39 Cervical Lymph Node Metastases of Squamous Cell Carcinoma from an Unknown Primary Site

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Abstract

Cancer of unknown primary (CUP) is a well-recognized clinical disorder where the primary site cannot be identified after a standard diagnostic approach and it accounts for 3–5 % of all tumors. CUP is distinguished into two different clinicopathological entities, favorable or unfavorable. The subset of squamous cell carcinoma metastatic to cervical lymph nodes constitutes the 5 % of all head-and-neck cancers. For detection of the primary site, all patients need a detailed clinical examination and imaging investigation including PET scans, panendoscopy with directed biopsies, and possibly bilateral tonsillectomy. Lymph nodal stage, extracapsular spread, and HPV status are considered as the most prominent prognostic factors. Although, randomized trials are lacking concerning the optimal therapeutic management, combined-modality treatment is offering the most encouraging results. Surgery alone is indicated in N1 or N2a stages. Radiotherapy is used as a single modality for early-stage pN1 without extracapsular extensions or combined with neck dissection as postoperative therapy in more advanced disease. Chemoradiation can also be given in a neoadjuvant setting followed by surgery in certain cases as well in patients with comorbidities. Prognosis in general is encouraging with 5-year progression-free and overall survival rates of 85 % and 75 %, respectively.

Keywords

Cancer of unknown primary • Metastatic squamous cell carcinoma • Cervical nodes • Treatment • Prognosis

39.1 Introduction

Cancer of unknown primary (CUP) represents a heterogeneous group of malignancies presenting with distant metastases without an identified primary tumor at diagnosis. The nature of CUP remains unanswered. The primary tumor may either have a slow growth rate or it may possibly involute.

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In a general medical oncology service, metastatic carcinoma of unknown primary site is not a rare diagnosis. CUP accounts for 3–5 % of all tumors. Similarly, in a head-and-neck or otolaryngology department, the proportion of patients presented with cervical lymph node metastatic disease of not known origin follows more or less the same pattern.

Today, the definition of CUP includes patients who present with histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT scan) of the abdomen and pelvis and in certain cases mammography, magnetic resonance imaging (MRI), and position emission tomography (PET scan) fail

J. Bernier (ed.), *Head and Neck Cancer*, DOI 10.1007/978-3-319-27601-4_39

to identify the primary site. Recently, gene expression-profiling platforms were shown to accurately assign CUP to a primary tissue of origin with, however, unknown impact on patient outcome [1–3].

In general, CUP is associated with dismal prognosis with a median survival of 9–12 months. Nowadays, CUP patients are divided into various subsets of favorable or unfavorable prognosis. Patients with cervical lymph node metastases from an unknown primary site of squamous cell histology (SQ-CUP) belong to the favorable prognostic subsets of CUP [1, 2].

Every medical or surgical specialty could come across to a CUP patient, and therefore they should be aware of the optimal diagnostic and therapeutic approach of these patients.

39.2 Incidence

In 1957, the first definition of cervical lymph node metastasis of an unknown primary site was reported by Comess et al. [4].

Cervical lymph node metastases from SQ-CUP constitute approximately 5 % (range 1–10 %) of all head-and-neck cancers [5]. The annual incidence of SQ-CUP tumors is 0.34 cases per 100,000 per year [6]. Median age is around 57–60 years (range 30–80 years) and almost 80 % of the patients are males. They usually carry a history of chronic tobacco or alcohol use.

Squamous cell histology is the most common type representing the 75 % of the cases, followed by undifferentiated carcinoma and adenocarcinoma [7]. Regarding the distribution of involved cervical lymph nodes, jugulodigastric nodes are the most commonly affected (71 %) followed by midjugular nodes (22 %) [8].

In this chapter only patients with squamous cell histotype will be discussed, since patients with other histological types are managed differently and carry different prognosis.

39.3 Diagnostic Evaluation

The diagnostic approaches in patients with SQ-CUP refer firstly to the establishment of the histopathological type of the tumor and secondly to the detection of the primary tumor site.

Therefore, the diagnostic maneuvers include (a) physical examination, (b) fine-needle aspiration (FNA) or biopsies, (c) endoscopic examination, and (d) imaging studies.

