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"Influencia de la localización topográfica del tumor primario, edad de los pacientes, estadio T y espesor de infiltración tumoral en la capacidad de metastatización del carcinoma epidermoide de cavidad oral."

"Influence of topographic location, patients age, T-stage and tumor thickness on the metastatic capacity of squamous cell carcinoma of the oral cavity."

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A Lorena y Claudia,

por ser la luz que ilumina mi camino

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RESUMEN

El cáncer oral es uno de los diez tipos de cáncer más frecuentes en el mundo, constituyendo alrededor del 3% de todos los tumores malignos en los países desarrollados. El carcinoma epidermoide representa el tipo de cáncer que más frecuentemente afecta la cavidad oral. Las localizaciones más interesadas son, lengua oral, suelo de la boca, mucosa vestibular oral, encía insertada superior e inferior, trígono retromolar y paladar duro. Alcohol y tabaco representan los factores etiológicos más frecuentemente asociados con este tipo de enfermedad. Además, en los últimos años, el virus del papiloma humano (HPV) está siendo considerado como un importante factor etiológico y pronóstico en el cáncer de orofaringe. Desafortunadamente, el tratamiento del cáncer oral no ha conseguido mejorar significativamente el pronóstico de los pacientes en estos últimos años. El tratamiento quirúrgico suele basarse en la tumorectomía de la lesión primaria ± disección cervical ganglionar. Sin embargo, no existen muchos estudios que analicen la distribución topográfica de las metástasis cervicales en relación a la localización del tumor primario en la cavidad oral. Además, el papel de muchos factores pronósticos clásicamente relacionados con esta enfermedad son objeto de controversia hoy en día.

El objetivo de esta tesis es analizar la distribución topográfica de las metástasis cervicales en relación a la localización topográfica del tumor primario con el fin de crear un protocolo de actuación quirúrgica que tenga en cuenta de las diferencias en el comportamiento biológico de los tumores en función de su localización en la cavidad oral y reducir la yatrogenia asociada a la cirugía. Además, este estudio también pretende analizar el impacto de estadio T, estadio N, espesor de infiltración tumoral, invasión linfovascular, invasión perineural, desbordamiento capsular y márgenes quirúrgicos en el pronóstico de la enfermedad y supervivencia de los pacientes.

Se evaluaron de manera retrospectiva las historias clínicas de un total de 532 pacientes que cumplieron los criterios de inclusión para ser analizados en el presente estudio.

Los resultados de este trabajo demuestran que el nivel IIA es el nivel que es el más frecuentemente afectado por metástasis cervicales de carcinomas epidermoides de lengua. También se evidenció una elevada tasa de metástasis ocultas aisladas en nivel IV (7.4%) en pacientes diagnosticados con carcinoma epidermoide lingual y sin evidencia clínica y/o radiológica de afectación cervical antes de la cirugía. Sin embargo, el carcinoma epidermoide maxilar superior metastatiza preferentemente en el nivel Ib.

En este trabajo de tesis, también se evidenció que estadio T, estadio N, espesor de infiltración tumoral >0.4 cm, invasión linfovascular, invasión perineural, desbordamiento capsular y márgenes quirúrgicos representan factores de mal pronóstico y tiene un impacto negativo sobre la supervivencia global de los pacientes.

ABSTRACT

Oral cancer is one of the most common types of cancer in the world. It represents about 3% of all malignant tumors in developed countries. Specifically, squamous cell carcinoma is the most common type of cancer that usually affects the oral cavity. Oral tongue, floor of the mouth, buccal mucosa, mandibular and maxillary gingiva, retromolar zone and hard palate are the most frequently involved areas. Alcohol and tobacco represent the classic risk factors associated with this type of disease. Recently, human papillomavirus (HPV) is being considered as an important etiological r and prognostic factor in oropharyngeal cancer. Unfortunately, surgical and medical treatment failed to significantly improve the prognosis of patients during the last years. Surgical treatment is usually based on the extirpation of the primary lesion ± cervical lymph node dissection. However, there are not many studies analyzing the topographic distribution of cervical metastases in relation to the location of the primary tumor in the oral cavity. Similarly, the importance of several prognostic factors classically related to this disease is controversial.

The main goal of this study is to analyze the topographic distribution of cervical metastases in relation to the topographic location of the primary tumor with the aim to create a surgical protocol that considerate the different biological behavior of tumors with different location in the oral cavity. Moreover, this study also analyzes the impact of T stage, N stage, tumor thickness, vascular invasion, perineural invasion, extracapsular spread and surgical margins on overall survival.

The clinical records of 532 patients were retrospectively evaluated for this study.

According to our results, level IIA was the cervical level most frequently affected by cervical metastases of squamous cell carcinomas of the tongue. Furthermore, a high rate of isolated occult metastases was also found at level IV (7.4%) in patients with squamous cell carcinoma of the tongue and without clinical and / or radiological evidence of cervical

involvement before surgery. In contrast, squamous cell carcinoma of the upper jaw usually metastasizes at level Ib.

Moreover, our study also confirmed that T stage, N stage, tumor thickness> 0.4 cm, vascular invasion, perineural invasion, extracapsular and surgical margins (close and infiltrated) represent poor prognostic factors and have a negative impact on overall survival.

LISTADO DE ABREVIATURAS

HPV: virus del papiloma humano

OMS: Organización Mundial Sanidad

RMN: Resonancia Magnética

AJCC: American Joint Committee on Cancer

RT: Radioterapia

QT: Quimioterapia

ILV: Invasión linfovascular

N0: Ausencia de afectación ganglionar cervical

N+: afectación ganglionar cervical

OSCC: Oral squamous cell carcinoma

SCC: squamous cell carcinoma

cTNM: TNM clínico

pTNM: TNM patológico

ECS: Extracapsular spread

ESOHND: Extended supraomohyoid neck dissection

UICC: International Union Against Cancer

TT: Tumor Thickness

HNSCC: Head and neck squamous cell carcinoma

Gy: Gray

INTRODUCCIÓN

El cáncer oral es uno de los diez tipos de cáncer más frecuentes en el mundo, constituyendo alrededor del 3% de todos los tumores malignos en los países desarrollados (1). El carcinoma de células escamosas representa el tipo de cáncer que más frecuentemente afecta la cavidad oral (2). Las localizaciones más interesadas son, lengua oral, suelo de la boca, mucosa vestibular oral, encía insertada superior e inferior, trígono retromolar y paladar duro (3). Alcohol y tabaco representan los factores etiológicos más frecuentemente asociados con este tipo de enfermedad. Además, en los últimos años, el virus del papiloma humano (HPV) está siendo considerado como un importante factor etiológico y pronóstico en el cáncer de orofaringe (4). Desafortunadamente, el tratamiento del cáncer oral no ha conseguido mejorar significativamente el pronóstico de los pacientes a pesar de los avances en la cirugía, radioterapia y quimioterapia, y la supervivencia a 5 años de los pacientes afectados es aproximativamente del 40- 60% (5). Uno de los factores que más pesantemente contribuye a la gran agresividad del cáncer oral es su capacidad de metastatización a distancia. Este tipo de cáncer difunde casi exclusivamente por vía linfática y los ganglios cervicales son los más frecuentemente interesados (6). Pulmón, hueso y cerebro podrían también estar afectados en menos del 10% de pacientes en estadios más avanzados (7). En este sentido, el compromiso ganglionar es el principal factor pronóstico independiente en el carcinoma escamoso de cavidad oral y la presencia de adenopatías metastásicas cervical reduce la sobrevivencia de casi un 50% (8).

Tamaño Tumoral, localización del tumor primario y espesor de infiltración tumoral son factores que parecen jugar un papel importante en la capacidad de metastatización del tumor primario y, consecuentemente, se consideran factores de mal pronóstico (9). El análisis de estos factores tiene una gran importancia en la práctica clínica y determina el tipo de tratamiento al que será sometido el paciente. Además de la extirpación tumoral, otros tratamientos como el vaciamiento cervical, la radioterapia y la quimioterapia se

pueden utilizar para reforzar la estrategia terapéutica en presencia de factores de mal pronóstico (10). Por ejemplo, el tamaño tumoral (estadio T) es un factor fundamental a la hora de decidir el tipo de tratamiento que se aplicará. Tumores más grandes recibirán un tratamiento más agresivo a nivel local y regional debido al mayor riesgo de metastatización. La localización topográfica del tumor primario es otro factor determinante para la elección del tratamiento. Los tumores de la lengua, por ejemplo, presentan mayor tendencia a la diseminación cervical, peor pronóstico y esquemas terapéuticos más agresivos (11). Con respecto al espesor tumoral, numerosos estudios afirman que tumores con espesor de infiltración >0,5 cm muestran mayor riesgo de afectación cervical y, por lo tanto, necesitan una actitud terapéutica más enérgica (12). Sin embargo, el real significado clínico y pronóstico de todos estos factores no ha sido aún aclarado completamente y los mecanismos de metastatización a distancia del carcinoma epidermoide de cavidad oral restan en gran parte desconocidos. Tumores muy pequeños pueden mostrar una marcada tendencia a la metastatización cervical y numerosos estudios han evidenciado que tumores con espesor de infiltración >0,3 cm pueden tener un alto riesgo de diseminación a distancia (13). Igualmente, otros estudios han demostrado la elevada agresividad de los tumores de suelo de la boca y de mucosa yugal (14). Por lo tanto, existe gran controversia en la literatura sobre cuales sean los mecanismos que condicionan la capacidad de diseminación a distancia del carcinoma epidermoide cavidad oral. Un atento análisis de estos factores podría tener un importante impacto clínico y contribuir a la reducción de la morbilidad asociada al tratamiento quirúrgico de este tipo de cáncer.

1.1 Epidemiología

El cáncer oral constituye un importante problema sanitario debido a su difusión, a la alta mortalidad y a los problemas funcionales y estéticos provocados por su tratamiento. De acuerdo con los últimos informes de la OMS, la prevalencia e incidencia del carcinoma epidermoide de cavidad oral sería en continuo aumento países desarrollados y en vía de desarrollo. Especificadamente, el cáncer oral es el undécimo cáncer más común, y representa aproximadamente el 3% de todos los cánceres y un 2% de las muertes por cáncer en todo el mundo (15).

1.2 Diagnóstico

El diagnóstico final y definitivo del carcinoma epidermoide de cavidad oral es histológico a través del minucioso estudio de una muestra del tejido patológico. Sin embargo, una correcta exploración clínica de los pacientes y la radiología son fundamentales para realizar un diagnóstico completo y estadiar la patología. El carcinoma epidermoide de cavidad oral suele manifestarse como una úlcera que no cura, una masa exofítica, una tumoración submucosa que no llega a ulcerar la mucosa oral o una alteración de la coloración de la mucosa oral. Por lo tanto, cualquier lesión sospechosa que afecte a la cavidad oral y que no se cure en un plazo de 2-3 semanas debería biopsiarse con el fin de asegurar un diagnóstico lo más precoz posible. TAC y RMN son fundamentales una vez que los exámenes histológicos hayan confirmado la sospecha clínica de carcinoma epidermoide y permiten completar el estadiaje clínico de estos tumores y decidir la actitud terapéutica a seguir (16). El TAC es el más sensible para valorar la infiltración de las estructuras óseas del macizo facial en relación de cercanía con el tumor primario, mientras que la RMN permite valorar la infiltración de las estructuras “blandas” adyacentes al

tumor (17). Ambas pruebas presentan similar especificidad y sensibilidad en evaluar la posible diseminación cervical de la enfermedad.

1.3 Estadiaje

El estadio del carcinoma epidermoide de cavidad oral depende del tamaño de la lesión primaria y de la diseminación cervical o a distancia de la patología. El estadio es extremadamente importante y presenta una correlación directa con el tipo de tratamiento al que será sometido el paciente y con el pronóstico de la enfermedad. La clasificación más comúnmente utilizada para el estadiaje de este tipo de cáncer es la TNM, propuesta por American Joint Committee on Cancer (AJCC) (Tablas 1 y 2) (18) (19).

1.4 Tratamiento

El tratamiento del carcinoma epidermoide de cavidad oral depende el estadio de la enfermedad (20). La cirugía sigue representando un pilar fundamental y suele ser el tratamiento de inicio en caso de tumores resecables y que no afecten estructuras vitales (21). La radioterapia constituye un tratamiento adyuvante a la cirugía y suele emplearse cuando el tumor presenta determinadas características de mal pronóstico como, por ejemplo, estadio T o N avanzado, infiltración perineural o vascular, márgenes quirúrgicos afectos o presencia de metástasis cervicales con desbordamiento capsular (22). El papel de la quimioterapia es secundario en este tipo de patología, aunque suele asociarse a la RT como tratamiento adyuvante en el caso de que el examen histológico evidenciara la presencia de márgenes quirúrgicos infiltrados, metástasis cervicales con desbordamiento capsular o diseminación a distancia. Solo en el caso que el tumor primario se considere quirúrgicamente o funcionalmente irresecable la RT y la QT se emplearan como la

primera modalidad de tratamiento (23). Un caso especial es representado por los carcinomas epidermoides con afectación exclusiva de orofaringe. De hecho, en estos tumores se mostrarían mejores tasas de respuesta a la RT y QT y mejores pronósticos de supervivencia. Por lo tanto, el tratamiento con QT y RT está transformándose en el tratamiento de elección en los tumores de orofaringe y base de lengua que no afecten simultáneamente otras localizaciones de la cavidad oral (24).

Con respecto al tratamiento quirúrgico, las actuales línea guías prevén una extirpación del tumor primario con un margen de seguridad de 0.5 cm de tejido sano alrededor de la lesión. Además, de la cirugía del tumor primario con márgenes oncológicos, el vaciamiento cervical representa otro pilar fundamental del tratamiento quirúrgico del carcinoma epidermoide de cavidad oral. Especificadamente, la cirugía de vaciamiento cervical se recomienda en casos de tumores con avanzado estadio T (T3 o T4), infiltración tumoral >0.5 cm y/o sospecha clínica o radiológica de afectación cervical (25). Desafortunadamente no hay evidencia sobre la distribución topográfica de las metástasis cervicales con respecto a la localización del tumor primario en la cavidad oral y esto obliga los cirujanos a ser particularmente agresivos en el tratamiento de esta patología. Existen varios tipos de vaciamiento cervical y, cada uno de ellos, presenta una especial indicación según el estadiaje clínico y radiológico del paciente previo a la cirugía. En este sentido, en el caso de que no exista sospecha clínica y/o radiológica de afectación cervical se indicaría un vaciamiento selectivo de tipo supraomohioideo incluyendo los niveles cervicales I-III (26). Este concepto es válido para todas las localizaciones de la cavidad oral con excepción de la lengua. De hecho, los carcinomas epidermoides de lengua suelen presentar peor pronóstico y mayor agresividad local y regional. Numerosos estudios han evidenciado una comunicación directa entre este órgano y el nivel cervical IV hasta en caso de pacientes con escasa evidencia clínica y/o radiológica de afectación linfática. Por

estas razones, se aconseja realizar un vaciamiento supraomohioideo extendido al nivel IV aunque no se haya evidencia clínica o radiológica de la afectación de este nivel antes de la cirugía en pacientes diagnosticados con carcinoma epidermoide de lengua (27). Sin embargo, en caso de pacientes con sospecha clínica o radiológica de afectación cervical es mandatorio realizar un vaciamiento "funcional" donde se incluyan los niveles desde el I al V (28).

Con respecto a la Radioterapia, tanto el cáncer primario como los ganglios linfáticos cervicales pueden incluirse en los campos de radiación. Generalmente se utilizan dosis de 66-70 Gray (Gy) (1Gy = 100 rads) fraccionadas 30-36 dosis de 2Gy administradas durante 5 días a la semana durante 6-7 semanas. A pesar que la radioterapia permita preservar los órganos, no está exenta de complicaciones (mucositis, xerostomía, candidiasis, osteorradionecrosis y limitación de la apertura oral) y, al mismo tiempo, ha demostrado menores tasas de curaciones cuando comparada con la cirugía como primera modalidad de tratamiento. Consecuentemente, se utiliza casi de forma exclusiva como tratamiento adyuvante cuando se evidencien factores de mal pronóstico (29).

La QT suele utilizar fármacos citotóxicos como el cisplatino y el 5-fluoracil y el Cetuximab. Sin embargo, esta modalidad de tratamiento no ha demostrado un aumento en las tasas de supervivencia a los 5 años, control del tumor primario y/o reducción del potencial metastásico (30). El rol de la quimioterapia sería el de potenciar los efectos de la radioterapia sensibilizando las células neoplásicas y facilitando el efecto del tratamiento radiante. Como se ha explicado anteriormente, la QT es generalmente utilizada junto con la RT en los casos en los que la cirugía es desestimada o cuando existan factores de mal pronóstico como metástasis a distancia, metástasis cervicales con desbordamiento capsular o márgenes afectos (31).

1.5 Supervivencia

A pesar de los avances con respecto a las técnicas de cirugía extirpativa y reconstructiva, radioterapia y quimioterapia, el pronóstico de los pacientes con carcinoma epidermoide de cavidad oral no ha mejorado en las últimas décadas. Las tasas de curación del cáncer oral dependen del estadio de la enfermedad acercándose al 80% en estadios precoces y bajando hasta el 20% en pacientes con estadios avanzados y afectación loco-regional y/o a distancia (32). Por lo tanto, la detección precoz aumenta significadamente los porcentajes de curación y la esperanza de vida de los pacientes. Sin embargo, a pesar de su elevada incidencia y prevalencia, el carcinoma epidermoide de cavidad oral representa una patología desconocida para la opinión pública y, en muchos casos, para muchos profesionales de la salud. Esto suele provocar un notable retraso diagnóstico e incita a promover campañas nacionales e internacionales para sensibilizar la opinión pública sobre este problema sanitario.

De acuerdo a numerosos estudios el principal factor relacionado con el retraso diagnóstico sería atribuible al propio paciente y al desconocimiento que una lesión crónica que afecte a la cavidad oral pueda ser provocada por un cáncer (33).

1.6 Factores pronósticos

Numerosos son los factores pronósticos clásicamente asociados con la supervivencia de los pacientes con carcinoma epidermoide de la cavidad oral. En este sentido, el estadio de la enfermedad es uno de los factores que más se ha relacionado con la evolución de este tipo de patología. Paciente en estadios precoces presentan elevadas tasas de curación (80-90% en estadio I y 65-80% en estadio II). Estadio T y Estadio N factores extremadamente importantes y tienen un peso relevante a la hora de decidir entre las varias tipologías de tratamiento (34). La afectación cervical (N+) se asocia a una

reducción de hasta el 50% en termino de supervivencia global (35). Otro factor determinante en el pronóstico de este tipo de cáncer es el espesor tumoral. La literatura clásica considera que aquellos tumores con espesor de infiltración >0,5 cm presentan mayor capacidad de diseminación linfática y afectación cervical. Este valor es de fundamental importancia, ya que determina la necesidad de incluir el vaciamiento cervical en la estrategia de tratamiento que se aplicará al paciente (36). De hecho, la disección de los ganglios linfáticos cervicales no se realiza en tumores en estadios precoces con espesor de infiltración <0.5 cm. En el caso de que se sospeche que el espesor de infiltración sea >0.5, el vaciamiento cervical debería asociarse siempre a la cirugía de extirpación del tumor primario, incluso en los casos en los que no se haya evidencia clínica y/o radiológica de extensión cervical de la patología (37). A pesar de la importancia de este factor para la decisión de la modalidad del tratamiento y de su influencia en el pronóstico, existe controversia en la literatura moderna sobre este valor. Numerosos autores han observado que tumores con espesor de infiltración tumoral de 0.3 o 0.4 cm podrían evidenciar un riesgo similar de diseminación linfática cuando comparados con tumores con espesor de infiltración > 0,5 cm y, por lo tanto, similar pronóstico (38). En este sentido, muchos autores están aconsejando modificar el cut-off de 0.5 cm a la hora de considerar el espesor de infiltración tumoral como factor pronóstico de esta enfermedad. Debido a la gran controversia existente en la literatura con respecto a este valor, determinar el real impacto del espesor de infiltración tumoral en la capacidad de diseminación cervical y en el pronóstico de la enfermedad ha sido uno de los aspectos centrales de este trabajo de tesis. Los márgenes quirúrgicos se consideran como otro factor clave con respecto a la supervivencia global de esta patología. Generalmente, se aceptan 3 grupos de márgenes quirúrgicos: 1- libre, el tumor está a más de 0.5 cm del margen de resección; 2- estrecho, el tumor está entre 0.2 y 0.5 cm del margen de

resección; 3- infiltrado, el tumor está a menos de 0.2 cm del margen de resección (39). Esta clasificación tiene un notable valor pronóstico y es clave a la hora de decidir el tipo de tratamiento adyuvante que se aplicará al paciente. En este sentido, tumores con márgenes libre no suelen requerir tratamiento adyuvante en ausencia de otros factores de mal pronóstico. Sin embargo, se aconseja administrar radioterapia en caso de pacientes con márgenes estrechos y radio- y quimio-terapia en caso de pacientes con márgenes infiltrados. Según algunas series, la supervivencia bajaría entre un 20 y 40% en caso de márgenes estrechos y hasta un 60% en casos de márgenes infiltrados (40). Sin embargo, existe cierta controversia en relación con el real valor del margen quirúrgico que debería de considerarse como libre de enfermedad. Muchos autores consideran que márgenes de 0.3 cm podrían ser suficientes, especialmente en determinadas localizaciones de la cavidad oral, y que no se relacionarían con mayores tasas mortalidad y peor pronóstico. La determinación de la influencia de los márgenes quirúrgicos en el pronóstico de la enfermedad ha sido otro de los pilares de este trabajo de tesis. Infiltración linfovascular y perineural son dos criterios histopatológicos relacionados con el tumor primario que muestran importante relación con el pronóstico de la enfermedad (41). La invasión linfovascular (ILV) se define como la presencia de células cancerosas en un espacio con revestimiento endotelial definido (como los vasos linfáticos o los vasos sanguíneos) en la cavidad oral. La infiltración perineural se define como la penetración de las vainas nerviosas superficiales por parte de células cancerígenas. De acuerdo con algunas series, invasión linfovascular y perineural traducirían una mayor tendencia a la metastatización del tumor primario y podrían asociarse a una reducción de hasta el 50% de la supervivencia global (42). Por lo tanto, la presencia de estos factores en el análisis histológico postoperatorio impone la aplicación de esquemas de tratamiento adyuvante más agresivos. Otro factor, que recientemente, está adquiriendo mayor importancia

pronostica es la edad de los pacientes (43). Numerosos estudios han documentado que este tipo de cáncer mostraría peor pronóstico en paciente jóvenes (< 45 años). La principal razón de esta asociación podría ser debida a la ausencia de los tradicionales factores de riesgos (tabaco y alcohol) en este grupo de pacientes. En estos casos, parece que la etiopatogenia del carcinoma epidermoide estaría relacionada con una marcada predisposición genética de los pacientes y menor sensibilidad a los tratamientos adyuvantes usualmente empleados para tratar esta patología (44).

