

# Metastatic Squamous Cell Carcinoma of the Neck with Unknown Primary Site

JOSÉ FRANCISCO GALLEGOS-HERNÁNDEZ<sup>1\*</sup>, FRANCISCO GERARDO ROSALES-SOTO<sup>1</sup> AND IVÁN CRUZ-ESQUIVEL<sup>2</sup>

<sup>1</sup>Department of Head and Neck Tumors, Hospital de Oncología, CMN SXXI, IMSS, Mexico City, Mexico; <sup>2</sup>Department of Oncological Surgery, Centro de Oncología Estatal, Campeche, Camp., Mexico

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## ABSTRACT

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When node metastases are identified in the neck, but the clinical assessment using imaging and endoscopic procedures does not enable identifying the primary site, the established diagnosis is metastasis with unknown primary site. In these cases the majority of patients have the malignancy confined to the supraclavicular area, thus making it unnecessary to perform a systematic search.

The majority of metastases are squamous cell carcinoma, the most common tumor originating in the mucous membranes of the head and neck.

The lack of a primary site forces us to not only treat the neck, but also probable primary sites and the contralateral neck. However, the morbidity brought about by this treatment is currently questioning its routine use.

The great majority of patients cannot be treated with only one therapeutic treatment and must be subjected to surgery, radiotherapy, or an association of chemoradiotherapy, but the key to the therapeutic decision is correct staging.

Intensity modulated radiotherapy, and the value of the human papilloma virus and Epstein Barr virus in the etiology of head and neck cancer have changed the therapeutic approach to this entity. The purpose of this study is to offer readers the latest diagnostic-therapeutic bases for this neoplasia. (J CANCEROL. 2015;2:161-9)

Corresponding author: José Francisco Gallegos Hernández, gal61@prodigy.net.mx

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### Correspondence to:

\*José Francisco Gallegos Hernández  
Departamento de Tumores de Cabeza y Cuello  
Hospital de Oncología  
Centro Médico Nacional Siglo XXI, IMSS  
Avda. Cuauhtémoc, 330  
Col. Doctores, C.P. 06725  
Mexico, D.F., Mexico  
E-mail: gal61@prodigy.net.mx

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## INTRODUCTION

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It is quite common for head and neck cancer consulting rooms to receive referred patients with lateral tumors of the neck without any clinical evidence of their cause, or with a background of having been subjected to a biopsy of a mass in the neck whose histopathological report is “metastasis of squamous cell carcinoma”, and this entity forces us to identify the origin of the metastasis. If after having exhausted all clinical, endoscopic, and imaging study techniques the primary site is still unidentified, the patient is grouped under the entity known as “metastatic cancer with unknown primary site” (MCUP).

The diagnosis and treatment of MCUP have changed radically over the last 10 years as a result of better technology to identify the primary tumor, knowledge of the oncological behavior of these patients, identification of risk factors, and development of treatment techniques that improve the quality of life without prejudicing neoplastic control.

Examples of this progress are: the use of positron emission tomography-chemotherapy (PET-CT) in the diagnosis-staging process; the possibility of reducing the aggressiveness of the treatment based on the presence or not of human papillomavirus (HPV, currently recognized as a good prognosis factor); the identification of patients with a high risk of recurrence who not only require adjuvant treatment with radiotherapy, but also the association of chemoradiation treatment; the screening of patients based on the ganglionic status for dissection of the neck that is not only less aggressive, but also more selective in extension; and the increased use of intensity modulated radiotherapy that considerably reduces the severity of undesirable effects and thus improves the quality of life<sup>1,2</sup>.

The purpose of this article is to analyze the diagnosis-therapeutic methods used in these patients based on current clinical evidence.

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## EPIDEMIOLOGY

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The MCUP are more frequent in male patients between the fifth and seventh decade of life, generally among people who smoke and drink alcohol, and represent approximately 5% of neoplasias of the head and neck area.

The neck levels where they are more commonly presented are II, III, and IV and the most frequently found stage is cN2b followed by cN1b<sup>1</sup>.

