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INCIDENCE OF CERVICAL METASTASES IN LEVEL IIB AND V ACCORDING TO LOCATION AND STAGE OF ORAL AND SALIVARY GLAND TUMOURS

FINAL DEGREE PROJECT

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INDEX

ABSTRACT

Objectives: clinical stage, location and histopathological features in oral cancer influence in cervical nodal spread. Establishing the patterns of cervical spread and the involvement of the level IIb according to the location of tumours could reduce the morbidity of cervical surgery.

Material: a descriptive study of oral squamous carcinomas (SCC) diagnosed in Tarragona from January 2018 to December 2021 and the incidence of metastasis in cervical level IIb has been analysed.

Results: 213 patients were diagnosed of oral SCC. The most frequent location was the tongue, followed by the oral floor and oropharynx. In surgical patients with cervical dissection (n=87), the percentage of cervical metastases at the IIb level according to the location of the tumour regardless of T stage (T1-T4) was: in mobile tongue carcinomas 3,7%, in oral floor 5%, in mandibular carcinomas 10%, in oropharyngeal carcinomas (tongue base and soft palate) 22,2%, in maxillary carcinomas 33,3% and in parotid carcinomas up to 50%. In stage T1, only in one patient with cervical dissection and in 9,7% of patients with T2 stage, metastases were found at level IIb, all of them oropharyngeal and parotid carcinomas.

Conclusions: level IIb dissection in patients with early stages T1-T2 has been studied to decrease the morbidity of this level in cervical surgery. In T1-T2 of oropharyngeal, parotid and maxillary carcinomas we found metastasis at level IIb, so dissection of level IIb should be performed regardless of tumour stage in these locations. According to other locations in T1-T2 tumours (mobile tongue, oral floor, yugal mucosa), studies with a greater number of patients are needed to assess the percentage of metastasis in level IIb and whether dissection of this level could be avoided. In more advanced stages T3-T4, level IIb involvement is more frequent and level IIb dissection should be performed regardless the location. When level IIa is involved, it has a statistically significant influence on level IIb involvement.

Keywords: IIb, oral cancer, metastasis

RESUM

Objectius: estadi clínic, localització i característiques histopatològiques en la influència del càncer oral en la propagació dels ganglis cervicals. Establir els patrons de propagació cervical i la implicació del nivell IIb segons la localització dels tumors podria reduir la morbiditat de la cirurgia cervical.

Material: s'ha analitzat un estudi descriptiu dels carcinomes escamosos orals (SCC) diagnosticats a Tarragona des de gener de 2018 fins a desembre de 2021 i la incidència de metàstasi a nivell cervical IIb.

Resultats: 213 pacients van ser diagnosticats de SCC oral. La localització més freqüent va ser la llengua, seguida del sòl oral i l'orofaringe. En pacients quirúrgics amb dissecció cervical (n=87), el percentatge de metàstasis cervicals a nivell IIb segons la localització del tumor independentment de l'estadi T (T1-T4) va ser: en carcinomes mòbils de la llengua 3,7%, al sòl oral 5%, en carcinomes mandibulars 10%, en carcinomes d'orofaringe (base de llengua i paladar tou) 22,2%, en carcinomes maxil·lars 33,3% i en carcinomes de paròtide fins al 50%. En l'estadi T1, només en un pacient amb dissecció cervical i en un 9,7% dels pacients amb estadi T2, es van trobar metàstasis a nivell IIb, tots ells carcinomes d'orofaringe i paròtide.

Conclusions: s'ha estudiat la dissecció de nivell IIb en pacients amb estadis inicials T1-T2 per disminuir la morbiditat d'aquest nivell en cirurgia cervical. En T1-T2 dels carcinomes d'orofaringe, paròtide i maxil·lar hem trobat metàstasis al nivell IIb, per la qual cosa s'hauria de realitzar la dissecció del nivell IIb independentment de l'estadi del tumor en aquestes localitzacions. Segons altres localitzacions en tumors T1-T2 (llengua mòbil, sòl oral, mucosa jugal), calen estudis amb un major nombre de pacients per avaluar el percentatge de metàstasi a nivell IIb i si es podria evitar la dissecció d'aquest nivell. En els estadis més avançats T3-T4, l'afectació de nivell IIb és més freqüent i la dissecció de nivell IIb s'hauria de realitzar independentment de la ubicació. Quan està implicat el nivell IIa, té una influència estadísticament significativa en l'afectació del nivell IIb.

Paraules clau: IIb, càncer oral, metàstasi

1. OBJECTIVES

1. Descriptive study of the incidence of oral carcinoma in patients.
2. Incidence of metastasis in cervical levels IIb and V according to tumour location of oral cavity and salivary gland tumours.
3. Incidence of cervical metastasis at levels IIb and V according to tumour stage of oral cavity and salivary gland tumours.
4. Survival in patients with oral and salivary gland tumours.

2. INTRODUCTION

2.1. DESCRIPTION: HEAD AND NECK TUMOURS

Cancers that are known collectively as head and neck cancers usually begin in the squamous cells that line the mucosal surfaces of the head and neck (for example, those inside the mouth, throat, and voice box). These cancers are referred to as squamous cell carcinomas of the head and neck. Head and neck cancers can also begin in the salivary glands, sinuses, or muscles or nerves in the head and neck, but these types of cancer are much less common than squamous cell carcinomas (1, 2).

2.1.1. What is the squamous cell carcinoma?

Squamous cell carcinomas (SCCs), also known as epidermoid carcinomas, comprise a number of different types of cancer that result from squamous cells. These cells form on the surface of the skin, on the lining of hollow organs in the body, and on the lining of the respiratory and digestive tracts.

Typical SCC has nests of squamous epithelial cells arising from the epidermis and extending into the dermis (Annex I). The malignant cells are often large with abundant eosinophilic cytoplasm and a large, often vesicular, nucleus. Variable keratinisation (keratin pearls etc) is present (Annex II).

2.1.2. Where can the cancers of the head and neck be formed?

- **Oral cavity:** includes the lips, the front two-thirds of the tongue, the gums, the lining inside the cheeks and lips, the floor (bottom) of the mouth under the tongue, the hard palate (bony top of the mouth), and the small area of the gum behind the wisdom teeth.
- **Throat (pharynx):** the pharynx is a hollow tube about 5 inches long that starts behind the nose and leads to the oesophagus. It has three parts: the nasopharynx (the upper part of the pharynx, behind the nose); the oropharynx (the middle part of the pharynx, including the soft palate [the back of the mouth], the base of the tongue, and the tonsils); the hypopharynx (the lower part of the pharynx).
- **Voice box (larynx):** the voice box is a short passageway formed by cartilage just below the pharynx in the neck. The voice box contains the vocal cords. It also has a small piece of tissue, called the epiglottis, which moves to cover the voice box to prevent food from entering the air passages.
- **Paranasal sinuses and nasal cavity:** the paranasal sinuses are small hollow spaces in the bones of the head surrounding the nose. The nasal cavity is the hollow space inside the nose.
- **Salivary glands:** the major salivary glands are in the floor of the mouth and near the jawbone. The salivary glands produce saliva. Minor salivary glands are located throughout the mucous membranes of the mouth and throat.

(See illustration in Annex III)

Cancers of the brain, the eye, the oesophagus, the thyroid gland, and the skin of the head and neck are not usually classified as head and neck cancers.

If a squamous cell carcinoma of the head and neck is going to spread, it almost always does so locally and/or to the lymph nodes in the neck. Sometimes, cancerous squamous cells can be found in the lymph nodes of the upper neck when there is no evidence of cancer in other parts of the head and neck, possibly because the original primary tumour is too small. When this happens, the cancer is called metastatic squamous cell carcinoma with unknown (occult) primary.

2.1.3. What causes cancers of the head and neck?

- **Alcohol and tobacco use** (including second-hand smoke and smokeless tobacco, sometimes called “chewing tobacco” or “snuff”) are the two most important risk factors for head and neck cancers, especially cancers of the oral cavity, hypopharynx, and voice box (3–7). People who use both tobacco and alcohol are at greater risk of developing these cancers than people who use either tobacco or alcohol alone (8, 9). Most head and neck squamous cell carcinomas of the mouth and voice box are caused by tobacco and alcohol use (8).
- **Infection with cancer-causing types of human papillomavirus (HPV), especially HPV type 16**, is a risk factor for oropharyngeal cancers that involve the tonsils or the base of the tongue (10–12). In the United States, the incidence of oropharyngeal cancers caused by HPV infection is increasing, while the incidence of oropharyngeal cancers related to other causes is falling (10). About three-quarters of all oropharyngeal cancers are caused by chronic HPV infection (13, 14).

Other known risk factors for specific cancers of the head and neck include the following:

- **Paan** (betel quid): the use of paan in the mouth, a common custom in Southeast Asia, is strongly associated with an increased risk of mouth cancers (15, 16).
- **Occupational exposure:** occupational exposure to wood dust is a risk factor for nasopharyngeal cancer (17, 18). Certain industrial exposures, including exposures to asbestos and synthetic fibres, have been associated with cancer of the voice box, but the increase in risk remains controversial (19). People working in certain jobs in the construction, metal, textile, ceramic, logging, and food industries may have an increased risk of cancer of the voice box (20). Industrial exposure to wood dust, nickel dust, or formaldehyde is a risk factor for cancers of the paranasal sinuses and nasal cavity (21–23).
- **Radiation exposure:** radiation to the head and neck, for noncancerous conditions or cancer, is a risk factor for cancer of the salivary glands (24–26).
- **Epstein-Barr virus infection:** infection with the Epstein-Barr virus is a risk factor for nasopharyngeal cancer (27) and cancer of the salivary glands (28, 29).
- **Ancestry:** Asian ancestry, particularly Chinese ancestry, is a risk factor for nasopharyngeal cancer (17, 18).
- **Underlying genetic disorders:** some genetic disorders, such as Fanconi anaemia, can increase the risk of developing precancerous lesions and cancers early in life (30).