Por lo tanto, a pesar de los numerosos estudios realizados, existe cierta controversia entre el real impacto de los "clásicos" factores pronósticos del carcinoma epidermoide de cavidad oral y la supervivencia global. Principal objetivo de este trabajo de tesis doctoral es analizar la distribución topográfica de las metástasis cervicales en relación a la localización del tumor primario en la cavidad oral y estudiar la relación de numerosos factores pronósticos de esta patología con la supervivencia global.

1.7 Definición de metástasis ocultas

Por metástasis ocultas se entiende la evidencia histológica de metástasis ganglionar, en uno o más niveles cervicales, en pacientes con carcinoma epidermoide de cavidad oral que no mostraban datos clínicos y/o radiológicos de afectación cervical antes de la cirugía (45). La presencia de metástasis ocultas al examen histopatológico postoperatorio empeora el pronóstico de esta patología y reduce notablemente la supervivencia de los pacientes (46). De acuerdo con numerosos autores, el espesor de infiltración tumoral podría estar relacionado con la presencia de metástasis ocultas. Especificadamente, tumores con espesor de infiltración >0.5 cm y sin evidencia clínica o radiológica de afectación cervical (cN0) podrían presentar un riesgo de metástasis ocultas del 15-20%. Por esta razón, tumores con espesor de infiltración >0.5 son solitamente tratados con

tumorectomía de la lesión primaria y vaciamiento ganglionar cervical aunque no existan otros datos que sugieran presencia de extensión cervical de la patología (47).

Bibliografía

1- Lingen MW, Kalmarr JR, Karrison T, Serbit PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol 2008;44(1):10-22.

2- Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002; 52:195-215.

3- Warnakulasuriya S. Review Global Epidemiology of Oral and Oropharyngeal Cancer. Oral Oncol 2004; 25:309-16.

4- Soung Min Kim. Human papilloma virus in oral cancer. J Korean Assoc Oral Maxillofac Surg. 2016 Dec; 42(6): 327–336.

5- Isaäc van der Waal. Are we able to reduce the mortality and morbidity of oral cancer; Some considerations. Med Oral Patol Oral Cir Bucal. 2013 Jan; 18(1): e33–e37.

6- Waseem Jerjes, Tahwinder Upile, Aviva Petrie, Andrew Riskalla, Zaid Hamdoon, Michael Vourvachis, Kostas Karavidas, Amrita Jay, Ann Sandison, Gareth J Thomas, Nicholas Kalavrezos, Colin Hopper. Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. Head Neck Oncol. 2010; 2: 9.

7- Liu JC, Bhayani M, Kuchta K, Galloway T, Fundakowski C. Patterns of distant metastasis in head and neck cancer at presentation: Implications for initial evaluation. Oral Oncol. 2019 Jan; 88:131-136.

8- Sivanandan R, Kaplan MJ, Lee KJ, Lebl D, Pinto H, Le QT, et al: Long-term results of 100 consecutive comprehensive neck dissections: implications for selective neck dissections. Arch Otolaryngol Head Neck Surg 2004; 130: 1369e1373.

9- Balasubramanian D, Ebrahimi A, Gupta R, Gao K, Elliott M, Palme CE, et al: Tumour thickness as a predictor of nodal metastases in oral cancer: comparison between tongue and floor of mouth subsites. Oral Oncol 2014; 50: 1165e1168.

10- Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004; 350:1937–44.

11- Bello IO, Soini Y, Salo T: Prognostic evaluation of oral tongue cancer: means, markers and perspectives (I). Oral Oncol 2010; 46:630e635.

12- Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a metaanalysis of reported studies. Cancer 2009; 115(07):1489-1497.

13- Capote A, Escorial V, Muñoz-Guerra MF, Rodríguez-Campo FJ, Gamallo C, Naval L. Elective neck dissection in early-stage oral squamous cell carcinoma–does it influence recurrence and survival? Head Neck 2007; 29(01):3–11.

14- Lin CS, Jen YM, Cheng MF, et al. Squamous cell carcinoma of the buccal mucosa: an aggressive cancer requiring multimodality treatment. Head Neck 2006;28(02):150–157.

15- La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. Oral Oncology 1997; 33:302-312.

16- Yen TC, Chang JT, Ng SH, Chang YC, Chan SC, Wang HM, et al. Staging of untreated squamous cell carcinoma of buccal mucosa with 18F-FDG PET: Comparison with head and neck CT/MRI and histopathology. J Nucl Med. 2005; 46:775–81.

17- Ng SH, Yen TC, Liao CT, Chang JT, Chan SC, Ko SF, et al. 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: A prospective study of 124 patients with histologic correlation. J Nucl Med. 2005; 46:1136–43.

18- Head and neck tumours. In: Sobin LH, Wittekind C (eds), UICC TNM classification of malignant tumours, 5th ed. New York: John Wiley & Sons, 17e32, 1997.

19- Brierley J, Gospodarowicz MK, Wittekind CH, editors. TNM classification of malignant tumours. 8th edition. Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc.; 2017.

20- Vassiliou LV, Acero J, Gulati A, Hölzle F, Hutchison IL, Prabhu S, Testelin S, Wolff KD, Kalavrezos N. Management of the clinically N0 neck in early-stage oral squamous cell carcinoma (OSCC). An EACMFS position paper. J Craniomaxillofac Surg 2020; 48:711-718.

21- Agrawal A, El Naggar A, Gourin CG, et al. Sentinel lymph node biopsy accurately stages the regional lymph node for T1-T2 oral squamous cell carcinoma. Results of multi-institutional trial. J Clin Oncol. 2010;28:1395–400.

22- Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004; 350:1945–52.

23- Cooper JS, Pajak TF, Forastiere A, Jacobs J, Fu KK, Ang KK. Precisely defining high-risk operable head and neck tumors based on RTOG #85-03 and #88-24: targets for postoperative radiochemotherapy. Head Neck. 1998; 20:588–94.

24- Huang SH, O´Sullivan. Oral cancer: Current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal. 2013; 18(2): e233–e240.

25- Monroe MM, Gross ND. Evidence-based practice: management of the clinical node-negative neck in early-stage oral cavity squamous cell carcinoma. Otolaryngol ClinNorthAm 2012; 45(05):1181–1193.

26- Thiele OC, Seeberger R, Flechtenmacher C, Hofele C, Freier K. The role of elective supraomohyoidal neck dissection in the treatment of early, node-negative oral squamous cell carcinoma (OSCC): a retrospective analysis of 122 cases. J Craniomaxillofac Surg 2012; 40(01):67–70.

27- Feng Z, Li JN, Niu LX, Guo CB: Supraomohyoid neck dissection in the management of oral squamous cell carcinoma: special consideration for skip metastases at level IV or V. J Oral Maxillofac Surg 2014; 72: 1203e1211.

28- Lim YC, Koo BS, Lee JS, Choi EC. Level V lymph node dissection in oral and oropharyngeal carcinoma patients with clinically node-positive neck: is it absolutely necessary? Laryngoscope. 2006; 116(7):1232-5.

29- Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354:567–78.

30- Bhide SA, Ahmed M, Newbold K, Harrington KJ, Nutting CM. The role of intensity modulated radiotherapy in advanced oral cavity carcinoma. J Cancer Res Ther. 2012; 8 Suppl 1:S67–71.

31- Sher DJ, Thotakura V, Balboni TA, Norris CM, Haddad RI, Posner MR. Treatment of oral cavity squamous cell carcinoma with adjuvant or definitive intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2011; 81:e215–22.

32- Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, Sutton D, Errington D, Vaughan D. Survival following primary surgery for oral cancer. Oral Oncol. 2009; 45(3):201-11.

33- Groome PA, Rohland SL, Hall SF, Irish J, Mackillop WJ, O'Sullivan B. A population-based study of factors associated with early versus late stage oral cavity cancer diagnoses. Oral Oncol. 2011; 47:642-7.

34- Nobis CP, Otto S, Grigorieva T, Alnaqbi M, Troeltzsch M, Sch€ope J, et al: Elective neck dissection in unilateral carcinomas of the tongue: unilateral versus bilateral approach. J Craniomaxillofac Surg 2017; 45: 579e584.

35- Ergun S, Warnakulasuriya S, Duman N, et al. Micronuclear and sister chromatid exchange analyses in peripheral lymphocytes of patients with oral lichen planus–a pilot study. Oral Dis 2009;15 (07):499–504.

36- Orabona GD, Bonavolonta P, Maglitto F, Friscia M, Iaconetta G, Califano L: Neck dissection versus "watchful-waiting" in early squamous cell carcinoma of the tongue our experience on 127 cases. Surg Oncol 2016; 25:401e404.

37- Pentenero M, Gandolfo S, Carrozzo M: Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 2005; 27:1080e1091.

38- Woolgar JA. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncol 2006; 42:229e239.

39- Woolgar JA, Rogers S, West CR, Errington RD, Brown JS, Vaughan ED: Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. Oral Oncol 1999; 35:257e265.

40- Mitchell DA, Kanatas A, Murphy C, Chengot P, SmithAB, Ong TK. Margins and survival in oral cancer. Br J Oral Maxillofac Surg 2018; 56(9):820–829.

41- Zanoni DK, Migliacci JC, Xu B, et al. A proposal to redefine close surgical margins in squamous cell carcinoma of the oral tongue. JAMA Otolaryngol Head Neck Surg. 2017; 143:555–560.

42- Dik EA, Willems SM, Ipenburg NA. Resection of early oral squamous cell carcinoma with positive or close margins: relevance of adjuvant treatment in relation to local recurrence: margins of 3 mm as safe as 5 mm. Oral Oncol.2014; 50:611–615.

43- Garavello W, Spreafico R, Gaini RM. Oral tongue cancer in young patients: a matched analysis. Oral Oncol. 2007 Oct;43(9):894-7

44- Hilly O, Shkedy Y, Hod R, Soudry E, Mizrachi A, Hamzany Y, Bachar G, Shpitzer T. Carcinoma of the oral tongue in patients younger than 30 years: comparison with patients older than 60 years. Oral Oncol. 2013 Oct;49(10):987-90.

45- Crean SJ, Hoffman A, Potts J, Fardy MJ. Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck 2003; 25:758–762.

46- Ho CM, Lam KH, Wei WI, Lau SK, Lam LK: Occult lymph node metastasis in small oral tongue cancers. Head Neck 1992; 14: 359e363.

47- Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW: Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 1986; 152: 345e350.

JUSTIFICACIÓN

La novedad y relevancia de los estudios que planteamos viene dada por los siguientes puntos:

a) análisis de la distribución de las metástasis cervicales en relación a la localización topográfica del tumor primario. Los carcinomas epidermoides de cavidad oral se incluyen generalmente en un único grupo a pesar de la localización del tumor primario. La diferenciación de los tumores en base a su localización topográfica es fundamental para poder analizar las diferencias entre los varios subtipos. Esto podría tener importantes implicaciones a nivel terapéutico;

b) análisis del impacto del espesor tumoral y estadio T en la capacidad de metastatización cervical del carcinoma epidermoide de cavidad oral.

Recientemente, numerosos estudios han puesto en discusión los pilares que clásicamente han orientado la elección de las varias estrategias de tratamiento. Por lo tanto, un atento análisis del real impacto de estos factores en la capacidad de diseminación a distancia y, consecuentemente, en el pronóstico del carcinoma epidermoide de cavidad oral es mandatorio;

c) análisis de la influencia de la edad de los pacientes en la capacidad de diseminación a distancia y en el pronóstico;

d) proposición de un protocolo de tratamiento quirúrgico en base a localización topográfica del tumor primario, estadio T y espesor de infiltración tumoral. Los protocolos de tratamiento quirúrgicos actualmente utilizados no suelen discriminar en base a la localización del tumor primario. Una atenta consideración de este factor podría tener un impacto favorable sobre la morbilidad asociada con el tratamiento quirúrgico y sobre la supervivencia global.

La principal hipótesis de la que partimos es que espesor de infiltración >0,4 cm, estadio T, edad de los pacientes y localización topográfica tengan un considerable impacto en la capacidad de difusión a distancia y en el pronóstico del carcinoma epidermoide de cavidad oral. De modo que esperamos encontrar un valor de espesor de infiltración que identifique de manera más fiable el riesgo de diseminación del tumor. También nos proponemos evaluar si existe alguna diferencia en la capacidad de metastatización de los tumores en base a su localización al interno de la cavidad oral y a la edad de los pacientes. Otro objetivo de este estudio es analizar si el tamaño tumoral se asocia a una mayor tendencia a la diseminación metastática o si la capacidad de metastatización representa un factor intrínseco del tumor independiente de su tamaño.

OBJETIVOS

Objetivo general: Analizar la distribución topográfica de las metástasis cervicales en relación con la localización del tumor primario en la cavidad oral y valorar la eficacia de los actuales protocolos quirúrgicos de disección cervical. Además, el trabajo se propone analizar el impacto y el peso de los "clásicos" factores pronósticos del carcinoma epidermoide de cavidad oral y su relación con la supervivencia global.

Objetivo 1. Estudiar la distribución topográfica de las metástasis cervicales en carcinomas epidermoide de lengua.

Objetivo 2. Analizar el papel de factores relacionados con el tumor y su extensión en la supervivencia global del carcinoma epidermoide de lengua

Objetivos específicos:

2.1 Papel de los componentes TNM sobre la supervivencia global

2.2 Influencia de márgenes quirúrgicos sobre la supervivencia

2.3 Evaluar el papel de la disección linfática cervical en el pronóstico de la enfermedad.

2.4 Impacto de espesor de infiltración tumoral (>0.4 cm), invasión linfovascular, invasión perineural y desbordamiento capsular sobre la supervivencia global

Objetivo 3. Estudiar la distribución topográfica de las metástasis cervicales en carcinomas epidermoide del maxilar superior.

Objetivo 4. Analizar el papel de factores relacionados con el tumor y su extensión en la supervivencia global del carcinoma epidermoide del maxilar superior

Objetivos específicos:

4.1 Papel de los componentes TNM sobre la supervivencia global

4.2 Impacto de espesor de infiltración tumoral (>0.4 cm), invasión linfovascular, invasión perineural y desbordamiento capsular sobre la supervivencia global

4.3 Evaluar el papel de la disección linfática cervical en el pronóstico de la enfermedad.

Objetivo 5. Evaluar el papel de factores sociodemográficos, como la edad y el sexo, así como factores causales clásicos, tabaco y alcohol, en la etiopatogenia y pronostico del cáncer oral.

Objetivo 6. Evalua**r** el impacto de la cirugía de disección cervical selectiva en el pronóstico y supervivencia de pacientes con carcinoma epidermoide de lengua en estadio precoz (pT1N0M0)

Objetivos específicos

6.1 Evaluar la seguridad oncológica del "wacth and wait strategy" en pacientes con carcinoma epidermoide de lengua en estadio precoz.

6.2 Analizar el valor diagnóstico y de estadiaje del vaciamiento cervical en pacientes con carcinoma epidermoide de lengua en estadio precoz.

- Los objetivos 1 y 2 se analizan y responden en el artículo "**Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas**."

- Los Objetivos 3 y 4 se analizan y responden en el artículo "**Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?**"

- El objetivo 5 se analiza y responde en el artículo "**Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital.**"

- El objetivo 6, y los relacionados objetivos específicos, se analizan y responden en el artículo "**Neck dissection versus a watch and wait strategy in T1N0 tongue cancers.**"

OBJECTIVES

MAIN OBJECTIVE:

To analyze the topographic distribution of cervical metastases in relation to the location of the primary tumor in the oral cavity and to determine the efficacy of the current protocols of neck dissection. In addition, this study aims to analyze the impact and influence of the "classic" prognostic factors of squamous cell carcinoma of the oral cavity and its relationship with overall survival.

Objective 1. To study the topographic distribution of cervical metastases in squamous cell carcinomas of the tongue.

Objective 2. To analyze the impact of several factors related to the tumor and tumor extension on overall survival of patients affected by tongue squamous cell carcinoma.

Specific objectives:

2.1 Impact of TNM classification on overall survival

2.2 Influence of surgical margins on overall survival

2.3 To evaluate the role of neck dissection for patient prognosis

2.4 Impact of tumor thickness (> 0.4 cm), vascular invasion, perineural invasion and extracapsular spread on overall survival

Objective 3. To study the topographic distribution of cervical metastases in squamous cell carcinomas of the upper jaw.

Objective 4. To analyze the influence of several factors related to the tumor and tumor extension on overall survival of squamous cell carcinoma of the upper jaw.

Specific objectives:

4.1 Impact of TNM classification on overall survival

4.2 Impact of tumor thickness (> 0.4 cm), vascular invasion, perineural invasion and extracapsular spread on overall survival

4.3 To evaluate the impact of cervical neck dissection for patient prognosis.

Objective 5. To evaluate the impact of sociodemographic factors, such as age and sex, as well as the classic etiological factors (tobacco and alcohol) in the pathogenesis and prognosis of oral cancer.

Objective 6. To evaluate the impact of selective neck dissection on overall survival of patients with early stage squamous cell carcinoma of the tongue (pT1N0M0)

Specific objectives

6.1 To evaluate the oncological safety of the "watch and wait strategy" in patients with early stage squamous cell carcinoma of the tongue.

6.2 To analyze the diagnostic and staging value of neck dissection in patients with early stage squamous cell carcinoma of the tongue.

- Objectives 1 and 2 are analyzed in the paper "**Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas**."

- Objectives 3 and 4 are analyzed in the paper "**Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?**"

- Objectives 5 is analyzed in the paper "**Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital.**"

- Objectives 6, and the related specific objectives, is analyzed in the paper "**Neck dissection versus a watch and wait strategy in T1N0 tongue cancers.**"

PACIENTES Y MÉTODOS

En la siguiente tabla se exponen las características del diseño, número de pacientes y análisis de datos de los diferentes artículos que componen esta memoria de tesis.

ARTICULO	DISEÑO	Numero pacientes	VARIABLES	MÉTODOS
Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas	Estudio retrospectivo	117	Estadio T Estadio N Espesor de infiltración tumoral Invasión linfovascualr y perineural Desbordamiento extracapsular Margenes quirúrgicos Supervivencia global	Analisis del test del Chi-cuadrado y curvas de Kaplan-Meiers (ssps 23)
Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?	Estudio retrospectivo	29	Estadio T Estadio N Espesor de infiltración tumoral Invasión linfovascualr y perineural Desbordamiento extracapsular	Analisis del test del Chi-cuadrado y curvas de Kaplan-Meiers (ssps 23)

			Supervivencia global	
Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital.	Estudio retrospectivo Estudio comparativo entre pacientes con epidermoide de cavidad oral <45 años y >45 años	133	Edad de los pacientes Alcohol Tabaco Localización del tumor primario Características demográficas Características socio-económicas Estadio T Estadio N Recidiva local y loco-regional Supervivencia global	Analisis del test del Chi-cuadrado y curvas de Kaplan-Meiers (ssps 23)
Neck dissection versus a watch and wait strategy in T1N0 tongue cancers	Estudio retrospectivo Estudio comparativo entre pacientes con carcinoma	53	Espesor de infiltración tumoral Invasión linfovascualr y perineural	Analisis del test del Chi-cuadrado y curvas de Kaplan-Meiers

	epidermoide pT1N0 de lengua sometidos a tumorectomia y vaciamiento cervical vs tumorectomia y seguimiento clínico		Desbordamiento extracapsular Margenes quirúrgicos Recidiva local y loco-regional Supervivencia global	(ssps 23)

La metodología que se ha utilizado para la creación y la elaboración de cada uno de los proyectos de investigación se especifica más detalladamente en los artículos completos que se encuentran en los siguientes apartados.

RESULTADOS Y DISCUSIÓN

En los siguientes artículos publicados se presentan tanto los resultados como la discusión de los mismos.

Los resultados y discusión se han organizado en base a los 5 artículos publicados.

En el anexo 1 se pueden ver los índices de calidad de cada revista.

RESPUESTA POR OBJETIVOS 1 y 2

Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas.

Cariati P, Cabello Serrano A, Fernandez Solis J, Martinez Lara I**. Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas.** J Craniomaxillofac Surg. 2018; 46(1):155-161. **doi: 10.1016/j.jcms.2017.10.009.**

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Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas

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ABSTRACT

Purpose: The aims of this study were to evaluate the pattern of distribution of cervical metastasis in tongue cancer and to analyze the various therapeutic options available. Moreover, numerous histological features were analyzed to assess the impact of each factor on overall survival.
Materials and methods: A retrospective analysis was conducted using the records of patients diagnosed with oral tongue cancer between 2004 and 2010 in the HUVN. A total of 117 patients with squamous cell carcinoma of the tongue treated with glossectomy and selective neck dissection were included in the study. The pattern of distribution of cervical metastases and numerous histological features such as T-stage, N stage, surgical margins, tumor thickness, extracapsular spread (ECS) and vascular invasion were analyzed.
Results: Level IIA was the most affected, followed by level III. The rate of skip metastasis was 7,4%. T and N stage, tumor thickness, ECS, surgical margins and nerve and vascular invasion were associated with poorer outcomes in terms of overall survival ($p < 0,001$).
Conclusion: Cervical nodal involvement represents the major prognostic factor in tongue cancer. A total of 51,2% of N+ patients presented T1 and T2 tumors in this series. We recommend performing neck dissection at the early stages in clinically N0 patients when a tumor thickness >0,4 cm is suspected. Level IV should be included in the neck dissection of clinically N0 tongue cancer.

1. Introduction

Treatment of the clinically negative neck is controversial in early-stage tongue cancer. According to other studies, 20%–50% of these patients might develop cervical metastases (Cunningham et al., 1986). Several authors report that a "watchful waiting" strategy is sufficiently safe in T1 tongue tumors with a depth of infiltration ≤4 mm or low grade (Orabona et al., 2016). However, other authors recommend performing a selective neck dissection of the ipsilateral levels I–III in all patients with oral cavity cancer (Wolff et al., 2012). In this regard, numerous surgeons advise performing a selective neck dissection of level I–IV in N0 tongue cancers to reduce the risk of "skip metastasis" (Woolgar et al., 1999), a term that refers to involved nodes that are not in the orderly progression of the tongue cancer (Byers et al., 1997). Occasionally, the tumor drains to a level III or IV node as the first manifestation of metastatic disease. This phenomenon is anatomically possible, as reported by Rouviere. According to this author, the oral portion of the tongue might directly drain to level IV without going through the supraomohyoid triangle (Rouviere, 1938). The presence of lymph node metastasis diminishes locoregional control rates, and is the most important factor for prognosis in head and neck cancer (Feng et al., 2014). Thus, the initial treatment strategy is critical to ensure good patient outcomes. This study was conducted to evaluate the pattern of distribution of tongue cancer cervical metastasis and to discuss the various therapeutic options available. Moreover, numerous histological features were analyzed to evaluate the impact of each factor on overall survival.