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## PATHOGENICITY

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Over 80% of MCUP are squamous cell carcinoma so that the term MCUP refers to this type of malignancy; 20% of metastasis in the neck is comprised of various histologies such as adenocarcinoma, melanoma, undifferentiated carcinoma, and lymphoepithelioma<sup>2</sup>. Each of these histologies requires different assessment and they do not form part of the purpose of this review.

There are three main reasons why the primary tumor cannot be found:

- The cervical ganglions themselves are the origin of the neoplasia.
- The primary tumor is in contact with the metastatic adenopathies.
- The primary tumor is sufficiently small so that it cannot be identified with any diagnostic method; this is especially the case in difficult to assess areas such as Waldeyer’s tonsillar ring, the base of the tongue, tonsillar regions, or the lateral walls of the nasopharynx.

When making a diagnosis for metastasis of squamous cell carcinoma in ganglions of the neck and the initial assessment shows no primary tumor, the origin is practically limited to the supraclavicular area and so any diagnostic effort made in search of an infraclavicular primary tumor becomes unnecessary.

## DIAGNOSIS

Before making a diagnosis of MCUP tumor it is important to have histological or cytological evidence of metastatic cells of epithelial origin in a cervical ganglion or ganglions, and there must be absence of identification of the primary tumor in the physical examination of the oral cavity and the oropharynx using conventional means, absence of suspect areas in the mucosa of upper aerodigestive tract in triple endoscopy (naso-pharyngo-laryngoscopy, oesophagoscopy, and bronchoscopy) and finally, the PET-CT should not show any suspect areas, although its use is still open to controversy as it does not necessarily mean identification of the primary tumor and the cost-benefit ratio is debatable<sup>3,4</sup>.

### Clinical examination

A complete examination must be made of the cervicofacial area; the site of the metastasis in the neck gives a rather good idea of where the primary tumor could be found. In patients with metastasis at levels I and II, the mouth is the most probable site; at levels II and III it is the oropharynx and the supraglottic larynx; in the parapharyngeal region it is the hypopharynx and supraglottic larynx; at level IV, the larynx, hypopharynx, and neck section of the esophagus; and at level V, the nasopharynx. When the metastasis is bilateral it is important to dismiss the primary tumor being in the nasopharynx, a suspicion that is heightened if the histology is undifferentiated carcinoma or lymphoepithelioma.

Suspect areas are considered to be the presence of indurated plaques in the mucosa, areas of submucosal induration, ulcers, or areas that bleed spontaneously or on pressure. The presence of any suspect area indicates performing a biopsy<sup>5</sup>.

Taking random biopsies of the mucosa of the head and neck area has been a classic procedure during the diagnosis of MCUP tumor. However, its usefulness is questionable, and it is now contraindicated as the possibility of finding the primary tumor using this method is rather low and the morbidity, time, and cost involved exceed any benefit<sup>2</sup>.

It is considered that if complete assessment is negative for identification of the primary tumor, random biopsies are only positive in 3% of patients<sup>2</sup>.

### Endoscopic examination

Evaluation is preferred with fiber optics and this should include an examination of the nasopharynx, oropharynx with special attention to the vallecula area and base of the tongue, larynx with special attention to the pharyngeal/laryngeal wall, hypopharynx, and neck section of the esophagus and trachea. Should this method find any suspect region, a biopsy is indicated<sup>2</sup>.

When the metastasis is reported as undifferentiated carcinoma or lymphoepithelioma curette and cytology of the roof of the nasopharynx and the area of the torus tubarius is recommended, as the mucosa in this region is the most common site for the origin of this type of metastasis, identification of the Epstein Barr virus in this sample is also recommended as its presence identifies patients with the origin in this anatomical region<sup>6</sup>.

### Imaging techniques

There are three imaging techniques that enable adequate assessment of a patient with metastasis of unknown primary tumor.

