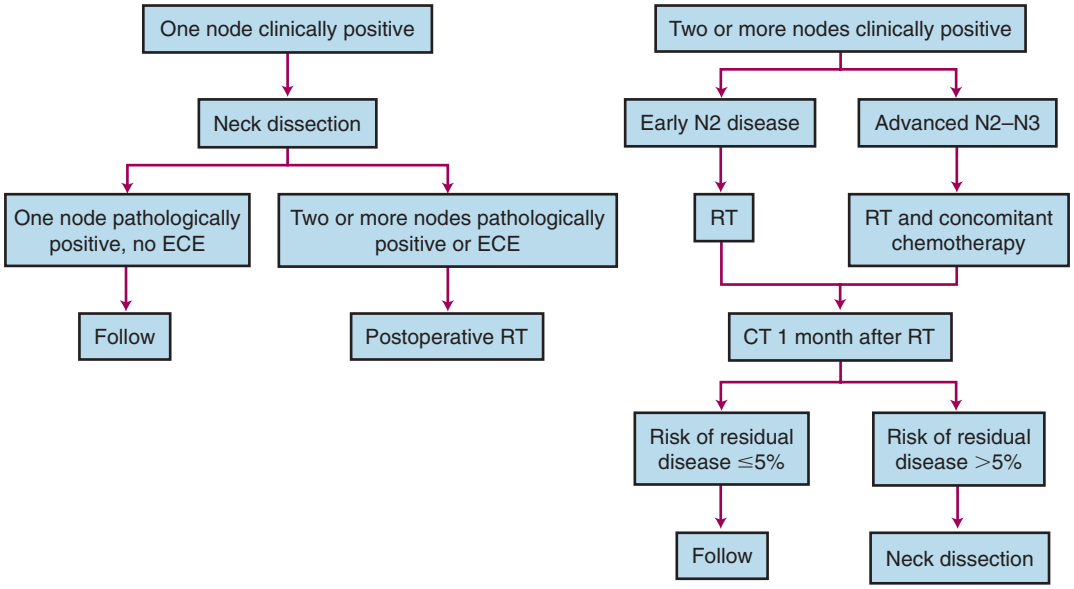


Figure 39-2 **Treatment algorithm.** *CT,* Computed tomography; *ECE,* extracapsular extension; *RT,* radiotherapy.

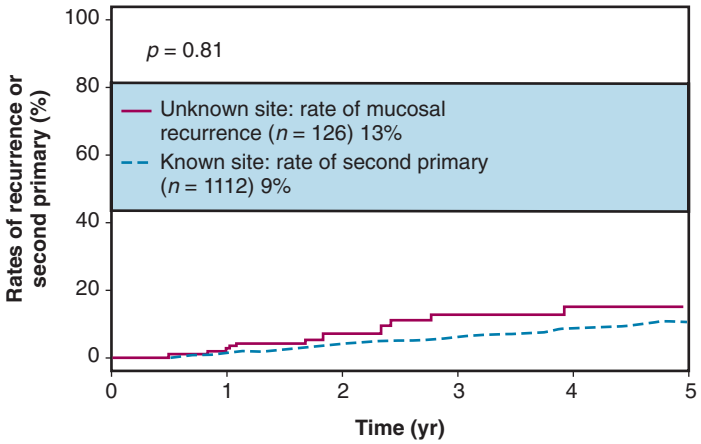


Figure 39-3 The rate of developing carcinomas in head and neck mucosal sites for patients treated for carcinomas with an unknown head and neck mucosal site compared to the rate for developing metachronous carcinomas in head and neck mucosal sites for patients treated for carcinomas with a known head and neck mucosal site.
From Erkal HS, Mendenhall WM, Amdur RJ, et al: Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys 50(1):55-63, 2001.[44]

surgery (224 patients). The ipsilateral oropharynx unintentionally received some irradiation in patients treated to the ipsilateral neck alone, depending on the treatment technique.[45] The 5-year rates of freedom from failure in the head and neck mucosa were as follows: surgery alone, 45%; RT with or without surgery to the ipsilateral neck, 77%; and RT to the head and neck mucosa with or without surgery 87%. Failure in the oropharynx, particularly the base of tongue, was the most common location of mucosal site failure.

