ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

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ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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MSc: "Clinical Trials: Design and Conduct"

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Τίτλος Διπλωματικής Εργασίας: The value of lymph node ratio as a prognostic factor affecting survival, in mixed cohorts of node-positive and node-negative patients with oral squamous cell carcinoma: A systematic review and meta-analysis.

Ονοματεπώνυμο Φοιτήτριας: Άρτεμις Κυριακοπούλου

Αριθμός Μητρώου: 20190063

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ΑΘΗΝΑ 2022

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ΑΘΗΝΑ 2022

Foreword

This thesis is a systematic review and meta-analysis of studies engaged in the fields of Oncology and Surgery. It is expected to contribute significantly to future research aiming at a more precise risk stratification of patients suffering from oral cancer, leading to establishment of effective patient-oriented treatment guidelines, that will guarantee longer and better survival. An intricate research requiring around 18 months to be properly designed and conducted in the Therapeutic Clinic of Alexandra Hospital, with no funding received, currently awaiting peer-review. Despite its complexity, it was the most interesting and rewarding journey, that would have never been feasible without the enthusiastic support and constant guidance from my supervisor, Assistant Professor Theodoros Sergentanis, whose scientific wealth and kind, inspiring nature motivated me to expand my knowledge, deepening into the field of systematic research. I would also like to express my gratitude to my dear friend and partner in this project, postgraduate student Zoi Gartagani, MD, for our excellent collaboration and mutual respect where contribution of independent researchers was necessary. Of course nothing would have been achieved without the valuable help and guidance provided by Professors Evangelos Terpos and Theodora Psaltopoulou, members of the selection board, from the very beginning. Chrysanthi Kotampasi, secretary at our postgraduate program, deserves special thanks for her never ending efforts to address any issues and support the whole educational process, under unprecedented difficulties the COVID-19 pandemic brought. Last but not least, I would like to thank my family, to whom my thesis is dedicated, for their psychological support and encouragement all this time.

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Abstract

Oral cavity cancer was the 16th most common type of cancer globally in year 2020, with an incidence rate of 377,713 new cases. Oral squamous cell carcinoma (OSCC) is the most usual type, with main predisposing factors tobacco exposure and alcohol consumption and nodal metastasis associated with poor prognosis**.** Lymph node ratio (LNR), representing the ratio of positive lymph nodes extracted during a neck dissection to the total nodal yield, is a well established prognostic factor for colorectal and breast cancer. During the last years, research has also proven the clinical implication of LNR in OSCC prognosis, aiming at a more precise disease classification. The main purpose of this study is to prove that LNR, as a dichotomous categorical variable, is an independent prognostic factor for OSCC. A systematic search was conducted in the following databases to result in 32 studies published between 2009 and 2020; PubMed, EMBASE, Cochrane library and ClinicalTrials.gov. Pooled relative risk/hazard ratio was calculated, along with 95% confidence intervals for the following endpoints; overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), distant metastasis-free survival (DMFS) and locoregional disease-free survival (LRDFS), according to random-effects models, including subgroup and meta-regression analyses. 20 cohort studies, including node-negative patients, were eligible for meta-analysis. Patients with high LNR versus those with low LNR, had shorter OS (RR: 2.38, 95% CI: 1.99- 2.85), DFS (RR: 2.04, 95% CI: 1.48- 2.81) and DSS (RR: 2.90, 95%CI: 2.35-3.57). LNR seems to be a significant, independent prognostic factor concerning OSCC patients, very likely to be incorporated in future classification systems for better risk stratification.

1. Introduction

1.1. Squamous cell carcinomas of the head and neck; definitions, sites affected and symptoms

A cancerous tumor is a mass formed by the sudden, uncontrollable differentiation and growth of healthy cells. Its ability to grow and spread to distant areas of the body makes it malignant. Malignant tumors affecting the mouth, throat, larynx, nose and sinuses, are generally described as "head and neck cancers". The majority of these are squamous cell carcinomas detected in the epithelium, a thin layer of tissue on the surface of structures in the head and neck consisting of flat squamous cells. If a malignancy affects the squamous layer only, then it is characterized as a carcinoma *in situ*. Sometimes cancer invades the layer of mucosa underneath the epithelium [1]. Other forms of head and neck cancer, more rarely observed, affect the salivary glands, sinuses or muscles and nerves. The salivary gland tumor is usually classified as adenocarcinoma, adenoid cystic carcinoma, or mucoepidermoid carcinoma [2].