2.1.4. Which are the head and neck cancer symptoms?

Head and neck cancer symptoms may include a lump in the neck or a sore in the mouth or the throat that does not heal and may be painful, a sore throat that does not go away, difficulty in swallowing, and a change or hoarseness in the voice. These symptoms may also be caused by other, less serious conditions. It is important to check with a doctor or dentist about any of these symptoms.

Symptoms of cancers in specific areas of the head and neck include:

- **Oral cavity:** a white or red patch on the gums, the tongue, or the lining of the mouth; a growth or swelling of the jaw that causes dentures to fit poorly or become uncomfortable; and unusual bleeding or pain in the mouth.
- **Throat (pharynx):** pain when swallowing; pain in the neck or the throat that does not go away; pain or ringing in the ears; or trouble hearing.
- **Voice box (larynx):** trouble breathing or speaking, pain when swallowing or ear pain.
- **Paranasal sinuses and nasal cavity:** sinuses that are blocked and do not clear; chronic sinus infections that do not respond to treatment with antibiotics; bleeding through the nose; frequent headaches, swelling or other trouble with the eyes; pain in the upper teeth; or problems with dentures.
- **Salivary glands:** swelling under the chin or around the jawbone, numbness or paralysis of the muscles in the face, or pain in the face, the chin, or the neck that does not go away.

2.1.5. How common are head and neck cancers?

Head and neck cancer is the sixth most common tumour in the world and accounts for 6% of all tumours worldwide (31). It is more common in men than in women (32) and its incidence has risen sharply in recent years in relation to HPV+ (33). 90% of head and neck tumours are squamous cell carcinomas (34). It is the most common cancer in developing countries (35). Overall survival at 5 years is 50%. Many head and neck cancers are not diagnosed until advanced stages, however 30% are diagnosed in early stages and have a higher survival rate (36).

Knowing the factors that influence the prognosis of oral cavity carcinomas is a very important part of the work that conditions the treatment, follow-up and survival of these patients: the patient's comorbidities, the patient's baseline situation, age, sex, histopathological factors of

the tumour itself (tumour type, tumour thickness, degree of differentiation, tumour infiltration, resection margins, perivascular, perineural and perilymphatic involvement), tumour location, pre- and post-surgical staging and the treatments performed: surgery, radiotherapy, chemotherapy and their combination.

2.1.6. How are head and neck cancers diagnosed and treated?

Diagnosis is clinical, radiological and anatomopathological. 90% of all head and neck cancers are squamous cell carcinoma (34). Proper diagnosis and staging are essential for correct treatment and improved survival (37).

In the treatment and management of oral cavity tumours, surgery, radiotherapy and chemotherapy in combination are used (38, 39). Early stages (I-II), which account for 40% of tumours, are usually treated with surgery or radiotherapy alone (38, 39). In advanced stages III-IVa-IVb, resectable or unresectable tumours, treatment is usually combined using sequential therapies (38, 39). In the treatment of these patients with cervicofacial oncological pathology, it is important to address two main aspects: functionality and aesthetics. Adequate and multidisciplinary oncological diagnosis and treatment must always be considered.

In surgical treatment we need to establish a precise reconstructive treatment, which must be individualised in each case and for which training and knowledge of techniques, often microsurgical, is necessary. As well as the factors that influence the post-surgical results and the complications of microsurgical reconstructions.

There are many studies on risk factors and survival in head and neck cancer patients. These are necessary to improve the prognosis, diagnosis and treatment of these patients, as well as the feasibility of reconstructions and disease-free survival rates.

2.2. CERVICAL LEVELS

- **Level I**: submental (**Ia**) and submandibular (**Ib**).
- **Level II**: upper internal jugular nodes.
- **Level III**: middle jugular nodes.
- **Level IV**: low jugular nodes.

- **Level V**: posterior triangle nodes.
- **Level VI**: central compartment.
- **Level VII**: superior mediastinal nodes.

(See in Annex IV)

2.3. TUMOUR STAGING FOR ORAL CAVITY CANCERS (AJCC 8th ed.)

(See in Annex V)

3. MATERIAL AND METHODS

3.1. TYPE OF STUDY

This is a descriptive and retrospective cohort study of patients with oral cavity and salivary gland cancer in the province of Tarragona from January 2018 to December 2021. We analyse the variables of epidemiology, location, stage, treatments carried out and survival. We also study the incidence of metastasis in level IIb and V according to stage and location of oral and salivary gland tumours.

3.2. STUDY CANDIDATES AND SAMPLE SIZE

The patients who are candidates for the study are all patients diagnosed with squamous cell carcinoma of the oral cavity and salivary glands, treated at the Joan XXIII University Hospital by the Oral and Maxillofacial Surgery Service, who underwent surgery and who met the inclusion criteria.

For this purpose, 213 patients with head and neck tumours were retrospectively collected in an Excel database.

Inclusion criteria:

- Surgical patients with histological diagnosis of oral cavity and salivary gland squamous cell carcinoma at the Joan XXIII University Hospital treated between January 2018 and December 2021.

Exclusion criteria:

- Patients with a diagnosis of tumours other than squamous carcinoma.
- No surgical patients.
- Patients who have been lost during following.

3.3. STATISTICAL METHODOLOGY: DATA COLLECTION AND VARIABLES

Data collection was done through the clinical history of each patient with squamous cell carcinoma of the oral cavity and salivary glands treated by the Oral and Maxillofacial Surgery service at the Joan XXIII University Hospital, from January 2018 to December 2021, collecting the characteristics, location and stage of the tumour, in particular the incidence of cervical metastasis at levels IIb and V.

3.3.1. VARIABLES

The variables subject to study are as follows:

Dependent variables: metastasis at level IIb and metastasis at level V.

Independent variables: gender, age, tumour location, tumour stage, recurrence date.

3.3.2. BIVARIATE ANALYSIS

For the bivariate analysis of the qualitative independent variables (location, stage, metastasis IIa) with the dichotomous qualitative dependent variables' outcome (metastasis at levels IIb and V) with the study population following a normal distribution, we used Pearson's X2 test. For variables not following a normal distribution, we used Fisher's exact X2 test.

3.3.3. SURVIVAL STUDIES AND ROC CURVES

We analysed overall survival in patients with oral cavity and salivary gland squamous cell carcinoma by performing ROC curves.

4. RESULTS

4.1. DESCRIPTIVE RETROSPECTIVE OBSERVATIONAL AND COHORT STUDY

4.1.1. GENDER, NUMBER OF PARTICIPANTS AND AVERAGE AGE OF PATIENTS WITH HEAD AND NECK TUMOURS

213 patients were diagnosed of squamous cell carcinoma from January 2018 to December 2021. 146 were men and 67 were women. The mean age of the men was 59,66 years and the mean age of the women was 67,26 years. (See table 1 in Annex VI)

4.1.2. LOCATION OF HEAD AND NECK TUMOURS

The most frequent location of oral cavity tumours was the tongue (31%), the oral floor (23%) and the oropharynx (10,3%). The less frequent was the lip (1,1%), trigon (2,3%) and parotid (4,6%). (See table 2 in Annex VII)

4.1.3. CERVICAL INVOLVEMENT

Hardly the half of surgical patients (46%) with oral squamous cell and salivary gland carcinoma had cervical involvement. (See table 3 in Annex VIII)

4.1.4. LEVEL IIB INVOLVEMENT

Only 9 patients (10,3%) with oral squamous cell and salivary gland carcinoma had level IIb involvement. (See table 4 in Annex IX)

4.1.5. TUMOUR STAGE T1-T4

The predominant tumour stage in the patients in our study who underwent surgery was T2 (34,9%), meaning that the size of the tumour was between 2-4 cm. (See table 5 in Annex X)

4.2. BIVARIATE ANALYSIS

4.2.1. LEVEL IIB

4.2.1.1. LEVEL IIB INVOLVEMENT BY LOCATION

When the primary tumour was located in the parotid, half of the patients had level IIb involvement. The second most frequent location with involvement of level IIb was the maxilla (33,3%) and the third was the oropharynx (22,2%). (See table 6 in Annex XI)

4.2.1.1.a. LEVEL IIB INVOLVEMENT IN MAXILLARY CANCER BY STAGE

When the maxillary cancer was at T3, 100% of patients had level IIb involvement. When the maxillary cancer was at T4, 20% of patients had level IIb involvement. The reason is because only one patient with T3 stage underwent surgery, in contrast of five patients with T4 stage that were operated. The results were without statistical significance ($p>0.05$). (See table 7 in Annex XII)

4.2.1.1.b. LEVEL IIB INVOLVEMENT IN OROPHARYNGEAL CANCER BY STAGE

In oropharyngeal cancer, all tumours had level IIb involvement when the stage was T4. None of them had level IIb involvement with T2 and T3. The results were without statistical significance ($p>0.05$). (See table 8 in Annex XIII)

4.2.1.1.c. LEVEL IIB INVOLVEMENT IN PAROTID CANCER BY STAGE

Half of the patients had level IIb involvement when the parotid tumour was at stage T2. This was because the four patients operated with parotid carcinomas were at T2 stage. The results were without statistical significance ($p>0.05$). (See table 9 in Annex XIV)