Complications

The main complication of radiation therapy for patients treated for an unknown head and neck primary tumor is xerostomia. The likelihood of long-term problems with altered taste or difficulty swallowing is relatively low. IMRT may be used to reduce the dose to the contralateral parotid gland so long as the patient does not have bilateral clinically positive neck nodes. It is difficult to limit the dose to the parotid if there are positive nodes in the same side of the neck without risking underdosing the adenopathy and increasing the risk of a marginal miss.[32] The risk of bone exposure, radiation myelitis, or radiation-induced malignancy is low.

The complications of neck irradiation include subcutaneous fibrosis and lymphedema of the larynx and submentum. The latter complications may be minimized by sparing an anterior strip of skin when designing the parallel-opposed lateral portals used to encompass the suspected primary site. This will also reduce the risk of desquamation, particularly in patients who receive concomitant chemotherapy. A 5-mm-wide midline block in the en face low-neck field may also diminish the likelihood of postirradiation edema. The probability of complications is directly related to radiation dose and volume.

Complications of neck dissection include hematoma, seroma, lymphedema, wound infection, wound dehiscence, chyle fistula, damage to cranial nerves VII, X, XI, and XII, carotid exposure, and carotid rupture. The incidence of complications after neck dissection is probably higher when the operation follows a course of radiation therapy.

The incidence of postoperative complications in a series of 143 patients treated with radiation to the primary lesion and neck followed by unilateral neck dissection was 23%.[36] Seventeen patients (12%) required a second operation and four patients (3%) experienced fatal complications.[36] The incidence of complications was higher for maximum subcutaneous doses higher than 60 Gy. Taylor et al[46] updated the University of Florida experience with an analysis of the incidence of moderate (2+) and severe (3+) wound complications in a series of 205 patients who underwent a planned unilateral neck

