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REVIEW ARTICLE

Management of Squamous Cancer Metastatic to Cervical Nodes With an Unknown Primary Site

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ABSTRACT

Squamous cell carcinoma of an unknown primary (SCCUP) of the head and neck is a rare disease. As a diagnosis of exclusion, the manner in which it is assigned merits consideration. Despite the development and refinement of several techniques designed to locate an occult tumor, including cross-sectional anatomic imaging, functional imaging, and transoral surgical techniques, delineating SCCUP remains an active clinical problem. Its relative rarity has prevented prospective study of the entity. Hence, investigators must rely on retrospective analyses to understand the disease and its appropriate treatment. The current understanding of SCCUP differs substantially from when it was initially described decades ago. The most common site of a small primary tumor initially thought to represent SCCUP is the tonsil or base of the tongue, and an increasing percentage are associated with human papilloma virus. Modern treatment of SCCUP by neck dissection alone, neck dissection followed by radiation with or without concurrent chemotherapy, or primary chemoradiation according to initial nodal disease burden produces extraordinarily low recurrence rates. Whether the potential mucosal primary site and/or the contralateral neck should be electively treated is controversial. Efficacy data seem to be similar; therefore, an evaluation of the toxicity of both treatment paradigms is warranted.

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INTRODUCTION

Squamous cell carcinoma of unknown primary of the head and neck (SCCUP) is defined as metastatic disease in the lymph nodes of the neck without any evidence of a primary tumor of the upper aerodigestive tract[1] after appropriate investigation.[2] SCCUP reportedly accounts for 1% to 4% of all cancers of the head and neck.[3] Recent experience suggests that an increasing proportion of SCCUP is associated with human papilloma virus (HPV).[4] The incidence is increasing at a rate similar to that of known-primary oropharyngeal cancer.[5]

SCCUP is a diagnosis of exclusion, and what constitutes appropriate investigation is subject to change. Methods to identify a small primary tumor have advanced in the 70 years since the condition was initially described. Increasingly sophisticated imaging and biopsy techniques have limited the number of patients in whom SCCUP is diagnosed. When evaluating the literature about SCCUP, clinicians should remain aware that the same disease might be classified as either SCCUP or a small primary tumor depending on the institution or the diagnostician.

PATIENT PRESENTATION AND TISSUE CONFIRMATION

The most common presenting symptom in SCCUP is a painless neck mass, and the most common neck stage at diagnosis is N2a or N2b[3,4,6-19] (Table 1). Nearly 40% of patients come to medical attention with a single enlarged lymph node, which is most commonly located in level 2,[6] suggesting an occult oropharyngeal primary tumor location.[21] Lymphadenopathy in level 3, without involvement of level 2, suggests a primary site in the supraglottic larynx or hypopharynx because primary tumors in these locations more commonly drain to the mid neck.[7] Metastatic nodes limited to the low neck, that is, level 4 and/or the supraclavicular fossa, are seldom the result of a primary site above the clavicles.[22]

Fine-needle aspiration (FNA) of the lymph node is the preferred initial approach to diagnosis. When clinical findings suggest SCCUP, nondiagnostic FNA results should be repeated, perhaps with sonographic guidance. Open biopsy to confirm or assign the diagnosis is discouraged because of possible spillage of the tumor and disruption of fascial planes that act as a natural barrier to tumoral spread.[23] Ill-considered open

Table 1. Nodal Stage at Diagnosis of Squamous Cell Carcinoma of an Unknown Primary

Authors	No.	NX	N1	N2a	N2b	N2c	N3
Grau et al[3]	263	2	46	82	32	8	93
Keller et al[4]	35	0	5	10	6	6	8
Ligey et al[7]	95	16	9	22	33	0	15
Frank et al[8]	52	3	5	11	23	6	4
Chen et al[9]	60	0	5	26	20	0	9
Demiroz et al[10]	41	0	4	10	18	0	9
Wang et al[11]	157	60	22	20	14	24	17
Iganej et al[12]	106	0	14	27	39	2	24
Colletier et al[13]	136	10	31	49	25	3	18
Reddy et al[14]	52	0	9	16	7	5	15
Perkins et al[15]	46	0	3	10	22	2	9
Cuaron et al[16]	85	0	21	12	40	4	8
Sher et al[17]	24	0	2	9	10	1	2
Marcial-Vega et al[18]	72	0	12	14	18	12	16
Sinnathamby et al[19]	69	3	6	9	24	3	24
Wallace et al[20]	179	0	18	48	46	11	56
All							
No.	1,472	94	212	375	377	87	327
%	100	6	14	25	26	6	22

biopsy may limit or define future treatment, promote the development of scar tissue, necessitate a second operation if accurate pathologic staging is pursued, and increase morbidity because the biopsy wound must be excised in a second operation and/or covered in a high-dose radiation volume. When necessary, open biopsy should be performed by a surgeon prepared to complete definitive surgical management, that is, to finish neck dissection, as part of the same procedure if indicated.