4.2.1.2. LEVEL IIB INVOLVEMENT BY T-STAGE

The stage where we found more level IIb involvement was T4 (20% of the surgical T4 tumours of oral cavity and salivary glands), which means that the tumour had invaded nearby structures in the mouth or the muscles and bones that form the mouth or the base of the skull, and/or it encased the internal arteries. The results were without statistical significance ($p>0.05$). (See table 10 in Annex XV)

4.2.1.3. LEVEL IIB INVOLVEMENT BY LEVEL IIA INVOLVEMENT

When level IIa was involved, 38,5% of patients had also level IIb involvement. When level IIa was not involved, only 10,3% of patients had level IIb involvement. In the Pearson's Chi-square table, we see that the results were significant, because p=0,000 (p<0.005). (See table 11 in Annex XVI)

4.2.1.4. LEVEL IIB INVOLVEMENT BY GENDER

From all of the cases, only 10,2% of the men and only 10,5% of the women had level IIb involvement. The results were without statistical significance (p>0.05). (See table 12 in Annex XVII)

4.2.2. LEVEL V

4.2.2.1. LEVEL V INVOLVEMENT BY TUMOUR LOCATION

Level V involvement was only found in patients with the primary tumour in the mandible (10%) and on the floor of the mouth (5%). In the remaining locations, we found no level V involvement. The results were without statistical significance (p>0.05). (See table 13 in Annex XVIII)

4.2.2.2. LEVEL V INVOLVEMENT BY T-STAGE

In our study, level V involvement was found only in one patient with advanced stage (T4), without statistical significance (p>0.05). (See table 14 in Annex XIX)

4.2.2.3. LEVEL V INVOLVEMENT BY GENDER

Women had a slightly higher level of V involvement (2,6%) compared to men (2%), without statistical significance (p>0.05). (See table 15 in Annex XX)

4.3. SURVIVAL STUDIES AND ROC CURVES

4.3.1. RECURRENCES

Recurrence	Persistence	2n primary tumour
34 patients (14,5%)	15 patients (7,4%)	5 patients (2%)

4.3.2. SURVIVAL OF SURGICAL PATIENTS

Total number	Recurrence number	Censored	
		Number	Percentage
124	23	101	81,5%

The median survival was 54 months (4 years), with a survival rate of 81,5%.

(See ROC Curve in Annex XXI)

4.3.3. SURVIVAL OF CHEMOTHERAPY/RADIOTHERAPY PATIENTS

Total number	Recurrence number	Censored	
		Number	Percentage
63	26	37	58,7%

The median survival was 26,98 months (2 years and 3 months), with a survival rate of 58,7%.

(See ROC Curve in Annex XXII)

4.4. REVIEW OF THE LITERATURE

4.4.1. METASTASIS IN LEVEL IIB: LOCATION OF THE PRIMARY ORAL CAVITY TUMOUR AND STAGING

Reference	Study	Population	Intervention Follow-up	Results	Conclusions
Kou Y, Zhao T, Huang S, Liu J, Duan W, Wang Y, Wang Z, Li D, Ning C, Sun C. Cervical level IIb metastases in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. Onco Targets Ther. 2017 Sep 11;10:4475-4483. **(48)**	Systematic review and meta-analysis	Patients with oral squamous cell carcinoma (n = 2001)	Elective neck dissection	Patients with level IIb metastases = 112 (6%)	Due to the low frequency of level IIb nodal metastases in oral squamous cell carcinoma patients and rare occurrence of isolated level IIb, level IIb dissection could be avoided when the primary lesions were in early stages (T1 and T2), with the exception of tongue cancer.
Lea J, Bachar G, Sawka AM, Lakra DC, Gilbert RW, Irish JC, Brown DH, Gullane PJ, Goldstein DP. Metastases to level IIb in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. Head Neck. 2010 Feb;32(2):184-90. **(49)**	Systematic review and meta-analysis	Patients with oral squamous cell carcinoma (n = 332)	Elective neck dissection	Patients with level IIb metastases = 20 (6%)	Level IIb nodal metastases are relatively uncommon in previously untreated SCC of the oral cavity (6%). Furthermore, isolated level IIb nodal disease is uncommon. However, it is recommended that dissection of level IIb remain the standard of care in oral cavity squamous cell cancer.

Yang H, Son NH, Lee SH, Kim D, Kim HJ, Cha IH, Nam W. Predictive modelling of level IIb lymph node metastasis in oral squamous cell carcinoma. Sci Rep. 2021 Sep 2;11(1):17562. **(50)**	Predictive study with univariate and multivariate analyses	Patients with oral squamous cell carcinoma (n = 541)	Analysis of independent risk factors for level IIb metastases = level IIa metastasis and lymphovascular permeation	Patients in area under curve = 0.697 (P < .0.001) Sensitivity = 66.7% Specificity = 77.4%	Level IIb dissection should be performed in patients with level IIa metastasis and LVP. However, thorough consideration of the oncologic safety of omitting level IIb dissection is compulsory.
Gross BC, Olsen SM, Lewis JE, Kasperbauer JL, Moore EJ, Olsen KD, Price DL. Level IIB lymph node metastasis in laryngeal and hypopharyngeal squamous cell carcinoma: single-institution case series and review of the literature. Laryngoscope. 2013 Dec;123(12):3032-6. **(51)**	Retrospective cohort study and review of the literature	Patients with laryngeal or hypopharyngeal squamous cell carcinoma (n = 65)	Treated with surgery at Mayo Clinic (Rochester, Minnesota) from 2004 through 2010	Patients with level IIb lymph node metastases in elective neck dissections = 4% Patients with level IIb lymph node metastases in therapeutic neck dissections = 17%	The rate of occult IIb metastasis in laryngeal and hypopharyngeal squamous cell carcinoma is exceedingly low. In a clinically node-negative case, the ipsilateral and contralateral level IIB nodal packet should not be dissected. For clinically node-positive cases, ipsilateral level IIb dissection should be performed; contralateral IIb dissection should be performed only when indicated.
Santoro R, Franchi A, Gallo O, Burali G, de' Campora E. Nodal metastases at level IIb during neck dissection for head and neck cancer: clinical and pathologic evaluation. Head Neck. 2008 Nov; ;30(11):1483-7. **(52)**	Prospective cohort study	Patients with head and neck cancer (n = 114)	Elective neck dissection	Patients with level IIb metastases = 5 (3.3%) Incidence of positive level IIb in N0 = 2% Incidence of positive level IIb in N+= 5%	The incidence of metastases at level IIb is low, also in the N+ necks, therefore dissection of this level could be unnecessary in N0 necks. Furthermore, an interesting statistical association between the presence of metastases at level IIb and at level IIa was recorded.
Ghantous Y, Akrish S, Abd-	Prospective	Patients with oral	Selective neck	Patients with level IIB	Neck dissecting, including dissecting

Elraziq M, El-Naaj IA. Level IIB Neck Dissection in Oral Squamous Cell Carcinoma: Science or Myth? J Craniofac Surg. 2016 Jun;27(4):1035-40. **(53)**	cohort study	squamous cell carcinoma (n = 70)	dissection	metastases = 17 (4%)	level IIb, remains the keystone of treating OSCC. Its prognostic and therapeutic value exceeds its associated morbidity; therefore, dissecting level IIb is recommended in treating OSCC in clinically N0 patients.
Dabholkar JP, Kapre NM. Level IIb Neck Dissection in Oral Cavity Cancers- When Should One Address it..? Indian J Surg Oncol. 2016 Sep;7(3):303-6. **(54)**	Non-randomized prospective observational study	Patients with oral cavity cancer (n = 65)	Appropriate surgery for primary tumour and neck dissection	Patients with level IIB positive for metastases = 7 (10.44 %)	Level IIb dissection can be avoided in N0 necks. For therapeutic neck dissections, Level IIb should be cleared if there are positive nodes at level IIa.
Hosokawa S, Mochizuki D, Takahashi G, Okamura J, Imai A, Ishikawa R, Takizawa Y, Yamatodani T, Misawa K, Mineta H. Relevance of Level IIb Neck Dissection in Patients with Head and Neck Squamous Cell Carcinomas. World J Surg. 2019 Dec;43(12):3059-3064. **(55)**	Prospective cohort study	Patients with head and neck squamous cell carcinoma (n = 181)	Elective neck dissection	Overall prevalence of patients with level IIb metastases = 2.4% Prevalence of positive level IIb in cN0= 0% Prevalence of positive level IIb in cN+= 10.34%	Our findings suggest that level IIb neck dissection in patients with head and neck squamous cell carcinomas may be required only if preoperative examination reveals multilevel or level IIa metastasis or suspicious level IIb metastasis.
Kim YH, Koo BS, Lim YC, Lee JS, Kim SH, Choi EC. Lymphatic metastases to level IIb in hypopharyngeal	Prospective analysis of a case series	Patients with hypopharyngeal squamous cell carcinoma (n = 50)	Surgical treatment for a primary lesion and simultaneous	Patients with positive level IIb in N0 = 2 (3%) Patients with positive level IIb in N+= 32	Level IIb LN pads may be preserved during elective neck dissection in the treatment of patients with cN0 necks with HPSCC. This area should be removed during therapeutic neck

squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2006 Oct;132(10):1060-4. **(56)**		Neck dissections = 93	neck dissection from January 1998 to February 2004	(11%)	dissection in the treatment of cN+ necks.
Gross BC, Olsen SM, Lewis JE, Kasperbauer JL, Moore EJ, Olsen KD, Price DL. Level IIB lymph node metastasis in oropharyngeal squamous cell carcinoma. Laryngoscope. 2013 Nov;123(11):2700-5. **(57)**	Retrospective cohort study	Patients with oropharyngeal squamous cell carcinoma (n = 348)	Surgically managed at Mayo Clinic from 2004 through 2010	Patients with level IIb metastasis in elective neck dissections = 2.5% Patients with level IIb metastasis in therapeutic neck dissections = 25%	Level IIb neck dissection can be omitted in early stage (T1 or T2) cN0 OPSCC. In patients with a cN0 neck and advanced OPSCC (T3 or T4), primary tumour in the tonsil, or ipsilateral cN+ and contralateral cN0 neck, level IIb dissection should be considered. Level IIb dissection should be performed routinely in patients with cN+ OPSCC.
Sezen OS, Kubilay U, Haytoglu S, Unver S. Frequency of metastases at the area of the supraretrospinal (level IIB) lymph node in laryngeal cancer. Head Neck. 2007 Dec;29(12):1111-4. **(58)**	Retrospective cohort study	Patients with squamous cell carcinoma of the larynx (n = 63) Neck dissections = 98	Laryngectomy and neck dissection between January 2000 and June 2004	Patients with level IIb metastasis = 6 (9.52%)	If the level IIa shows positive metastatic changes, perioperative pathologic examination by frozen section that includes level IIb could be an alternative approach. This area may not be routinely dissected during the surgical management of laryngeal carcinoma with no palpable lymph nodes.
Wiegand S, Esters J, Müller HH, Jäcker T, Roessler M, Fasunla JA, Werner JA, Sesterhenn AM. Relevance of level I and IIB neck dissection in laryngeal cancer. J Laryngol Otol. 2012 Aug;126(8):795-9. **(59)**	Retrospective review	Patients with laryngeal cancer (n = 73)	Level I and IIb neck dissection	Patients with level IIb metastases in cN0 = 1 Patients with level IIb metastases in cN+ = 3	Dissection of neck levels I and IIb is justifiable in laryngeal cancer patients with clinically detectable neck nodes and suspicious lymph nodes in the respective level or level IIa. However, in patients without clinically detectable neck nodes, preservation of levels I and IIb is oncologically safe, economical and reduces the risk of comorbidity.

Sakai A, Okami K, Sugimoto R, Ebisumoto K, Yamamoto H, Maki D, Atsumi T, Saito K, Iida M. Evaluating the significance of level IIb neck dissection for hypopharyngeal cancer. Head Neck. 2013 Dec;35(12):1777-80. **(60)**	Retrospective review	Patients with hypopharyngeal cancer (n = 34) Neck dissections = 51	Neck dissection from April 2008 to April 2011	Patients with level IIb metastasis in elective neck dissections = 0% Patients with level IIb metastasis in therapeutic neck dissections = 13.3%	Preservation of level IIb during neck dissection was possible in N0 cases of hypopharyngeal cancer.
Lim YC, Lee JS, Koo BS, Choi EC. Level IIb lymph node metastasis in laryngeal squamous cell carcinoma. Laryngoscope. 2006 Feb;116(2):268-72. **(61)**	Prospective analysis of a case series	Patients with laryngeal squamous cell carcinoma (n = 65) Total of neck dissections = 125	Surgical treatment of the primary lesion with simultaneous neck dissection from January 1999 to December 2002	Patients with level IIb metastases in cN0 = 1% Patients with level IIb metastases in cN+ = 37%	Level IIb lymph node pads may be preserved in elective neck dissection in patients with LSCC. However, this area should be removed thoroughly during therapeutic neck dissection in the treatment of clinically node-positive necks.
Wiegand S, Esters J, Müller HH, Jäcker T, Roessler M, Werner JA, Sesterhenn AM. Is it necessary to dissect levels I and IIB in hypopharyngeal cancer? Acta Otolaryngol. 2010 Jun;130(6):747-52. **(62)**	Retrospective analysis	Patients with hypopharyngeal cancer	Primary surgical treatment for hypopharyngeal cancer and neck dissection	Patients with level IIb metastases in cN0 = 1/14 Patients with level IIb metastases in cN+ = 2/36	The low incidence of metastases in levels I and IIb in patients with hypopharyngeal cancer in cases of cN0 and cN+ neck and the fact that all patients with metastases in levels I and IIb received postoperative radiotherapy justifies the preservation of levels I and IIb in patients with hypopharyngeal cancer to improve functional results and reduce the operating time.
Villaret AB, Piazza C, Peretti G, Calabrese L, Ansarin M,	Prospective cohort study	Patients with head and neck primary	Unilateral or bilateral neck	Prevalence of level IIB metastases = 5.6%	Sublevel IIb dissection is strongly recommended for all patients with cN+

Chiesa F, Pellini R, Spriano G, Nicolai P. Multicentric prospective study on the prevalence of sublevel IIb metastases in head and neck cancer. Arch Otolaryngol Head Neck Surg. 2007 Sep;133(9):897-903. **(63)**		tumours (n = 297) Total of neck dissections = 443 (151 unilateral and 146 bilateral)	dissection with therapeutic or elective intent between 2003 and 2005	The chi(2) test = significantly higher risk for LN metastases at sublevel IIb in patients affected by parotid gland primary tumours (33%), tumours of the skin or scalp (25%), unknown primary tumours (14%), and cancers of the oral cavity (10%) (P = .02) and in those clinically staged as cN+ (P < .001).	tumours and in those affected by tumour of the parotid gland, skin, and scalp scheduled for elective ND. Patients affected by laryngeal cancer scheduled for elective ND can be considered the ideal candidates for preservation of sublevel IIB. However, whether this policy could be associated with a better functional outcome remains to be demonstrated by prospective studies on a large series of patients.
Gutierrez CN, Chatzopoulos K, Garcia JJ, Janus JR. Review of treatment modalities and outcomes of patients with basal cell adenocarcinoma. Am J Otolaryngol. 2020 May-Jun;41(3):102414. **(64)**	Retrospective review	Patients with basal cell adenocarcinoma of the parotid gland (n = 13)	Radiation therapy, neck dissection or no treatment from 1.01.1996 to 08.01.2018	Patients with nodal involvement or distant metastases = 0	Elective neck dissections are not necessarily following resection of T1/T2N0M0 basal cell adenocarcinoma for the prevention of local or regional recurrence. No longer performing neck dissections for T1/T2N0M0 BCAC would reduce the morbidity associated with the treatment of this rare parotid tumour.
Pfisterer MJ, Vazquez A, Mady LJ, Khan MN, Baredes S, Eloy JA. Squamous cell carcinoma of the parotid gland: a	Multicenter study	Patients with squamous cell carcinoma of the parotid gland (n = 2545)	Elective neck dissection	END in N0 = 78.3% patients with higher disease-specific survival Omission of END = x3	Parotid SCC is uncommon, and data on treatment decisions are limited. Our study profiles the demographic, clinicopathologic, incidence, and survival features of this entity. Perhaps most notably, our results support the

population-based analysis of 2545 cases. Am J Otolaryngol. 2014 Jul-Aug;35(4):469-75. **(65)**				patients with greater hazard of death	practice of END of the N0 neck.
Bartella AK, Kloss-Brandstätter A, Kamal M, Teichmann J, Modabber A, Hölzle F, Lethaus B. "IIb or not IIb" - The necessity of dissection in patients with oral squamous cell carcinoma. J Craniomaxillofac Surg. 2016 Oct;44(10):1733-1736. **(66)**	Retrospective study	Patients with OSCC (n = 183)	Neck dissection	Patients with metastases in level IIb = 3.3% (none of them as exclusive metastases) Most LN metastases = levels I and IIa at ipsilateral sites, significantly related to tumour size ($p < 0.01$) and the infiltration of lymph vessels ($p < 0.001$) Locations of primary cancer sites in metastatic disease = soft palate, alveolar crest of the lower jaw and buccal mucosa	Lymph node metastases of OSCC in level IIb remain rare, especially as exclusive metastases and in clinically N-negative necks. The findings of this study support the hypothesis of sparing neck dissection in level IIb in cases of clinically negative necks.
Li Y, Liu K, Ke Y, Zeng Y, Chen M, Li W, Liu W, Hua X, Li Z, Zhong Y, Xie C, Yu H. Risk Factors Analysis of Pathologically Confirmed	Retrospective study	Patients with OSCC (n = 161)	Neck dissection	Patients with level IIb metastases = 1 (2.9%) Univariate analysis = no significant effect on cervical lymph	The growth pattern, degree of differentiation, depth of invasion, neutrophil/lymphocyte ratio, and the short/long axis diameter ratio of lymph nodes were the independent risk factors for pathological cervical lymph

Cervical Lymph Nodes Metastasis in Oral Squamous Cell Carcinoma Patients with Clinically Negative Cervical Lymph Node: Results from a Cancer Center of Central China. J Cancer. 2019 Jun 2;10(13):3062-3069. **(67)**	node metastasis (P>0.05) Multivariate Logistic regression analysis = independent risk factors for cervical lymph node metastasis (P<0.05)	node metastasis in oral squamous cell carcinoma patients with cN0. If patients with the above risk factors receive nonstandard radical neck dissection or no dissection, it may be necessary for them to receive the corresponding regional postoperative radiotherapy.

SCC: squamous cell carcinoma; OSCC: oral squamous cell carcinoma; HPSCC: hypopharyngeal squamous cell carcinoma; LSCC: laryngeal squamous cell carcinoma; BCAC: basal cell adenocarcinoma; ND: neck dissection; END: elective neck dissection; N0: node negative; N+: node positive; cN0: clinically node negative; cN+: clinically node positive; LN: lymph node; LVP: lymphovascular permeation; SNB: sentinel node biopsy; UADT: upper aerodigestive tract.