39.3.1 Physical Examination

A painless and unilateral cervical mass is the most common clinical presentation. The site of palpable cervical lymph nodes could be useful in suggesting the possible primary tumor site. In patients with squamous cell histotype, the jugulodigastric and midjugular lymph nodes are most commonly involved, whereas metastatic adenocarcinoma is more frequently diagnosed in the low cervical or supraclavicular areas.

In addition, based on the metastatic lymph node level, several probable sites of the primary tumors can be predicted, that is:

(a) If submandibular nodes (level I) are involved, the primary site could be in the floor of the mouth, lips, and anterior tongue. (b) If jugulodigastric or upper jugular nodes (level II) are affected, search for a primary tumor in the epipharynx, base of the tongue, tonsils, nasopharynx, and larynx. (c) If middle and lower jugular nodes (levels III and IV) are involved, the most likely primaries are located in the hypopharynx or larynx. (d) If supraclavicular nodes (level V) are the metastatic sites, the possible primary tumors could be derived from the lungs, thyroid, breast, gastrointestinal, or genitourinary system [8, 9] (Table 39.1).

The most commonly involved level is level II (30–50 %), followed by level I and III (10–20 %) and levels IV and V (5–10 %).

39.3.2 Cytology and Histopathology

Fine-needle aspiration (FNA) is most commonly used as a first step diagnostic procedure to establish malignancy. The diagnostic accuracy of FNA in these patients is close to 95 % [10].

Incisional biopsy of enlarged cervical nodes remains controversial since higher rates of local recurrence has been observed due to seeding of tumor cells along the tract [11, 12]. However, open biopsy is indicated if the mass is suspected to be lymphoma, sarcoma, melanoma, or adenocarcinoma.

While traditional histochemistry has been established as a useful technique in other tumor types, it has not proven

Table 39.1 Location of neck nodes and possible site of primary tumor

Level	Neck nodes involved	Possible primaries
I	Submental, submandibular nodes	Mouth's floor, lips, anterior tongue
II	Jugulodigastric/upper jugular nodes	Epipharynx, base of tongue, tonsils, nasopharynx, larynx
III	Middle jugular nodes	Supraglottic larynx, inferior pyriform sinus, post-cricoid region
IV	Inferior jugular nodes	Hypopharynx, subglottic larynx, thyroid, esophagus
V	Supraclavicular	Lungs, thyroid, breast, gastrointestinal system

particularly helpful in the diagnostic workup of SQ-CUP. Advanced molecular techniques such as in situ hybridization or polymerase chain reaction could be useful as surrogate markers in detecting Epstein-Barr virus (EBV) or human papillomavirus (HPV), differentiating a nasopharyngeal or oropharyngeal primary cancer, respectively [13, 14].

39.3.3 Endoscopic Examination

If history, physical examination, and imaging studies are unrevealing to identify a primary site, the patient should undergo a panendoscopy under anesthesia with the use of a flexible nasopharyngoscope. Blind biopsies from the nasopharynx, tongue base, tonsil, and pyriform sinus are recommended. Esophagoscopy and bronchoscopy are also parts of panendoscopic examination [8, 15].

39.3.4 Imaging Studies

Imaging investigation in SQ-CUP patients include CT scan, MRI, and PET scan. The goals of performing imaging studies in these patients include, first, the detection of primary site in the head-neck region or in the lungs and, second, the staging evaluation of lymph nodal status before any local-regional treatment.

Imaging should be performed prior to any invasive procedure or treatment in order to avoid any diagnostic misinterpretation.

CT scan is considered as the imaging study of choice, because it has a low cost and offers detailed anatomical information. Primary tumor detection rate is approximately 22 % [16, 17].

MRI has a higher accuracy in identifying the primary site of 36 %. Due to better soft tissue definition compared to CT scan, it makes it more useful for investigating the area of the nasopharynx and oropharynx [18, 19].

PET has also been used in patients with SQ-CUP. In both prospective studies and meta-analysis, ^{18}F-FDG PET showed a diagnostic accuracy in detecting the primary site up to 28 % with sensitivity and specificity of 84 % and modification of treatment plans in almost 30 % of the patients [20–23].

A disadvantage of FDG-PET, however, is its lack of anatomic information with precise localization of FDG accumulation. Therefore, the application of combined FDG-PET/CT or MRI could offer a greater value for the detection of primary site.

Recently, there is evidence that narrow band imaging with magnifying endoscopy might be useful in the detection of unknown head-and-neck primary sites. A detection rate of 45–55 % has been reported [24, 25].