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2. Materials and methods

Between the years 2004 and 2010, a total of 117 previously untreated patients with squamous carcinoma of the oral tongue were diagnosed and treated with at least a glossectomy and selective neck dissection at HUVN. The neck dissections included levels I–IV in patients with clinically negative neck. However, the neck was recorded as clinically positive (N+) if any of the investigations suggested that nodal metastasis was present. In these cases, neck dissection was extended to level I–V.

The series comprised 79 males (67,6%) and 38 females (32,4%). Patient ages ranged between 19 and 81 years, with a mean of 59.36 years. The clinical stage of the primary tumor was established following the recommendations of the International Union Against Cancer (UICC) (Sobin and Wittekind, 1997). All patients underwent an accurate clinical exploration and a computed tomography (CT) scan of the cervicofacial area before surgery.

A total of 88 (75%) patients were classified as N0 and 29 (25%) as N (+) before surgery. However, following the pathological examination, node involvement was evidenced in 14 (15,9%) of clinically N0 patients. Thus, a total of 43 (36,7%) patients presented with nodal involvement following histological examination. A total of 48 (41%) of the primary tumors were T1, 37 (31,6%) were T2, 13 (11,1%) were T3, and 19 (16,2%) were T4 (Table 1). Free surgical margins were observed in 90 cases (76,9%), "close" in 21 (17,9%) and involved in 6 (5,1%).

An apron flap incision was used to guarantee better access to level IV and the posterior triangle (level V). In the case of unilateral neck dissection, a horizontal incision from the mastoid curving inferiorly upwards towards the upper border of the thyroid was performed 3–4 cm caudal to the mandibular margin. Moreover, a vertical incision was performed from the posterior zone of the cervicotomy to the skin of the clavicular zone in the case of particularly long necks. In the case of bilateral neck dissection, the incision is performed from mastoid to mastoid. In our study, neck levels were differentiated according to the classification proposed by the American Head and Neck Society. According to this classification, level IV includes the nodes located around the lower third of the internal jugular vein extending from the inferior border of the cricoid cartilage to the clavicle below. The medial boundary is the lateral border of the sternohyoid muscle, and the lateral boundary is the posterior border of the sternocleidomastoid muscle. In contrast, level V is represented by the nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The superior boundary is the apex formed by the convergence of the sternocleidomastoid and trapezius muscle, the inferior boundary is the clavicle, the medial boundary is the posterior border of the sternocleidomastoid, and the posterior lateral boundary is the anterior border of trapezius muscle (Robbins et al.). In this regard, it is worth noting that we perform the dissection of level V only in clinically positive tongue cancers or when macroscopic node metastases are evidenced during surgery. If node metastases are diagnosed with the postoperative pathological analysis, the patient will receive postoperative radiotherapy but will not receive second surgery. In fact, we do not usually analyze intraoperatively lymph nodes via frozen section.

In order to identify the lymphatic territories most affected by tongue cancer, we decided to perform a split neck dissection. More specifically, the surgical team identified, labeled, and separated the operation specimens in the surgical field before immersion in formalin. The specimens were examined and dissected by a single pathologist.

In addition, several pathological features as T-stage, N stage, surgical margins, tumor thickness, ECS and vascular invasion were analyzed. Tumor thicknesses were divided into two groups, <0,4 cm and >0,4 cm. At the time of analysis, all surviving patients had at least 5 years of follow-up.

It is important to note that all patients with positive neck dissection and/or poor prognostic factors (T3, T4, ECS, surgical margins, nerve and vascular invasion) were treated with radiation therapy (RT) with or without QT.

Statistical analysis was conducted using SPSS version 23 software. Frequency and percentages were used to evaluate the pattern of distribution of cervical metastases. A correlation test was carried out in order to analyze the relationship between variables. The Chi-square test was used to compare the differences among the groups of N0 and N+. In addition, a Kaplan–Meier test was carried out to obtain an overall 5-year survival analysis. Specific contingency tables allowed for the calculation of the impact of each factor on patient survival. The P value was set at 0.05.

Table 1
Pattern of distribution of cervical metastases in the present series.

Neck level	Number of metastases	Isolated metastases
IA	7 (8,6%)	
IB	11 (13,5%)	
IIA	30 (37,1%)	14
IIB	3 (3,7%)	0
III	17 (20,9%)	5
IV	10 (12,3%)	1
V	3 (3,7%)	0

3. Results

In our sample, 43 of 117 patients presented with node involvement after histological examination (36,7%). Eight (18,6%) of these 43 tumors were T1, 14 (32,6%) T2, 7 (16,3%) T3, and 14 (32,6%) T4 (Table 1). Of the patients, 74 (63,2%) were classified as N0, 20 (17,1%) as N1, 7 (6%) as N2a, 12 (10,3%) as N2b, and 4 (3,4%) as N2c. In all, 81 cervical nodes were infiltrated by tongue cancer cells. IIA was the most affected level, with 30 (37,1%) metastases being found at this level. It is interesting to note that 14 of these metastases were isolated metastases, whereas level III was positive in 17 cases (20.9%). The isolated metastases at this level were 5. Seven (8,6%) positive nodes were identified at level IA and 11 (13,5%) at level IB. Level IV was affected in 10 cases (12,3%). Interestingly, 1 of these represented an isolated metastasis in a clinically N0 patient (1,2% of all metastases). Finally, lymph nodes of level IIB and V were affected in 3 cases each (3,7%).

With respect to pathological features, our findings indicate that T stage and tumor thickness >0,4 cm are directly related to node involvement ($p < 0,01$) (Table 1). Smaller tumors were significantly more frequent in the N0 group, with 40 T1 tumors being diagnosed in this group. However, only 8 T1 tumors were evident in the N+ group. In contrast, T4 tumors were more common in the group of patients with nodal involvement. Of the 19 T4 tumors observed, 14 of the affected patients belonged to the N+ group. Major T stages were associated with more severe cervical affectation, greater numbers of affected or closed margins, and major tumor thickness ($p < 0,01$). Similarly, tumors with thickness <0,4 cm were more frequent in the group of patients with N0 ($p < 0,01$). Specifically, 34 of 74 (45,9%) tumors found in group N0 patients presented a tumor thickness <0,4 cm. However, only 1 tumor (2,3%) from the group of N+ patients showed a tumor thickness <0,4 cm (Tables 1 and 3). In addition, a negative correlation between tumor thickness and surgical margins was also found. In fact, greater thickness was associated with poorer outcomes in terms of clear margins ($p < 0,01$).

Regarding overall survival, patient outcomes were significantly related to several pathological features such as T stage ($p < 0,01$) (Fig. 1), depth of invasion ($p < 0,01$) (Fig. 2), node involvement

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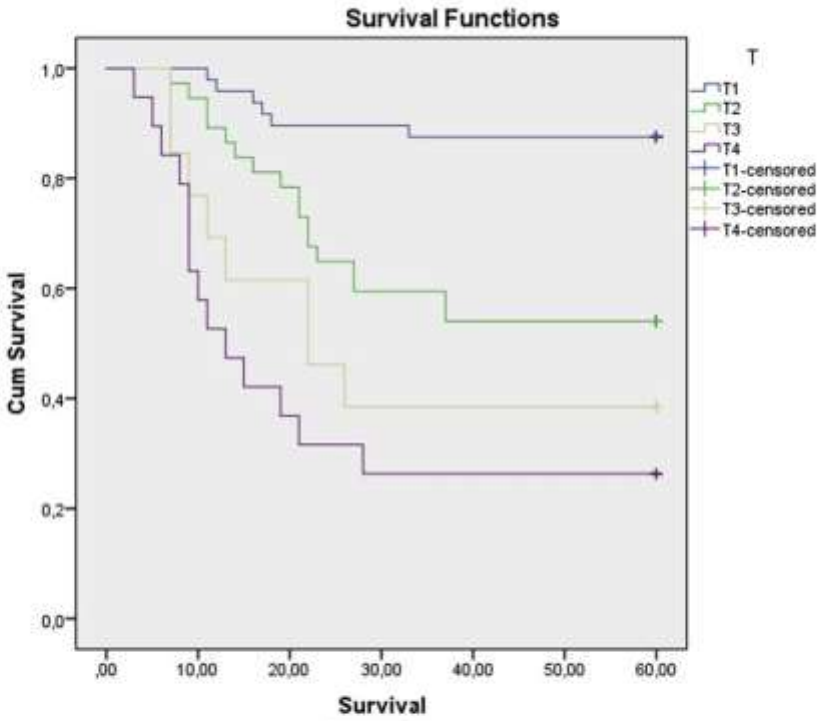

Fig. 1. Relationship between T-stage and overall survival. A more advanced T-stage is associated with worse survival rates.

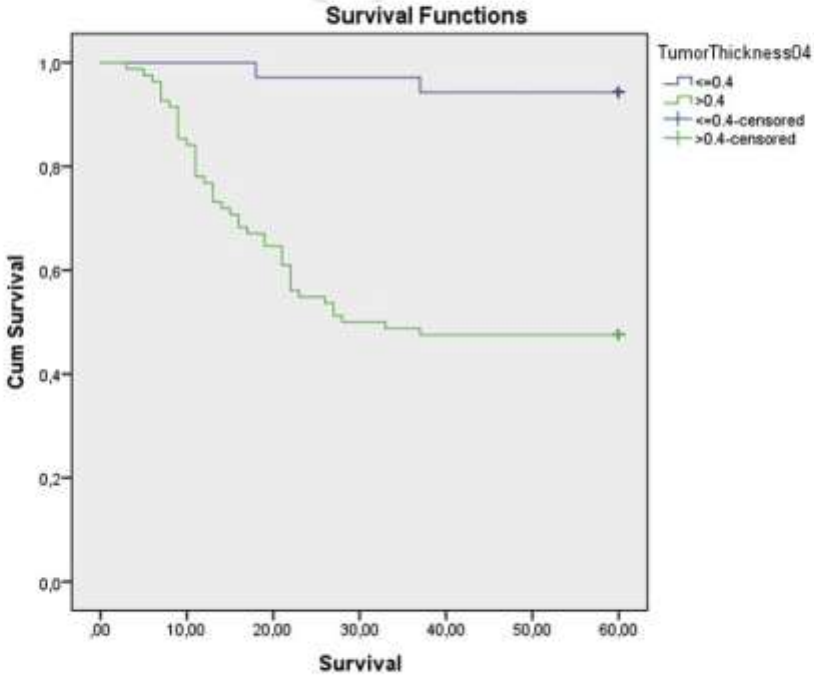

Fig. 2. Relationship between tumor thickness and overall survival. Patients with tumor thickness ≤0,4 cm showed a 5-year overall survival of 94,3%. In contrast, the 5-year overall survival of patients with tumor thickness ≥0,4 cm was 47,6% ($p < 0,01$).

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(Fig. 3), ECS ($p < 0,01$) (Fig. 4), N stage ($p < 0,01$) (Fig. 5), surgical margins ($p < 0,01$), and nerve and vascular invasion ($p < 0,01$) (Table 2). The 5-year overall survival rate was 61,5%. However, patients in group N0 showed better outcomes. In particular, 5-year overall survival was 73% in N0 patients and 42% in N+ patients, whereas we observed a 5-year overall survival rate of 65% for N1 and 21,7% for N2 (Fig. 5) (Table 2).

4. Discussion

Our data confirm that cervical nodal involvement represents the major prognostic factor in tongue cancer (Sivanandan et al., 2004). N+ patients showed the poorest outcomes in terms of overall survival and rapid disease evolution. In this regard, several other authors have reported comparable outcomes. For instance, Woolgar et al. reported a 5-year survival probability of 81% in N0 patients, 64% for patients with intranodal metastases, and 21% for patients with metastases and ECS (Woolgar et al., 1999). Similarly, Ho et al. reported a 5-year overall survival rate of 20% in patients with occult neck metastasis (Ho et al., 1992). Due to the abundant lymphatics of the tongue, 20%–50% of patients with tongue cancer could develop metastases in cervical lymph nodes (Spiro and Strong, 1974). In our study, an average of 7,23 lymph nodes could be identified in the different levels (from 3 to 16 lymph nodes for each level). In addition, 28,3 was the average number of lymph nodes found in each neck dissection. These data are comparable with outcomes reported by Koerdt et al. (2016). Of 117 patients, 43 presented nodal involvement at histopathological examination (36,7%). The majority of these tumors were T4 (32,6%) and T2 (32,6%). In contrast, the incidence of T1 and T3 tumors were 18,6% and 16,3% respectively. Thus, small tumors T1 and T2 generated 51,2% of all metastases.

However, treatment of the clinically negative neck is controversial. Selective neck dissection (SND) is usually the surgical treatment for N0 disease. However, it is not completely clear whether level IV and V should be included in the neck dissection of tongue cancers. Feng et al. asserted that supraomohyoid neck dissection is adequate to treat cN0 and cN+ oral squamous cell carcinoma (Feng et al., 2014), and Shah et al. also reported that supraomohyoid dissection is sufficiently safe to manage N0 patients. According to these authors, if a supraomohyoid dissection had been performed, 3.5% patients would have had nodal metastasis left behind in level IV or V, and only 1,5% would have had an isolated level of involvement outside the supraomohyoid triangle (level I, II, or III) (Shah et al., 1990). Similarly, Yuen et al. affirm that selective I–III neck dissection is the treatment of choice for N0 oral tongue carcinomas (Yuen et al., 1997).

The term "skip metastasis" refers to the condition in which the disease bypasses levels I or II or both and goes directly to levels III or IV. Byers et al. reported a skip metastasis rate of 15,8% in a series of 270 tongue cancer cases. Thus, they concluded that supraomohyoid neck dissection is inadequate for a complete pathologic evaluation of all the nodes at risk to treat patients with squamous carcinoma of the oral tongue (Byers et al., 1997).

In our sample, 6 of the 81 metastases (7,4%) bypassed levels I and II and might be considered skip metastases. These data are comparable with those of other studies in the field. Balasubramanian et al. reported a skip metastasis rate of 5,7% in a series of

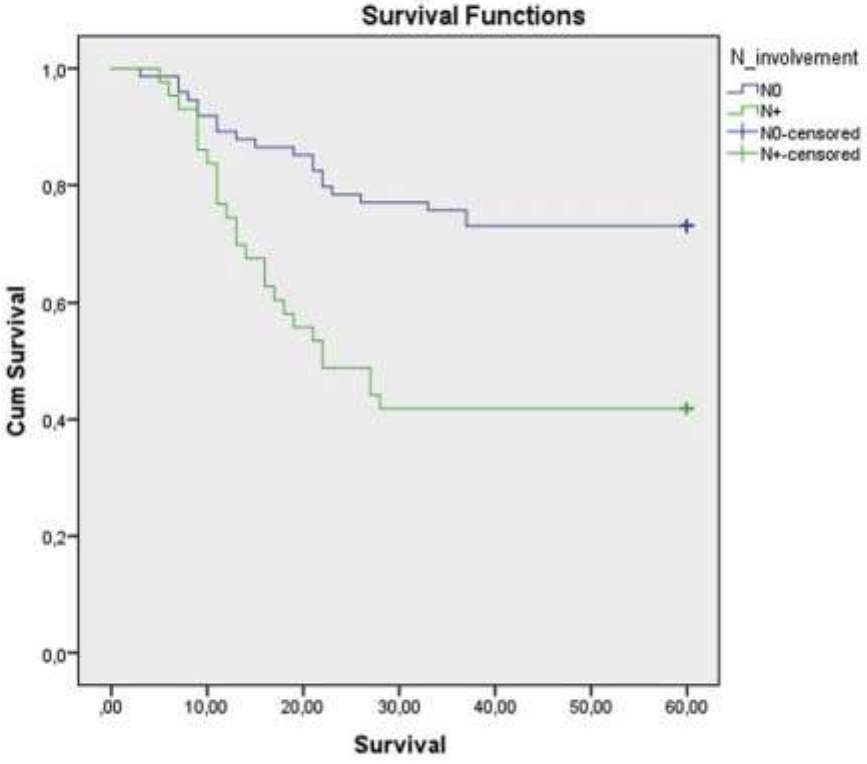

Fig. 3. Outcomes in relation to node involvement.

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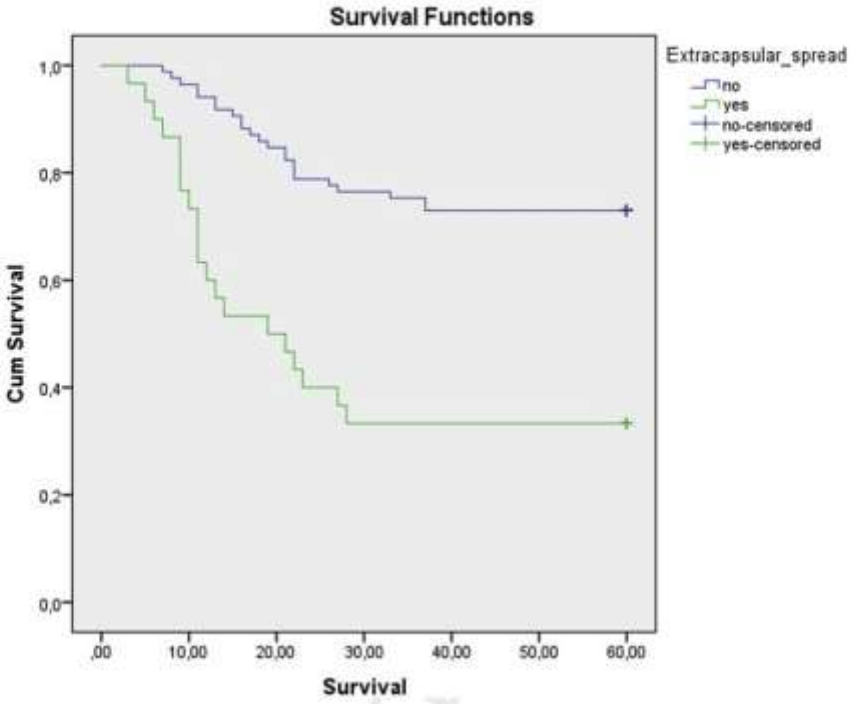

Fig. 4. Outcomes in relation to extracapsular spread (ECS).

52 tongue cancer cases (Balasubramanian et al., 2014). Lim et al. showed that the tongue presents a higher risk of developing skip metastases at level IV than other tumors of the mouth. The rate of skip metastases at level IV in tongue tumors was 4,3% in this series (Lim et al., 2006). In the same vein, Woolgar et al. emphasized the importance of including level IV in neck dissections for all tumors involving the tongue, even when the neck is clinically negative (Woolgar et al., 1999).

In our opinion, level IV should be included in neck dissection of clinically N0 tongue cancers. In fact, this procedure is not associated with major complications. Moreover, the extra time taken to dissect level IV is no more than 15 min. According to the data in the literature, the rate of complications associated with extended supraomohyoid neck dissection (ESOHND) fluctuates around 3,6%, and it confers no long-term disadvantage to the patients (Crean et al., 2003). Considering that nodal involvement is strongly related to overall survival, we believe that the risks related to surgery are lower than the benefits offered by level IV dissection. In this regard, Crean et al. demonstrated that the inclusion of level IV in neck dissection might remove occult level IV metastatic injuries from an extra 10% of patients in whom this cancer would otherwise have remained undiscovered with a standard supraomohyoid neck dissection (Crean et al., 2003). Another important issue is the need to extend the neck dissection to the contralateral neck. The literature is also contradictory with respect to this issue. For instance, Nobis et al. recommend performing a bilateral extended neck dissection (END) with tongue cancers at early stages (Nobis et al., 2017). However, the authors found evidence of nodal metastasis in only 4 of 45 cases treated with bilateral neck dissection (8.9%; 3 cases ipsilateral, 1 case contralateral neck). In this regard, we advise performing a bilateral selective I–IV neck dissection in cases of clinically N0 tongue cancers if the tumor is near or crosses the middle line.

With respect to the other variables analyzed, tumor thickness showed a negative correlation with surgical margins and a positive correlation with N-stage and T-stage. Higher tumor thickness was associated with poorer outcomes in terms of surgical margins, cervical affectation, and tumor size. This reflects the aggressive behavior of cancers with greater thickness of infiltration. The present study had a "close" margin rate of 21%. This differs from other studies in the field. For example, Orabona et al. reported close or positive margins in 7,6% of patients. However, this study analyzed squamous cell carcinoma of the tongue only at an early stage (Orabona et al., 2016). Similarly, Hicks et al. reported close margins in 7% of patients undergoing partial glossectomy. In this study, T3 and T4 tumors also represented only 8,4% of all tumors analyzed (Hicks et al., 1998). A variety of factors must be evaluated to explain our poorer results in terms of surgical margins. One possible explanation lies in the fact that almost 30% of patients in the present series had T3/4 tumors, and it is more difficult to achieve free margins in the advanced stages.

Also interesting is the relationship between tumor thickness and nodal involvement (Table 3). In our sample, infiltration thickness >0,4 cm was associated with a higher rate of cervical metastases. Specifically, 42 of 43 patients with N+ (97,7%) presented with a tumor thickness >0,4 cm ($p < 0,01$). In contrast, 34 of 74 N0 patients (45,9%) showed a tumor thickness <0,04 ($p < 0,01$). This outcome is also comparable with the findings of other studies (Spiro et al., 1986; Pentenero et al., 2005; Woolgar, 2006).