The most common benign cause of a painless neck mass is a branchial cleft cyst,[24] a congenital abnormality that may manifest in adulthood. The cystic nature of HPV-associated lymph nodes[25] may obscure radiographic distinction between carcinoma and branchial cleft cysts. The most useful determinant is age, as branchial cleft cysts usually appear in late childhood or early adulthood.[26] Primary presentation in an adult is rare.[27] By contrast, the median age at diagnosis for HPV-associated oropharyngeal cancer is in the late 50s.[28] National Comprehensive Cancer Network guidelines recommend that a painless neck mass in an adult older than 40 years of age should be considered malignant until proven otherwise.[2]

The most common malignant causes of a neck mass not originating from the upper aerodigestive tract are papillary thyroid cancer and cutaneous squamous cell carcinoma of the lymph nodes. If an FNA report suggests thyroid cancer, thyroid ultrasonography with biopsy of suspicious nodules should be pursued. Metastases of cutaneous squamous cell carcinoma nodal can be p16-positive[29]; however, the location of the presenting node and patient demographics can aid in determining whether a particular case represents SCCUP. For instance, cutaneous carcinoma metastases are rarely present in level 2, and cutaneous carcinoma metastases are more common in the elderly and patients who are immunocompromised. Nodal material can be tested for HPV DNA, which is generally not present in p16-positive metastases of cutaneous carcinoma.

DIAGNOSIS

The manner in which the diagnosis of SCCUP is assigned is important because it is one of exclusion. Increasing the intensity and morbidity of diagnostic maneuvers will aid in identifying more small primary cancers and in reducing the apparent incidence of SCCUP.

Imaging

Cross-sectional imaging of the neck such as contrast-enhanced (CT) and/or magnetic resonance imaging has demonstrably changed the detection of small primary cancers, informing the distribution of SCCUP. Before CT was invented and fiberoptic endoscopy became widely available, surgical endoscopy was commonly performed to identify small primary tumors first classified as SCCUP in areas difficult to examine, such as the nasopharynx and the hypopharynx.[23] Early investigations with CT and endoscopy demonstrated that primary tumors suspected on CT scans were often not actual neoplasms, emphasizing the continued need for examination under anesthesia and confirmatory biopsy of small tumors. Still, CT could depict small cancers in approximately 25% of patients whose small cancer was not discovered during head and neck examination.[30] Larger modern series involving treatment with anatomic imaging and fiberoptic endoscopy for all presenting candidates emphasize the importance of cross-sectional imaging. Among patients in whom no primary site was detected by examination, a mucosal primary tumor is twice as likely to be found in those with anatomic images suggestive of tumor than in those without suggestive imaging results, with rates of 62% versus 29%, respectively.[21]

Despite the known physiologic uptake of [^{18}F]fluorodeoxyglucose in the head and neck,[31] initial retrospective reports suggested that the addition of positron emission tomography (PET) and/or CT could depict small primary tumors in approximately 25% of patients who had previously received a diagnosis of SCCUP on the basis of anatomic

neck images and, often, examination under anesthesia (EUA).[32] Later prospective analysis demonstrated that the addition of PET and/or CT led to the detection of 29% more mucosal cancers after anatomic neck imaging and, in most patients, EUA suggested SCCUP.[33] Furthermore, PET and/or CT can demonstrate either distant metastases of SCCUP or a primary tumor not of the upper aerodigestive tract when FDG uptake occurs below the clavicles. Although these analyses demonstrate some benefit of PET and/or CT in the identification of small mucosal tumors, the relatively high false-positive rate of 16% to 20% emphasizes the continued need for diagnostic biopsy. Because positive PET and/or CT findings must be confirmed, the imaging study should be performed before the patient is examined under anesthesia.