Table 39.2 Nodal staging in patients with SQ-CUP

Nodal disease	Nodal characteristics
N1	Single ipsilateral node <3 cm
N2a	Single ipsilateral node 3–6 cm
N2b	Multiple ipsilateral nodes <6 cm
N2c	Bilateral or contralateral nodes <6 cm
N3	Lymph node >6 cm

39.4 Prognostic Factors

The prognostic outcome of patients with SQ-CUP is based on several endpoints such as the overall survival, disease-free survival, distant failure, or local-regional control.

Numerous treatment and patient- or tumor-related variables have been implicated. However, the most prominent prognostic factors correlated with disease outcome are two tumor-related variables, the lymph nodal stage and the extracapsular spread [5].

Table 39.2 demonstrates the neck nodal staging.

39.5 Treatment

The optimal therapeutic management of patients with SQ-CUP remains controversial as a result of the absence of randomized studies comparing treatment options. Therefore, the treatment is mainly based on nonrandomized evidence as well as on institutional policies.

39.5.1 Surgery

Surgical therapy includes excisional biopsy, neck dissection ("radical," "modified," or "selective"), and tonsillectomy.

"Radical neck dissection" refers to the removal of the levels I–V neck nodes, which at the same time sacrifices the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. "Modified radical neck dissection" removes the same nodal levels but spares the rest of the neck structures. It is important to notice though that preservation of spinal accessory nerve saves shoulder mobility. "Selective neck dissection" targets specific nodal groups and it is considered as the safest operational procedure.

Patients with N1- or N2a-limited disease without extracapsular extension could be treated with surgery alone. Local-regional control rates range from 80 % to 90 %, median nodal recurrence rate about 34 %, and 5-year overall survival rate up to 65 % [26–29].

Therefore, neck dissection alone is advocated only for patients with N1 and N2a disease without extracapsular spread, whereas postoperative irradiation is indicated in

cases with an incisional or excisional biopsy and in patients with extracapsular extension.

Tonsils are considered as one of the commonest site of a hidden primary site in patients with SQ-CUP. Although the true incidence is not known, it is estimated to be between 18 % and 40 % [30].

Various reports suggest that directed random biopsies or unilateral or even bilateral tonsillectomy should be part of the screening for detection of the occult primary tumor [30–34]. It is interesting that in 10 % of the cases, the primary tonsilar lesion is located in contralateral to the metastatic cervical nodes [30].

Nowadays, several specialized centers recommend bilateral tonsillectomy (screening tonsillectomy) as standard procedure in the investigation of patients presented with subdigastric, mid-jugulocarotid, or submandibular nodal metastases.

39.5.2 Radiotherapy

Radiotherapy (RT) in SQ-CUP is used as:

(a) A single modality for early-stage pN1 without extracapsular extension (involved field RT) or after excisional or incisional biopsy of the neck before definitive treatment
(b) Combined with neck dissection as postoperative RT in stages N1 with extracapsular extension or stages N2–N3
(c) Initial chemoradiation followed by operation (in those patients who do not achieve a clinical or metabolic (PET), complete response) in stage N1 with extracapsular extension, stages N2–N3, and large nodes fixed to the adjacent structures (e.g., to the carotid sheath)
(d) Chemoradiation in patients with comorbidities, which make them unable to tolerate radical surgery

Although the value of irradiation of the potentially (occult) primary sites has not been confirmed by randomized studies, some authors have observed that mucosal irradiation reduced both the emergence of primary tumor and regional recurrence but without affecting overall survival [35–38]. A higher 5-year overall survival rate has been reported, although in a retrospective study, for patients treated with extensive radiotherapy including neck nodes and the entire pharyngeal mucosa relatively to those treated by more limited volumes (57.6 % vs. 24 % $p<0.01$) [39]. However extensive bilateral and mucosal RT seems not to be indicated for all patients, particularly if close follow-up is provided.