A positive correlation was also found between T stage and N-stage. In our sample, N0 patients showed a significantly lower percentage of T3 and T4 tumors than N+ patients. T3 and T4 tumors

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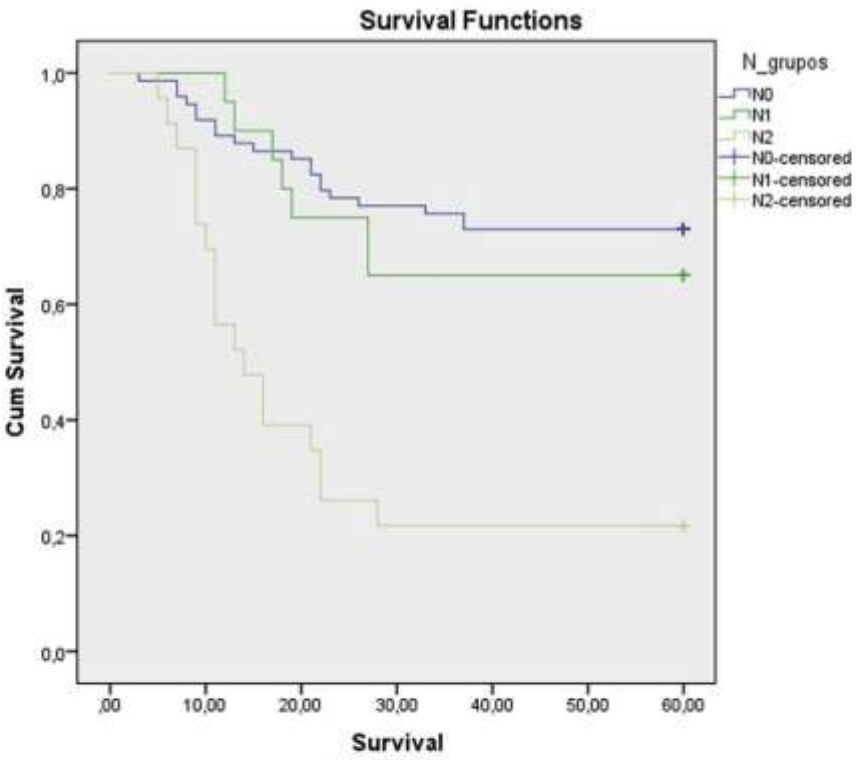

Fig. 5. Outcomes in relation to N-stage.

represented 14,9% of all tumors in the N0 group. However, this percentage rose to 48,9% in the group of patients with N+ (Table 1). T stage and N stage are strongly related and have a negative impact on overall survival (Table 2). These data are supported by the work of several other authors. Hicks et al. reported that the incidence of nodal metastasis increased with clinical T stage (T1, 6%; T2, 36%; T3, 50%; and T4, 67%) (Hicks et al., 1998). El-Husseiny et al. reported that involved regional lymph nodes and T3/4 tumors were associated with poor overall survival in tongue cancer (El-Husseiny et al., 2000). Mitchell et al. also found that higher T and N stage was significantly associated with poorer outcomes for patients with tongue cancer (Mitchell and Crighton, 1993). Bello et al. reported that T and N stage are interconnected and mutually influence the prognosis of tongue cancer (Bello et al., 2010). In our sample, overall survival at 5 years was 61%. However, these data differed between patients with N0 and N+ disease. Overall survival was 73% in the group of N0 patients and 42% in the N+ group (65% for N1 and 21,7% for N2), a pattern of findings that has been reported by other authors. For instance, El-Husseiny et al. described a comparable 5-year overall survival rate of 73% in patients with uninvolved nodes and 40% for patients with involved nodes (El-Husseiny et al., 2000). The work of Mitchell et al. indicated an overall survival rate of 93% and 87% for T1 and T2 N0 tongue cancers. However, overall survival was 33% in patients with a clinically positive neck (Mitchell and Crighton, 1993).

In addition to T and N stage, tumor thickness, ECS, surgical margins and nerve and vascular invasion appear to influence overall survival in our sample. According to Woolgar, all these factors are associated with poor outcomes, with ECS having a

Table 2
Histological features related to the presence of lymph node metastasis.

Feature	N0	N+	p
T-stage	40 T1 (54,1%) 23 T2 (31,1%) 6 T3 (8,1%) 5 T4 (6,8%)	8 T1 (18,6%) 14 T2 (32,6%) 7 T3 (16,3%) 14 T4 (32,6%)	<0.01
Tumor thickness <0,04 mm	45,9%	2,3%	<0.01
Tumor thickness >0,04 mm	54,1%	97,7%	<0.01
Overall survival	73%	42%	<0.01

Table 3
Relationship between T-stage, node involvement, and N-stage with tumor thickness.

Feature	TT < 0,4 cm	TT > 0,4 cm	p
T-stage			
T1	26/35 (74,2%)	22/82 (26,8%)	<0,001
T2	9/35 (26,7%)	28/82 (34,1%)	
T3	0/35	13/82 (15,8%)	
T4	0/35	19/82 (23,1%)	
Node involvement			
–	34/35 (97,1%)	40/82 (48,7%)	<0,001
+	1/35 (2,8%)	42/82 (52,2%)	
N-stage			
N0	34/35 (97,1%)	40/82 (48,6%)	<0,001
N1	1/35 (2,8%)	19/82 (23,1%)	
N2	0/35	23/82 (28,3%)	
Surgical margins			
Clear	35/35 (100%)	55/82 (67%)	<0,01
Close	0/35	21/82 (25,6%)	
Involved	0/35	6/82 (7,3%)	

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Table 4
Outcome in relation to histological features.

Feature	Overall survival	p
T stage		
T1	87,5%	<0,01
T2	54,1%	
T3	38,5%	
T4	26,3%	
Node involvement		
N–	73%	<0,01
N+	42%	
N-stage		
N0	73%	<0,01
N1	65%	
N2	21,7%	
ECS		
–	72,6%	<0,01
+	33,3%	
Nerve and vascular invasion		
–	69,5%	<0,01
+	30%	
Surgical margins		
Clear	68,1%	<0,01
Close	45%	
Involved	16,7%	

particularly negative impact on patient survival. These authors reported a survival probability of 21% for patients with metastasis and ECS. In our series, the 5-year overall survival rate of patients with cervical metastasis and ECS was 33,3% (Table 4).

5. Conclusion

To summarize, this report raises three central points. First, 7,4% of all metastases documented in our study could be regarded as instances of "skip metastasis." This justifies the inclusion of level IV in neck dissection of N0 tongue cancers. Second, T stage and tumor thickness are strongly related to cervical involvement. However, 51,2% of N+ patients presented with T1 (18,6%) and T2 (32,6%) tumors. Hence, we recommend performing neck dissection at the early stages in clinically N0 patients when a tumor thickness >0,4 cm is suspected. Third, tumor thickness also reflects the technical difficulty of tumor extirpation. In particular, greater infiltration thicknesses make it difficult to obtain clear surgical margins.

Uncited reference

Howaldt et al., 1993.

References

Balasubramanian D, Ebrahimi A, Gupta R, Gao K, Elliott M, Palme CE, et al: Tumour thickness as a predictor of nodal metastases in oral cancer: comparison between tongue and floor of mouth subsites. Oral Oncol 50: 1165–1168, 2014

Bello IO, Soini Y, Salo T: Prognostic evaluation of oral tongue cancer: means, markers and perspectives (1). Oral Oncol 46: 630–635, 2010

Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P: Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck 19: 14–19, 1997

Crean SJ, Hoffman A, Potts J, Fardy MJ: Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck 25: 758–762, 2003

Cunningham MJ, Johnson JT, Myers EN, Schramm Jr VL, Thearle PB: Cervical lymph node metastasis after local excision of early squamous cell carcinoma of the oral cavity. Am J Surg 152: 361–366, 1986

El-Husseiny G, Kandil A, Jamshed A, Khafaga Y, Saleem M, Allam A, et al: Squamous cell carcinoma of the oral tongue: an analysis of prognostic factors. Br J Oral Maxillofac Surg 38: 193–199, 2000

Feng Z, Li JN, Niu LX, Guo CB: Supraomohyoid neck dissection in the management of oral squamous cell carcinoma: special consideration for skip metastases at level IV or V. J Oral Maxillofac Surg 72: 1203–1211, 2014

Hicks Jr WL, North Jr JH, Loree TR, Maamoun S, Mullins A, Orner JB, et al: Surgery as a single modality therapy for squamous cell carcinoma of the oral tongue. Am J Otolaryngol 19: 24–28, 1998

Ho CM, Lam KH, Wei WI, Lau SK, Lam LK: Occult lymph node metastasis in small oral tongue cancers. Head Neck 14: 359–363, 1992

Howaldt HP, Frenz M, Pitz H: Proposal for a modified T-classification for oral cancer. The DOSAK. J Craniomaxillofac Surg 21: 96–101, 1993

Koerdt S, Röckl J, Rommel N, Mücke T, Wolff KD, Kesting MR: Lymph node management in the treatment of oral cancer: analysis of a standardized approach. J Craniomaxillofac Surg 44: 1737–1742, 2016

Lim YC, Koo BS, Lee JS, Lim JY, Choi EC: Distributions of cervical lymph node metastases in oropharyngeal carcinoma: therapeutic implications for the N0 neck. Laryngoscope 116: 1148–1152, 2006

Mitchell R, Crighton LE: The management of patients with carcinoma of the tongue. Br J Oral Maxillofac Surg 31: 304–308, 1993

Nobis CP, Otto S, Grigorieva T, Alnaqbi M, Troeltzsch M, Schöpe J, et al: Elective neck dissection in unilateral carcinomas of the tongue: unilateral versus bilateral approach. J Craniomaxillofac Surg 45: 579–584, 2017

Orabona GD, Bonavolontà P, Maglitto F, Friscia M, Iaconetta G, Califano L: Neck dissection versus "watchful-waiting" in early squamous cell carcinoma of the tongue our experience on 127 cases. Surg Oncol 25: 401–404, 2016

Pentenero M, Gandolfo S, Carrozzo M: Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 27: 1080–1091, 2005

Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al. Neck dissection classification update: revisions proposed by the American Head.

Rouviere H: Anatomy of the human lymphatic system. Ann Arbor, MI: Edward Brothers, 34, 1938

Shah JP, Candela FC, Poddar AK: The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer 66: 109–113, 1990

Sivanandan R, Kaplan MJ, Lee KJ, Lebl D, Pinto H, Le QT, et al: Long-term results of 100 consecutive comprehensive neck dissections: implications for selective neck dissections. Arch Otolaryngol Head Neck Surg 130: 1369–1373, 2004

Head and neck tumours. In: Sobin LH, Wittekind C (eds), UICC TNM classification of malignant tumours, 5th ed. New York: John Wiley & Sons, 17–32, 1997

Spiro RH, Strong EW: Surgical treatment of cancer of the tongue. Surg Clin N Am 54: 759–765, 1974

Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW: Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 152: 345–350, 1986

Wolff KD, Follmann M, Nast A: The diagnosis and treatment of oral cavity cancer. Deutsch Arzteblatt Int 109: 829–835, 2012

Woolgar JA: Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncol 42: 229–239, 2006

Woolgar JA, Rogers S, West CR, Errington RD, Brown JS, Vaughan ED: Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. Oral Oncol 35: 257–265, 1999

Yuen AP, Wei WI, Wong YM, Tang KC: Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. Head Neck 19: 583–588, 1997

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RESPUESTA POR OBJETIVOS 3 y 4

Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?

Cariati P, Cabello-Serrano A, Monsalve-Iglesias F, Fernadez-Solis J, Martinez-Lara I. **Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?** Curr Probl Cancer. 2019 Aug;43(4):336-343. **doi: 10.1016/j.currproblcancer.2018.10.004**

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Is a "watch and wait strategy" safe to manage clinically N0 squamous cell carcinoma of the upper jaw?

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Watch and wait strategy
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Supraomohyoid neck dissection
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ABSTRACT

Purpose: The main aim of the present study is to analyze the behavior of squamous cell carcinoma (SCC) of maxillary gingiva, alveolus, and hard palate and to determine the utility of selective neck dissection in clinically N0 patients at early stages.

Material and method: Twenty-nine previously untreated patients with SCC of maxillary gingiva, alveolus, and hard palate were diagnosed and treated with at least a tumorectomy and selective neck dissection at HUVN and included in the study.

Results: A total of 34.4% of patients (10/29) showed nodal involvement at postoperative histopathologic exam. Several pathologic features such as N involvement, N stage, T stage, and locoregional failure all have a negative impact on overall survival.

Discussion: SCC of maxillary gingiva, alveolus, and hard palate shows an aggressive behavior that is comparable with other oral cavity cancers. A more aggressive treatment is thus required for improving locoregional control and overall

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survival. Supraomohyoid neck dissection may be useful in cT2N0M0.

Introduction

Management of the clinically negative neck can be difficult in patients with squamous cell carcinoma (SCC) of maxillary gingiva, alveolus, and hard palate. Specifically, to "watch and wait" represents the strategy of choice to control the neck in clinically N0 patients. This approach is based on the low risk of occult cervical metastases attributable to this malignancy.[1] In fact, elective treatment of the neck is largely indicated if the risk of presenting occult cervical metastases is greater than 15%-20%.[2,3] However, recent studies have demonstrated that SCC of the upper jaw should be considered to be as aggressive as other carcinomas of the oral cavity.[4-7] In this regard, Beltramini et al reported a node involvement rate of 21% in a series of 69 patients with SCC of the maxillary gingiva, alveolus, and hard palate. According to these authors, elective neck dissection should be indicated in patients with the following characteristics: (1) T3/T4 stage, (2) if cervicotomy is needed for microvascular reconstruction, and (3) in case of patients with poor compliance to a close follow-up.[1] In the same vein, Montes et al affirmed that SCC of maxillary gingiva, alveolus, and hard palate presents aggressive cervical metastatic behavior. These authors found a node involvement in 42.9% of 14 patients. Interestingly, 20% of these showed lymph node involvement at presentation and 21.4% developed a cervical failure during follow-up. Thus, the authors recommended an elective neck dissection even in clinically N0 patients because of the high risk of occult metastases.[4] Moreover, more clinicians are recommending a more aggressive treatment regimen to improve overall survival.[8-10] The main aim of the present study is to analyze the behavior of SCC of this specific area and to determine the utility of selective neck dissection in clinically N0 patients at early stages.

Materials and methods

Between 2000 and 2012, 29 previously untreated patients with SCC of maxillary gingiva, alveolus, and hard palate were diagnosed and treated with at least a tumorectomy and selective neck dissection at HUVN. The neck dissections included levels I-III in patients with clinically negative neck. However, the neck was recorded as clinically positive (N+) if there were any clinical or radiologic suspicion of node involvement. In these cases, an elective neck dissection of levels I-V was carried out.

The male:female ratio was 1.07:1 (15 males/14 females). Patient ages ranged between 47 and 81 years, with a mean of 70.1 (S.D: 8.401). The clinical stage of the primary tumor was determined by using the recommendations of the fifth edition of the UICC TNM classification of malignant tumors.[11] A careful clinical exploration and a CT scan of the cervicofacial area were carried out in order to ascertain the clinical stage of each patient before surgery.

A split neck dissection was performed in order to identify the lymphatic territories most affected by SCC of the upper jaw. More specifically, the surgical team identified, labeled, and separated the operation specimens in the surgical field before immersion in formalin. The specimens were examined and dissected by a single pathologist. In our study, neck levels were differentiated according to the classification proposed by the American Head and Neck Society.[12]

It is important to stress all patients with positive neck dissection and/or poor prognostic factors (T3, T4, ECS, surgical margins, nerve, and vascular invasion) received adjuvant treatment with RT ± QT.

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Several pathologic features such as T stage, N stage, tumor thickness, surgical margins, and locoregional failure were also considered. Tumor thicknesses were divided into 2 groups: <0.4 cm and >0.4 cm. At the time of analysis, all surviving patients had at least 5-year follow-up.

Statistical analysis was conducted using SPSS 23v. Frequency and percentages were used to evaluate the pattern of distribution of cervical metastases. A correlation test was carried out in order to analyze the relationship between variables. Chi-square was performed to compare the differences among N0 and N+ patients, and specific contingency tables allowed for the calculation of the impact of each factor on patient survival. The *P* value was set at 0.05. Finally, a Kaplan-Meier test was carried out to obtain an overall 5-year survival analysis.

Results

Hence, 29 patients were included in this study. The male:female ratio was 1.07:1 (15 males/14 females). Patient ages ranged between 47 and 81 years, with a median age of 69.7 (S.D: 7.603).

T stage

In our sample, 9 of the 29 tumors were classified as T1 (31%), 9 as T2 (31%), 2 as T3 (6.9%), and 9 as T4 (31%). T stage was found to have a strong relationship with N involvement ($P < 0.05$), N stage ($P < 0.05$), and tumor thickness ($P < 0.01$). Moreover, a nonsignificant trend toward association between T stage and 5-year overall survival was also observed ($P = 0.06$; Fig 1). Specifically, 5-year overall survival was 88.9% for T1, 66.7% for T2, 50% for T3, and 44.4% for T4. In relation to tumor thickness, 8 of the 9 T1 (88.8%) tumors presented a tumor thickness <0.4 cm. In contrast, only 1 of 9 T2 (11.1%) showed a depth of invasion<0.4 cm. In the same line, all T3 and T4 tumors presented a tumor thickness >0.4 cm. With respect with N involvement, only 1 of the 9 T1 (11.3%) tumors were associated with positive nodes at postoperative histopathologic examination. Positive nodes were found in 22.2% of T2 patients (2/9), 100% of T3 (2/2), and 55.5% of those with T4 tumors (5/9).

Tumor thickness

Tumor thickness emerged as an extremely significant prognostic factor. This factor was significantly related to T stage ($P < 0.01$), node involvement ($P < 0.05$), and N stage ($P < 0.05$). In addition, tumor thickness was strongly associated with the risk of developing a local or regional failure during follow-up ($P < 0.01$). Specifically, no patients with a depth of invasion <0.4 cm experienced a local or regional recurrence (Table 1).

Table 1
Histological features related to the presence of lymph node metastasis.

	N0	N+	*P*
T stage	8 T1 (88.8%) 7 T2 (77.7%) 0 T3 (0%) 4 T4 (44.4%)	1 T1 (11.1%) 2 T2 (22.2%) 2 T3 (100%) 5 T4 (55.5%)	<0.01
Tumor thickness <0.04 mm	47.3%	0%	<0.01
Tumor thickness >0.04 mm	52.6%	100%	<0.01
Overall survival	89.5%	20%	<0.01

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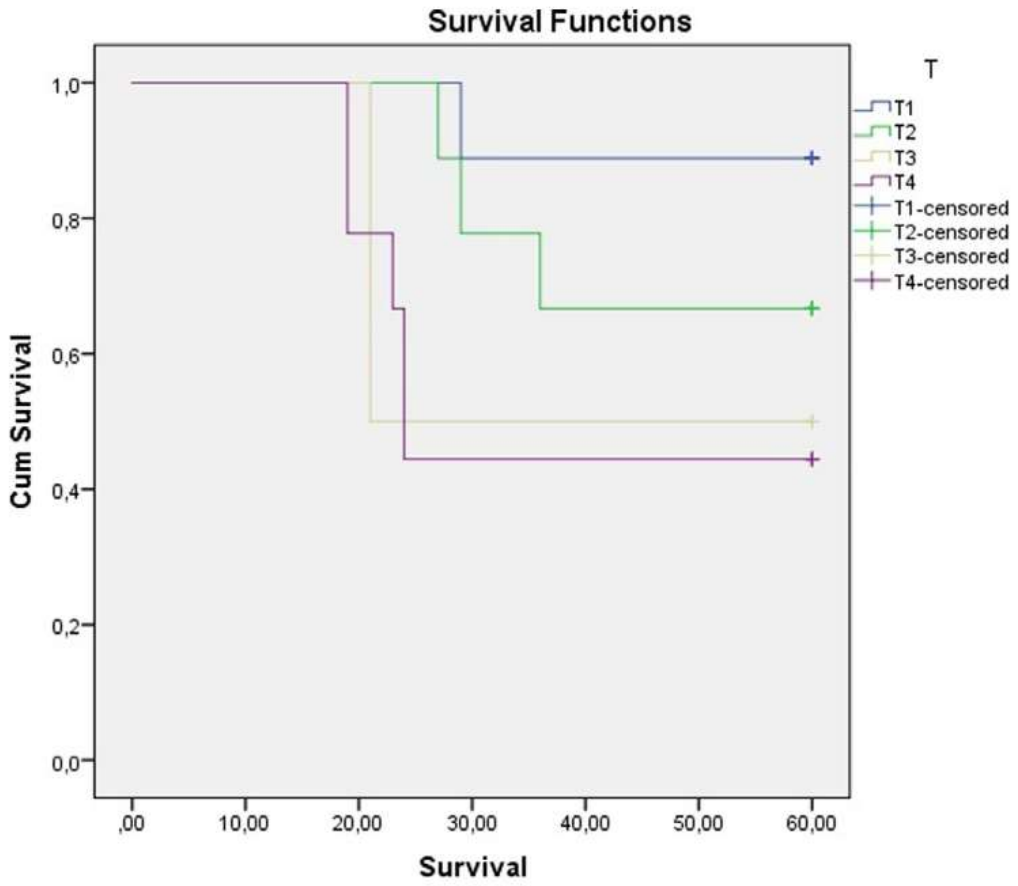

Fig. 1. Outcomes in relation to T stages.

N involvement

Nineteen patients were classified as N0 (65.5%) and 10 as N+ (34.4%). N involvement proved to be the most important prognostic factor in our series. Overall survival was 65.5% at 5 years. However, overall survival was 89.5% in N0 patients and 20% in N+ patients ($P < 0.01$). T stage and tumor thickness were strongly related to the risk of presenting positive cervical nodes ($P < 0.05$). Interestingly, 10 of the 19 N0 patients (47.3%) presented a tumor thickness <0.4cm. However, no tumors with a depth of invasion <0.4 cm were found in the group of N+ patients. N involvement showed a nonsignificant trend toward association with the risk of developing a recurrence during follow-up ($P = 0.06$).

A total of 47 nodes were affected by carcinogenic cells. Level I was the most commonly affected area (55.3%; 26 of 47 affected nodes) followed by level II (34%; 16 of 47 nodes). Level III was affected in 8.5 % of cases (4 of 47 nodes). A total of 2.1% and 0% positive nodes were observed at level IV (1 of 47 nodes) and level V (0 of 47 nodes), respectively. Importantly, no isolated metastases were found at level III or IV ("skip metastasis"). All patients with involvement of these regions also presented metastatic disease at levels I or II.

Occult cervical metastases

Twenty-three patients (79.3%) were preoperatively classified as N0 and 6 (20.6%) as N (+). However, node involvement was evidenced in 17.3% of patients classified as N0 before surgery

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Table 2
Outcome in relation to histological features.

Feature	Overall survival	*P*
T stage		0.063
T1 (n = 9)	88.9%	
T2 (n = 9)	66.7%	
T3 (n = 2)	50%	
T4 (n = 9)	44.4%	
Node involvement		0.009
N− (n = 19)	89.5%	
N+ (n = 10)	20%	
N-stage		0.01
Overall (n = 29)	65.5%	
N0 (n = 19)	89.5%	
N1 (n = 7)	28.6%	
N2 (n = 3)	0%	
ECS		0.01
− (n = 26)	73.1%	
+ (n = 3)	0%	

(4/23). Consequently, occult cervical metastases were evidenced in 13.7% of all patients (4/29). One of these 4 tumors was staged as T1 (25%), 1 as T2 (25%), and 2 as T4 (50%). A total of 14 positive lymph nodes were found in these 4 patients. Level I was the anatomical area most frequently affected. A total of 64.2% of occult cervical metastases affected this area (9 of 14 positive nodes). However, levels II and III tumors were affected in 21.4% (3 of 14) and 14.2% (2 of 14), respectively. No positive nodes were observed at levels IV or V in patients classified as clinically N0.