EUA: Direct Laryngoscopy and Directed Biopsy

If the history and findings from complete head and neck examination, fiberoptic laryngoscopy, and/or imaging alert the multidisciplinary team to a potential primary site, comprehensive mucosal sampling during EUA may not be necessary. With preprocedural identification of a potential mucosal primary tumor, the site or sites of interest should be examined with biopsy first and samples submitted for frozen-section analysis. If carcinoma is confirmed and visual and/or manual evaluation of the rest of the upper aerodigestive tract does not suggest additional primary sites, tonsillectomy and additional biopsy is unnecessary.

If preprocedural findings do not suggest potential biopsy targets, directed biopsy is recommended. Studies performed before sophisticated pretreatment assessments suggested that as many as 40% of patients thought to have SCCUP after physical examination had a primary tumor discovered at EUA. Because present-day selection of mucosal sites for biopsy is predicated on radiographic and biomarker evaluation, it is difficult to estimate the yield of directed biopsy in the modern era. Nonetheless, for level 2 and 3 nodes, biopsy of the nasopharynx—both sides of the base of the tongue and both pyriform sinuses—is typically recommended. Many tonsillar cancers begin in the crypts[34] and may not be readily seen. Therefore, tonsillectomy is recommended if sufficient tonsillar tissue is present. Bilateral tonsillectomy has been advocated.[35]

As detailed elsewhere in this article, many nasopharyngeal and oropharyngeal carcinomas are caused by viruses. Nasopharyngeal cancer has a distinct geographic distribution. Although plasma Epstein-Barr virus (EBV) DNA is useful in monitoring patients with diagnosed nasopharynx cancer, plasma EBV levels are rarely elevated in North American patients with an initial diagnosis of SCCUP. EBV can be detected in FNA specimens,[36] and such evaluation is recommended to direct biopsy when clinicians are treating patients in an area where EBV-associated nasopharynx cancer is endemic. The incidence of oropharyngeal cancer is rapidly increasing in the United States because of an increase in HPV-associated disease.[37] HPV can also be[38] detected from an FNA specimen. Given the frequency of this disease, it is recommended for all patients in whom SCCUP is diagnosed.

Tonsillectomy and Base-of-Tongue Resection

The tonsil and the base of the tongue are the most common sites for a small primary tumor initially thought to represent SCCUP.[21] A lymph node that tests positive for p16 and/or HPV DNA further suggests a primary tumor of either a tonsil or the base of the tongue. Despite the morbidity associated with tonsillectomy in adults, ipsilateral tonsillectomy rather than deep tonsil biopsy is typically included in the initial evaluation of a patient with SCCUP.[39] Contralateral tonsillectomy is sometimes performed, with strong institutional bias. Both the spread of occult contralateral tonsil cancer[35] and the synchronous presentation of bilateral tonsil cancer[40] are cited as justifications for contralateral tonsillectomy. However, unilateral treatment for a known primary T1 tonsil cancer is common practice,[41,42] without progression in the contralateral side of the neck or tonsil. Therefore, the extremely low rates of mucosal emergence in the absence of a contralateral tonsillectomy suggest that the procedure is unnecessary.

Before transoral surgical techniques were developed,[43,44] no procedure similar to the palatine tonsillectomy was available to evaluate the base of the tongue. In the last decade, several institutions have reported results from transoral surgical techniques to evaluate SCCUP either after conventional EUA failed[45] or in the initial surgical procedure.[46] Investigators from some series do not explicitly identify the percentage of patients with a primary site suspected on the basis of imaging and/or physical examination before the transoral procedure, and others do not pursue tonsillectomy before using transoral surgical techniques. However, the results are impressive (Table 2). Rates of mucosal detection range from 63% to 100% and are generally 2× to 3× greater than the yield encountered with diagnostic palatine tonsillectomy, which is 24% to 39%. The long-term toxicity of this procedure, like palatine tonsillectomy, is anticipated to be low. Head and neck surgeons increasingly incorporate transoral techniques in their

Table 2. Transoral Surgical Techniques to Identify the Primary Cancer

Authors	No.	Years	Previous, %			Transoral Surgery Yield, %*
			EUA (tonsillectomy)	CT or MRI	PET/CT	
Mehta et al[45]	10	2009-2011	100 (100)	100	100	100†
Nagel et al[46]	36	2002-2011	100 (0)	—	—	86
Graboyes et al[47]	65	2001-2012	100 (0)	100	65	89
Durmus et al[48]	11‡	2008-2012	100 (0)	100	100	63
Patel et al[49]	18‡	2010-2013	100 (13)	81 or 6§	57	72

Abbreviations: CT, computed tomography; EUA, examination with anesthesia; MRI, magnetic resonance imaging; PET, positron emission tomography.
*In either the tonsil of the base of the tongue.
†All in the base of the tongue.
‡Data are limited to patients without examination and/or imaging highly suggestive of primary tumor before lingual and/or palatine tonsillectomy.
§81% for CT, 6% for MRI.