### **Ultrasonography**

Ultrasonography of the neck enables identifying the characteristics of the adenopathies, and may guide fine needle or open biopsy to the most suspicious site, thus reducing the rate of false negatives<sup>7</sup>. The sensitivity of ultrasonography is 85% and the specificity is 90%<sup>3,7</sup>.

### **Tomography**

Tomography enables high-sensitivity (90%) identification of the size of the metastasis, its number, and the presence of ganglion capsule rupture and invasion of soft tissues<sup>2</sup>. Whenever greater precision is required in the assessment of the tumoural invasion of soft tissues or the infiltration of the vascular axis of the neck, magnetic resonance imaging (MRI) is a useful method.

### **Positron emission tomography**

This technique has a sensitivity of 69% for identification of the primary tumor, especially in palatine amygdala and base of the tongue, and it is more sensitive than tomography or magnetic resonance<sup>8</sup>. A PET-CT should be performed before any invasive procedure of therapeutic character in order to reduce the rate of false positives. The identification of a site suspected of being the origin of the tumor means that it must be histologically demonstrated. Generally this involves fine-needle or cutting needle aspiration biopsy guided by an imaging technique such as tomography. However, its cost and relatively low sensitivity have led some authors to question its routine usefulness for staging patients with head and neck cancer<sup>4</sup>.

The identification of the site originating the metastasis enables staging the patient and treating them in consequence and dismissing, for obvious reasons, the diagnosis of MCUP.

If the primary tumor is not identified with these methods, ipsilateral tonsillectomy is indicated as the site of the metastasis of the primary tumor could be in the tonsillar crypts<sup>2,8,9</sup>. Examination of the tonsillar tissue is important as the identification of occult squamous cell carcinoma would enable concentrating the therapeutics in the oropharynx and so avoiding radiotherapy of all the cervico-facial mucosa.

### **Biopsy**

The recommended biopsy method for neck tumor is an ultrasound-guided minimally invasive fine-needle or cutting-needle method. Even for tangible metastasis, ultrasound guiding enables identifying the site with the greatest possibility of viable tumor and so avoids obtaining samples from sites with tumoural necrosis that usually offer no diagnosis. Open biopsy, although not the first procedure to be performed, can be considered in three situations:

- When the initial clinical assessment of the patient has been completed and it is not possible to obtain a minimally invasive biopsy; nevertheless, it is not recommended as an initial procedure.
- When ultrasound-guided fine-needle aspiration biopsy (FNAB) or cutting needle biopsy are not diagnostic or it is not possible to perform them.
- Whenever there is a suspicion that the primary tumor may be of oropharyngeal origin (tonsillar) in order to identify the presence of HPV in the ganglionic tissue and it is not possible to perform a cutting-needle biopsy.

Two precise recommendations must be fulfilled before resorting to an open biopsy:

- The incision in the neck must always be made so as not to compromise the definite incision for neck dissection.
- Care must be taken to prevent neoplastic spread in the wound when dissecting the tumor mass and so contaminating the surgical area as in these cases classic radical dissection is required and this implies morbidity for the patient.

### **Value of the human papillomavirus**

At present, HPV is probably the third causal agent in importance, after alcohol use and smoking, of squamous cell carcinoma of the upper aerodigestive tract<sup>10</sup> and is recognized as an agent with cause-effect relationship, especially in patients with oropharyngeal squamous cell carcinoma. Various subtypes have been related but VPH16 is the most common<sup>11</sup>. The value of HPV as a prognosis factor is being investigated, but it seems that in individuals with oropharynx cancer that do not smoke or drink alcohol and are positive to HPV DNA, the prognosis is better than for those who do not have it, probably because the chronic lesion of the mucosa induced by intoxication is less and not necessarily due to any protective role of the HPV<sup>12,13</sup>.

The presence of HPV DNA in metastatic ganglionic tissue implies that the primary tumor be much more frequently originating in the oropharyngeal mucosa and it has been suggested that due to better prognosis in these patients and the origin site being identified, treatment of MCUP can be modified to limit the radiotherapy fields to the neck and oropharynx, thus avoiding unnecessary radiation of all the cervicofacial mucosa and consequently reducing the morbidity inherent to this treatment<sup>14</sup>.