N stage

Ten patients were classified as N+ in our study. Of these, 7 were staged as N1 (70%), 1 as N2a (10%), and 2 as N2b (20%). As stated previously, N stage was significantly associated with both T stage ($P < 0.05$) and tumor thickness ($P < 0.05$). No patients classified as N1 or N2 presented a depth of invasion <0.4 cm. In addition, N stage was significantly related to overall survival ($P < 0.05$). Five-year overall survival rates were 89.5%, 28.6%, and 0% for N0, N1, and N2 patients, respectively (Table 2).

Local and cervical failure

In our series, 51.7% of the patients (15/29) experienced a local or cervical recurrence. In particular, local and cervical failures were observed in 24.1% (7/29) and 27.6% (8/29) of patients, respectively. Tumor thickness >0.4 cm and close/involved surgical margins were significantly associated with a higher rate of locoregional failure (<0.01). In addition, patients that experienced a local or cervical failure showed the worst outcomes in terms of overall survival ($P = 0.06$; Fig 2). Overall survival was 57.1% in the case of local recurrence and 25% in the case of cervical relapse.

Overall survival

Overall survival was 65.5% in the present study. Nodal involvement proved to be the most significant prognostic factor ($P < 0.01$). T stage and locoregional failure showed a nonsignificant trend toward association with overall survival ($P = 0.06$).

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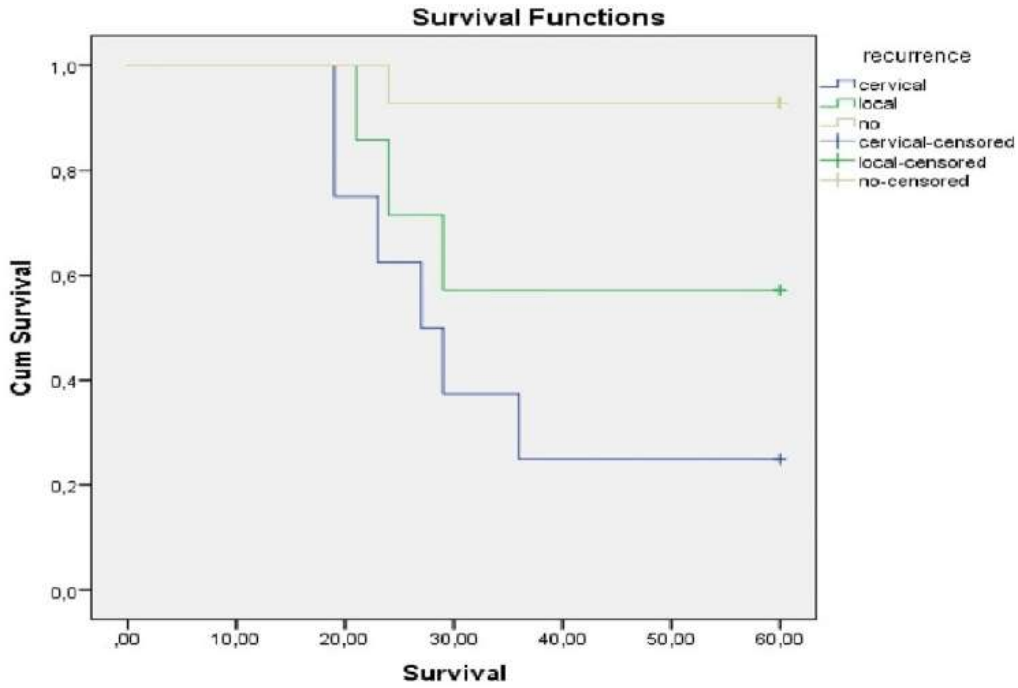

Fig. 2. Outcomes in relation to recurrence.

Discussion

Management of the clinical N0 neck is controversial in oral cancer, particularly in the case of SCC of maxillary gingiva, alveolus, and hard palate. The low incidence of cervical metastases has historically been considered a hallmark of this disease and "watch and wait" strategy is typically used to control the neck at early stages (T1N0M0/T2N0M0).[1] However, many authors have recently suggested that maxillary SCC should be considered to be equally aggressive as other carcinomas of the oral cavity. For instance, Beltramini et al demonstrated node involvement in 21.5% of 65 patients, while 12.3% of patients (8/65) were classified as N+ at the first observation. However, 19.4% of the patients classified as N0 (6/31) experienced a cervical failure during the first year of follow-up.[1] Mourouzis et al found evidence of cervical disease in 6 of 17 patients with maxillary SCC (35.2%). Four of these patients (23.5%) were classified as N+ at presentation. However, 2 of 13 clinically N0 patients (15.3%) experienced a cervical recurrence during the first 18 months of follow-up.[13] Similarly, Ogura et al reported lymph node involvement in 6 of 21 patients at presentation (28.5%). However, 8 of 15 patients considered as clinically N0 (53.3%) developed cervical metastases during the first 2 years of follow-up.[14] In the same vein, Morris et al reported cervical involvement in 28.4% of 139 patients.[15] In our series, node involvement was evidenced in 10 of 29 patients (34.4%), with 6 of these 10 patients classified as N+, showing node involvement at presentation. However, 4 were initially classified as N0. Thus, occult metastases were observed in 13.7% of our patients (4/29). Interestingly, level I was the most affected level and 55.3% of all positive nodes were found at this level. Only 1 patient presented positive nodes at level IV (2.1%). However, this patient also showed affectation of level II and level III. Thus, no skip metastases were evidenced in the present study. Similarly, level I was the most affected area in the 6 N+ patients previously classified as clinically N0. Node involvement represents one of the most significant prognostic factors in oral oncology. In our series, N+ patients also showed drastically worse outcomes. In particular, while overall survival was 65.5% in the present study, this rate was 89.5% in N0 patients compared with only 20% in N+ patients

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($P < 0.01$). These data are also comparable with other studies in the field. According to the literature, the overall survival rate for SCC of maxillary gingiva, alveolus, and hard palate ranges between 49% and 69%.[16,14] For instance, Mourouzis et al reported an overall survival rate of 58% in 17 patients with SCC of this anatomical region. Moreover, N+ patients showed the worst outcomes (50% vs 69.2%).[13] In our study, N involvement showed a significant relationship with T stage and tumor thickness. Only 1 of 9 T1 tumors (11.3%) was associated with positive cervical nodes. In contrast, node involvement was evidenced in 22.2% of T2 (2/9), 100% of T3 (2/2), and 55.5% of T4 (5/9). With respect to tumor thickness, no tumors of the N+ group of patients presented a thickness <0.4 cm. Moreover, N involvement was also associated with a higher risk of suffering a local or cervical recurrence during follow-up.

The recurrence rate was 51.7% (15/29) in the present report. In particular, local and cervical failures were observed in 24.1% (7/29) and 27.6% (8/29) of patients, respectively. Tumor thickness and involved/affected margins were both strongly associated with a higher risk of recurrence.

Thus, considering the high rate of node involvement (34.4%) and occult metastases (13.7%) observed, we recommend a more aggressive treatment of SCC of maxillary gingiva, alveolus, and hard palate, even at early stages. Elective treatment of the cervical nodes is widely accepted in oral oncology when the risk of occult metastases exceeds 15%-20%. In our series, 22.2% (2/9) of patients with T2 tumors showed lymph node involvement after postoperative histopathologic examination. Taking this into consideration, we advise performing selective I-III neck dissection in patients with cT2N0M0 SCC of maxillary gingiva, alveolus, and hard palate. Due to the low rate of positive nodes found at levels IV and V in clinically N0 patients, we believe that supraomohyoid neck dissection could be a sufficiently safe treatment for patients with no evidence of cervical affectation before surgery. However, we recommend performing a selective I-V neck dissection in the case of N+ patients. This approach might reduce the number of undiagnosed occult metastases and improve overall survival. A "watch and wait strategy" should be considered only in the case of T1 tumors. This is supported by the fact that in our series only 1 of the 9 T1 tumors (11.1%) presented node involvement.

To summarize, this report highlights 3 central points of interest. First, SCC of maxillary gingiva, alveolus, and hard palate shows an aggressive behavior that is comparable with other oral cavity cancers. Second, a more aggressive treatment is thus required for improving locoregional control and overall survival. In particular, supraomohyoid neck dissection might be useful in treating cT2N0M0. Third, several pathologic features such as N involvement, N stage, T stage, and locoregional failure all have a negative impact on overall survival.

This study presents some limitation. First, it is a retrospective study with the consequent limitations that this may cause. Second, the sample is small. However, there are not many reports that analyze in detail the involvement of this specific anatomical area. Further researches are essential to better understand the behavior of maxillary SCC.

Conflict of interest

None.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.10.004.

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References

1. Beltramini GA, Massarelli O, Demarchi M, et al. Is neck dissection needed in squamous-cell carcinoma of the maxillary gingiva, alveolus, and hard palate? A multicentre Italian study of 65 cases and literature review. *Oral Oncol.* 2012;48:97–101 Epub 2011 Oct 10. doi:10.1016/j.oraloncology.2011.08.012.
2. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg.* 1994;120:699–702.
3. Haddadin KJ, Soutar DS, Oliver RJ, et al. Improved survival for patients with clinicallyT1/T2. N0 tongue tumors undergoing a prophylactic neck dissection. *Head Neck.* 1999;21:517–525.
4. Montes DM, Schmidt BL. Oral maxillary squamous cell carcinoma: management of the clinically negative neck. *J Oral Maxillofac Surg.* 2008;66:762–766. doi:10.1016/j.joms.2007.12.017.
5. Feng Z, Li JN, Li CZ, et al. Elective neck dissection versus observation for cN0 neck of squamous cell carcinoma primarily located in the maxillary gingiva and alveolar ridge: a retrospective study of 129 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;116:556–561. doi:10.1016/j.oooo.2013.07.011.
6. Simental Jr AA, Johnson JT, Myers EN. Cervical metastasis from squamous cell carcinoma of the maxillary alveolus and hard palate. *Laryngoscope.* 2006;116:1682–1684.
7. Koshkareva Y, Liu JC, Lango M, et al. Cervical metastasis in squamous cell carcinoma of the hard palate and maxillary alveolus. *Ear Nose Throat J.* 2016;95:E6–11.
8. Yang Z, Deng R, Sun G, et al. Cervical metastases from squamous cell carcinoma of hard palate and maxillary alveolus: a retrospective study of 10 years. *Head Neck.* 2014;36:969–975 Epub 2013 Sep 18. doi:10.1002/hed.23398.
9. Lin HW, Bhattacharyya N. Survival impact of nodal disease in hard palate and maxillary alveolus cancer. *Laryngoscope.* 2009;119:312–315. doi:10.1002/lary.20054.
10. Eskander A, Givi B, Gullane PJ, et al. Outcome predictors in squamous cell carcinoma of the maxillary alveolus and hard palate. *Laryngoscope.* 2013;123:2453–2458. doi:10.1002/lary.24079.
11. *UICC TNM Classification of Malignant Tumours.* New York: John Wiley & Sons; 1997:17 ± 32.
12. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg.* 2002;128:751–758.
13. Mourouzis C, Pratt C, Brennan PA. Squamous cell carcinoma of the maxillary gingiva, alveolus, and hard palate: is there a need for elective neck dissection. *Br J Oral Maxillofac Surg.*. 2010;48:345–348 Epub 2009 Aug 7. doi:10.1016/j.bjoms.2009.07.012.
14. Ogura I, Kurabayashi T, Sasaki T, et al. Maxillary bone invasion by gingival carcinoma as an indicator of cervical metastasis. *Dentomaxillofac Radiol.* 2003;32:291–294.
15. Morris LGT, Patel SG, Shah JP, et al. High rates of regional failure in squamous cell carcinoma of the hard palate and maxillary alveolus. *Head Neck.* 2011;33:824–830.
16. Yorozu A, Sykes AJ, Slevin NJ. Carcinoma of the hard palate treated with radiotherapy: a retrospective review of 31 cases. *Oral Oncol.* 2001;37:493.

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RESPUESTA POR OBJETIVOS 5

Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital.

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Oral and oropharyngeal squamous cell carcinoma in young adults: A retrospective study in Granada University Hospital

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Abstract

Background: This study aims to evaluate and analyze the clinical features and outcomes of oral and oropharyngeal squamous cell carcinoma (SCC) in patients < 45-years old in our center.

Material and Methods: A retrospective analysis was conducted using the records of patients diagnosed with oral and oropharyngeal SCC between 1998 and 2011 in the University Hospital of Granada (Spain). The analysis identified 33 patients with oral and oropharyngeal SCC with an age of <45 years. Moreover, during the years studied, a further 472 patients were diagnosed with oral and oropharyngeal SCC in our center. Thus, 100 SCC patients with an age of >45 years were randomly selected from the same database. A retrospective analysis was conducted to determine specific features including sites of occurrence, risk factors, sex distribution, socio-economic status, T stage at diagnosis, nodal involvement, degree of tumor differentiation, locoregional failure and overall survival at 5 years was. Further, the results of both groups were compared.

Results: The male-female ratio was 1.2:1 in the group of young adults and 2.03:1 in the group of patients with an age of >45 years. No significant differences were found in terms of site, nodal involvement, locoregional failure, and overall survival. However, there were statistically significant differences between the two groups in terms of features such as risk factors, socio-economic status, T stage at diagnosis, and degree of tumor differentiation. The overall 5-year survival rate was 62% for patients >45 years old, whilst for the group of young adults this rate was 48.4% (p= 0.17).

Conclusions: The poor association between the common risk factors and oral and oropharyngeal cancers in young adults suggests that other pathogenic mechanisms should be investigated. For young patients, the data show evidence of poorer outcomes in terms of overall survival (p=0.17), and locoregional failure (p=0.23). Nevertheless, the literature shows that the results in this field are particularly inconsistent, and further research is therefore needed to provide more in-depth knowledge of the disease in this age group.

Key words:

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. It represents 5-6% of all cancers and usually occurs during the sixth and seventh decades of life (1,2). The use of tobacco and alcohol are strongly associated with the occurrence of this malignancy (3). Unfortunately, despite progress in treatment protocols the prognosis still remains poor (4). Furthermore, several reports have described an increased incidence of HNSCC in young people (5). This is particularly true for certain locations such as the oral cavity (6). The key reason for this epidemiological change is unknown. Interestingly, numerous authors have confirmed that the association between oral and oropharyngeal SCC and use of alcohol and tobacco is less evident in young people (7). In particular, the results of various studies suggest that the majority of young patients, especially women, report only slight or no exposure to these risk factors (8). Due to this apparent absence of significant habits in young people, factors such as immune deficiency, genetic factors and dietary factors have been considered as the main etiological agents (9), whilst the involvement of Herpes simplex virus and human papilloma virus have also been studied (10). However, HPV seems to be associated only with pharyngeal and oropharyngeal squamous cell carcinoma (2,9).

With respect to disease free and overall survival rates the data are even more inconsistent. In this regard, many authors refer to survival rates that are comparable with older patients (11,12). However, others have suggested that oral and oropharyngeal SCC show rapid disease progression and poorer prognosis in young people (13,14).

-Aim of the study

We conducted a retrospective analysis to examine a series of parameters such as sites of occurrence, tobacco and alcohol consumption, sex distribution, socio-economic status, T stage at diagnosis, degree of tumor differentiation, locoregional failure and overall survival at 5 years in Spanish patients aged < 45-years with oral and oropharyngeal SCC. In addition, we compared these results with a group of patients aged >45 years with oral and oropharyngeal SCC.

Material and Methods

The medical records of 33 patients aged <45 years with oral and oropharyngeal SCC were retrospectively analyzed. These patients were diagnosed between 1998 and 2011 at the Granada University Hospital (Spain). During this time, 472 patients were diagnosed with oral and oropharyngeal SCC in this center. Thus, another 100 patients aged >45 years with oral and oropharyngeal SCC were randomly selected from the same database. We carried out a retrospective study to gather data on specific features such as sites of occurrence, risk factors, sex distribution, socio-economic status, T stage at diagnosis, nodal involvement, degree of tumor differentiation, locoregional failure and overall survival at 5 years. Finally, the outcomes of both groups were compared. SCC of the lip was excluded since it can originate from skin rather than mucosa. Furthermore, patients with an incomplete clinical history were also omitted.

We divided the sites into the tongue, floor of the mouth, buccal mucosa, alveolus, gingiva, and oropharynx. The World Health Organization classification was used to assess the histopathological type. The UICC TNM system for head and neck cancers was used to determine the features of the primary tumor, nodal involvement, and distant metastasis (15). The degree of differentiation of the tumor was defined according to the classification proposed by Bryne (16). Local recurrence was considered as the appearance of the same malignancy located in the vicinity of the primary tumor beds. Regional recurrence referred to cervical metastases diagnosed during follow-up (17). Socioeconomic status was established through the analysis of specific characteristics such as household income, education, and occupation (18). Patient follow-up was conducted with a clinical exploration every 3 months during the first year after surgery, every 6 months during the second and third years, and once per year thereafter.

The SPSS version of statistical software was used for data analysis. Descriptive statistics such as mean and standard deviations (SD) were used to calculate the average age of the patients. Frequency and percentages for sex distribution, sites, risk factors, socio-economic status, T stage at diagnosis, nodal involvement, degree of tumor differentiation, locoregional failure and overall survival at 5 years were calculated. The Chi-square was used to compare the difference between the two groups. The P value was set at 0.05. A Kaplan–Meier test was carried out for an overall 5-year survival analysis.

Further, we conducted a paired-matched analysis between the groups using a propensity score analysis. This test allows a pseudo-randomization of the groups based on definite variables. Specifically, patients were divided in five groups according with tumor site, clinical stage of disease and degree of tumor differentiation to reduce the heterogeneity of the participants. In addition, a logistic regression multivariate analysis was performed to consider the effect of confounding factors such as tumor site, clinical stage, degree of tumor differentiation and node.

Results

-Socio-economic and demographic data

A total of 133 patients were identified. Of the group of patients aged >45 years, 67 were males and 33 were females. The male-female ratio was 2.03:1. Patient ages ranged between 46 and 97 years, with a mean of 64.32.

In addition, we also observed that 67% of these patients came from a low social class with little education, 25 % were categorized as middle class, and 8 % upper class. However, of the group of patients aged >45 years, 18 were males and 15 females. The male-female ratio was 1.2:1. Patient ages ranged between 19 and 45 years, with a mean of 33.71. In this group, 30. 3 % (n=10) came from a low social class with little education, 54.5 % (n=18) were categorized as middle class and 15. 1% (n=5) were upper class.

To summarize, in young people SCC is more frequent in patients from the middle-upper classes ($p< 0,01$). Moreover, the male-female ratio is more balanced than in the group aged >45 years.

-Risk Factors

87 % of patients >45 years of age had been smokers or drinkers throughout life. Among these, 69 % presented both risk factors, 13 % were only smokers and 5 % only drinkers. Thus, only 13% of patients aged >45 years had not reported exposure to alcohol and tobacco.

However, in the group of patients aged <45 years only 48.4% (n=16) were smokers throughout life. Among these, 25% (n=4) also reported high alcohol consumption. In contrast, 51.5 % (n=17) of young adults had no exposure to identifiable risk factors.

Our data therefore show that alcohol and tobacco have a poor correlation with SCC in young adults ($p< 0,01$).

-Site

In the group aged >45 years, the tongue was the area most commonly affected (35%, n=35). Other sites involved were the floor of the mouth (20%, n=20), the retromolar region (14%, n=14), buccal mucosa (9 n=9), oropharynx (8%, n=8), maxilla (7%, n=7), palate (5%, n=5), and gingiva (2%, n=2).

In the group aged <45 years, the tongue also represented the most affected area (54.5%, n=18). Other sites affected by SCC were the floor of the mouth (15,1%, n=5), buccal mucosa (12.1%, n=4), oropharynx (9.09%, n=3), alveolar ridge (3.03 %, n=1), maxilla (3.03 %, n=1), and gingiva (3.03 %, n=1).

In conclusion, the tongue was the most affected zone, with no significant differences between the two groups ($p= 0,11$).

-T stage at diagnosis

In accord with the UICC TNM system, T2 and T3 were the most frequent stages of presentation in patients aged >45 years with 37% (n=37) and 29% (n=29) respectively, whereas the rate of T1 and T4 was 27% (n=27) and 7% (n=7).

In contrast, T1 was the most frequent stage of presentation in patients aged <45 years (57.5%, n=19) followed by T2 (27.2%, n=9), T3 (3.03% n=2) and T4 (3.03% n=3) ($p< 0.01$).

-Nodal involvement (histological examination)

Nodal involvement was evident in 33% (n=33) of patients aged >45 years. However, in patients <45 years old, the neck lymph system was affected in 48.4% (n=16) of the cases. There was no significant association between nodal involvement and age ($p=0,06$).

-Degree of tumor differentiation

66% (n=66) of patients aged >45 years presented a moderately differentiated SCC, whilst well-differentiated and poorly-differentiated SCC were observed in 8% (n=8) and 26% (n=26) of cases respectively.

Moderately differentiated SCC was also the most common degree of differentiation in patients aged <45 years (51.5%, n=17). Well-differentiated SCC was evident in 39.3% of cases (n=13), whilst poorly differentiated SCC was observed in only 9.09% (n=3) of patients.

In short, moderately differentiated is the most common subtype of SCC in both groups. However, well-differentiated subtypes are more frequent in young patients ($p< 0,01$).

-Locoregional failure

The rate of locoregional failure was 34% (n=34) for patients aged >45 years, whilst young patients experienced locoregional failure in 45.4% of cases (n=15). In this regard, there was no significant association between locoregional failure and age ($p=0.23$).

-Overall Survival

An overall 5-year survival rate was estimated using the Kaplan–Meier survival analysis. With a mean follow up of 41.7 months (95 % CI: 37.5, 45.9), the 5-year overall survival rate for patients aged >45 years was 62% (n=62). However, the younger group had a mean follow up of 38.3 months (95 % CI: 29.9, 46.7) and a 5-year overall survival rate of 48.4% (n=16). There was no evidence of a significant association between overall survival and age ($p=0,17$).

The paired-matched analysis showed worse prognosis for young people in all sub-groups (Tables 1,2-Figs. 1,2). Unfortunately, due to the small sample of subgroups, these results did not present statistical significance ($p>0.05$). In the same line, the logistic regression multivariate analysis evidenced an increased mortality rate in patients <45 years old (OR= 1.734; 0.789-3.832) and the adjustment for confounding factors (tumor site, clinical stage, degree of tumor differentiation and node) pointed out that node involvement (OR=3,183; IC 95% 1,430-7.083; $p <0,05$) and age <45 (OR= 3,9181, IC 95% 1.288-11.916; $p <0,05$) represent the major risk factors for patient mortality in our study (Table 3).