Radiotherapy portals encompass the sites shown in Table 39.3, according to the level of the neck affected (Fig. 39.1) [41, 42]. The dose usually given with standard fractionation (dose per fraction of 1.8–2 Gy) is for the neck, 65–70 Gy to the involved nodal stations and 50 Gy for the uninvolved sites, and for the mucosal sites usually 50–60 Gy. In case of clinically suspicious mucosal sites, a dose of 60–64 Gy is recommended. However IMRT (integrated

Table 39.3 Occult primary sites to be included in radiotherapy fields, according to the level of the enlarged lymph nodes

Levels of the neck	Sites to be irradiated
I	Oral cavity, Waldeyer's ring, oropharynx, both sides of the neck. Protection of larynx
II, III, (upper) V	Nasopharynx, oropharynx, hypopharynx, larynx, both sides of the neck, to the level of the clavicles
IV only	Waldeyer's ring, larynx, hypopharynx, both sides of the neck
Lower level V	Larynx, hypopharynx, both sides of the neck, generous regional portal to include adjacent apex of the axilla
Preauricular	Radiotherapy alone (or combined with parotidectomy). Squamous cell carcinoma is suggestive of skin cancer

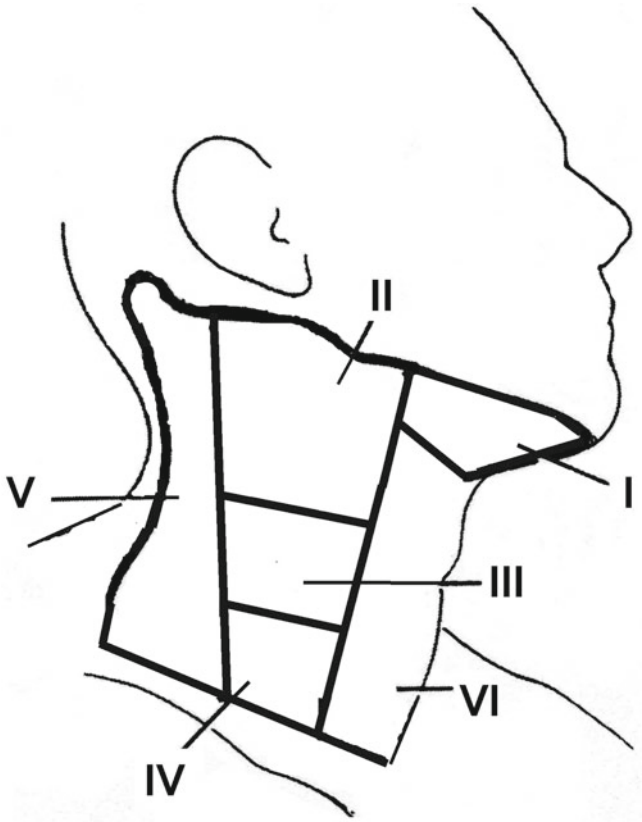

Fig. 39.1 The head-and-neck lymph node areas are currently classified into six levels (I–VI): I, submandibular and submental; II, jugulodigastric (base of skull to hyoid); III, deep cervical (hyoid to cricoid); IV, Virchow's nodes (cricoid to clavicle); V, accessory spinal (superior and inferior posterior triangle). VI, Supraclavicular The lymphatics of the head and neck follow several drainage pathways depending on their origin (see also Table 39.3). This is an important information for the design of radiotherapy portals in squamous cell cancer of the neck, of unknown primary. The figure roughly illustrates the six levels. For detailed description, see reference [40]

boost intensity-modulated radiotherapy) allows treatment to be given keeping overall treatment time as short as 6 weeks and allows boost doses of hypofractionated radiation (2.2 Gy/fraction) to be given to gross nodal disease simultaneously with standard-fraction radiation (range, 1.8–2 Gy) to sites at risk of harboring microscopic disease [43].

In a report from MD Anderson Cancer Centre [43] on IMRT, among a total of 52 patients, 26 patients had undergone neck dissection, 13 before and 13 after IMRT; 14 patients had undergone excisional biopsy and presented for IMRT without evidence of disease. Fourteen patients had received chemotherapy. All patients underwent IMRT to targets on both sides of the neck and pharyngeal axis. After a median follow-up time of 3.7 years, the 5-year actuarial rate of primary mucosal tumor control and regional control was 98 % and 94 %, respectively. The 5-year actuarial disease-free and overall survival rate was 88 % and 89 %, respectively.