The identification of HPV or protein p16 in cervical metastasis identifies patients whose primary tumor

originates in the oropharynx, and as a result reduces the number of patients with "metastasis of truly unknown primary tumor"<sup>15</sup>.

When the ganglion biopsy shows a non-keratinizing or undifferentiated carcinoma, the most probable site of origin is the nasopharynx. The detection of Epstein-Barr virus DNA in either the nasopharyngeal mucosa or ganglionic tissue helps to determine that the origin of the malignancy is nasopharyngeal and so establishes the specific treatment for the neoplasias with this origin. However, it has not been demonstrated that the determination of this virus has any prognostic value<sup>16</sup>.

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## **TREATMENT**

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The treatment for MCUP has evolved and is expected to be much more selective within the next few years. Historically, patients with this complaint were subjected to a classic radical dissection of the neck if possible, followed by radical radiotherapy of the entire neck and all mucous membranes of the cervicofacial area, from the nasopharynx to the hypopharynx (pan-mucosal irradiation)<sup>16</sup>.

It is currently being debated whether all patients should routinely receive this treatment due to the morbidity implied by radiotherapy of the mucosa of the head and neck area, the basis of this treatment being that the possibility of the tumor appearing during follow-up is minimum. However, current understanding of various predictive factors, such as the metastasis site, histological type, and presence of HPV, enables us to distinguish different risk groups<sup>14</sup>.

There is not yet sufficient evidence to exclude routine classic treatment. However, everything seems to indicate that prognostic factors play an important role in the screening and identification

of patients for treatment, with the most important factors being the stage, ganglionic status, topographic image of the metastasis, the site of neck metastasis, and the presence or not of HPV<sup>17</sup>.

It has not been demonstrated that surgery followed by radiotherapy or chemoradiotherapy is better than rescue surgery (that performed after radiotherapy or chemoradiotherapy) and so it is the morbidity that decides the therapeutic sequence based on the ganglionic stage at the time of diagnosis; this means it is possible to distinguish two large groups.

### **cN1-cN2A**

With limited disease in patients with a unique metastasis of up to 4 cm, both surgery and radiotherapy offer the same control rate; if there is no presence of HPV, either of the two treatments is sufficient. Dissection of the neck should include the five levels and conserve non-ganglionic structures (modified radical neck dissection)<sup>18</sup>; radiotherapy should include the whole of the affected neck and, if the virus is present, the oropharynx should be included in the field of radiation. The presence of ganglionic necrosis detected by tomography could be an indication for initial surgical treatment as these patients have a lower response rate to radiotherapy<sup>2</sup>.