Discussion

Oral and oropharyngeal SCC are rare in young adults. In fact, patients below 45 years of age account for only 6% of oral and oropharyngeal SCC cases (14). However, many studies suggest that oral and oropharyngeal SCC is increasing in young adults worldwide (6,19,20,21). In particular, several reports have presented evidence for

Table 1: Results.

	≤ 45 years old (n=33)	> 45 years old (n=100)	*p*
Gender	M/F ratio= 1.2:1	M/F ratio= 2.03:1	
Risk Factors	48,4%	87%	< 0,01
Site	Tongue 35%, (n=35) Floor of the mouth 20%, (n=20) Retromolar region 14%, (n=14) Buccal mucosa 9% (n=9) Oropharynx 8% (n=8) Maxilla 7% (n=7) Palate 5% (n=5) Gingiva 2% (n=2)	Tongue 54,5%, (n=18) Floor of the mouth 15,1% (n=5) Buccal mucosa 12,1%, (n=4) Oropharynx 9,09%, (n=3) Alveolar ridge 3,03 %, (n=1) Maxilla 3,03 %, (n=1) Gingiva 3,03 % (n=1)	*p*= 0,11
T stage at diagnosis	T1 57,5%, (n=19) T2 27,2%, (n=9) T3 3,03% (n=2) T4 3,03% (n=3)	T1 27% (n=27) T2 37% (n=37) T3 29% (n=29) T4 7% (n=7)	*p*< 0,01
Nodal involvement at diagnosis	48,4% (n=16)	33% (n=33)	*P*=0,06
Degree of tumor differentiation	Moderately differentiated 51,5% (n=17 Well differentiated 39,3% (n=13) Poorly differentiated 9,09% (n=3)	Moderately differentiated 66% (n=66) Well differentiated 8% (n=8) Poorly differentiated 26% (n=26)	*p*< 0,01
Locoregional failure	45,4% (n=15)	34% (n=34)	*p*=0,23
Overall survival	48,4% (n=16)	62% (n=62)	*P*=0,17

Table 2: Paired-matched analysis. Young patients showed a higher mortality rate in in all subgroups.

	Q1	Q 2	Q 3	Q 4	Q 5
<45	27,80%	70%	100%	100%	100%
>45	12,50%	40,60%	21,40%	55,60%	39,30%

the rising incidence of tongue cancers in young people (2). The reasons for this increase are not known. Interestingly, numerous authors have noted only a weak correlation between oral and oropharyngeal SCC in young people and typical risk factors such as tobacco and alcohol use (22). The relatively low exposure to these risks raises the possibility that other factors might be involved in the etiology of this disease (2). Our results also revealed that 51.5% of patients below the age of 45 reported no history of exposure to alcohol or tobacco. However, 87% of patients aged over 45 had been smokers or drinkers throughout life, a result that is compatible with the findings of other studies in the field.

The tongue appeared to be the most affected area in both groups, with the floor of the mouth representing the second-most affected region in the two groups. In contrast,

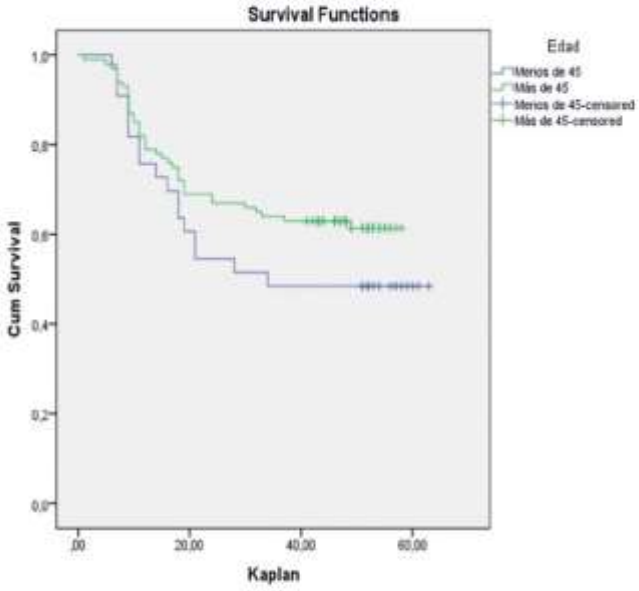

Fig. 1. Survival analysis with Kaplan-Meier.

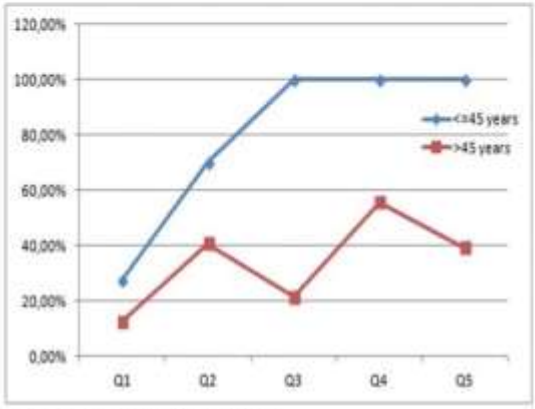

Fig. 2. Mortality rate in each subgroup.

Table 3. Logistic regression multivariate analysis. The prognosis of oral and oropharyngeal SCC is worse in patients aged < 45-years. The adjustment for confounding factors indicated that node involvement and age <45 years represent the major risk factors for patient mortality in our study.

	B	OR	IC95%	*p*
Age <45	1,365	3,918	1,288-11.916	0,016
Positive node	1,158	3,183	1,430-7.083	0,005

SCC of alveolar ridge and maxilla are relatively rare in young people. These findings are also comparable with other outcomes reported in the literature (23,10).

Other relevant information is related to the degree of tumor differentiation. In this regard, our data show that moderately differentiated cancers were the most common subtypes in both groups. However, well-differentiated tumors were relatively more prevalent in the younger age group (39.3% vs. 8%), a trend that has also been observed by other authors (10,24). However, it is not known whether the degree of tumor differentiation could represent a marker of poor prognosis for young patients.

Importantly, the majority of the young patients (57,5%) presented T1 stage at the time of diagnosis, whereas patients aged >45 years showed a higher rate of T2 and T3. In accord with these data, the majority of other authors have reported a higher proportion of T1 and T2 tumors in young people (25). Thus, smaller cancers are more common in young patients. Nevertheless, our results revealed a higher rate of nodal involvement (48.4%) at presentation in the group of young adults (Table 1) compared with a rate of only 33.3% in patients aged >45 years. In this respect, the literature is inconclusive, with the majority of studies being based on small samples. O'Regan et al reported a rate of nodal involvement of 50% in patients aged <40 years (10), whilst Soon et al. reported a nodal involvement rate of higher than 50% (19). However, Sarkaria et al described lower rates of nodal affectation in young patients. To be more specific, these authors studied the behavior of oral and oropharyngeal SCC in young people, analyzing 14 studies for a total of 132 patients aged <40 years. Interestingly, their results showed a high prevalence of early stage disease at presentation (64% stage I and II). In spite of this, the percentage of locoregional failure and overall survival was 57% and 47% (14). Hence, these results are comparable with our data. With regard to overall survival, our results revealed a poor prognosis for young people (p=0.17). However, it is important to note that the literature has yielded particularly inconsistent results in this field (5,7,24,26,27,28). Thus, the characteristics of SCC in young adults appear to be poorly understood. Unfortunately, the vast majority of studies are based on small samples and this has hindered progress in terms of advancing our knowledge of the phenomenon.

Conclusions

SCC in young adults could have specific characteristics. In particular, the weak association with the common risk factors and the increasing prevalence of the disease in females suggest that other pathogenic mechanisms might be involved in this group of patients. Our results revealed that whilst the majority of young patients presented smaller tumors at diagnosis, the rate of nodal involvement at presentation was higher in this group. Similarly, young people showed poor outcomes in terms of locoregional failures and overall survival. Unfortunately, due to the restricted sample of almost all the studies, current knowledge regarding the characteristics of SCC in young people is limited, and the findings in the literature are often contradictory. Thus, considering that the incidence of OSCC is rapidly rising in young people, further research will be critical in order to improve the management of these cases.

References

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer. 1993 Jun 19;54(4):594-606.

2. van Monsjou HS, Wreesmann VB, van den Brekel MW, Balm AJ. Head and neck squamous cell carcinoma in young patients. Oral Oncol. 2013 Dec;49(12):1097-102. doi: 10.1016/j.oraloncology.2013.09.001.

3. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer. 2008 Jul;44(10):1345-89. doi: 10.1016/j.ejca.2007.12.015.

4. Gonzalez-Garcia R, Naval-Gias L, RomanRomero L, et al. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: a retrospective analytic study of 500 patients. Head & Neck 2009; 31: 1168–80.

5. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people – a comprehensive literature review. Oral Oncol. 2001; 37: 401–18.

6. Schantz SP, Yu GP. Head and neck cancer incidence trends in young Americans, 1973-1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg. 2002 Mar;128(3):268-74.

7. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case-control study in Southern England. J Oral Pathol Med. 2004 Oct;33(9):525-32.

8. Tsukuda M, Ooishi K, Mochimatsu I, Sato H. Head and neck carcinomas in patients under the age of forty years. Jpn J Cancer Res. 1993 Jul;84(7):748-52.

9. de Castro Junior GI, dos Santos-Silva AR, Aparecida de Azevedo Koike Folgueira M, Toporcov T. Tongue cancer in the young. Curr Opin Oncol. 2016 May;28(3):193-4. doi: 10.1097/CCO.0000000000000285.

10. O'Regan EM, Timon C, Sheils O, Codd M, O'Leary JJ, Toner M. Squamous cell carcinoma of the head and neck in young Irish adults. Br J Oral Maxillofac Surg. 2006 Jun;44(3):203-6. Epub 2005 Jul 7.

11. Hilly O, Shkedy Y, Hod R, Soudry E, Mizrachi A, Hamzany Y, Bachar G, Shpitzer T. Carcinoma of the oral tongue in patients younger than 30 years: comparison with patients older than 60 years. Oral Oncol. 2013 Oct;49(10):987-90. doi: 10.1016/j.oraloncology.2013.07.005.

12. Pytynia KB, Grant JR, Etzel CJ, Roberts DB, Wei Q, Sturgis EM. Matched-pair analysis of survival of never smokers and ever smokers with squamous cell carcinoma of the head and neck. Pytynia KB, Grant JR, Etzel CJ, Roberts DB, Wei Q, Sturgis EM.

13. Garavello W, Spreafico R, Gaini RM. Oral tongue cancer in young patients: a matched analysis. Oral Oncol. 2007 Oct;43(9):894-7. Epub 2007 Feb 16.

14. Sarkaria JN, Harari PM. Oral tongue cancer in young adults less than 40 years of age: rationale for aggressive therapy. Head Neck. 1994 Mar-Apr;16(2):107-11.

15. Sobin LH, Wittekind CH, International Union Against Cancer (UICC). TNM Classification of Malignant Tumors, 5th edn. John Wiley & Sons, Inc, New York 1997; 20–4.

16. Bryne M. Is the invasive front of an oral carcinoma the most im-

portant area for prognostication? Oral Dis. 1998; 4:70-77.
17. Huang TY1, Hsu LP, Wen YH, Huang TT, Chou YF, Lee CF, Yang MC, Chang YK, Chen PR. Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins. Oral Oncol. 2010 Jan;46(1):49-55. doi: 10.1016/j.oraloncology.2009.10.011.
18. Matthews KA, Gallo LC. Psychological perspectives on pathways linking socioeconomic status and physical health. Ann Rev Psychol. 2011;62:501–30.
19. Son YH, Kapp DS. Oral cavity and oropharyngeal cancer in a younger population. Review of literature and experience at Yale. Cancer. 1985 Jan 15;55(2):441-4.
20. Davis S, Severson R. Increasing incidence of cancer of the tongue in the United States among young adults. Lancet 1987;17:910–1.
21. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008;26:612–9.
22. Golas SM. Trends in palatine tonsillar cancer incidence and mortalsty rates in the United Staten. Community Dent Oral Epidemiol. 2007;35:98–108.
23. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007;110:1429–35.
24. Hirota SK, Braga FPF, Penha SS, Sugaya NN, Migliari DA. Risk-factors for oral squamous cell carcinoma in young and older Brazilian patients: a comparative analysis. Med Oral Patol Oral Cir Bucal 2008; 13: E227–31.
25. Bundgaard T, Bentzen SM, Wildt J et al. Histopathologic, stereologic, epidermiologic, and clinical parameters in the prognostic evaluation of squamous cell carcinoma of the oral cavity. Head Neck 1996; 18: 142–5
26. Annertz K1, Anderson H, Biörklund A, Möller T, Kantola S, Mork J, Olsen JH, Wennerberg J. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer. 2002 Sep 1;101(1):95-9.
27. Chitapanarux I, Lorvidhaya V, Sittitrai P et al. Oral cavity cancers at a young age: analysis of patient, tumor and treatment characteristics in Chiang Mai University Hospital. Oral Oncol 2006; 42: 83–8.
28. Blanchard P, El Khoury C, Temam S, Casiraghi O, Mirghani H, Lévy A, Gorphe P, Even C, De Felice F, Nguyen F, Janot F, Tao Y. Oral cavity cancers among young people: Clinical results and prognostic analysis. Cancer Radiother. 2016 Apr;20(2):91-7. doi: 10.1016/j.canrad.2015.09.013.

Conflicts of Interest

Non-conflict of interest to declare.

RESPUESTA POR OBJETIVOS 6

Neck dissection versus a watch and wait strategy in T1N0 tongue cancers

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Neck dissection versus a watch and wait strategy in T1N0 tongue cancers

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Key-words. Outcomes; tongue; cancer; oncology

Abstract. *Purpose*: The aim of this study was to evaluate the impact of neck dissection on T1N0M0 tongue cancers. Numerous histological features were analyzed to assess the impact of each one on overall survival.
Materials and methods: The study included 53 patients with squamous cell carcinoma of the tongue who were treated with tumorectomy and selective neck dissection or neck observation. The patients were divided into two groups: patients who underwent tumorectomy and neck dissection (n=31) and patients treated with tumorectomy and neck observation (n=22).
Results: The rate of occult metastasis was 16,1% in the group of patients who underwent neck dissection. No statistically significant difference was found between overall survival and the type of neck treatment ($p>0,05$). Node involvement and recurrence were two important prognostic factors in clinical T1N0M0 tongue cancers ($p<0,05$).
Conclusion: Considering the high rate of occult metastases in our series (16,1%), we recommend performing neck dissection in cT1N0M0 tongue cancers with a tumor thickness >0,4 cm. Even though the type of neck treatment failed to show a significant relationship with overall survival, neck dissection might offer important prognostic information.

Introduction

The choice of neck treatment in clinical N0 tongue cancer remains controversial.[1] The incidence of occult cervical metastases in early oral SCC ranges from 14% to 45%, and node involvement is the most important prognostic factor.[2,3] Although CT or MRI screening of clinical N0 patients could help detect nonpalpable metastases, the recurrence rate in N0 patients with the "watch and wait" strategy ranges from 23.7% to 42%.[4,5] Neck dissection might be extremely helpful in reducing the negative impact of occult metastasis on overall survival. Due to its possible complications, neck dissection is only recommended in patients who have an estimated risk of metastasis greater than 15% to 20%, since nerve injuries, cervical scarring, and chronic shoulder pain might negatively impact the patient's quality of life.[6,7] The relatively good survival rate for T1N0 tongue cancer serves to further increase this controversy. The main aim of the present work was to analyze the benefits of neck dissection versus neck observation in terms of survival and nodal control in clinically T1N0 tongue cancers.

Materials and methods

Ethical considerations: The ethical aspects of the study were considered. No private patient data are discussed in this paper. The study was a retrospective analysis of the outcomes observed in our department.

Between 2001 and 2011, 53 previously untreated patients with clinical T1N0M0 squamous cell carcinoma of the oral tongue were diagnosed and treated with, at a minimum, a tumorectomy and selective neck dissection or observation at HUVN. The clinical stage of the primary tumor was established following the recommendations of the UICC.[8] All patients underwent an accurate clinical examination and a CT scan of the cervicofacial area before surgery. The neck dissections included levels I-IV; neck dissection was performed if any of the preoperative findings suggested the presence of nodal metastasis or tumor thickness >0,4 cm.

The patients were divided into two groups: patients that underwent tumorectomy and neck dissection (n=31) and patients who were treated with tumorectomy and neck observation (n=22). In

Conflicts of interest: None
IRB: N/A (IRB approval was not required for this retrospective study.) All patients provided informed consent that authorized the use of their clinical data.

our study, neck levels were differentiated according to the classification proposed by the American Head and Neck Society.[8] Several histopathological features were analyzed, such as tumor thickness, pathological N, recurrence rate, and surgical margins. We also analyzed the relationships of these factors with each other and their associations with overall survival. Finally, we examined the impact of neck dissection on overall survival. Importantly, all patients with positive neck dissection and/or poor prognostic factors (ECS, surgical margins, nerve and vascular invasion) were treated with radiotherapy +/- chemotherapy.

Statistical analysis was conducted using SPSS v23. Frequency and percentages were used to evaluate the distribution pattern of cervical metastases, and correlation tests were carried out in order to analyze the relationships between variables. Chi-square tests were used to compare the differences in the groups (neck dissection versus neck observation). A Kaplan–Meier test was performed for the 5-year overall survival analysis. Specific contingency tables allowed us to calculate the impact of each factor on patient survival. A p value less than or equal to 0.05 was considered to indicate significance.

Results

The series included 38 men (71,7%) and 15 women (28,3%) (n=53). The mean patient age was 65.3 (SD = 11,410), and the range was 36 to 83 years.

Tumor thickness

Tumor thickness was an important prognostic factor. In our series, 25 tumors were ≤0,4 cm thick, and 28 were >0,5 cm thick. The tumor thickness in all of the patients treated with neck observation was ≤0,4 cm (22/22); in the neck dissection group, tumor thickness was >0,4 cm in 28 of 31 patients (90,3%) and ≤0,4 cm in the other 3 patients (9,6%). The depth of infiltration was significantly related to recurrence rate ($p<0,05$) and to node involvement ($p<0,01$). In particular, only 3 of 25 patients (12%) with tumor thickness ≤0,4 cm experienced local (1/25) or cervical (2/25) recurrence. However, 11 of 28 patients (39,2%) with tumor thickness >0,4 cm had local (7/28) or cervical (4/28) relapse during follow-up. With respect to node involvement in the neck dissection group, all cervical metastases were observed in patients with a depth of infiltration greater than >0,4 cm. No significant correlation was found with respect to surgical margins ($p>0,05$) or overall survival ($p>0,05$). Interestingly, 5 of the 8 deceased patients (62,5%) showed tumor thickness >0,4 cm.

Occult metastases

In our series, 5 of 31 patients (16,1%) who were previously staged as clinically N0 and who had undergone neck dissection presented with node involvement at the postoperative histopathological exam. The thickness of all of these tumors >0,4 cm. A total of 7 cervical nodes had been infiltrated by tongue cancer cells. The most affected level was IIA, with 4 (57,1%) metastases found at this level, while 2 positive nodes were identified at level IB (28,5%) and 1 positive node found at level IV (14,2%). Interestingly, the metastasis found at level IV, which was isolated and showed no signs of extracapsular spread, was observed in a 35-year-old man with no risk factors for oral squamous cell carcinoma. The primary tumor measured 1,7 × 1,7 cm, and the depth of infiltration was 0,9 cm. Hence, it was classified as T1N1M0 with free surgical margins. However, the pathology showed particularly aggressive behavior, and a substantial loco-regional relapse was observed 6 months after surgery. The patient died during the 17th month of follow-up.

Recurrence

Recurrence was also an important prognostic factor in early stage tongue cancer. Recurrence was significantly related to tumor thickness ($p<0,05$), surgical margins ($p<0,05$), and overall survival ($p<0,01$). In our sample, 14 patients (26,4%) experienced recurrence during follow-up: 8 were local or regional recurrences (57,1%), while the other 6 recurrences affected only the neck (42,8%). It is important to note that recurrence during follow-up was significantly related to overall survival ($p<0,01$). Indeed, all of the patients that suffered a cervical recurrence died. Moreover, 2 of the 8 patients (25%) with local or regional recurrence also died during the first 5 years of follow-up, while 5 out of 14 patients that suffered a recurrence were diagnosed as N0 after surgery. In particular, 4 local recurrences and 1 cervical recurrence were

observed in this group of patients (5/14; 35,7%). In addition, 2 cervical and 2 local recurrences occurred in N+ patients (4/14; 28,5%). Finally, 3 cervical and 2 local relapses (5/14; 35,7%) were observed in patients treated with neck observation. Hence, 9 out of 31 patients (29%) underwent neck dissection, and 5 out of 22 patients (22,7%) treated with neck observation presented with recurrence during follow up. However, statistical analysis found no significant relationship between recurrence and the type of neck treatment (p>0,05).

Surgical margins

While 6 patients (11,3%) had close margins, 47 of 53 patients showed free surgical margins (88,6%). Importantly, 4 of 6 patients with close surgical margins underwent surgery to expand the margins, while the other 2 patients were treated with radiotherapy. Surgical margins showed a significant relationship with the risk of suffering local or cervical recurrence during follow up (p<0,05). In fact, 3 of 8 patients (37,5%) with local or regional recurrence had a close margin after surgery. However, all cervical relapses were observed in patients with free surgical margins. No significant correlation was found between surgical margins and either tumor thickness or overall survival (p>0,05).

In our series, 22 patients were treated with neck observation and 31 with neck dissection, with 26 of the neck dissections being carried out at the same time as the primary surgery. Neck dissection was performed a second time in 5 patients due to a depth of infiltration >0,4 cm at histological analysis. No significant correlation was found between the type of neck treatment (observational vs. neck dissection) and overall survival or cervical recurrence (p>0,05) (Fig. 1, Table 1). Notably, 3 of 22 patients (13,6%) treated with neck observation and 5 of 31 patients (16,1%) treated with neck dissection died during follow-up. Importantly, 2 of the patients who died that were in the group treated with neck observation presented with a tumor thickness of 0,4 cm. Neck dissection was not performed on these two patients due to their age. Moreover, according to our protocols, neck dissection was only performed on patients with T1 tumors >0,4 cm thick. The third patient who died belonged to the neck observation group and had a tumor thickness of 0,3 cm. The surgical margins were free in all three of these cases, but the patients suffered substantial cervical relapse.