Table 3. Association of Human Papilloma Virus With Squamous Cell Carcinoma of an Unknown Primary

Authors	No.	Years	p16-Positive, %
Keller et al[4]	35	1990-2010	74
Demiroz et al[10]	17	1994-2008	59
Nagel et al[46]	52	1996-2011	78
Graboyes et al[47]	71	2001-2012	92*
Durmus et al[48]	22	2008-2012	95*
Desai et al[51]	41	2000-2007	27
Compton et al[52]	25	2002-2009	28

*Most patients in these two series had a small oropharyngeal primary tumor found with transoral techniques, which, therefore, does not represent true squamous cell carcinoma of an unknown primary. The information gained by including them is uncertain.

initial examination performed with anesthesia if frozen-section analysis of directed biopsy samples does not demonstrate a tumor.[46,47] However, in view of the low rate of mucosal emergence when a patient is treated with surgery alone, the clinical significance of these base-of-the-tongue tumors is dubious. The benefit of small primary tumor identification is postulated to be a reduction, and in rare circumstances elimination, of radiation treatment volumes. Although the surgical community has expressed some enthusiasm for this approach, whether such volume reductions meaningfully decrease toxicity is unknown. Therefore, whether additional efforts to find the occult primary tumor are justified is also unknown. Further consideration of this as a deintensification technique will depend on an evaluation of ongoing prospective experiences.

HPV

The tonsil and the base of the tongue are the most common locations for a small primary tumor initially thought to represent SCCUP[21] and for HPV-associated tumors.[50] Multiple investigators have sought to determine the incidence of HPV-associated SCCUP (Table 3). Although the two series that included small oropharyngeal primaries found by means of transoral techniques[47,48] demonstrated the highest rate of HPV association, many SCCUP are clearly associated with HPV. The incidence of HPV-associated SCCUP seems to be increasing.[4]

INITIAL TREATMENT

Most patients with SCCUP are treated with multimodality therapy. As with oropharyngeal cancer, multimodality therapy, most commonly, is resection followed by adjuvant radiation with or without chemotherapy, or primary chemoradiotherapy with or without post-therapeutic neck dissection. Similar to patients with known primary mucosal cancer of the head and neck,[53] those with SCCUP do well with either approach, and institutional bias often determines treatment. Effectiveness data seem to be similar. Therefore, an evaluation of the toxicity of both treatment paradigms is warranted.

SURGERY

Initial surgical treatment for SCCUP is neck dissection. The presentation of the disease determines the extent of the dissection. Management of SCCUP with surgery alone requires accurate identification of patients at low risk for both mucosal emergence and regional recurrence. Data about the outcome of surgery alone are sparse because of the relatively limited number of patients for whom it is appropriate.

In the largest series of neck dissection alone, outcomes for 104 patients treated between 1948 and 1968 were reported.[6] During this same time, 52 patients were treated with primary radiation, and 28 were treated with surgery and postoperative radiation therapy. In general, patients treated with neck dissection alone had a lower disease burden in the neck. Almost all patients underwent examination with biopsy and general anesthesia. Treatment predated cross-sectional imaging and the recent increase in HPV-associated cancers. Among patients treated with an operation alone, the mucosal progression rate was 18%. The recurrence rate in the ipsilateral neck was 13% for patients with NX-1 disease, and 32% for patients with N2-3 disease. Data from other series[3,11,12,54,55] substantiate that both mucosal progression and contralateral neck failure are uncommon in selected patients, even without radiation (Table 4). The most common sites of recurrence reported for SCCUP, even in the absence of pretreatment imaging, transoral diagnostic techniques, and radiation, are in the ipsilateral neck and distally. The notable exception to this is a Danish experience[3] that demonstrated high rates of mucosal emergence and neck recurrence. Because the stated policy of the Danish health system during the study period was to approach head and neck cancer with

Table 4. Primary Surgery Alone for the Treatment of Squamous Cell Carcinoma of an Unknown Primary