### **cN2B-cN3**

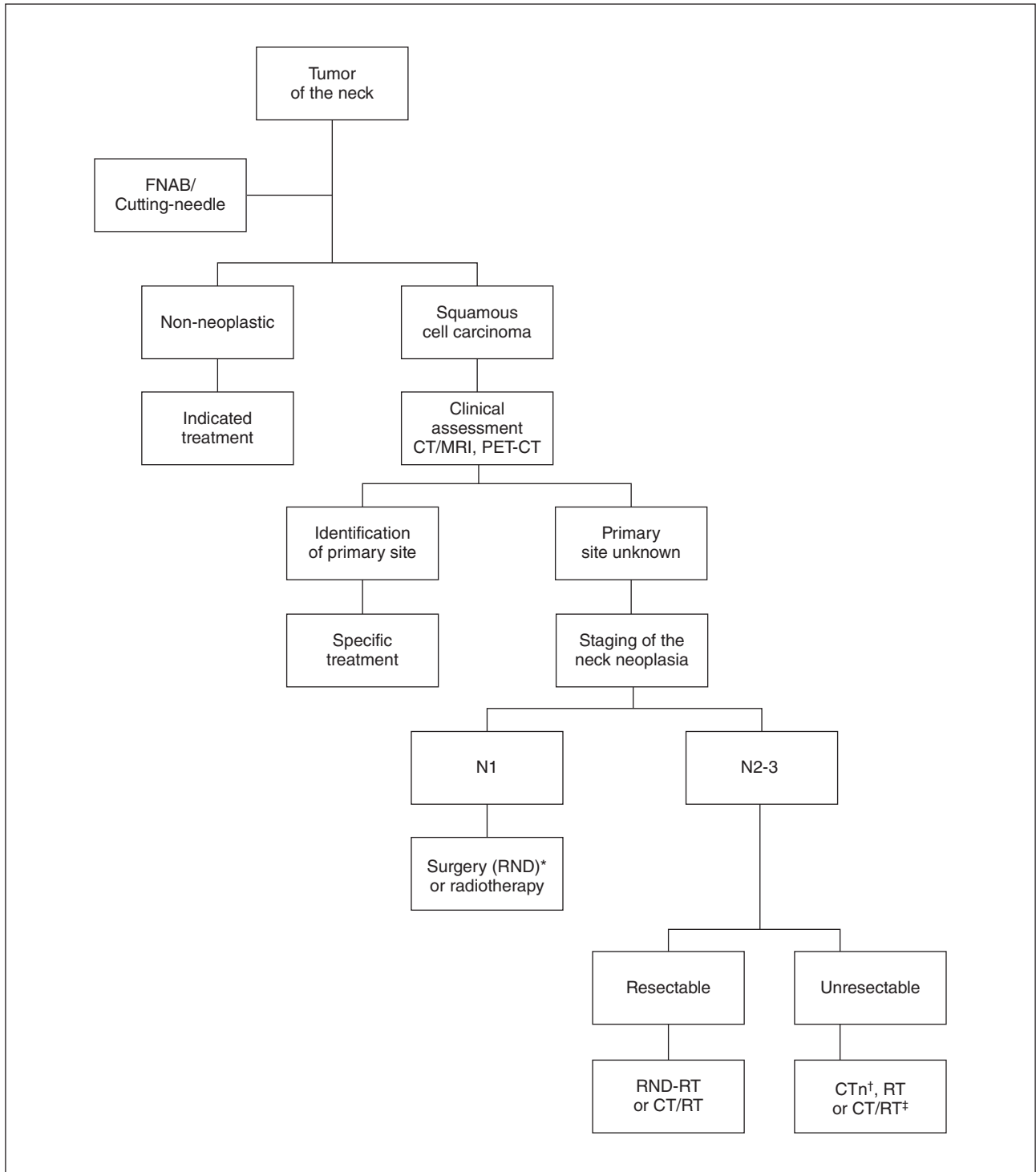
Voluminous disease in this group of patients of a single therapeutic variety is insufficient to gain regional control, the therapeutic alternatives being radiotherapy followed by surgery, chemoradiotherapy followed by surgery, or initial surgery if the malignancy is resectable.

In patients with multiple ganglionic metastases or metastasis of more than 4 cm (cN2B), treatment

should be initiated with neck dissection, the radicalism depending on the tumor volume and the infiltration of ganglionic structures at the time of diagnosis. This procedure enables correct histopathological staging, determining prognosis factors in the dissected ganglions, and the selection of patients to decide between adjuvant radiotherapy or concomitant chemoradiotherapy if the prognosis factors are adverse (multiple metastasis with ganglion capsule rupture and infiltration of soft tissues or insufficient surgical resection)<sup>18,19</sup>. The inconvenience of initiating treatment with radiotherapy or chemoradiotherapy is that the possibility of neoplastic persistence is high and the complication rate of neck dissection as rescue treatment is much higher.