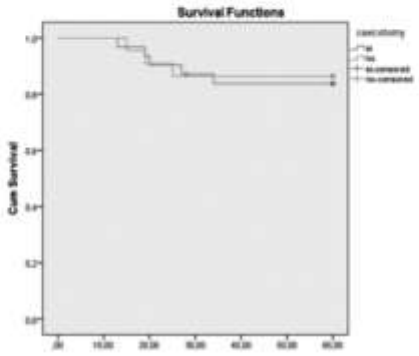

Figure 1

Outcomes according to type of neck treatment (observational or neck dissection).

Table 1

Outcomes according to histological features and type of neck treatment

Feature	Overall survival	p value
Node involvement		<0,01
N-	96,4%	
N+	20%	
Recurrence		<0,01
Local or regional	75%	
Cervical	0%	
Surgical margins		>0,05
Clear	85,1%	
Close	83,3%	
Tumor thickness		>0,05
≤0,4 cm	88%	
>0,4 cm	82,1%	
Neck treatment		>0,05
Observation	86,54%	
Neck dissection	83,9%	

Overall survival

The 5-year overall survival rate was 84,9% in our series and showed a strong relationship with both node involvement (p<0,01) and recurrence (p<0,01). Overall survival was 96,2% for N0 and 20% for N+ disease (Fig. 2). Only 1 of 5 patients with node involvement was alive after 5 years of follow up, and only 1 patient died of 26 patients classified as having N0 disease after neck dissection. With respect to recurrence, overall survival was 100% in patients without recurrence, 75% in patients with local or regional recurrence, and 0% in patients with cervical recurrence. No significant relationships were found between the type of neck

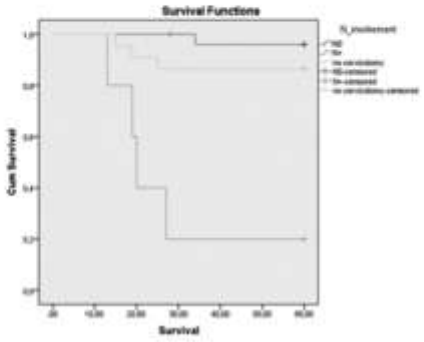

Figure 2
Outcomes according to node involvement.

treatment and overall survival, recurrence rate, or surgical margins (p>0,05).

Discussion

In this series, node involvement and recurrence were two important prognostic factors for stage T1 tongue squamous cell carcinoma. Notably, although overall survival was 84,9%, it was 0% in patients that suffered a cervical recurrence, 20% in patients classified as N+, and 75% in patients that experienced a local or regional relapse. Tumor thickness emerged as an important predictor of the behavior of Stage I tongue cancer and was also significantly related to recurrence rate. Although there was no statistically significant difference between tumor thickness and overall survival, it is interesting to note that 5 of 8 patients who died presented with tumors that were >0,4 cm thick. In addition, only 12% of patients with a depth of infiltration ≤0,4 cm suffered a local or cervical relapse. In contrast, 39,2% of patients with tumors that were >0,4 cm thick experienced recurrence during the first 5 years of follow-up.

In terms of neck dissection, our analysis revealed that overall survival was approximately the same in the neck dissection group (83,9%) and in the neck observation group (86,4%; p>0,05). Unfortunately, relatively few studies have analyzed the behavior of Stage I tongue cancer, and most of these studies included patients with Stage I and Stage II cancer. For instance, Feng et al. studied the impact of neck dissection on the overall survival of 229 patients with T1N0M0 (n=109) and T2N0M0 (n=120) tongue cancers and found that neck dissection improved the overall survival of T2N0M0 patients (79,2% vs. 61,9%). They also found that in the group of patients with a T1 tumor, overall survival was better for those who underwent neck dissection than for those treated with neck observation (87,2% vs 76%). However, the difference they observed in the T1 subgroup was not statistically significant.[10] Orabona et al. also studied the behavior of 117 tongue cancers classified as Stage I and II (T1N0M0/T2N0M0) before surgery and found that a "watchful waiting" strategy might be appropriate for T1 stage tumors with a depth of infiltration ≤0,4 cm or low grade (G1 or G2) tumors. Specifically, 5-year overall survival was 100% in patients with T1 tumors that were ≤0,4 cm thick, and only 15% of these patients showed regional recurrence.[11] Kelner et al. also reported that a watch and wait strategy might be considered to be an adequate treatment for appropriately selected patients with early stage tumors (Stage I and II).[12]

In contrast, other authors have suggested that neck dissection might be useful even for patients with Stage I tongue cancer.[13-14] Indeed, neck dissection is also considered a staging procedure that can provide an indication for adjuvant treatment.[15] For instance, Yu et al. reported a 5-year survival rate of 100% in patients after elective neck dissection versus 68,7% in the observational group.[14] Kligerman et al. suggested that neck dissection should remain mandatory for early stage oral squamous cell carcinomas. According to these authors, neck dissection should be particularly useful in patients with a tumor thickness >0,4 cm.[16] Other studies have demonstrated that elective neck dissection has a therapeutic effect in the early treatment of nodal diseases at Levels I, II and III.[17-19] Hence, the data that are currently available in the literature are controversial in terms of whether neck dissection is warranted.[19]

While several studies have reported better survival rates for patients who underwent neck dissection versus those treated only with neck observation, the majority of these studies considered both T1 and T2 lesions.[20-21] In our series, mortality was slightly higher in the group that received neck dissection, and we believe that the greater number of tumors with a depth of infiltration >0,4 cm in the neck dissection group might explain this result. However, our findings suggest that neck dissection may not

be useful in improving the overall survival rate of patients with T1 lesions. Indeed, 4 of 5 patients (80%) with node involvement after neck dissection died during follow-up. Hence, neck dissection did not increase the likelihood of survival for patients with tumors that initially affected the cervical nodes. In our opinion, this might be due to specific intrinsic tumor characteristics that are not related to tumor thickness or to other studied factors. We firmly believe that only particularly aggressive tumors are able to metastasize at the T1 stage. In these cases, the disease should be considered highly aggressive from the beginning, and the use of radiotherapy and chemotherapy might be helpful in improving outcomes in terms of overall survival. This may be particularly relevant in young patients who have no risk factors for oral squamous cell carcinoma. Considering the high rate of occult metastases in our series (16,1%), we recommend performing neck dissection in cT1N0M0 tongue cancers with a tumor thickness >0,4 cm. Indeed, tumor thickness was found to have a strong relationship with node involvement and recurrence rate. Moreover, neck dissection could be very useful for identifying patients with particularly aggressive tumors and for guiding adjuvant treatment. Even though the type of neck treatment failed to show a significant relationship with overall survival, neck dissection might offer important prognostic information. Moreover, it is important to note that 2 patients who died (25%) had tumors that were 0,4 cm thick. In both patients, the cause of death was attributed to substantial cervical recurrence. It is therefore reasonable to think that neck dissection could have offered important information about the behavior of the disease; given this possibility, the cut-off for tumor thickness that prompts neck dissection could be even lower. However, further studies are needed to attain more in-depth knowledge regarding the behavior of early stage tongue squamous cell carcinoma. The vast majority of studies are based on small samples, and larger samples may provide a better understanding of this phenomenon.

Conclusion

Considering the high rate of occult metastases in our series (16,1%), we recommend performing neck dissection in patients with cT1N0M0 tongue cancers that are >0,4 cm thick. Even though the neck treatment type failed to show a significant relationship with overall survival, neck dissection might offer important prognostic information.

References

1. Ho CM, Lam KH, Wei WI, Lau SK, Lam LK. Occult lymph node metastasis in small oral tongue cancers. *Head Neck*. 1992;14:359-363.
2. Brazilian Head and Neck Cancer Study Group. Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Brazilian Head and Neck Cancer Study Group. *Am J Surg*. 1998;176(5):422-427.
3. Pimenta Amaral TM, Da Silva Freire AR, Carvalho AL, Pinto CA, Kowalski LP. Predictive factors of occult metastasis and prognosis of clinical stages I and II squamous cell carcinoma of the tongue and floor of the mouth. *Oral Oncol*. 2004;40(8):780-786.
4. Brugère JM, Mosseri VF, Mamelle G, David JM, Buisset E, Vallicioni J, de Raucourt D, Szpirglas HJ, Asselain BJ. Nodal failures in patients with NO/N+ oral squamous cell carcinoma without capsular rupture. *Head Neck*. 1996;18(2):133-137.
5. Okamoto M, Nishimine M, Kishi M, Kirita T, Sugimura M, Nakamura M, Konishi N. Prediction of delayed neck metastasis in patients with stage I/II squamous cell carcinoma of the tongue. *J Oral Pathol Med*. 2002;31(4):227-233.
6. Cappiello J, Piazza C, Giudice M, De Maria G, Nicolai P. Shoulder disability after different selective neck dissections (levels II–IV versus levels II–V): a comparative study. *Laryngoscope*. 2005;115:259-263.
7. Erisen L, Basel B, Irdesel J, Zarifoglu M, Coskun H, Basut O, Tezel I, Hizalan I, Onart S. Shoulder function after accessory nerve-sparing neck dissections. *Head Neck*. 2004;26(11):967-971.
8. Sobin LH, Wittekind C. Head and neck tumours. In: *UICC TNM Classification of Malignant Tumours, 5th Edition*. John Wiley & Sons, New York, 1997;17-32.
9. Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, Som P, Wolf GT. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg*. 2002;128(7):751-758.
10. Feng Z, Li JN, Li CZ, Guo CB. Elective neck dissection versus observation in the management of early tongue carcinoma with clinically node-negative neck: a retrospective study of 229 cases. *J Craniomaxillofac Surg*. 2014;42:806-810. doi: 10.1016/j.jcms.2013.11.016
11. Orabona GD, Bonavolontà P, Maglitto F, Friscia M, Iaconetta G, Califano L. Neck dissection versus "watchful-waiting" in early squamous cell carcinoma of the tongue our experience on 127 cases. *Surg Oncol*. 2016;25(4):401-404. doi: 10.1016/j.suronc.2016.09.005.
12. Kelner N, Vartanian JG, Pinto CA, Coutinho-Camillo CM, Kowalski LP. Does elective neck dissection in T1/T2 carcinoma of the oral tongue and floor of the mouth influence recurrence and survival rates? *Br J Oral*

Maxillofac Surg. 2014;52(7):590-597. doi: 10.1016/j.bjoms.2014.03.020.
13. Yuen AP, Ho CM, Chow TL, Tang LC, Cheung WY, Ng RW, Wei WI, Kong CK, Book KS, Yuen WC, Lam AK, Yuen NW, Trendell-Smith NJ, Chan YW, Wong BY, Li GK, Ho AC, Ho WK, Wong SY, Yao TJ. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck*. 2009;31(6):765-772. doi: 10.1002/hed.21033.
14. Yu S, Li J, Li Z, Zhang W, Zhao J. Efficacy of supraomohyoid neck dissection in patients with oral squamous cell carcinoma and negative neck. *Am J Surg*. 2006;191:94-99.
15. Kerrebijn JD, Freeman JL, Irish JC, Witterick IJ, Brown DH, Rotstein LE, Gullane PJ. Supraomohyoid neck dissection. Is it diagnostic or therapeutic? *Head Neck*. 1999;21(1):39-42.
16. Kligerman J, Lima RA, Soares JR, et al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *Am J Surg*. 1994;168:391-394.
17. Dias FL, Kligerman J, Matos de Sá G, et al. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. *Otolaryngol Head Neck Surg*. 2001;125:23-29.
18. Canis M, Pfluger S, Ihler F, Matthias C, Kron M, Steiner W. Impact of elective neck dissection vs observation on regional recurrence and survival in cN0-staged patients with squamous cell carcinomas of the upper aerodigestive tract. *Arch Otolaryngol Head Neck Surg*. 2012;138(7):650-655. doi: 10.1001/archoto.2012.1026.
19. Abu-Ghanem S, Yehuda M, Carmel NN, Leshno M, Abergel A, Gutfeld O, Fliss DM. Elective Neck Dissection vs Observation in Early-Stage Squamous Cell Carcinoma of the Oral Tongue With No Clinically Apparent Lymph Node Metastasis in the Neck: A Systematic Review and Meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142(9):857-865. doi: 10.1001/jamaoto.2016.1281
20. Lin TC, Tsou YA, Lin MH, Hua CH, Tseng HC, Bau DT, Tsai MH. Impact of neck dissection in early tongue and buccal cancer without neck extension. *B-ENT*. 2011;7(2):97-102.
20. Tsai CY, Lai YS, Chen MK. Prediction of lymph node metastasis in T1/T2 tongue squamous cell carcinoma. *B-ENT*. 2014;10(3):179-184.

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DISCUSIÓN

Por “skip metástasis” o metástasis en salto, se entienden aquellas metástasis que afectan el nivel cervical III y/o IV sin evidencia de patología en niveles ganglionares I, II y III. No hay evidencia sobre el mecanismo que puede producir una metástasis en salto y varias teorías se han formulado en los últimos años para explicarlo. De acuerdo con algunos autores, un sistema de drenaje linfático alternativo entre algunos órganos como la lengua y el nivel cervical IV podría explicar este fenómeno. Según otros autores, la existencia de metástasis en salto podría relacionarse con la presencia de micro-metástasis (no detectables con las técnicas histopatológicas empleadas rutinariamente) en los niveles cervicales superiores. El fenómeno de las ”skip metástasis” ha sido clásicamente relacionado con el carcinoma epidermoide de lengua y representaría uno de los factores que contribuyen al peor pronóstico observado en los tumores que afectan esta localización de la cavidad oral. Este concepto tiene importantes repercusiones en la estrategia de tratamiento. En este sentido, el vaciamiento cervical tipo supraomohioideo (niveles I, II y III) es normalmente el empleado para el tratamiento de pacientes con carcinoma epidermoide de cavidad oral sin evidencia clínica ni radiológica de metástasis cervicales (N0) y que presentan los factores de riesgos de extensión metastásica cervical (T3, T4, N+, espesor infiltración >0.5 cm). Sin embargo, debido a la posible presencia de skip metástasis, este tipo de tratamiento podría ser insuficiente para el manejo de pacientes con carcinoma epidermoide lingual clasificados clínicamente como N0. Desafortunadamente, existe gran controversia en la literatura con respecto a este concepto y no hay consenso sobre cuál es el tipo de tratamiento más eficaz para estos casos. De acuerdo con los datos evidenciados en el presente estudio, 6 de las 81 (7.4%) metástasis detectadas en pacientes con carcinoma epidermoide de lengua afectaron el nivel III o IV sin evidencia de patología en los niveles cervicales superiores. Es interesante destacar que este valor es notablemente mayor (33.2%) en los casos en los que el examen

histopatológico postquirúrgico demuestra la presencia de patología metastásica en alguno de los niveles cervicales altos en pacientes que habían sido clasificados clínicamente como N0. Por lo tanto, estos datos confirman la necesidad de realizar un vaciamiento cervical extendido al nivel IV en los pacientes con carcinoma epidermoide de lengua incluso en ausencia de signos clínicos y radiológicos de afectación cervical antes de la cirugía. Esta estrategia de tratamiento podría ser fundamental para aumentar la supervivencia global de esta enfermedad. Es importante enfatizar que todos los pacientes incluidos en este estudio fueron sometidos a un vaciamiento cervical dividido por niveles (split neck dissection). Esto ha permitido un meticuloso y preciso análisis de la localización de las metástasis cervicales en cada caso. Además, el 51.2% de los pacientes que mostraron afectación cervical en el examen histopatológico postoperatorio presentaban un tumor clasificado como T1 (18.6%) o T2 (32.6%) con espesor de infiltración >0.4 cms. Esto justificaría la realización de un vaciamiento cervical en pacientes con carcinoma epidermoide de lengua en estadio precoz y con espesor de infiltración tumoral >0.4cms.

El nivel Ib fue el nivel cervical más frecuentemente afectado en el carcinoma epidermoide de maxilar superior. Específicamente, el 55.3% de todas las adenopatías metastásicas observadas en este grupo de pacientes afectaban este nivel cervical. Además, el 17.3% de los pacientes de este grupo presentaron metástasis ocultas en el examen histopatológico postoperatorio. Por metástasis oculta se entiende la presencia de patología metastásica en ausencia de evidencia clínica o radiológica de afectación cervical antes de la cirugía. Éste es un dato notablemente importante. De hecho, la literatura es muy controvertida sobre la necesidad de realizar cirugía de vaciamiento cervical en pacientes con carcinoma epidermoide de maxilar superior clasificados como clínicamente N0. Sin embargo, estos resultados respaldan la necesidad de realizar vaciamiento cervical selectivo a partir del

estadío T2N0M0 con el objetivo de aumentar la supervivencia global de esta enfermedad.

El análisis de nuestros resultados evidencia que el espesor de infiltración tumoral es uno de los factores pronósticos más importantes en el carcinoma epidermoide de cavidad oral. De hecho, tumores con espesor de infiltración >0.4 cms mostraron un riesgo significativamente mayor de presentar afectación cervical y peor pronóstico ($p<0.005$) independientemente de la localización del tumor primario en la cavidad oral. Este dato es comparable con numerosos estudios publicados al respecto. En este sentido, el valor pronóstico del espesor de infiltración tumoral ha sido notablemente enfatizado en la 8th edición de la AJCC (American Joint Committee on Cancer) (Anexo 2). Nuestro estudio evidenció que en numerosas ocasiones tumores clasificados como T2 presentaron peor pronóstico que tumores clasificados como T3. La razón principal que podría explicar estos resultados es que muchos de los cánceres clasificados en estos años como T2 deberían haber sido clasificados como T3 según la última clasificación de la AJCC y, por lo tanto, habrían podido recibir esquemas de tratamiento no apropiados Este dato apoya la hipótesis que el espesor tumoral es un factor pronóstico extremadamente importante para el carcinoma epidermoide de cavidad oral, especialmente en el caso de carcinomas linguales.

Con respecto a la edad de los pacientes, nuestros resultados han demostrado un peor pronóstico para el grupo de pacientes menores de 45 años de edad (48,4% vs 62%). Además, se observó que el peso de los clásicos factores de riesgos (alcohol y tabaco) es menos importante para el grupo de pacientes menores de 45 años ($p<0.005$). También se evidenció que los pacientes del grupo menor de 45 años son más propensos a abandonar los factores de riesgos (alcohol y tabaco) tras el diagnóstico de la enfermedad con respecto a los pacientes del grupo mayor de 45 años de edad. Otro dato significativo es que la relación hombre/mujer es más proporcional en el grupo de pacientes jóvenes (ratio h/m=

1.2:1 vs ratio h/m= 2.03:1). Estos resultados apoyan la hipótesis de que la predisposición genética sea el factor más relevante a la hora de desarrollar la enfermedad para los pacientes jóvenes y esto podría explicar el peor pronóstico y la escasa respuesta al tratamiento quirúrgico y adyuvante observados en este grupo.

Otro dato significativo evidenciado por nuestro estudio es que la cirugía de vaciamiento cervical no aumenta la supervivencia en pacientes con carcinoma epidermoide de lengua clasificados como pT1N0M0. Sin embargo, el vaciamiento cervical ofrece importantes datos diagnósticos y pronósticos y es la única herramienta que permite completar el estadiaje de la enfermedad. Por lo tanto, a luz de los resultados presentados, sería aconsejable realizar cirugía de vaciamiento cervical en pacientes con T1N0M0 y espesor de infiltración >0.4 cms.

La principal limitación de este trabajo es su carácter retrospectivo. Ulteriores estudios, con carácter multicéntrico y prospectivos, podrían confirmar y ampliar estos resultados permitiendo un mayor conocimiento de esta enfermedad con las consecuentes repercusiones clínicas sobre el pronóstico de los pacientes afectados por esta patología.

DISCUSSION

The term “skip metastasis" refers to those metastases that affect cervical level III and/or IV without evidence of pathology at nodal levels I, II and III. There is no evidence regarding the mechanism underlying skip metastasis, and in recent years, several theories have been proposed to explain this phenomenon. For instance, some authors have suggested an alternative lymphatic drainage system between certain organs such as the tongue and cervical level IV, whilst other authors propose the existence of a link between skip metastases and the presence of micro-metastases (not detectable with the histopathological techniques routinely employed) in the upper cervical levels.

The phenomenon of "skip metastasis" has been classically related to squamous cell carcinoma of the tongue and represents one of the factors contributing to the poorer prognosis observed in tumours affecting this location of the oral cavity. This concept has important repercussions for the treatment strategy. In particular, supraomohyoid neck dissection (levels I, II and III) is routinely used for the treatment of patients with squamous cell carcinoma of the oral cavity without clinical or radiological evidence of cervical metastasis (N0) and who present the risk factors of cervical metastatic extension (T3, T4, N+, infiltration thickness >0.5 cm). However, due to the possible presence of skip metastasis, this type of treatment could be insufficient for the management of patients with squamous cell carcinoma of the tongue clinically classified as N0. Unfortunately, there is considerable controversy in the literature regarding this concept and there is no consensus on the most effective type of treatment for these cases. According to the data evidenced in the present study, 6 of the 81 (7.4%) metastases detected in patients with squamous cell carcinoma of the oral tongue affected level III or IV without evidence of pathology in the upper cervical levels. It is interesting to note that this value is notably higher (33.2%) in cases in which the post-surgical histopathological examination demonstrates the presence of metastatic pathology in any of the upper cervical levels in

patients who had been clinically classified as N0. Therefore, these data confirm the need to extend the neck dissection at level IV in patients with squamous cell carcinoma of the tongue, even in the absence of clinical and radiological signs of cervical involvement before surgery. This treatment strategy could be essential for increasing overall survival of patients affected by this disease. It is important to emphasize that all patients included in this study were subjected to a split neck dissection. This has allowed a meticulous and precise analysis of the location of the cervical metastases in each case.

In addition, 51.2% of the patients who showed cervical involvement in the postoperative histopathological examination presented a tumour classified as T1 (18.6%) or T2 (32.6%) with an infiltration thickness >0.4 cm. This would justify the realization of neck dissection in patients with early stage squamous cell carcinoma of the tongue carcinoma with an infiltration thickness >0.4cms.

The level Ib was the most frequently affected cervical level in maxillary squamous cell carcinoma. Specifically, 55.3% of all cervical metastasis observed in this group of patients affected this cervical level. In addition, 17.3% of the patients included in this group presented occult metastases on postoperative histopathological examination. Occult metastasis is understood to be the presence of metastatic pathology in the absence of clinical or radiological evidence of cervical involvement prior to surgery. This fact is of considerable significance. In fact, there is a great deal of controversy in the literature about the need to perform neck dissection in patients with squamous cell carcinoma of the upper jaw classified as clinically N0. However, our results support the need to perform selective neck dissection from stage T2N0M0 with the aim of increasing overall survival of this disease.