				Previous, %			%*			
Authors	No.	Years	NX/N1, %	EUA (with biopsy)	CT or MRI	PET	Mucosal Emergence	Ipsilateral Neck Failure	Contralateral Neck Failure	Distant Failure
Grau et al[3]	23	1975-1995	43	94 (55)	30 CT, 7 MRI	1	54	42		—
Jesse et al[6]	104	1948-1968	43	Almost all (usually)	0	0	20	24	16	—
Wang et al[11]	57	1953-1988	> 50	All	All pts from 1982 to 1988	0	11	12	—	13
Iganej et al[12]	29	1969-1994	17	100 (all after the late 1970s)	59	0	28	34	3	0
Coker et al[54]	26	1949-1976	35	69 (unknown)	0	0	12	8	4	16
Coster et al[55]	24	1965-1987	54	46 (unknown)	0	0	4	25	8	4

Abbreviations: CT, computed tomography; EUA, examination with anesthesia; MRI, magnetic resonance imaging; PET, positron emission tomorgraphy; pts, patients.
*Values for mucosal emergence, contralateral or ipsilateral neck failure, and distant failure reflect crude reporting.

primary radiation, these results likely reflected an uncertain selection bias.

Findings from detailed analyses suggest that ultimate control above the clavicles with salvage treatment is greater than 90% for patients with N1 disease without nodal extracapsular spread (ECS), and the current standard of care is to treat such patients with surgery alone. In practice, N1 SCCUP without ECS has been a rare condition, one that affected less than one patient every 2 years in a large series from referral centers.[4,8,9,10,13] In view of the known good prognosis for HPV-associated N2a disease in a patient who never smoked who was treated with single modality radiation alone[28] and the somewhat arbitrary distinction of 3 cm separating an N1 node from and N2a node,[56] surgery alone could possibly be adequate treatment for selected T0N2a SCCUPs as well. As discussed in this review and accompanying articles, deintensification treatment of tumors with a good prognosis will be a focus of inquiry in the future.

RADIATION WITH OR WITHOUT NECK DISSECTION

Most patients with SCCUP receive radiation. Most also undergo neck dissection. Reports of retrospective series rarely indicate whether neck dissection was performed before or after radiation as a component of combined-modality therapy. The timing of the neck dissection does not appear to influence disease-free survival.

SCCUP was historically treated with a three-field technique.[57] All mucosal sites and both sides of the neck were treated. This was supplanted by larynx-sparing techniques without a subsequent increase in mucosal failures in the blocked larynx and/or hypopharynx.[58] Today, salivary-preservation intensity-modulated radiation therapy has become the standard radiation technique for SCCUP.[8] This affords considerable flexibility to the radiation oncologist when determining which tissues receive radiation.

Unilateral Versus Bilateral Neck Irradiation

In most retrospective series involving radiation for SCCUP, both definitive and adjuvant, a few patients receive unilateral treatment. Because the percentage of patients treated unilaterally is almost always smaller than those treated bilaterally (Table 5), unilateral therapy seems to represent a departure from common practice. Despite this, mucosal emergence and contralateral neck recurrence are rare.[3,14,15,18,19,59,60]

EORTC 22205 was the single prospective randomized study of SCCUP. This was a phase III trial in which researchers compared comprehensive bilateral neck and mucosal radiation to 50 Gy, followed by a 10-Gy boost to the ipsilateral neck and ipsilateral neck radiation, with 60 Gy alone. Planned accrual was 600 patients; however, the trial was closed after 2 years because of poor accrual, and no results have been reported.

Routine bilateral neck radiation produces gratifying oncologic results (Table 6). Mucosal emergence occurs in fewer than 10%. Contralateral neck failure is extremely rare. In modern series, the most common source of recurrence is distant metastatic disease.

Mucosal Targets

The oropharynx is where an occult primary tumor is most commonly found. Therefore, the oropharynx has uniformly been treated if the mucosa is irradiated.[3,8,9,13-17,20,61] In view of the low but documented incidence of bilateral tonsil cancer[35] and emerging transoral investigations demonstrating primary tumors in the contralateral base of tongue, the current standard is to treat mucosal surfaces bilaterally. Although HPV is most directly associated with oropharynx cancer,[62] other primary tumors with involved lymph nodes above the clavicles may stain for the p16 protein[29,63] as well.