According to Laura Q.M. Chow (2020), squamous cell carcinomas can form in the following subsites of the head and neck, depicted in Figure 1 [2]:

- The **oral cavity**, which includes the lips, buccal mucosa, anterior tongue, floor of mouth, hard palate, upper and lower gingiva, and retromolar trigone.
- The **pharynx**, which includes the nasopharynx, oropharynx and hypopharynx.
- The **larynx**, which includes the supraglottic larynx, glottic larynx and subglottic larynx.
- The **nasal cavity** and **paranasal sinuses** (maxillary, ethmoid, frontal and sphenoid).

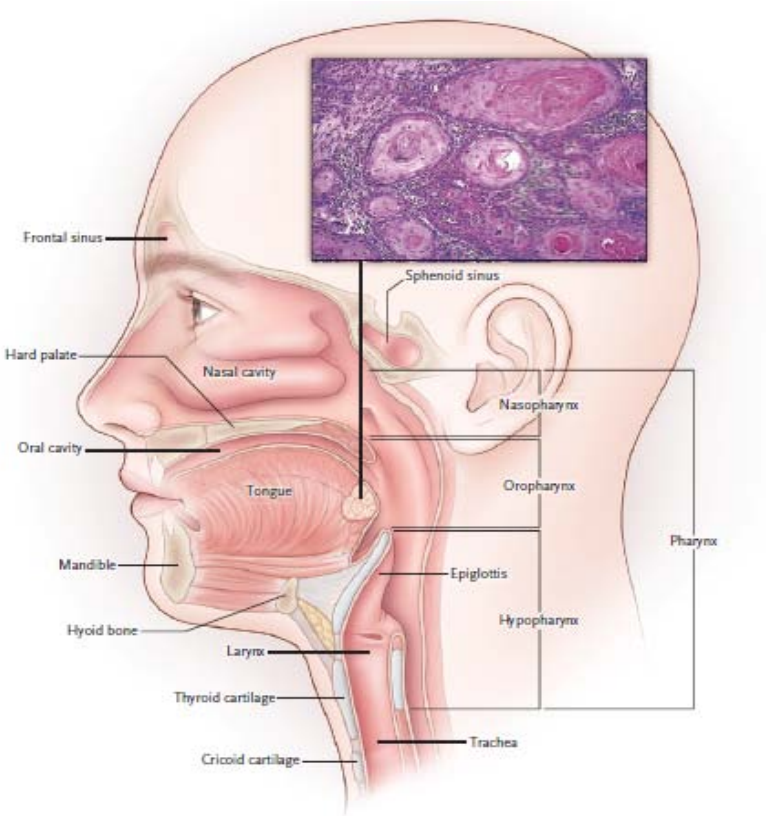

Figure 1. Anatomical sites of squamous cell carcinoma of the head and neck and typical histologic features (inset) [2].

Quite often, this type of carcinoma metastasizes to the lymph nodes in the neck and in some cases, the original primary tumor may be that small in size, that cancerous cells are firstly traced in the lymph nodes of the upper neck. Thus, the carcinoma is characterized as metastatic with unknown (occult) primary [2].

In general, common head and neck cancer symptoms may include a lump in the neck or a sore in the mouth or throat that does not heal, may be painful, a sore throat that does not go away, difficulty in swallowing, and a change or hoarseness of the voice. The National Cancer Institute [3] provides a list of area-specific symptoms that may alarm a person to visit their doctor.

1.2. Causal factors and epidemiology

Tobacco use and alcohol are the two most important risk factors for head and neck cancer. 254 reports on cigarette smoking and cancer, published between 1961 and 2003, were included in the 2004 International Agency for Research on Cancer (IARC) Monograph on *Tobacco Smoke and Involuntary Smoking*. Gandini S. et al. [4] conducted in 2007 a systematic meta-analysis of these observational studies, and defined current smoking status as a significant risk factor for cancers of the oral cavity (RR: 3.43; 95% CI: 2.37–4.94, p=0.001). The correlation between former smoking status and risk of oral cancer development was not statistically significant (RR: 1.40; 95% CI: 0.99-2.00, p=0.098). Smoking and alcohol consumption seem to be independently associated with the risk of head and neck cancer [5]. A pooled individual data analysis of 15 case-control studies showed that among never drinkers, cigarette smoking was associated with an increased risk of head and neck cancer. Stratification by cancer site did not reveal any statistically significant correlations regarding oral cancer, for either hypothesis. Association between secondhand smoke exposure and risk of oral cancer has been proven as well [6]. The duration of exposure of more than 10 or 15 years increases the risk of oral cancer.