In the above study [43], the nodal targets in the head and neck included the retropharyngeal nodes and both sides of the neck based on the approach that a significant proportion of patients with neck metastases have an occult malignancy in the pharyngeal axis. Inclusion of the neck node levels was determined by the involvement of the side of the neck. The dose prescribed to the entire mucosa of the pharyngeal axis was 54 Gy at 1.8 Gy/fraction. On the side of the neck containing disease, the uninvolved nodes at levels IB and V were treated electively to 54–60 Gy. The median dose prescribed to the CTV for gross nodes with a margin of 0.5–1 cm was 66 Gy (range, 60–72). The median dose prescribed to the dissected necks was 60 Gy (range, 60–70). The prescribed dose to the uninvolved contralateral neck was 54 Gy; level II–IV nodes were treated and included in either the IMRT fields or a separate low-neck field. The nodes at levels IB and V were not treated in the uninvolved sides of the neck.

If the operative bed extended into the low-neck field, or if gross adenopathy was present within 1 cm of the junction, a boost dose of 6–10 Gy was delivered to the neck on the involved side using either an appositional electron beam or photons.

Sites of gross nodal disease were treated with 66 Gy in 30 fractions, with consideration of an electron boost to 70 Gy. Uninvolved, nonoperated lymph node-negative regions of the neck were treated to 54 Gy in 30 fractions. In postoperative RT positive neck was treated to 60 Gy in 30 fractions with or without a boost to the involved site to 64 Gy if ECE is present.

The most noteworthy advantage of IMRT in the treatment of head-and-neck cancer of unknown primary origin appears to be related to its ability to preserve salivary function. Local-regional control and survival are significantly improved after 3D-CRT or IMRT, but even with IMRT, the acute and late toxicity of extensive elective irradiation of potential primary sites and *both* sides of the neck is significantly more pronounced than when RT is limited to the involved neck [40]. The advantage of IMRT over 3D conformal is suggested by recent studies [43–50].

The use of systemic treatment is expected to yield similar improvement in outcome as has been observed for known head-and-neck primary tumors. Chemo-radiotherapy has been mainly suggested for patients with extracapsular spread of the disease or with stages N2b–N3. In case of initially bulky neck disease, induction chemotherapy followed by chemo-radiotherapy is sometimes given, although higher toxicity is expected and this is not supported by clinical studies. In the study by Sher et al. [48] on 24 patients treated by IMRT and concurrent or induction chemotherapy, the median involved nodal dose was 70 Gy and the median mucosal dose was 60 Gy. With a median follow-up of 2.1 years, the 2-year actuarial overall survival and local-regional control rate was 92 % and 100 %, respectively. Only 25 % of the patients had grade 2 xerostomia, although 11 patients (46 %) required esophageal dilation for stricture.

In another larger retrospective study by Chen et al. [49], with 51 patients treated either with conventional RT (24 patients) or with IMRT (27 patients), the proportions of those who also received chemotherapy were 54 % and 63 %, respectively. The 2-year estimates of overall survival, local-regional control, and disease-specific survival for the entire patient population were 86 %, 89 %, and 84 %, respectively, but there were no significant differences in any of these endpoints with respect to radiation therapy technique. However the incidence of severe xerostomia in the late setting was 58 % and 11 % among patients treated by conventional RT and IMRT, respectively ($p<0.001$). The percentages of patients who were G-tube dependent at 6 months after treatment were 42 % and 11 %, respectively ($p<0.001$).

An interesting finding from dosimetric analysis was that the use of IMRT resulted in significant improvements with respect to mean dose and V_{30} to the contralateral parotid gland. In addition, mean doses to the ipsilateral inner and middle ear structures were significantly reduced with IMRT ($p<0.05$ for all).

In another report [50], 25 patients were treated with IMRT with a median radiation dose of 70 Gy. The bilateral neck and ipsilateral putative pharyngeal mucosa were included in the target volume and, from the 25 patients, 18 (72 %) received platinum-based chemotherapy in a combined-modality setting. With a median follow-up of 38 months, the overall survival, disease-free survival, and local-regional control rates were all 100 % at 3 years. No occurrence of primary cancer was observed during the follow-up period. The reported rates of xerostomia reduced with the interval from the completion of treatment. Nine patients (36 %) reported grade 2 or greater xerostomia at 6 months, and only 2 (8 %) of them reported the same grade of salivary function toxicity after 24 months of follow-up.