Although authors of historic SCCUP series reported rates of mucosal nasopharynx treatment in excess of 90%, omitting the nasopharynx from the treatment field in selected patients is increasingly common. Early experience suggested that treatment of patients not of Asian descent with p16-positive/EBV-negative neck nodes with this technique did not result in increased mucosal failure.[61] However, treatment to the ipsilateral retrostyloid space and the retropharyngeal nodes, recently termed level VII,[64] with an intensity-modulated technique generally delivers a considerable dose to the nasopharynx regardless of whether it is included in the clinical target volume. Hence, the effect of avoiding the nasopharynx may be small.

The previous paragraphs apply to SCCUP limited to level 2 or with a predominance of tumor in level 2 and smaller volume disease in level 3. This is by far the most common presentation of SCCUP, which is estimated to be 70% to 80%. SCCUP without level II nodes is much more likely to have a mucosal primary site of the supraglottic larynx or hypopharynx; therefore, larynx-sparing radiation would not be appropriate.

Mucosal Dose

Dosing of radiation to the neck follows that from treatment paradigms for known primary cancer, namely, 66 to 70 Gy for gross disease, 60 to 66 Gy for adjuvant therapy to high-risk areas, and 45 to 54 Gy to areas at risk for microscopic spread not considered to be high risk. Radiation doses to the mucosa are more variable. Clinicians at many institutions appear to treat the mucosa with a dose similar to that of the closed EORTC 22205 trial, that is, 50 Gy given in 25 fractions or 54 Gy given in 30 fractions. The rationale for this seems that an area without gross tumor, but at the risk of subclinical disease being present merits treatment with a subclinical dose of radiation regardless of whether the site is in the neck or the mucosa.[8] Other institutions prefer to increase the dose to the ipsilateral oropharynx to 60 to 64 Gy. The rationale for this is the knowledge that the ipsilateral oropharynx is the most likely location of the primary tumor,[46] and, therefore, an additional intermediate dose level is indicated. In view of the good prognosis for this disease and the paucity of mucosal failure regardless of elective radiation dose, intensifying the dose to the oropharynx affords little discernable benefit.

Chemotherapy

An increasing number patients are receiving primary chemoradiotherapy in the treatment of SCCUP (Table 5) although patients with SCCUP rarely present with traditional indications for concurrent systemic therapy, such as unresectable disease[65] or organ preservation.[66] Although not specifically stated in reports of the high utilization of chemoradiotherapy regimens, use of similar regimens seems to suggest that a patient with T0N2b disease is equivalent to one with T2N2b disease. This is not justified. Locoregional control of both small primary TX-1 oropharynx cancer[67] and SCCUP (Table 5) in the absence of systemic chemotherapy is excellent; this limits the rationale for adding concurrent chemotherapy in the treatment of SCCUP T0 to prevent distant metastases. The main benefit of concurrent systemic

Table 5. Unilateral Neck Radiation for Squamous Cell Carcinoma of an Unknown Primary

Authors	No.*	Years	Previous, %			%					
			EUA (with biopsy)	CT or MRI	PET	Chemoradiation	Neck Dissection	Mucosal Emergence	Ipsilateral Neck Failure	Contralateral Neck Failure	Distant Failure†
Grau et al[3]	26 of 352	1975 to 1995	94 (55)	30 CT, 7 MRI	1	0	15	12‡	Not reported, LRC 31%	4	7
Reddy and Marks[14]	16 of 52	1974 to 1989	All	All CT after 1978	0	0	60, 15 ExBx	44§	19§	44§	15§
Perkins et al[15]	21 of 46	1989 to 2008	100 (100)	100	50	IND 9, CRT 22	80, 7.5 ExBx	9.5	0	5%§	22%§
Marcial-Vega et al[18]	19 of 72	1965 to 1987	97 (89)	6	0	0	36, 7 ExBx	5%	—	—	31
Sinnathamby et al[19]	48 of 69	1983 to 1992	84 (unknown)	55 CT	0	0	39, 23 ExBx	13%§	29	4	6
Glyyne-Jones et al[59]	34 of 87	1954 to 1986	94 (94)	0	0	0	7	6‡	24	2	18
Weir et al[60]	85 of 144	1970 to 1986	92 (68)	67 plain radiography and CT	0	0	0, 49 ExBx	7‡	46	3	8

Abbreviations: CRT, concurrent chemotherapy; CT, computed tomography; EUA, examination with anesthesia; ExBx, excisional biopsy; IND, induction chemotherapy; MRI, magnetic resonance imaging; LRC, local-regional control; PET, positron emission tomography.

*The number listed is the number of patients noted to receive unilateral neck radiation. The number in parentheses is the total number of patients noted in the citation.

†For the entire series.

‡Head and neck only.