The use of smokeless tobacco products, major source of carcinogenic nitrosamines, has been common in many countries for centuries, especially in Asia, North America and northern Europe [7]. Their consumption proposes an overall raised risk of oral cancer (RR: 1.8; 95% CI: 1.1–2.9, p<0.001) in the USA and northern Europe. In USA alone, relative risk equals to 2.6 (95% CI: 1.3–5.2, p<0.001), whereas in Nordic countries (Sweden and Norway) the association is not statistically supported (RR: 1.0; 95% CI: 0.7–1.3, p=0.4). A possible explanation lies in the different composition of the tobacco products historically consumed in the USA and the northern Europe, since those consumed in the USA were richer in nitrosamines. 6.6%, 52.5% and 68.2% of oral cancer cases in men in the USA, India and Sudan, respectively, are attributed to smokeless tobacco products.

Areca., or betel nut, is the conical fruit of the oriental palm tree (*Areca catechu)* and forms the basis of a variety of widely chewed products consumed by an estimated 200 to 400 million people of all ages, predominantly of low socioeconomic classes, mainly for its stimulant properties. Betel quid, also known as paan, is made by adding ingredients including slices of areca nut, slaked lime (calcium hydroxide), tobacco and spices (cardamom, saffron, and coconut), then folded into a triangular package and chewed or even swallowed. Areca nut contains alkaloids that produce carcinogenic nitrosamines [8]. Leukoplakia is a premalignancy that may evolve to a squamous cell carcinoma. A 10-year follow-up study concerning Indian villagers, where paan is a common habit, found the incidence of leukoplakia equal to 2.5 per 1,000 people [9]. There is evidence supporting that Areca nut alone is capable enough to lead to oral cancer, as proved by studies on populations who prefer not to add tobacco. The relative risk for oral cancer among those who chew Areca only in the Taiwanese population is 58.4 (95% CI: 7.6-447.6) [10]. In a Pakistani cohort studied between July 1996 and March 1998, risk of oral cancer was 9.9 times greater in users of tobacco-free paan than in non-users [11]. In another study from South Africa, 68% of cheek cancer cases and 84% of tongue cancer cases were attributed to Areca chewing [12].

The leaves of Khat (*Catha edulis*), contain cathinone, a natural amphetamine, that induces stimulant effects and feeling of euphoria. They are chewed by a large proportion of the African and Middle Eastern population [13]. Oral mucosal keratosis, a precancerous

lesion, has been reported in 50% of Khat users [14]. A 2-year follow-up study on head and neck cancer incidence in Saudi Arabia followed 28 non-smoking patients, 10 of whom presented with a history of having chewed Khat over a period of 25 years or longer. Since eight were diagnosed with oral cancer, a correlation was built between Khat chewing and the development of oral cancer [15]. Mate´ is a tea-like beverage brewed from the dried leaves and stemlets of the perennial tree *Ilex paraguariensis*. Compounds contained in Mate´ may act as cancer promoters [16].

Another risk factor for oropharyngeal cancers, that mostly involve the tonsils or the base of the tongue, is infection with cancer-causing types of human papillomavirus (HPV), especially HPV type 16. While HPV-negative squamous cell carcinomas are strongly associated with tobacco and alcohol use, HPV-positive ones have risk factors related to sexual behavior and are most commonly diagnosed in younger individuals (<60 years old). These particularities probably explain the better survival profile of the HPV-positive cancer patients [17]. Oropharyngeal squamous cell carcinoma cases tend to increase in the USA after the 1980s, despite the positive effect of campaigns against smoking, something that led research to investigate patients' HPV exposure. HPV status in the USA was determined for 271 cases of oropharyngeal cancer dating from 1984 to 2004, collected by three population-based cancer registries (Hawaii, Iowa and Los Angeles) participating in the Surveillance, Epidemiology and End Results (SEER) Residual Tissue Repositories Program. HPV prevalence increased from 16.3% during 1984 to 1989 to 72.7% during 2000 to 2004, more than four times, perhaps due to increasing oral HPV exposure over calendar time. Radiotherapy also demonstrated a protective effect concerning duration of survival (HR: 0.23; 95% CI: 0.09-0.59) [18]. Assuming full HPV vaccine coverage of the population and 100% vaccine efficacy, an estimated 24,858 (63.4%) HPV-associated cancers in the United States could be prevented annually with the 16/18 vaccines, with around 3,944 (10.1%) additional cancers preventable through the 9-valent vaccine. Oropharyngeal cancers could be prevented by 60.2% [19].

A variety of other causal factors concerning mainly nasopharyngeal carcinomas and cancer of the larynx has also been investigated. Some of these arise from occupational exposure [20]. Cancer of the salivary glands can also be provoked by radiation of the head and neck as treatment strategy for other malignant or non-malignant conditions [21]. The role of Epstein-Barr virus (EBV) infection as a risk factor for nasopharyngeal cancer has also been studied [22].