Main acute radiation toxicity consists of dysphagia and mucositis especially in patients treated with combined chemo-radiotherapy compared with those treated with radiotherapy alone. Xerostomia is the main late complication of radiotherapy. Other late effects are persisting edema of the larynx or skin, soft tissue fibrosis, necrosis, and osteoradionecrosis. Combining postoperative complications and post-chemotherapy toxicity can potentially affect the quality of life especially of the long-term surviving patients. This underlines the significance of advanced radiotherapy techniques, such as 3D conformal but mainly IMRT, regardless of any anticipated benefit on tumor control.

According to the abovementioned retrospective study from MD Anderson Cancer Centre [43], severe late complications were uncommon after IMRT combined with surgery and/or chemotherapy. The most severe toxicity was grade 3 dysphagia due to esophageal stricture, experienced by 2 out of 52 patients.

The HPV status of the tumor can be used as a marker of radiosensitivity. Several retrospective studies [51–54] and a prospective analysis of data from a clinical trial [53] confirmed that HPV positivity confers a 60–80 % reduction in risk of death from cancer relative to similarly treated HPV-negative tumors. HPV positivity, particularly in nonsmokers, might be considered (although not definitely confirmed so far) an indication for less intensive or single-modality treatments [40].

39.5.3 Chemotherapy

Concurrent chemo-radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck significantly improves response rate and overall survival [55–57]. In addition, the combination of platinum-based chemotherapy with cetuximab increased efficacy as first-line treatment in patients with recurrent or metastatic head-and-neck cancer [58]. All these studies are large well-conducted randomized studies published during the last few years.

Unfortunately, up to now, there are no randomized reports on the efficacy of chemo-radiotherapy in patients with SQ-CUP. To the best of our knowledge, there are only four retrospective studies with approximately 100 patients treated with various cytotoxic drugs (platinum or non-platinum). Chemotherapy was administered before, during, or after radiotherapy, and results in some studies were compared with historical controls [39, 59–61].

In the oldest study, complete response rate to combined treatment was 81 % and median survival was 24 months [59]. In the second study, the 5-year progression-free and overall survival rate was 87 % and 75 %, respectively [60]. In the third report, the local-regional control and overall survival rates were 95 % and 89 %, respectively [61]. In the last report published in 2007, chemotherapy was administered as neoadjuvant or concomitantly to radiotherapy in 52 % and 48 % of the patients, respectively. Disease-free survival and 5-year overall survival were 17 % and 26.5 %, respectively [39]. It is worthwhile to notice also that acute or late toxicities following aggressive combined treatment were acceptable in these small studies.

Based on these encouraging preliminary results, prospective multicentric studies in a larger number of SQ-CUP patients will be warranted, in order to establish the efficacy of concurrent chemo-radiotherapy in a cohort of patients with bulky neck disease.

39.6 Discovery of Primary Site

The incidence of the appearance of primary site is around 10 % (ranging between 5 % and 30 %), and it usually occurs within the first 2 years of treatment. Several authors consider primary tumors arising later than 5 years after primary diagnosis as second primaries [5, 15].

The most common sites of the appearance of primary tumors include the nasopharynx, base of the tongue, tonsil, and pyriform sinus. Patients undergoing bilateral tonsillectomy have threefold increase chance to discover the primary site in the tonsils [62]. On the contrary, patients treated with radiotherapy bilaterally to the neck as well as to mucosa sites seem to decrease considerably the appearance of mucosal primary sites [63].

39.7 Conclusions

SQ-CUP most commonly affects middle-aged men and typically presented as a painless neck mass. More than 90 % of these cases represent squamous cell carcinoma originating within Waldeyer's ring (nasopharynx, tonsil, and base of tongue). The other 10 % comprised of other histologies such as adenocarcinoma, undifferentiated carcinoma, or other variants. Following diagnosis of metastatic cervical disease, all patients require a thorough head-and-neck history and clinical examination, radiographic imaging including PET scan, panendoscopy with directed biopsies of Waldeyer's ring, and possibly bilateral tonsillectomy.

Lymph nodal stage and extracapsular spread are considered as the most prominent prognostic factors.

The optimal treatment of SQ-CUP has not yet been defined. Randomized trials are lacking. Definitely, combined-modality treatment is offering a better outcome. Surgery alone is indicated in early stages (N1 or N2a), whereas neck dissection followed by postoperative radiotherapy is indicated in more advanced disease. The extent of radiation portal coverage though remains controversial. The role of chemotherapy as neoadjuvant, concomitantly, or adjuvant modality is waiting to be elucidated. Nevertheless, the 5-year survival rates are still encouraging.

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