Table 16. Metastasis in level IIb: location of the primary oral cavity tumour and staging

4.4.2. METASTASIS IN LEVEL V

Reference	Study	Population	Intervention Follow-up	Results	Conclusions
Hasegawa T, Shibuya Y, Takeda D, Iwata E, Saito I, Kakei Y, Sakakibara A, Akashi M, Minamikawa T, Komori T. Prognosis of oral squamous cell carcinoma patients with level IV/V metastasis: An observational study. J Craniomaxillofac Surg. 2017 Jan;45(1):145-149. **(68)**	Observational study	Patients with oral squamous cell carcinoma with level IV/V metastases (n = 291)	Head and neck surgery between 1999 and 2013	Patients with level IV/V metastases = 23 (7.9%)	Oral tongue tumors, high N staging, and neck dissection upon the occurrence of metachronous neck metastasis or recurrence were risk factors for level IV/V metastasis and positive extracapsular spread, presence of multiple lymph metastases, and moderate or poor differentiation were poor prognostic factors.
Kainuma K, Yano T, Kitoh R, Naito T, Usami S. Prevalence of level V metastasis in head and neck squamous cell carcinoma. Acta Otolaryngol. 2013 Feb;133(2):218-24. **(69)**	Comparative study	Patients with HNSCC with cN0 and cN+ neck (n = 162) Total of neck dissections = 301	Selective level V neck dissection	Most common primary site = oral cavity (n = 51), larynx (n = 48), hypopharynx (n = 39), and oropharynx (n = 24) Overall prevalence of level V metastasis = 7.4%	Because of the low rate of level V metastasis, and from the viewpoint of standard postoperative radiotherapy, selective neck dissection without level V dissection may be possible in cases without clinical evidence of level V metastasis on both the ipsilateral and contralateral sides. In addition, degree of pathological differentiation and pN stage >N2b are suggested risk factors for level V metastasis.

OOSCC: oral and oropharyngeal squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; cN0: clinically node negative; cN+: clinically node positive.

Table 17. Metastasis in level V

4.4.3. ORAL CANCER SURVIVAL RATES BY STAGE

Reference	Study	Population	Intervention Follow-up	Results	Conclusions
Barros-Silva PG, Fontes-Borges MM, Costa-Dias C, Mota-Lemos JV, Socorro-Saldanha-Cunha MD, Fernandes-Souza E, Sousa-Dantas T, Bitu-Sousa F. Clinical-pathological and sociodemographic factors associated with the distant metastasis and overall survival of oral cavity and oropharynx squamous cell carcinoma. Med Oral Patol Oral Cir Bucal. 2020 May 1;25(3):e375-e382. **(70)**	Retrospective cross-sectional study	Patients with oral cavity and oropharynx squamous cell carcinoma (n =404)	Surgical treatment between 2000-2014	15-year survival rate of patients with OOSCC = 46.8%	Lymph node metastasis independently increased the prevalence of distant metastases and, along with male sex, older age, brown racial type and palliative treatment, was independently associated with poor prognosis in patients with OOSCC.
Zanoni DK, Montero PH, Migliacci JC, Shah JP, Wong RJ, Ganly I, Patel SG. Survival outcomes after treatment of cancer of the oral cavity (1985-2015). Oral Oncol. 2019 Mar;90:115. **(71)**	Observational study	Patients with oral squamous cell carcinoma of a tertiary cancer care center from 1985 to 2015 (n = 2082)	Median follow-up = 37.6 months	5-year OS = 64.4% 5-year DSS = 79.3% Most common subsite = tongue 51%	pN stage is the most powerful and consistent predictor of outcome in patients with OSCC treated with primary surgery and appropriate adjuvant therapy.

OSCC: oral squamous cell carcinoma; OOSCC: oral cavity and oropharynx squamous cell carcinoma; LN: lymph node; OS: overall survival; DSS: disease specific survival

Table 18. Oral cancer survival rates by stage

5. DISCUSSION

5.1. LOCATION OF HEAD AND NECK TUMOURS

In our study, the most frequent location of head and neck tumours was the tongue (31%), the floor of the mouth (23%) and the oropharynx (10,3%). According to the observational study of Zanoni et al. (71), the most common subsite was also the tongue (51%).

5.2. LEVEL IIB INVOLVEMENT

In our study only 9 patients (10,3%) with oral and salivary gland carcinoma had level IIb involvement. Studies from Kou et al. (48), Lea et al. (49), Gross et al. (51), Wiegand et al. (59) and Bartella et al. (66) also coincide in the low incidence of metastases in levels I and IIb in patients with oral squamous cell cancer.

Lea et al. (49) and Ghantous et al. (53) are the only studies that recommend that dissection of level IIb remains the standard of care in oral cavity squamous cell cancer, taking in consideration that isolated level IIb nodal disease is uncommon.

5.3. LEVEL IIB INVOLVEMENT BY LOCATION OF PRIMARY TUMOUR

We found that when the primary tumour is located in the parotid, half of the patients had level IIb involvement. The second most frequent location with involvement of level IIb was the maxilla (33,3%) and the third was the oropharynx (base of the tongue, soft plate and amygdala) (22,2%).

According to the multicenter study of Pfisterer et al. (65), occult metastases were reported in 12% to 48% of patients with all forms of parotid gland carcinoma, similar as the results of our study. The study of Bartella et al. (66) states that the locations of primary cancer sites in metastatic disease were the soft palate, alveolar crest of the lower jaw and buccal mucosa. Here should be noticed that in our study, the second most frequent location of primary tumour was the upper jaw/maxilla, instead of the lower jaw/mandible.

According to the systematic review by Kou et al. (48), the most common primary site for level IIb metastases was the tongue, and tongue cancer particularly had a tendency toward early metastasis (T1 and T2). The possible reason for the propensity of tongue SCC to metastasize

was that the tongue possesses extensive lymphatic network. That means that due to the low frequency of level IIb nodal metastases in oral squamous cell carcinoma patients and rare occurrence of isolated level IIb, level IIb dissection could be avoided when the primary lesions were in early stages (T1 and T2), with the exception of tongue cancer. In our study, we found that the base of the tongue (oropharynx) also involved level IIb.

5.4. LEVEL IIB INVOLVEMENT IN OROPHARYNGEAL AND PAROTID CANCER BY STAGE

The majority of the studies analysed, including Kou et al. (48), Yang et al. (50), Gross et al. (51), Santoro et al. (52), Dabholkar et al. (54), Hosokawa et al. (55), Kim et al. (56), Gross et al. (57), Sezen et al. (58), Wiegand et al. (59), Sakai et al. (60), Lim et al. (61), Wiegand et al. (62), Villaret et al. (63) and Gutierrez et al. (64), they all conclude that level IIb neck dissection can be omitted in early stage (T1 or T2) clinically node negative (cN0) oral squamous cell carcinoma.

In our study only one patient with oropharyngeal T1 carcinoma had metastasis at level IIb and two patients with T2 parotid carcinoma had level IIb involvement too. In the other locations in stages T1-T2 the carcinomas had no level IIb involvement.

In the retrospective cohort study performed by Gross et al. (57), patients with a cN0 neck and advanced OPSCC (T3 or T4), primary tumour in the oropharynx, or ipsilateral cN+ and contralateral cN0 neck, level IIb dissection should be considered. Additionally, Pfisterer et al. (65) recommends elective neck dissection of the N0 neck in parotid squamous cell carcinoma, justifying that parotid squamous cell carcinoma is uncommon, and data on treatment decisions are limited.

5.5. LEVEL IIB INVOLVEMENT BY T-STAGE

In our study, the stage where we found more level IIb involvement was T4 (20%), which means that the tumour had invaded nearby structures in the mouth or the muscles and bones that form the mouth or the base of the skull, and/or it encased the internal arteries. According to the systematic review by Kou et al. (48), oral squamous cell cancer patients with level IIb metastases were usually in terminal stages (T3 and T4) when diagnosed, as the results of our study.

Additionally, the retrospective study by Bartella et al. (66) states that lymph node metastases were significantly related to tumour size ($p<0.01$) and the infiltration of lymph vessels ($p<0.001$).

5.6. LEVEL IIB INVOLVEMENT BY LEVEL IIA INVOLVEMENT

According to our study, when level IIa was involved, 38,5% of patients also had level IIb involvement. According to the retrospective review by Wiegand et al. (59), of the patients with clinically detectable neck nodes, 3 of 21 patients had level I metastases and 3 of 25 patients had level IIb metastases; these 6 patients also had additional metastases in level IIa, which leads to the conclusion that dissection of neck levels I and IIb is justifiable in patients with clinically detectable neck nodes and suspicious lymph nodes in the respective level or level IIa.

According to Yang et al. (50), their predictive study indicates that the combined risk factors of level IIa metastasis and LVP significantly raised the level IIb metastasis rate. Additionally, Bartella et al. (66) states that lymph node metastases most likely occurred in levels I and IIa at ipsilateral sites.

5.7. LEVEL IIB INVOLVEMENT BY GENDER

In our study, from all of the cases, only 10,2% of the men and only 10,5% of the women had level IIb involvement, without statistical significance ($p>0.05$).

According to the retrospective study by Li et al. (67), univariate analysis showed that 21,3% of men and 15,2% of women had level IIb involvement, meaning that gender had no significant effect on cervical lymph node metastasis ($p>0.05$).

5.8. LEVEL V INVOLVEMENT BY TUMOUR LOCATION

In our study, level V involvement was only found in patients with the primary tumour in the mandible (10%) and on the floor of the mouth (5%). In the remaining locations, we found no level V involvement.

According to the comparative study by Kainuma et al. (69), the most common primary tumour sites by level V involvement was the oral cavity (n = 51), followed by the larynx (n = 48), hypopharynx (n = 39), and oropharynx (n = 24), from a total of 301 neck dissections.