Analysis of our results revealed that tumour thickness is one of the most important prognostic factors in oral squamous cell carcinoma. In fact, tumours with an infiltration thickness >0.4 cm showed a significantly higher risk of cervical involvement and poorer prognosis ($p<0.005$) regardless of the location of the primary tumour in the oral cavity. These data are comparable with those reported in numerous studies published on the subject. In this regard, the prognostic value of tumour infiltration thickness has been notably emphasized in the 8th edition of the AJCC (American Joint Committee on Cancer). Our study showed that on numerous occasions, tumours classified as T2 had a poorer prognosis than those classified as T3. The main explanation of these findings could be that many of the cancers classified as T2 should have been classified as T3 according to the latest AJCC classification and, therefore, could have been treated inappropriately. These data support the hypothesis that tumour thickness is an extremely important prognostic factor for squamous cell carcinoma of the oral cavity.

With regard to the age of the patients, our results indicate a poorer prognosis for the group of patients aged under 45 years (48.4% vs. 62%). In addition, it was observed that the weight of the classic risk factors (alcohol and tobacco) is less important for the group of patients under 45 years of age ($p<0.005$). It was also shown that patients in the group aged under 45 years are more likely to abandon the habits that constitute risk factors (alcohol and tobacco) following diagnosis of the disease when compared with patients in the group aged over 45 years. Another significant finding is that the male/female ratio is more equal in the group of young patients (m/f ratio = 1.2:1 vs. m/f ratio = 2.03:1). These results support the hypothesis that for younger patients the genetic predisposition is the most relevant factor for developing the disease, which could explain the poorer prognosis and response to surgical and adjuvant treatment observed in this group.

Another significant factor evidenced by our study is that neck dissection does not increase survival in patients with squamous cell carcinoma of the tongue classified as pT1N0M0. However, neck dissection offers important diagnostic and prognostic data and is the only tool that allows for fully establishing the staging of the disease. Therefore, in light of the results presented, it would be advisable to perform neck dissection in patients with T1N0M0 and tumour thickness >0.4 cm.

The main limitation of this work is its retrospective nature. Further studies of a multicentric and prospective nature could confirm and extend these results and allow for gathering greater knowledge of this disease, along with the consequent clinical repercussions for the prognosis of patients affected by this pathology.

CONCLUSIONES

Conclusión general: El carcinoma epidermoide de lengua metastatiza más frecuentemente en el nivel cervical IIA. Tumores con espesor de infiltración >0.4 cm, independientemente de su localización en la cavidad oral, presentan mayor tasa de metastatización linfática y peor pronóstico con respecto a tumores con espesor de infiltración <0.4 cm. Este dato sugiere la necesidad de realizar vaciamiento cervical en los carcinomas epidermoides con espesor de infiltración >0.4 cm con el objetivo de mejorar las tasas de supervivencia global. El carcinoma epidermoide de maxilar superior mostró elevada tasa de metastatización cervical (34.4%) en pacientes sin evidencia clínica y radiológica de afectación cervical. Independientemente de la localización del tumor primario en la cavidad oral, Estadio T, estadio N, espesor de infiltración tumoral >0.4 cm, invasión linfovascular y perineural, desbordamiento capsular y márgenes quirúrgicos representan factores de mal pronóstico e impactan negativamente en la supervivencia global de los pacientes ($p<0.005$). El vaciamiento cervical no aumenta la supervivencia global en pacientes con carcinomas epidermoides de lengua diagnosticados como pT1N0 ($p<0.05$).

Conclusión Articulo 1: El 7.4% de paciente afectados por carcinoma epidermoide de lengua y clasificados como clínicamente N0 antes de la cirugía presentaron una metástasis aislada en el nivel cervical IV. Este dato justificaría la realización de un vaciamiento cervical supraomohioideo extendido al nivel IV en pacientes clasificados como clínicamente N0. Estadio T, estadio N, espesor de infiltración tumoral >0.4 cm, invasión linfovascular y perineural, desbordamiento capsular y márgenes quirúrgicos representan factores de mal pronóstico e tienen un impacto negativo sobre la supervivencia global de los pacientes ($p<0.05$).

Conclusión Articulo 2: El cervical nivel Ib es el más afectado por metástasis cervicales del carcinoma epidermoide de maxilar superior y el 64.2% de todas las metástasis cervicales ocultas evidenciadas en nuestro estudio se localizaron en este nivel cervical. Este dato sugiere la necesidad asociar el vaciamiento cervical a la extirpación del tumor primario en pacientes con carcinoma epidermoide de maxilar superior a partir del estadio cT2N0. Estadio T, estadio N, espesor de infiltración tumoral >0.4 cm, invasión linfovascular y perineural, desbordamiento capsular y márgenes quirúrgicos representan factores de mal pronóstico e impactan negativamente en la supervivencia global de los pacientes ($p<0.005$).

Conclusión Articulo 3: El carcinoma epidermoide de cavidad oral no parece estar íntimamente relacionado con los "clásicos" factores de riesgo (alcohol y tabaco) en pacientes jóvenes (<45 años) ($p<0.005$). En estos casos, la etiopatogenia de la enfermedad parece estar más íntimamente relacionado con una intrínseca predisposición genética de los pacientes afectados. Los pacientes jóvenes (<45 años) mostraron peores tasas de supervivencia con respecto a pacientes > 45 años. Sin embargo, los resultados no alcanzaron significatividad estadística con respecto a la supervivencia global de los dos grupos de pacientes ($p=0.17$).

Conclusión Articulo 4: El vaciamiento cervical no aumenta la supervivencia global en pacientes con carcinomas epidermoides de lengua diagnosticados como pT1N0 ($p<0.05$). Estadio T, estadio N, espesor de infiltración tumoral >0.4 cm, invasión linfovascular y perineural, desbordamiento capsular y márgenes quirúrgicos representan factores de mal

pronóstico e impactan negativamente en la supervivencia global de los pacientes (<0.005).

CONCLUSIONS

General Conclusion: Squamous cell carcinoma of the oral tongue most frequently metastasizes to the cervical IIA level. Tumours with tumour thickness >0.4 cm — regardless of their location in the oral cavity — have a higher rate of lymphatic metastasis and a poorer prognosis than tumours with an infiltration thickness <0.4 cm. These data indicate the need to perform neck dissection in squamous cell carcinoma with tumour thickness >0.4 cm in order to improve overall survival rates. Squamous cell carcinoma of the upper jaw showed a high rate of cervical metastasis (34.4%) in patients without clinical and radiological evidence of cervical involvement. Regardless of the location of the primary tumour in the oral cavity, T stage, N stage, tumour infiltration thickness >0.4 cm, lympho-vascular and perineural invasion, extracapsular spread and surgical margins are factors associated with poor prognosis and negatively impact the overall survival ($p<0.005$). Neck dissection does not increase overall survival in patients with epidermoid tongue carcinomas diagnosed as pT1N0 ($p<0.05$).

Chapter 1 Conclusion: 7.4% of patients affected by tongue squamous cell carcinoma classified as clinically N0 before surgery presented isolated metastasis at the cervical level IV. These data justify to extend the neck dissection at Level IV in patients classified as clinically N0. T stage, N stage, thickness of tumour infiltration >0.4 cm, lympho-vascular and perineural invasion, extracapsular spread and surgical margins are all factors associated with a poor prognosis and have a negative impact on the overall ($p<0.05$).

Chapter 2 Conclusion: Cervical level Ib is the one most affected by cervical metastases of maxillary squamous cell carcinoma, and 64.2% of all occult cervical metastases evidenced in our study were located at this cervical level. These data indicate the need to perform neck dissection in patients with squamous cell carcinoma of the upper jaw from

stage cT2N0. T stage, N stage, tumour thickness >0.4 cm, lympho-vascular and perineural invasion, extracapsular spread and surgical margins all represent factors associated with a poor prognosis and impact negatively on patients' overall survival ($p<0.005$).

Chapter 3 Conclusion: Oral squamous cell carcinoma does not appear to be closely related to the "classic" risk factors (alcohol and tobacco) in young patients (<45 years) ($p<0.005$). In these cases, the etiopathogenesis of the disease seems to be more closely related to an intrinsic genetic predisposition of the affected patients. Young patients (<45 years) showed poorer survival rates with respect to patients > 45 years. However, this difference in overall survival between the two groups of patients did did not reach statistical significance ($p=0.17$).

Chapter 5 Conclusion: Neck dissection does not increase overall survival in patients with squamous cell carcinoma of the oral tongue diagnosed as pT1N0 ($p<0.05$). T stage, N stage, tumour infiltration thickness >0.4 cm, lympho-vascular and perineural invasion, extracapsular spread and surgical margins are all factors associated with a poor prognosis and which negatively impact the overall survival in this group of patients (<0.005).

ANEXO 1

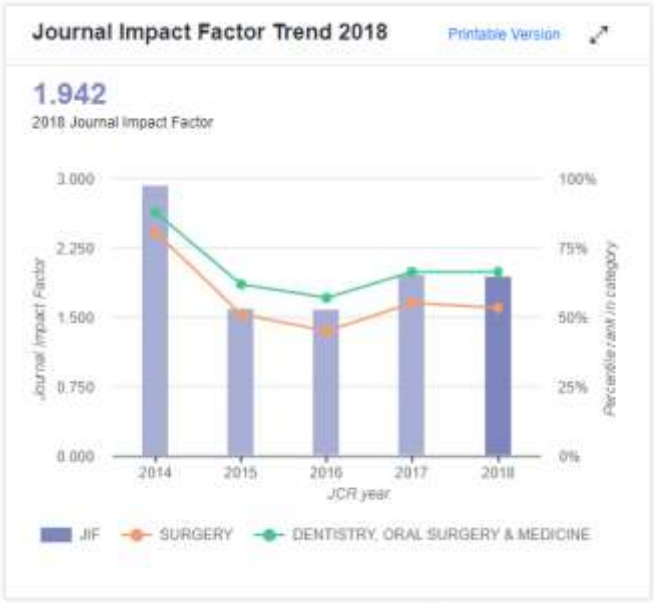
En este anexo representamos los índices de calidad de cada revista donde han sido publicados los artículos que componen la presente memoria de tesis doctoral.

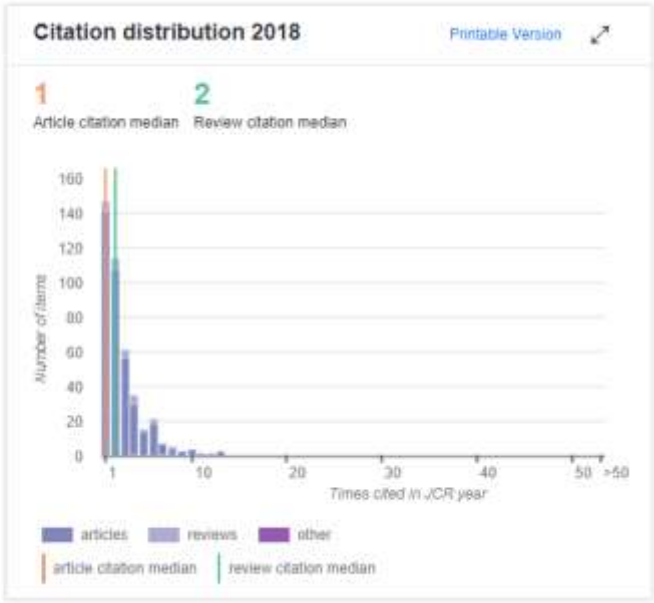
Journal of Cranio-Maxillofacial Surgery

Factor de impacto JCR: 1.942 (Primer tercil JCR)

Citaciones recibidas en 2018: 1109

Categorias: 1) Dentistry, Oral Surgery & Medicine (posición 31/91)



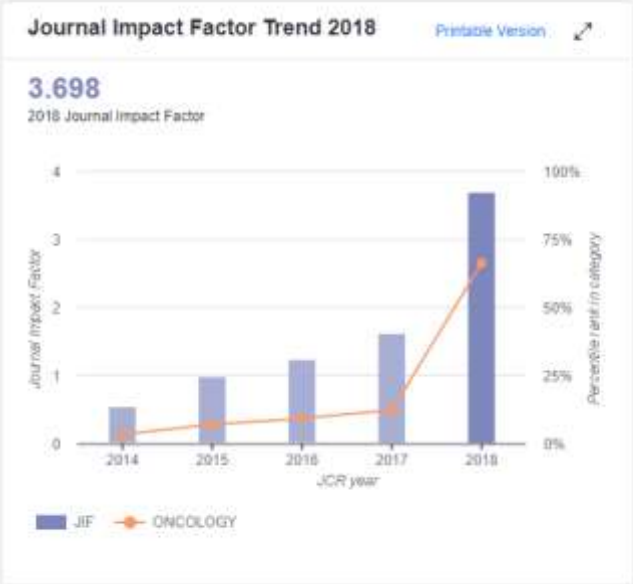


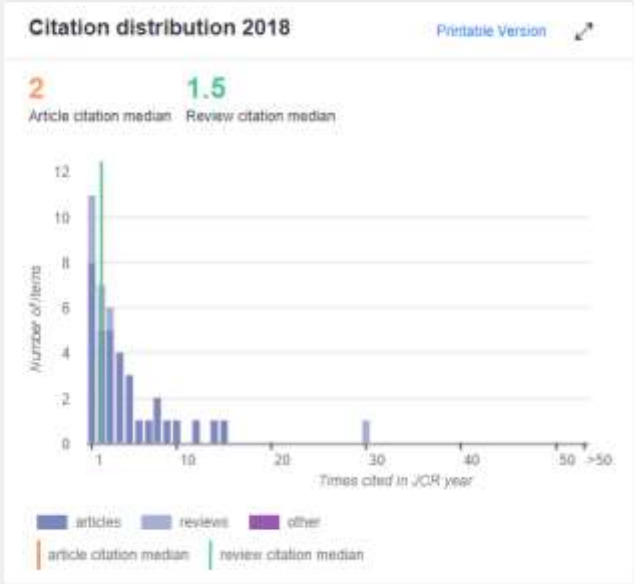
Current Problems in cancer

Factor de impacto JCR: 3.698 (Segundo Tercil JCR)

Citaciones recibidas en 2018: 196

Categorias: Oncology (posición 78/230)



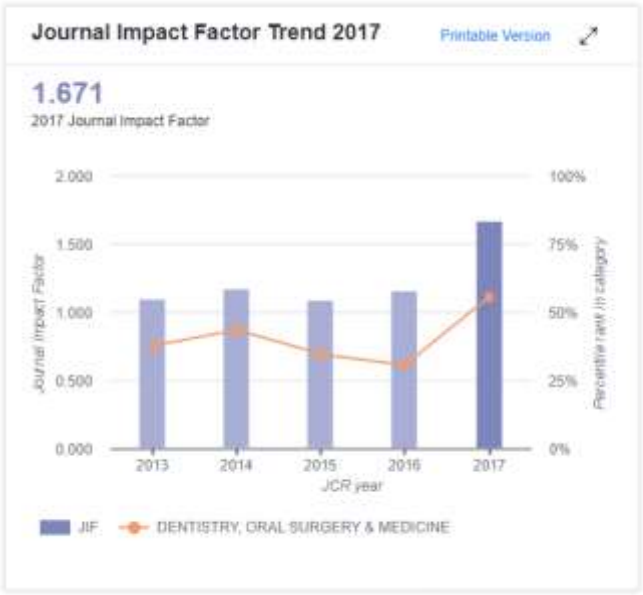


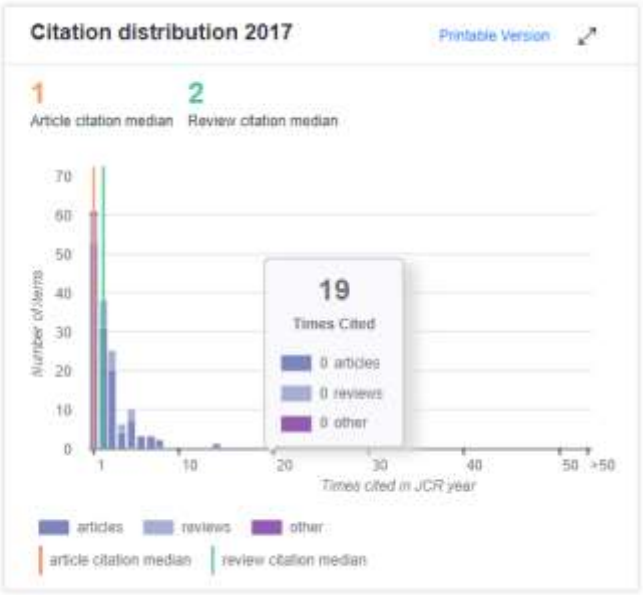
Medicina Oral Patologia Oral y Cirugia Bucal

Factor de impacto JCR: 1.671 (Segundo Tercil JCR)

Citaciones recibidas en 2017: 280

Categorias: Dentistry, Oral Surgery & Medicine (posición 41/91)



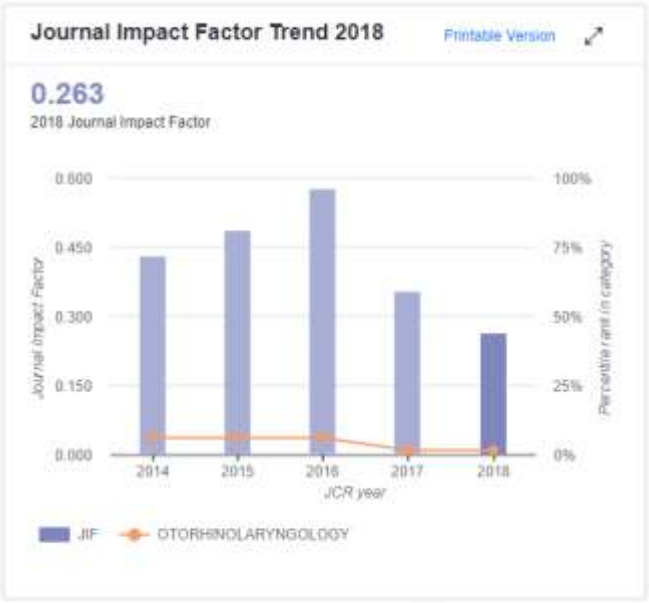


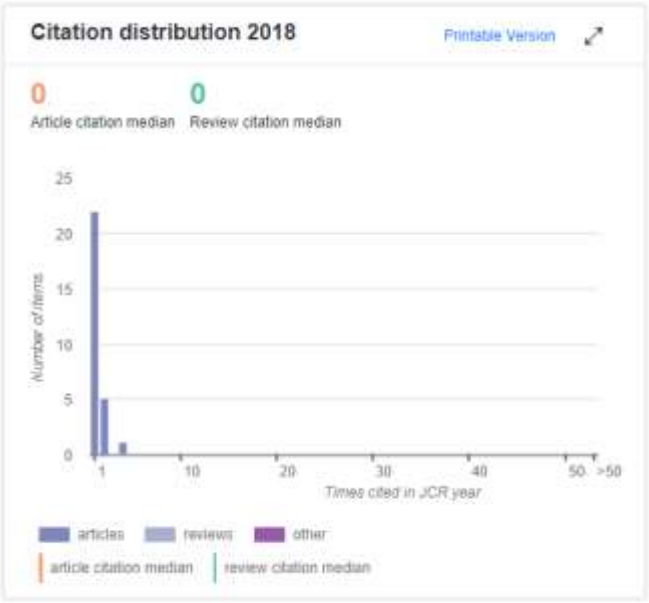
B-ENT

Factor de impacto JCR: 0.263 (Tercer Tercil JCR)

Citaciones recibidas en 2018: 53

Categorias: Otorhinolaryngology (posición 42/42)





ANEXO 2

En este anexo reportamos la 8th edición de la clasificación TNM de la AJCC (American Joint Committee on Cancer) para tumores malignos de cavidad oral (excluyendo la orofaringe).

Lip
1. External upper lip (vermilion border)
2. External lower lip (vermilion border)
3. Commissures
Oral Cavity
1. Buccal mucosa a. Mucosa of upper and lower lips (C00.3, 4) b. Cheek mucosa (C06.0) c. Retromolar areas (C06.2) d. Buccoalveolar sulci, upper and lower (vestibule of mouth)
2. Upper alveolus and gingiva (upper gum)
3. Lower alveolus and gingiva (lower gum)
4. Hard palate
5. Tongue a. Dorsal surface and lateral borders anterior to vallate papillae (anterior two thirds) b. Inferior (ventral) surface
6. Floor of mouth

Figura 1. Diferenciación entre las varias localizaciones de la cavidad oral (excluyendo la orofaringe).

T – Primary Tumour TX Primary tumour cannot be assessed T0 No evidence of primary tumour Tis Carcinoma in situ
T1 – Tumour 2 cm or less in greatest dimension and 5 mm or less depth of invasion*
T2 – Tumour 2 cm or less in greatest dimension and more than 5 mm but no more than 10 mm depth of invasion or Tumour more than 2 cm but not more than 4 cm in greatest dimension and depth of invasion no more than 10 mm
T3 – Tumour more than 4 cm in greatest dimension or more than 10 mm depth of invasion
T4a – (Lip) Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (of the chin or the nose)
T4a – (Oral cavity) Tumour invades through the cortical bone of the mandible or maxillary sinus, or invades the skin of the face
T4b – (Lip and oral cavity) Tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery
* Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4a.

Figura 2. Estadio T clínico

N – Regional Lymph Nodes
NX – Regional lymph nodes cannot be assessed
N0 – No regional lymph node metastasis
N1 – Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension
N2 – Metastasis described as: N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension
N3a – Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
N3b – Metastasis in a single or multiple lymph nodes with clinical extranodal extension*
* The presence of skin involvement or soft tissue invasion with deep fixation/tethering To underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extranodal extension. Midline nodes are considered ipsilateral nodes.
M – Distant Metastasis
M0 – No distant metastasis
M1 – Distant metastasis

Figura 3. Estadio N y M clínicos

pT – correspond to the clinical T categories
pN – Regional Lymph Nodes
NX – Regional lymph nodes cannot be assessed
N0 – No regional lymph node metastasis
N1 – Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension
N2 – Metastasis described as: pN2a Metastasis in a single ipsilateral lymph node, less than 3 cm in greatest dimension with extranodal extension or, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension pN2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension pN2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension
N3a – Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
N3b – Metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension or, multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension*
pT – correspond to the clinical T categories
pN – Regional Lymph Nodes
NX – Regional lymph nodes cannot be assessed

Figura 4. Estadio T y N patológicos

Stage
Stage 0 – Tis N0 M0
Stage I – T1 N0 M0
Stage II – T2 N0 M0
Stage III – T3 N0 M0 T1/T2/T3 N1 M0
Stage IVa – T4a N0/N1 M0 T1/T2/T3/T4a N2 M0
Stage IVB – Any T N3 M0 T4b Any N M0
Stage IVC – Any T Any N M1

Figura 5. Estadios de la enfermedad según el TNM