A clinical review published in 2019 investigated the incidence trends of lip, oral and pharyngeal cancers (LOPCs) from 1990 to 2017, using the latest Global Burden of Disease (GBD) study data, taken from population cancer registries in 195 countries [23]. Incidence trends were mapped and comparisons were made according to sex, age groups, regions, and countries. The calculated variable of interest was the estimated annual percentage change (EAPC), as the average change of age-standardized incidence rate per year. A negative EAPC describes a decreasing trend, while a positive EAPC describes an increasing trend. Variables were considered statistically significant when the 95% confidence interval excluded 0.

Globally, researchers estimated that the absolute number of incident lip and oral cavity cancers increased from around 186,000 in 1990 to 389,800 in 2017 (109% increase), with an EAPC value of 0.26 (95% CI: 0.16–0.37). The increasing incidence of lip and oral cavity cancers may be attributed to population growth and aging, hence an increased need for access to medical services such as screening tests that trace previously undiagnosed population. The

younger age groups were found to make the largest contribution to the overall worldwide increase perhaps due to their increasing oral HPV exposure in the course of time.

Among women, considerable increases in lip and oral cavity cancers and other pharyngeal cancers were found. This phenomenon is probably explained by the increasing trend of early introduction of women to smoking habits, in developing countries [24]. Comparisons by sex are graphically represented in the following box plot (Figure 2) [23].

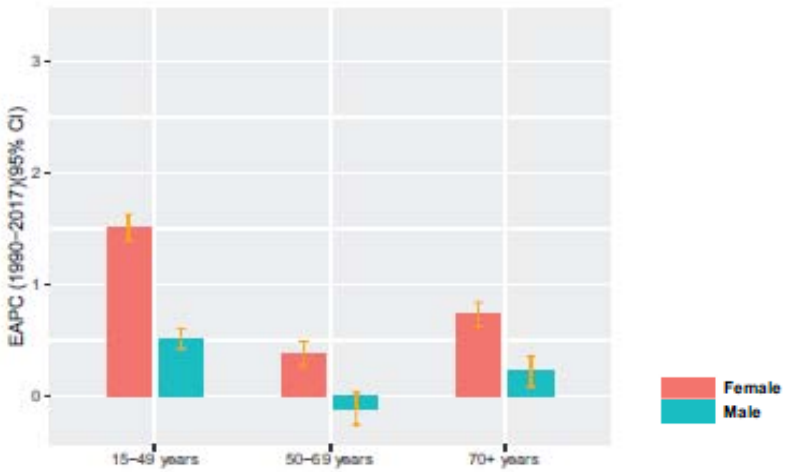

Figure 2. Temporal trends in lip and oral cavity cancers estimated annual percentage change (EAPC) from 1990 to 2017 in women (red) and men (blue) for three age groups (15-49 y, 50-69 y and 70+ y) [23].

Increasing trends for lip and oral cavity cancers were found in all sociodemographic index (SDI) levels (Figures 3,4) [23]. Inadequate prevention programs (e.g., HPV vaccination) may explain the more rapid increase in low and middle SDI regions [25].

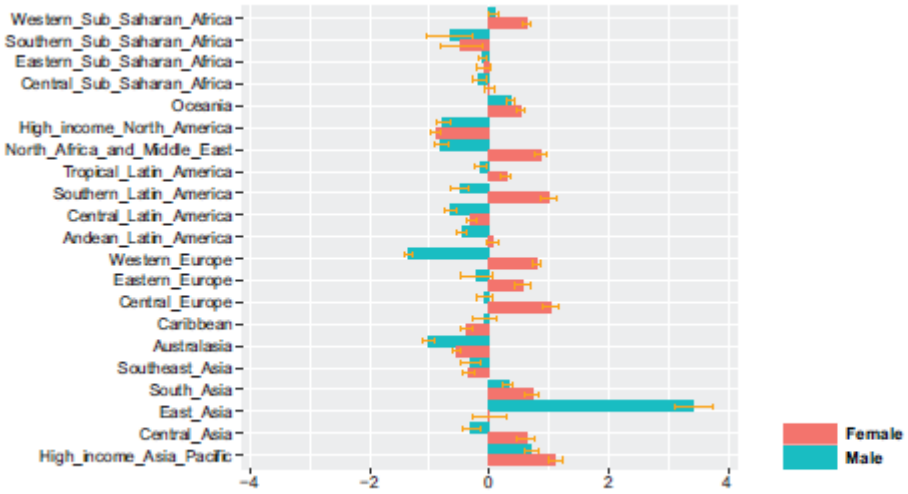

Figure 3. Estimated annual percentage change (EAPC) of lip and oral cavity cancers from 1990 to 2017 for 21 geographical regions in women (red) and men (blue) [23].