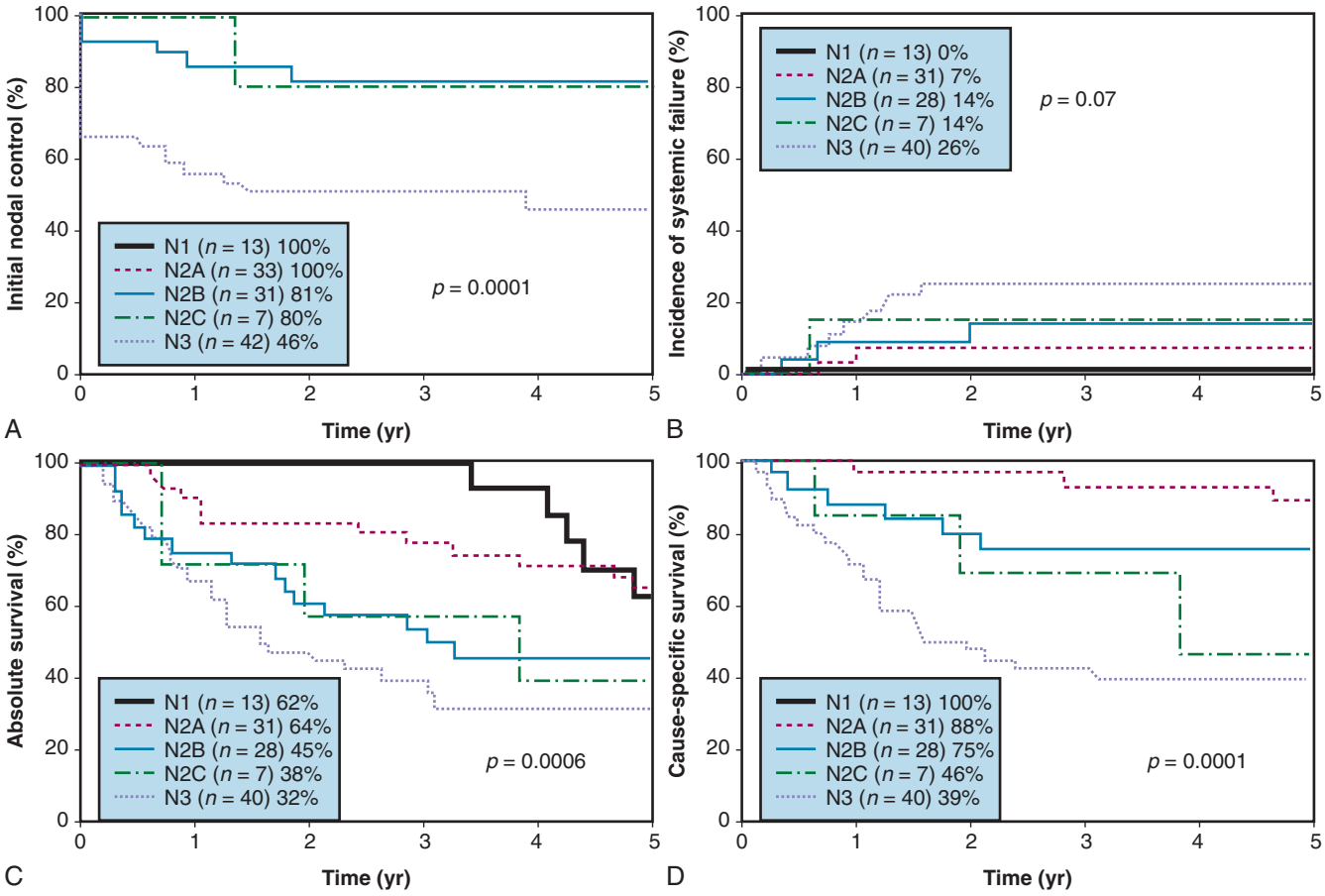


Figure 39-4 Disease and survival outcomes according to N category after initial treatment. **A,** Nodal control rates. **B,** Systemic failure (distant metastases). **C,** Absolute survival. **D,** Cause-specific survival.
From Erkal HS, Mendenhall WM, Amdur RJ, et al: Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys 50(1):55-63, 2001.[44]
[Figure 3-6, pp 58–60]

dissection after radiation therapy. Radiation therapy was given once daily in 123 patients, twice daily in 80 patients, and with both techniques in the remaining 2 patients. The incidence of wound complications tended to increase with total dose and dose per fraction.

CONCLUSIONS

The diagnostic evaluation of patients with squamous cell carcinoma of the head and neck from an unknown primary site includes multiple head and neck examinations by experienced examiners, FNA of the neck node, CT from the skull base to the clavicles, direct laryngoscopy and biopsies, and an ipsilateral tonsillectomy. The primary site will be detected in approximately 40% to 50% of patients and will be located in the oropharynx in more than 80% of patients. The management of these patients is controversial. Treatment usually includes irradiation of both sides of the neck (levels II, III, IV, and V) and the potential mucosal primary sites. The likelihood of 5-year survival is approximately 50% and is related to the extent of disease in the neck.

ACKNOWLEDGMENTS

The authors thank the research support staff of the Department of Radiation Oncology for their preparing the manuscript for publication.