5.9. LEVEL V INVOLVEMENT BY T-STAGE

According to our study, level V involvement was found only in one patient with advanced stage (T4), without statistical significance ($p>0.05$). The observational study performed by Hasegawa et al. (68) says that oral tongue tumours, high N staging, and neck dissection upon the occurrence of metachronous neck metastasis or recurrence were risk factors for level IV/V metastasis and positive extracapsular spread, presence of multiple lymph metastases, and moderate or poor differentiation were poor prognostic factors.

5.10. ORAL CANCER SURVIVAL RATES BY STAGE

In our study we found that the median survival in surgical patients was 4 years, with a survival rate of 81,5%, and in chemotherapy/radiotherapy patients the median survival was 2 years and 3 months, with a survival rate of 58,7%.

The retrospective study of Barros-Silva et al. (70) states that the 15-year survival rate of patients with OOSCC was 46,8% and that lymph node metastasis independently increased the prevalence of distant metastases and, along with male sex, older age, brown racial type and palliative treatment, was independently associated with poor prognosis in patients with OOSCC.

6. CONCLUSIONS

1. In early stages (T1-T2), most patients with oral and salivary gland tumours have no level IIb involvement, while in more advanced stages (T3-T4), level IIb involvement is more frequent and level IIb dissection should be performed regardless the location.
2. When the primary tumour is in the parotid, maxilla or oropharynx (soft plate, base of the tongue and amygdala), level IIb dissection should be performed regardless the stage (T1-T4) of the tumour.
3. Level IIa involvement influences statistically significant level IIb involvement.
4. Level V is rarely affected, only in advanced stages (T4). The results of our study are not significant.
5. Overall survival of surgical patients is longer than that of non-surgical patients who only underwent chemotherapy or radiotherapy.

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8. ANNEXES

ANNEXES I, II. HISTOLOGY OF SQUAMOUS CELL CARCINOMA

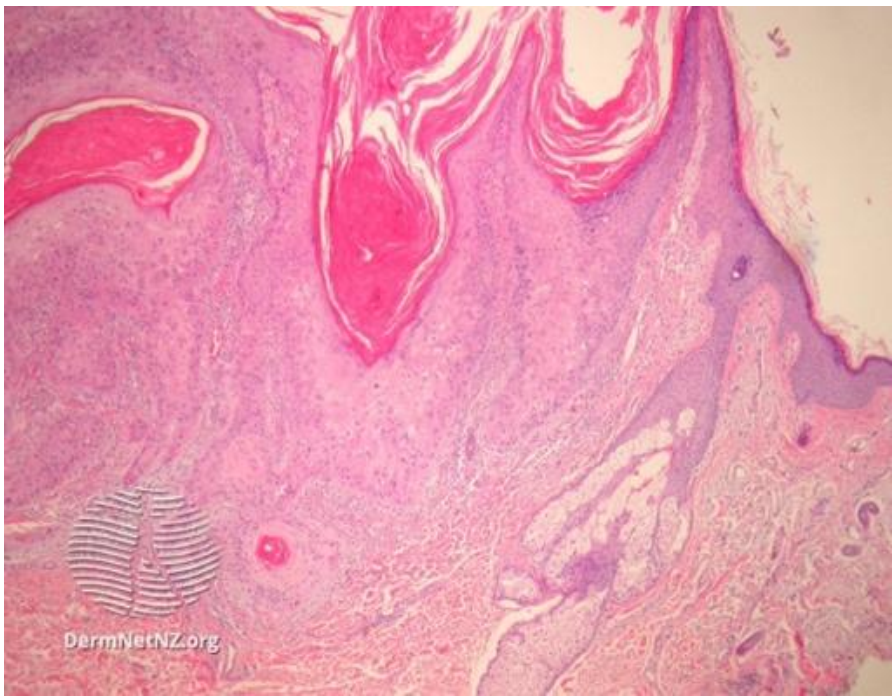

Figure 1. Squamous epithelial cells. (42)

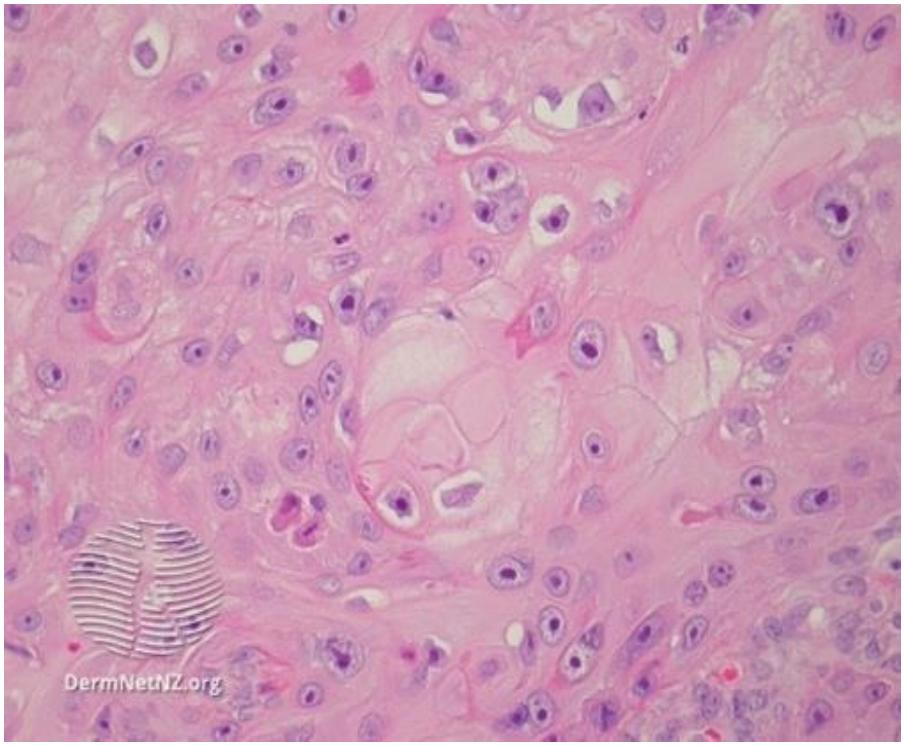

Figure 2. Cells with keratinisation. (42)

ANNEX III. ILLUSTRATION OF HEAD AND NECK CANCER REGIONS

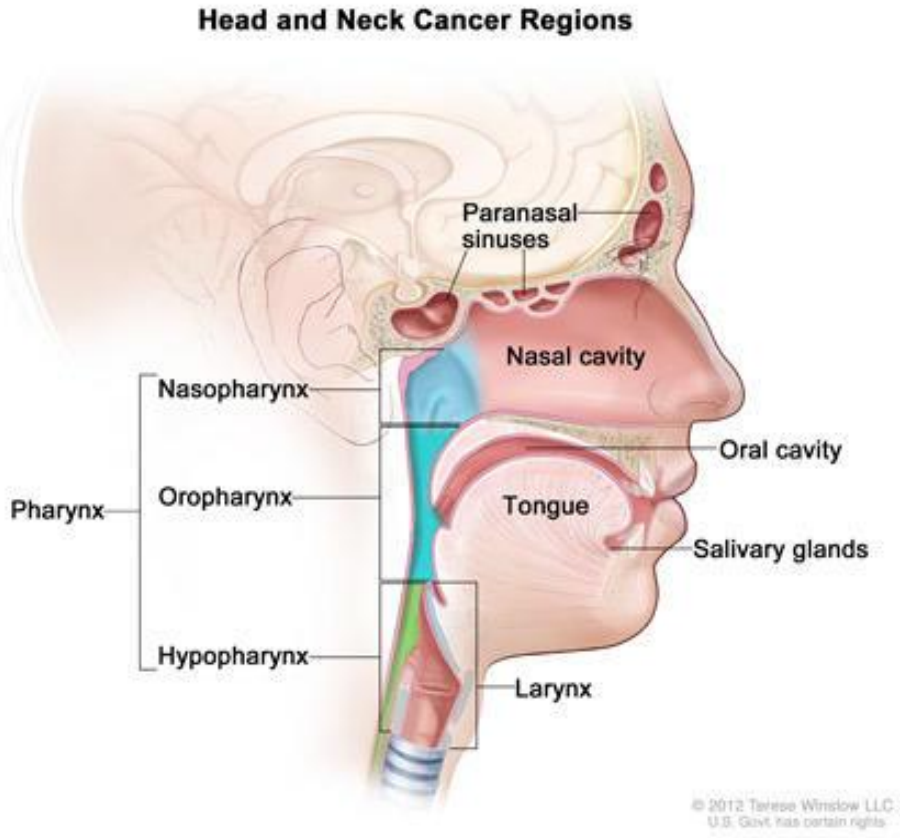

Figure 3. Head and neck cancer regions. Illustrates location of paranasal sinuses, nasal cavity, oral cavity, tongue, salivary glands, larynx, and pharynx (including the nasopharynx, oropharynx, and hypopharynx). (40)