In patients with very voluminous disease (cN3), clinical and imaging techniques should be used to evaluate the extension of the tumor to anatomical structures that make it non-resectable (common or internal carotid artery, pre-vertebral fascia, soft parts of the neck or cervical spine), and in this case there are two therapeutic alternatives; (i) chemoradiotherapy, or (ii) induction chemotherapy based on cisplatin and evaluation of the response and, based on this result, deciding between ganglionic dissection if response is partial but permits dissection, radiotherapy if the response is partial and the resection is not possible, and chemoradiotherapy if response is complete<sup>20</sup>. The objective is to offer the best possible control rate with the least possible morbidity.

In patients where the initial treatment is to be radiotherapy or chemoradiotherapy, there is still debate about whether or not they should be subjected to routine surgery irrespective of the response. This proposal is based on the fact that the rate of persistent occult metastases is between 15 and 25% and their later clinical manifestation makes rescue impossible. On the other hand, the neck dissection after these treatments implies a high complication rate<sup>2</sup>.



**Figure 1.** Algorithm showing the therapeutic route for metastasis of squamous cell carcinoma of the neck with unknown primary origin.

\*Surgery is preferred over radiotherapy; it pathologically stages the patient and enables distinguishing risk groups.

†Neoadjuvant chemotherapy based on one or two cycles of platinum enables some patients to be offered surgery before radiotherapy and thus reducing the morbidity.

‡Clinical response and/or PET-CT identifies patients as candidates for radical neck dissection.

CTn: neoadjuvant chemotherapy; RND: radical neck dissection; CT: chemotherapy; RT: radiotherapy; FNAB: fine-needle aspiration biopsy; MRI: magnetic resonance imaging; PET: positron emission tomography.

There are two alternatives in these patients:

- When the metastases are initially staged as cN2 or higher, dissection should be made at the five levels of the neck, preserving non-ganglionic structures (internal jugular vein, sternocleidomastoid muscle and accessory spinal nerve); patients with cN1 and complete response should undergo clinical and ultrasonographic monitoring.
- Deciding treatment based on PET-CT; in patients with complete clinical response, assessment with PET-CT six weeks after the end of treatment enables selecting candidates for follow-up<sup>21</sup>.

### Classical treatment

This is still a valid alternative, in spite of the biological cost “pan-mucosal” irradiation implies, in patients where there is no presence of HPV, who have solid, non-cyst like metastasis, with high histological stage, lymphoepithelioma, or undifferentiated with expression of the Epstein Barr virus, as these patients have a very high risk of a primary nasopharyngeal tumor.

Figure 1 shows the recommended algorithm for diagnosis and treatment selection in patients with metastasis of unknown primary tumor.

The follow-up of patients treated for MCUP depends on the type of treatment and the initial stage. Patients who received no treatment at the probable primary sites or with advanced stages (> cN1) should undergo fibro-endoscopy in the consulting rooms on a quarterly basis in the first year, and physical examination with oropharyngeal palpation and neck ultrasound; PET-CT is useful on an annual basis for the first three years.

In patients with treatment of the entire cervicofacial mucosa and in patients with initial stages,

surveillance should take place every four months during the first year and then every six months up to five years.

It is very important that the patient is required to abandon the habits of smoking and drinking alcohol as continuing implies a higher tumor recurrence rate.

The prognosis depends on the initial cervical stage. In patients with initial stages (N1-2) survival at five years is 70%; however, this drops to 30% in patients with N3. Continuing with the habit of smoking or drinking favors a worse prognosis.

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### CONCLUSIONS

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The presence of metastasis in cervical ganglions with unknown primary tumor is a relatively uncommon entity. Diagnosis is based on physical examination, minimally invasive biopsy with fine-needle or cutting-needle aspiration, fibroendoscopic assessment, and imaging based on tomography or MRI and PET-CT. The impossibility of identifying the primary tumor with these methods implies diagnosis of this entity. Treatment depends on factors inherent to the tumor and the general condition of the patient. In initial stages a single variety is sufficient to obtain oncological control, high-risk stages require surgery and radiotherapy, and in very high-risk patients concomitant treatment with chemoradiation therapy based on cisplatin is indicated before or after surgery.

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