REFERENCES

1. Mendenhall WM, Mancuso AA, Amdur RJ, et al: Squamous cell carcinoma metastatic to the neck from an unknown head and neck primary site. Am J Otolaryngol 22:261–267, 2001.
2. Hinerman RW, Amdur RJ, Morris CG, et al: Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes. Laryngoscope 118:1989–1996, 2008.
3. McGuirt WF, McCabe BF: Significance of node biopsy before definitive treatment of cervical metastatic carcinoma. Laryngoscope 88:594–597, 1978.
4. Parsons JT, Million RR, Cassisi NJ: The influence of excisional or incisional biopsy of metastatic neck nodes on the management of head and neck cancer. Int J Radiat Oncol Biol Phys 11:1447–1454, 1985.
5. Ellis ER, Mendenhall WM, Rao PV, et al: Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. Head Neck 13:177–183, 1991.
6. Robbins KT, Cole R, Marvel J, et al: The violated neck: Cervical node biopsy prior to definitive treatment. Otolaryngol Clin North Am 94:605–610, 1986.
7. Martin H, Morfit HM: Cervical lymph node metastasis as the first symptom of cancer. Surg Gynecol Obstet 76:133–159, 1944.
8. Macdonald MR, Freeman JL, Hui MF, et al: Role of Epstein-Barr virus in fine-needle aspirates of metastatic neck nodes in the diagnosis of nasopharyngeal carcinoma. Head Neck 17:487–493, 1995.
9. Begum S, Gillison ML, Nicol TL, et al: Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 13:1186–1191, 2007.
10. Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348–2354, 2009.
11. Al-Othman MOF, Morris CG, Hinerman RW, et al: Distant metastases after definitive radiotherapy for squamous cell carcinoma of the head and neck. Head Neck 25:629–633, 2003.