ANNEX IV. CERVICAL LEVELS

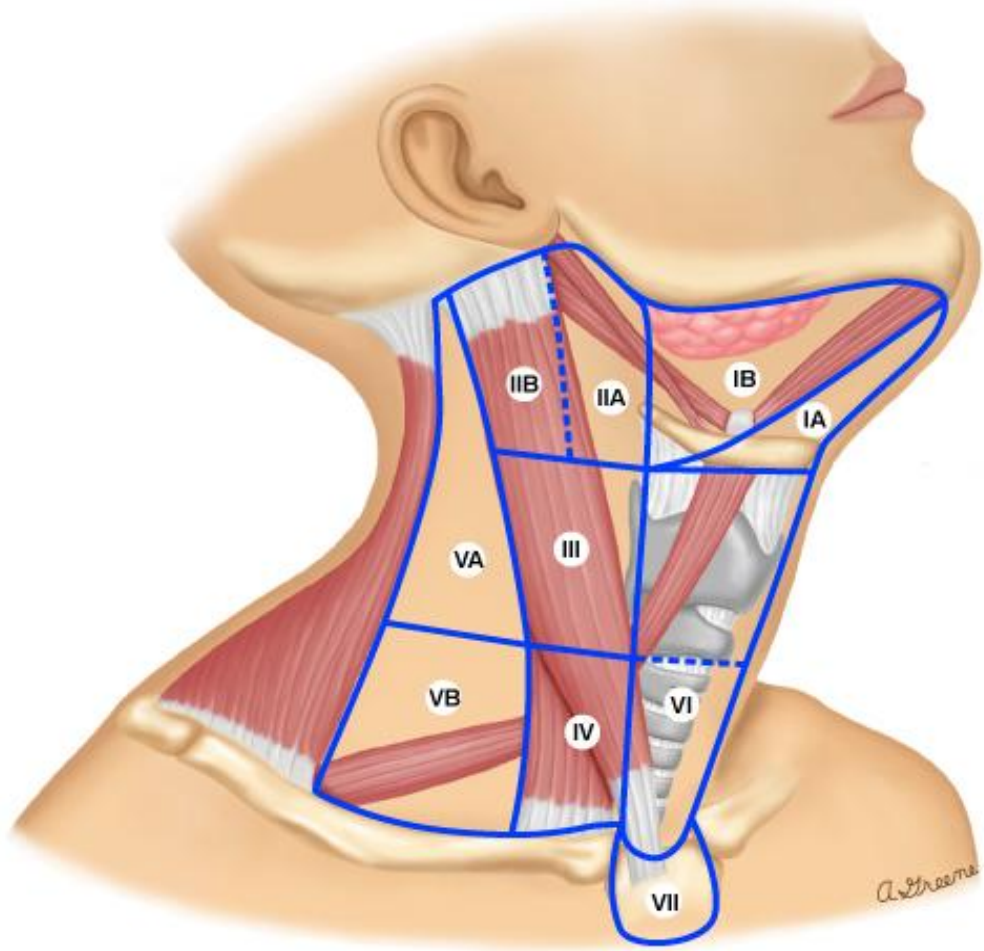

Figure 4. Cervical levels. (45)

ANNEX V. TUMOUR STAGING FOR ORAL CAVITY CANCERS (AJCC 8th ed.)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤ 2 cm and DOI ≤ 5 mm
T2	Tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm ***or*** tumor > 2 cm and ≤ 4 cm and DOI ≤ 10 mm
T3	Tumor > 4 cm ***or*** any tumor with DOI > 10 mm
T4 **T4a** **T4b**	Tumor invades adjacent structures only (e.g., through cortical bone of mandible or maxilla, or involves the maxillary sinus or skin of the face) Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

* DOI: depth of invasion. AJCC is currently discussing further refinement of T-stage stratification for small tumors (< 2 cm) with DOI > 10 mm.

Figure 5. Primary tumour (T) definition for oral cavity cancers. (46)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE-
N2 **N2a** **N2b** **N2c**	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE-; ***or*** metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE-; ***or*** in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE- Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE- Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE- Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE-
N3 **N3a** **N3b**	Metastasis in a lymph node > 6 cm and ENE-; ***or*** metastasis in any lymph node(s) with ENE+ clinically Metastasis in a lymph node > 6 cm and ENE- Metastasis in any lymph node(s) with ENE+ clinically

Figure 6. Clinical assessment of regional lymph nodes (cN). (46)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE-
N2 **N2a** **N2b** **N2c**	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE+; ***or*** metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE-; ***or*** metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE-; ***or*** in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE- Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE+; ***or*** metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE- Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE- Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE-
N3 **N3a** **N3b**	Metastasis in a lymph node > 6 cm and ENE-; ***or*** metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE+; ***or*** multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+; ***or*** a single contralateral node of any size and ENE+ Metastasis in a lymph node > 6 cm and ENE- Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE+; ***or*** multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+; ***or*** a single contralateral node of any size and ENE+

Figure 7. Pathological assessment of regional lymph nodes (pN). (46)

ANNEX VI. GENDER, NUMBER OF PARTICIPANTS AND AVERAGE AGE OF PATIENTS WITH HEAD AND NECK TUMOURS

Gender	Number of participants	Average age
Men	146	59,66 years
Women	67	67,26 years

Table 1. Gender, number of participants and average age of patients with head and neck tumours

ANNEX VII. LOCATION OF HEAD AND NECK TUMOURS

		Frequency	Percentage	Percentage valid	Percentage cumulative
Valid	Tongue	27	31,0	31,0	31,0
	Floor of the mouth	20	23,0	23,0	54,0
	Mandible	10	11,5	11,5	65,5
	Maxilla	6	6,9	6,9	72,4
	Jugal	8	9,2	9,2	81,6
	Trigon	2	2,3	2,3	83,9
	Oropharynx	9	10,3	10,3	94,3
	Parotid	4	4,6	4,6	98,9
	Lip	1	1,1	1,1	100,0
	Total	87	100,0	100,0	

Table 2. Percentage of the location of head and neck tumours

ANNEX VIII. CERVICAL INVOLVEMENT

		Frequency	Percentage	Percentage valid	Percentage cumulative
Valid	No	47	54,0	54,0	54,0
	Yes	40	46,0	46,0	100,0
	Total	87	100,0	100,0	

Table 3. Percentage of the cervical involvement

ANNEX IX. LEVEL IIB INVOLVEMENT

		Frequency	Percentage	Percentage valid	Percentage cumulative
Valid	Yes	9	10,3	10,3	10,3
	No	78	89,7	89,7	100,0
	Total	87	100,0	100,0	

Table 4. Percentage of the level IIb involvement

ANNEX X. TUMOUR STAGE T1-T4

		Frequency	Percentage	Percentage valid	Percentage cumulative
Valid	T1	20	23,0	23,3	23,3
	T2	30	34,5	34,9	58,1
	T3	16	18,4	18,6	76,7
	T4	20	23,0	23,3	100,0
	Total	86	98,9	100,0	
Lost	System	1	1,1		
Total		87	100,0		

Table 5. Percentage of the tumour staging

ANNEX XI. LEVEL IIB INVOLVEMENT BY LOCATION

			Level IIb involvement		Total
			Yes	No	
Tumour location	Tongue	Count	1	26	27
		% from Tumour location	3,7%	96,3%	100,0%
	Floor of the mouth	Count	1	19	20
		% from Tumour location	5,0%	95,0%	100,0%
	Mandible	Count	1	9	10
		% from Tumour location	10,0%	90,0%	100,0%
	Maxilla	Count	2	4	6
		% from Tumour location	33,3%	66,7%	100,0%
	Jugal	Count	0	8	8
		% from Tumour location	0,0%	100,0%	100,0%
	Trigon	Count	0	2	2
		% from Tumour location	0,0%	100,0%	100,0%
	Oropharynx	Count	2	7	9
		% from Tumour location	22,2%	77,8%	100,0%
	Parotid	Count	2	2	4
		% from Tumour location	50,0%	50,0%	100,0%
	Lip	Count	0	1	1
		% from Tumour location	0,0%	100,0%	100,0%
Total		Count	9	78	87

	% from Tumour location	10,3%	89,7%	100,0%

Table 6. Contingency table of the level IIb involvement by location

ANNEX XII. LEVEL IIB INVOLVEMENT IN MAXILLARY CANCER BY STAGE

			Level IIb involvement		Total
			Yes	No	
Stage	T3	Count	1	0	1
		% from Stage	100,0%	0,0%	100,0%
	T4	Count	1	4	5
		% from Stage	20,0%	80,0%	100,0%
Total		Count	2	4	6
		% from Stage	33,3%	66,7%	100,0%

Table 7. Contingency table of the level IIb involvement in maxillary cancer by stage

ANNEX XIII. LEVEL IIB INVOLVEMENT IN OROPHARYNGEAL CANCER BY STAGE

			Level IIb involvement		Total
			Yes	No	
Stage	T1	Count	1	4	5
		% from Stage	20,0%	80,0%	100,0%
	T2	Count	0	1	1
		% from Stage	0,0%	100,0%	100,0%
	T3	Count	0	2	2
		% from Stage	0,0%	100,0%	100,0%
	T4	Count	1	0	1
		% from Stage	100,0%	0,0%	100,0%
Total		Count	2	7	9
		% from Stage	22,2%	77,8%	100,0%

Table 8. Contingency table of the level IIb involvement in oropharyngeal cancer by stage

ANNEX XIV. LEVEL IIB INVOLVEMENT IN PAROTID CANCER BY STAGE

			Level IIb involvement		Total
			Yes	No	
Stage	T2	Count	2	2	4
		% from Stage	50,0%	50,0%	100,0%
Total		Count	2	2	4
		% from Stage	50,0%	50,0%	100,0%

Table 9. Contingency table of the level IIb involvement in parotid cancer by stage

ANNEX XV. LEVEL IIB INVOLVEMENT BY T-STAGE

			Level IIb involvement		Total
			Yes	No	
Stage	T1	Count	1	19	20
		% from Stage	5,0%	95,0%	100,0%
	T2	Count	3	28	31
		% from Stage	9,7%	90,3%	100,0%
	T3	Count	1	15	16
		% from Stage	6,2%	93,8%	100,0%
	T4	Count	4	16	20
		% from Stage	20,0%	80,0%	100,0%
Total		Count	9	78	87
		% from Stage	10,3%	89,7%	100,0%

Table 10. Contingency table of the level IIb involvement by stage

ANNEX XVI. LEVEL IIB INVOLVEMENT BY LEVEL IIA INVOLVEMENT

			Level IIb involvement		Total
			Yes	No	
Level IIa	Yes	Count	5	8	13
		% from Level IIa	38,5%	61,5%	100,0%
	No	Count	4	70	74
		% from Level IIa	5,4%	94,6%	100,0%
Total		Count	9	78	87
		% from Level IIa	10,3%	89,7%	100,0%

	Value	gl	Asymptotic sig. (bilateral)	Exact sig. (bilateral)	Exact sig. (unilateral)
Pearson's Chi-square	13,028[a]	1	,000		
Continuity correction[b]	9,707	1	,002		
Likelihood ratio	9,426	1	,002		
Fisher's exact statistic				,003	,003
Linear by linear association	12,878	1	,000		
N of valid cases	87				

a. 1 box (25.0%) have an expected frequency of less than 5. The minimum expected frequency is 1.34
b. Calculated only for a 2x2 table.