§Actuarial value reported in the citation. Otherwise, values of mucosal emergence, contralateral or ipsilateral neck failure, and distant failure reflect crude reporting.

Table 6. Bilateral Neck Radiation

Authors	No.*	Years	Previous, %			% †					
			EUA (with biopsy)	CT or MRI	PET	Chemoradiation	Neck Dissection	Mucosal Emergence	Ipsilateral Neck Failure	Contralateral Neck Failure	Distant Failure‡
Grau[3]	224	1975 to 1995	94 (55)	30, 7	1	0	9, 45 ExBx	8§	Not Reported, LRC 48	2	7
Keller et al[4]	35	1990 to 2010	100 (100)	100	40	11	89, 11 ExBx	3	0	0	8
Ligey et al[7]	36	1990 to 2007	— (19)	Varied, 2	17	6 IND, 39 CRT	83	6	19		30
Frank et al[8]	52, 46	1998 to 2005	100 (—)	100	50	15 IND, 12 CRT	50, 27 ExBx	2‖	4	2	8‖
Chen et al[9]	60	2001 to 2009	100 (100)	100 CT	32	53	70, 5 ExBx	3	5	2	16‖
Demiroz et al[10]	41	1994 to 2009	100 (100)	100 CT or MRI	66	61	54, 29 ExBx	5	5	0	20
Colletier et al[13]	136, 120	1968 to 1992	96 (83)	45	0	0	71, 29 ExBx	8‖	8	1	15‖
Reddy et al[14]	36	1974 to1989	All	All after 1978	0	0	63	8	31	14	15
Perkins et al[15]	25	1989 to 2008	100 (100)	100 CT or MRI	36	28	68, 8 ExBx	4	0	0	22
Cuaron et al[16]	85	1995 to 2012	—	—	—	49	66	1	8	5	13
Sher et al[17]	24	2004 to 2009	100 (100)	100 CT	100	29 IND, 100 CRT	25, 33 ExBx	0	0	0	4
Wallace et al[20]	179	1964 to 2006	87 (—)	74 CT, 8 MRI	9	1 IND, 5 CRT	61	8‖	19‖		14‖
Mourad[61]	68	1998 to 2010	All	—	—	56	44, 6 ExBx	2	3	0	0

Abbreviations: CRT, concurrent chemotherapy; CT, computed tomography; EUA, examination under anesthesia; ExBx, excisional biopsy; IND, induction chemotherapy; LRC, local-regional control; MRI, magnetic resonance imaging; PET, positron emission tomography.

*In two series, a small number of patients were treated unilaterally. The second number represents the total number of patients treated bilaterally. Outcomes of those treated unilaterally were not reported separately from those treated bilaterally. Data are based on all patients treated as reported in the citations.

†Values reported for mucosal emergence, ipsilateral or contralateral neck failure, and distant failure reflect crude reporting unless otherwise specified.

‡In all instances, distant metastases are reported as a single number in these citations regardless of different treatment techniques.

§Head and neck only.

‖Actuarial rate at 5 years.

therapy is locoregional control; the distant benefit is dubious.[65,68] This point is not trivial; the toxicity of chemoradiotherapy[69] may be justified to avoid operations with an adverse effect on speech and swallowing, but surgical therapy of SCCUP rarely involves an operation associated with more morbidity than neck dissection.

In the adjuvant setting, chemoradiotherapy appears to be administered for ECS, as extrapolated from prospective studies[68] that included no patients with SCCUP and relatively few with oropharyngeal cancer. In view of recent analyses,[70] it is reasonable to assume that the future interpretation of ECS on a pathology report will change from the binary present or absent to a grades describing the extent of ECS. The single SCCUP series in which the degree of ECS was analyzed showed that 32% of cases noted to have ECS on the pathology report had spread of less than 1 mm and behaved similar to cases without ECS when managed without chemotherapy.[4]

Although reports of toxicity in SCCUP are lacking because of the retrospective nature of the analyses, the addition of concurrent chemotherapy to radiation increases acute and late toxicity.[9] In the past two decades, treatment SCCUP has intensified as a result of the addition of concurrent systemic therapy to pharyngeal axis radiation. In light of practice patterns favoring deintensification for patients who have a good prognosis, a term that applies to most with SCCUP, chemoradiotherapy should not be used as a matter of course.