12. Mendenhall WM, Parsons JT, Mancuso AA, et al: Head and neck: management of the neck. In Perez CA, Brady LW, editors: Principles and practice of radiation oncology, Philadelphia, 1998, Lippincott–Raven, pp 1135–1156.
13. Mukherji SK, Drane WE, Mancuso AA, et al: Occult primary tumors of the head and neck: Detection with 2-[F-18] fluoro-2-deoxy-D-glucose SPECT. Radiology 199:761–766, 1996.
14. Johansen J, Buus S, Loft A, et al: Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumor. Results from the DAHANCA-13 study. Head Neck 30:471–478, 2008.
15. Mendenhall WM, Mancuso AA, Parsons JT, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Head Neck 20:739–744, 1998.
16. Greven KM, Keyes JW Jr, Williams DW, III, et al: Occult primary tumors of the head and neck. Lack of benefit from positron emission tomography imaging with 2-[F-18]Fluoro-2-deoxy-D-glucose. Cancer 86:114–118, 1999.
17. Safa AA, Tran LM, Rege S, et al: The role of positron emission tomography in occult primary head and neck cancers. Cancer J Sci Am 5:214–218, 1999.
18. Lapeyre M, Malissard L, Peiffert D, et al: Cervical lymph node metastasis from an unknown primary: Is a tonsillectomy necessary? Int J Radiat Oncol Biol Phys 39:291–296, 1997.
19. McQuone SJ, Eisele DW, Lee D-J, et al: Occult tonsillar carcinoma in the unknown primary. Laryngoscope 108:1605–1610, 1998.
20. Fletcher GH, Jesse RH, Healey JE, Jr, et al: Oropharynx. In MacComb WS, Fletcher GH, editors: Cancer of the head and neck, Baltimore, 1967, Williams & Wilkins, pp 179–212.
21. Jones AS, Cook JA, Phillips DE, et al: Squamous carcinoma presenting as an enlarged cervical lymph node. Cancer 72:1756–1761, 1993.
22. Coster JR, Foote RL, Olsen KD, et al: Cervical nodal metastasis of squamous cell carcinoma of unknown origin: Indications for withholding radiation therapy. Int J Radiat Oncol Biol Phys 23:743–749, 1992.
23. Weir L, Keane T, Cummings B, et al: Radiation treatment of cervical lymph node metastases from an unknown primary: An analysis of outcome by treatment volume and other prognostic factors. Radiother Oncol 35:206–211, 1995.
24. Mendenhall WM: Unknown primary squamous cell carcinoma of the head and neck. Curr Cancer Ther Rev 1:167–748, 2005.
25. Olsen KD, Caruso M, Foote RL, et al: Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in patients with lymph node involvement. Arch Otolaryngol Head Neck Surg 120:1370–1374, 1994.
26. Huang DT, Johnson CR, Schmidt-Ullrich R, et al: Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: A comparative study. Int J Radiat Oncol Biol Phys 23:737–742, 1992.
27. Mendenhall WM, Amdur RJ, Hinerman RW, et al: Postoperative radiation therapy for squamous cell carcinoma of the head and neck. Am J Otolaryngol 24:41–50, 2003.
28. Barker CA, Morris CG, Mendenhall WM: Larynx-sparing radiotherapy for squamous cell carcinoma from an unknown head and neck primary site. Am J Clin Oncol 28:445–448, 2005.
29. Reddy SP, Marks JE: Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: Results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. Int J Radiat Oncol Biol Phys 37:797–802, 1997.
30. McLaughlin MP, Mendenhall WM, Mancuso AA, et al: Retropharyngeal adenopathy as a predictor of outcome in squamous cell carcinoma of the head and neck. Head Neck 17:190–198, 1995.
31. Million RR, Cassisi NJ, Mancuso AA, et al: Management of the neck for squamous cell carcinoma. In Million RR, Cassisi NJ, editors: Management of head and neck cancer: A multidisciplinary approach, Philadelphia, 1994, J.B. Lippincott Company, pp 75–142.
32. Mendenhall WM, Mancuso AA: Radiotherapy for head and neck cancer—is the "next level" down? Int J Radiat Oncol Biol Phys 73:645–646, 2009.
33. Mendenhall WM, Riggs CE, Amdur RJ, et al: Altered fractionation and/or adjuvant chemotherapy in definitive irradiation of squamous cell carcinoma of the head and neck. Laryngoscope 113:546–551, 2003.
34. Peters LJ, Weber RS, Morrison WH, et al: Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. Head Neck 18:552–559, 1996.
35. Johnson CR, Silverman LN, Clay LB, et al: Radiotherapeutic management of bulky cervical lymphadenopathy in squamous cell carcinoma of the head and neck: Is postradiotherapy neck dissection necessary? Radiat Oncol Investig 6:52–57, 1998.
36. Mendenhall WM, Million RR, Cassisi NJ: Squamous cell carcinoma of the head and neck treated with radiation therapy: The role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 12:733–740, 1986.
37. Mack Y, Parsons JT, Mendenhall WM, et al: Squamous cell carcinoma of the head and neck: Management after excisional biopsy of a solitary metastatic neck node. Int J Radiat Oncol Biol Phys 25:619–622, 1993.
38. Ojiri H, Mancuso AA, Mendenhall WM, 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. Am J Neuroradiol 23:1012–1018, 2002.
39. Yeung AR, Liauw SL, Amdur RJ, et al: Lymph node-positive head and neck cancer treated with definitive radiotherapy: Can treatment response determine the extent of neck dissection? Cancer 2008.
40. Liauw SL, Mancuso AA, Amdur RJ, et al: Postradiotherapy neck dissection for lymph node-positive head and neck cancer: The use of computed tomography to manage the neck. J Clin Oncol 24:1421–1427, 2006.
41. Mendenhall WM, Villaret DB, Amdur RJ, et al: Planned neck dissection after definitive radiotherapy for squamous cell carcinoma of the head and neck. Head Neck 24:1012–1018, 2002.
42. Brizel DM, Prosnitz RG, Hunter S, et al: Necessity for adjuvant neck dissection is setting of concurrent chemoradiation for advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 58:1418–1423, 2004.
43. Colletier PJ, Garden AS, Morrison WH, et al: Postoperative radiation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site: Outcomes and patterns of failure. Head Neck 20:674–681, 1998.
44. Erkal HS, Mendenhall WM, Amdur RJ, et al: Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys 50:55–63, 2001.
45. Grau C, Johansen LV, Jakobsen J, et al: Cervical lymph node metastases from unknown primary tumours: Results from a national survey by the Danish Society for Head and Neck Oncology. Radiother Oncol 55:121–129, 2000.
46. Taylor JMG, Mendenhall WM, Parsons JT, et al: The influence of dose and time on wound complications following post-radiation neck dissection. Int J Radiat Oncol Biol Phys 23:41–46, 1992.