Table 11. Contingency table of the level IIb involvement by level IIa involvement

ANNEX XVII. LEVEL IIB INVOLVEMENT BY GENDER

			Level IIb involvement		Total
			Yes	No	
Gender	Men	Count	5	44	49
		% from Gender	10,2%	89,8%	100,0%
	Women	Count	4	34	38
		% from Gender	10,5%	89,5%	100,0%
Total		Count	9	78	87
		% from Gender	10,3%	89,7%	100,0%

Table 12. Contingency table of the level IIb involvement by gender

ANNEX XVIII. LEVEL V INVOLVEMENT BY TUMOUR LOCATION

			Level V involvement		Total
			Yes	No	
Tumour location	Tongue	Count	0	27	27
		% from Tumour location	0,0%	100,0%	100,0%
	Floor of the mouth	Count	1	19	20
		% from Tumour location	5,0%	95,0%	100,0%
	Mandible	Count	1	9	10
		% from Tumour location	10,0%	90,0%	100,0%
	Maxilla	Count	0	6	6
		% from Tumour location	0,0%	100,0%	100,0%
	Jugal	Count	0	8	8
		% from Tumour location	0,0%	100,0%	100,0%
	Trigon	Count	0	2	2
		% from Tumour location	0,0%	100,0%	100,0%
	Oropharynx	Count	0	9	9
		% from Tumour location	0,0%	100,0%	100,0%
	Parotid	Count	0	4	4
		% from Tumour location	0,0%	100,0%	100,0%
	Lip	Count	0	1	1
		% from Tumour location	0,0%	100,0%	100,0%
Total		Count	2	85	87
		% from Tumour location	2,3%	97,7%	100,0%

Table 13. Contingency table of the level V involvement by tumour location

ANNEX XIX. LEVEL V INVOLVEMENT BY T-STAGE

			Level V involvement		Total
			Yes	No	
T	T1	Count	0	26	26
		% from T	0,0%	100,0%	100,0%
	T2	Count	0	21	21
		% from T	0,0%	100,0%	100,0%
	T3	Count	0	9	9
		% from T	0,0%	100,0%	100,0%
	T4	Count	1	20	21
		% from T	4,8%	95,2%	100,0%
Total		Count	1	76	77
		% from T	1,3%	98,7%	100,0%

Table 14. Contingency table of the level V involvement by T-stage

ANNEX XX. LEVEL V INVOLVEMENT BY GENDER

			Level V involvement		Total
			Yes	No	
Gender	Men	Count	1	48	49
		% from Gender	2,0%	98,0%	100,0%
	Women	Count	1	37	38
		% from Gender	2,6%	97,4%	100,0%
Total		Count	2	85	87
		% from Gender	2,3%	97,7%	100,0%

Table 15. Contingency table of the level V involvement by gender

ANNEX XXI. ROC CURVE: SURVIVAL OF SURGICAL PATIENTS

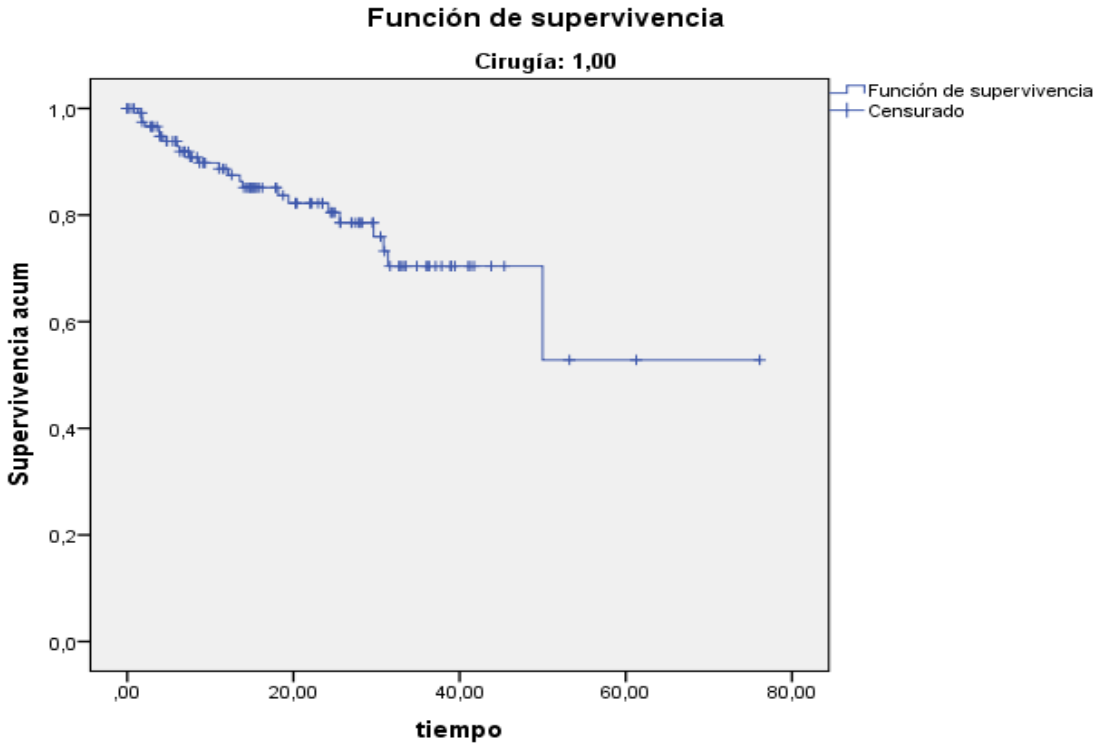

Figure 8. ROC curve: survival of surgical patients.

ANNEX XXII. ROC CURVE: SURVIVAL OF CHEMOTHERAPY/ RADIOTHERAPY PATIENTS

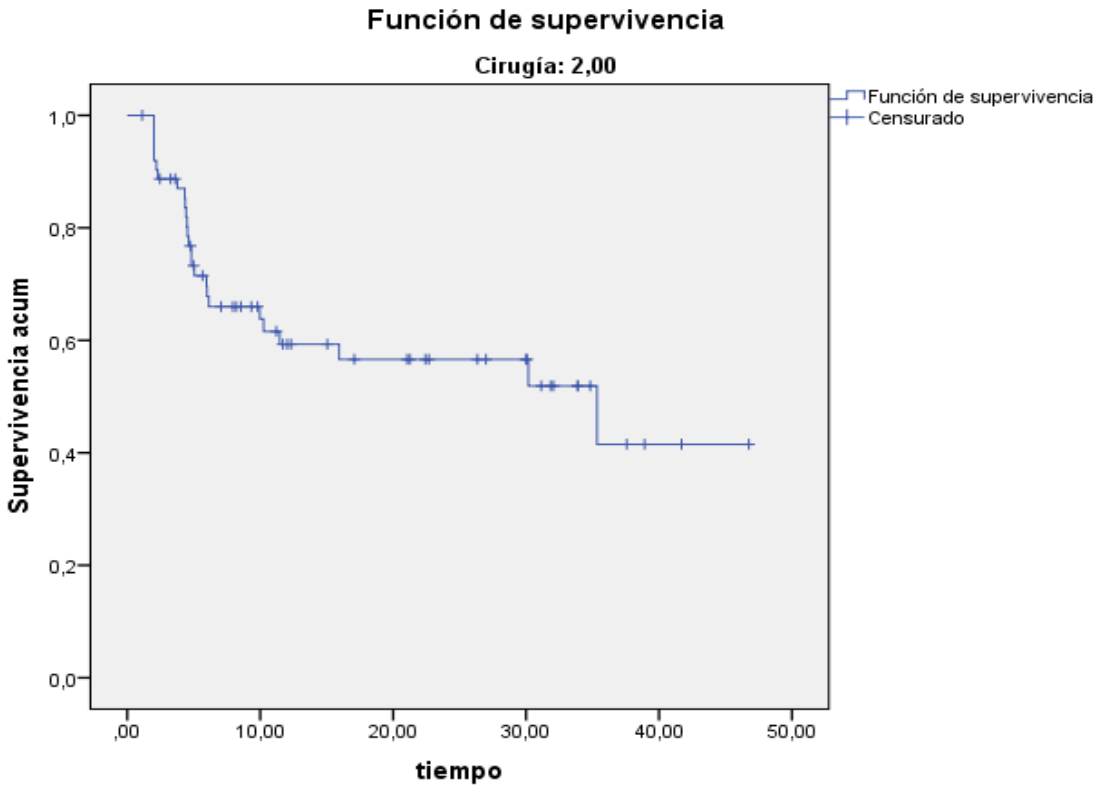

Figure 9. ROC curve: survival of chemotherapy/radiotherapy patients.