TREATMENT RECOMMENDATIONS

The rarity of SCCUP dictates that treatment recommendations are based on institutional bias. Treatment principles are summarized as follows:

- T0N1 SCCUP is a rare condition that does well regardless of primary treatment. Treatment for patients should involve a single modality. For most patients, this will be a neck dissection alone, although radiation alone would be expected to afford similarly good results.
- T0N2a SCCUP is a common presentation of SCCUP. Patients with a favorable risk factor profile, that is, p16 positive, smoking history of less than 10 pack-years, and no clinical and/or radiographic evidence of ECS, should be treated with single-modality therapy consisting of either surgery alone or radiation alone. T0N2a cases that are p16 negative or p16 positive associated with smoking history of more than 10 pack-years should receive surgery plus radiation. T0N2a with clinical and/or radiographic ECS should be managed with primary chemoradiotherapy. This is because adjuvant chemoradiotherapy will likely be required and thereby diminish the utility of the neck dissection. Approximately 12 weeks after the completion of chemoradiotherapy a PET and/or CT should be performed to evaluate the metabolic response of the initially involved nodes. Patients in whom a complete metabolic response in not achieved should be treated with neck dissection.
- T0N2b is a common presentation of SCCUP. Two commonly administered treatment regimens afforded good results in retrospective series. One is neck dissection followed by adjuvant radiation, and the other is primary chemoradiotherapy. The choice between these regimens is dictated by institutional bias. These two regimens impose different adverse effects on the patient's quality of life. It is unknown which is better. T0N2b with clinical and/or radiographic ECS should be managed with primary chemoradiotherapy. Adjuvant chemoradiotherapy will likely be required and thereby diminish the utility of the neck dissection. Approximately 12 weeks after the completion of chemoradiotherapy, PET and/or CT should be obtained to evaluate the metabolic response of the initially involved nodes. Patients in whom a complete metabolic response is not achieved should be treated with neck dissection.
- T0N2c is a rare diagnosis that should be managed with primary chemoradiotherapy. Approximately 12 weeks after the completion of chemoradiotherapy, a PET and/or CT should be obtained to evaluate the metabolic response of the initially involved nodes. Heminecks that do not demonstrate a complete metabolic response should be managed with neck dissection.
- T0N3 is a common presentation of SCCUP. It should be managed with primary chemoradiotherapy, as many N3 neck nodes harbor ECS. If findings from imaging and physical examination do not suggest ECS, patients can alternatively be treated with surgery followed by adjuvant radiation, with the understanding that many patients with T0N3 disease will ultimately be found to have ECS during surgical pathology and require adjuvant chemoradiotherapy, which diminishes the utility of neck dissection. Approximately 12 weeks after chemoradiotherapy is completed, PET and/or CT should be obtained to evaluate the metabolic response of the initially involved nodes. Patients without a complete metabolic response should be treated with neck dissection, and neck dissection, even with a favorable metabolic response, is not unreasonable.
- Patients with clinical or radiographic findings strongly suggestive of ECS should be treated with primary chemoradiotherapy.
- The wisdom of routine administration of adjuvant chemoradiotherapy for microscopic ECS on a p16-positive pathology report is unknown. In the future, prospective trials involving patients with p16-positive known primaries, a population similar to most patients with SCCUP, will inform the relevance of microscopic ECS in this population. In the absence of such data, any degree of ECS remains an indication for adjuvant chemoradiotherapy.
- The current standard of care at most institutions is radiation of the contralateral neck and mucosal subsites, although its use increases toxicity and is probably seldom necessary. Prospective efforts to identify patients for whom such volume reductions do not increase failures are warranted.

CONCLUSION

Modern SCCUP treatment confers disease control superior to that demonstrated in historic series. However, many patients included in early reports would likely have had their primary cancers identified in modern times as a result of improved diagnostic techniques. Most

SCCUPs in North America today are associated with HPV; therefore, future issues surrounding SCCUP will likely center on amelioration of toxicity. Although the difference in toxicity between neck dissection followed by risk-adapted radiation and primary radiation or chemoradiation remains to be defined, the importance of combined-modality therapy may decline. In the future, the number of patients for whom surgery or radiation alone is thought to be the best treatment will likely expand. The possibility that N1, N2a, and selected N2b SCCUPs could be treated with a single modality in the future warrants consideration. The single modality—surgery or radiation—that has the best therapeutic ratio should be defined. By applying general principles of head and neck oncology, oncologists can achieve disease control in the great majority of patients with SCCUP.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Squamous Cancer Metastatic to Cervical Nodes With an Unknown Primary Site

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