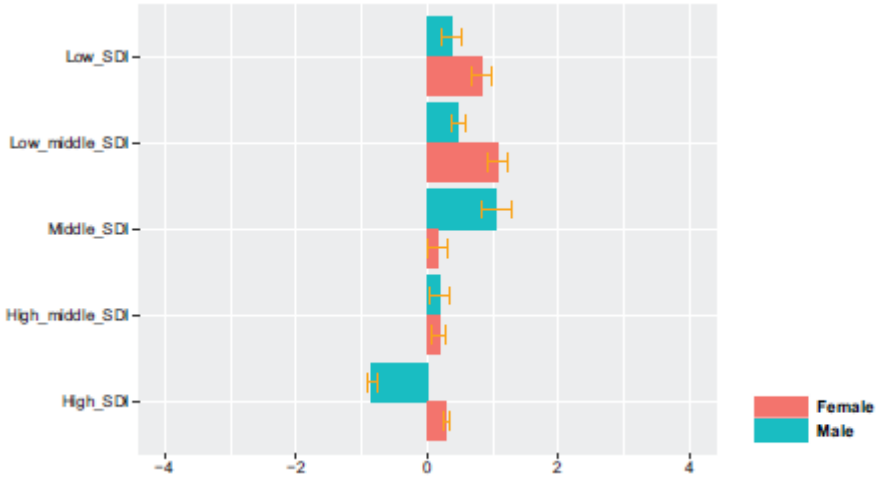

Figure 4. Estimated annual percentage change (EAPC) of lip and oral cavity cancers from 1990 to 2017 for 5 sociodemographic index (SDI) regions in women (red) and men (blue) [23].

Surveillance, Epidemiology and End Results Program is supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS) [26]. A graphical depiction of the incidence rate and mortality of oral cavity and pharynx cancers in the USA from 1975 to 2019 is provided, as well as a calculation of the 5-year survival rate, according to data from 2011 to 2018 (Figures 5,6) [26].

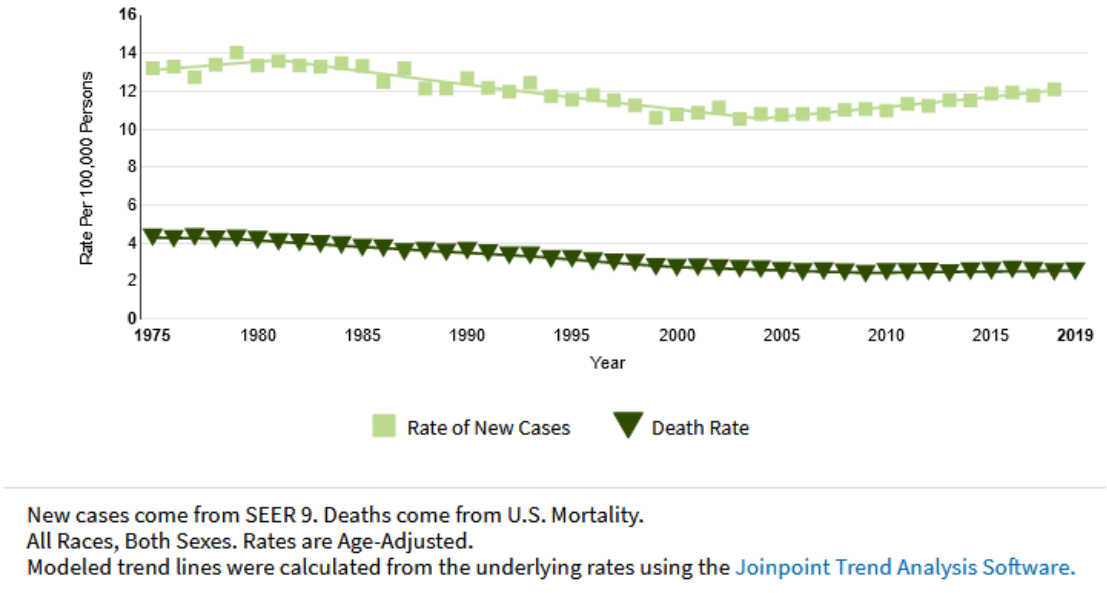

Figure 5. Incidence rate and mortality of oral cavity and pharynx cancers in the USA from 1975 to 2019 [26].

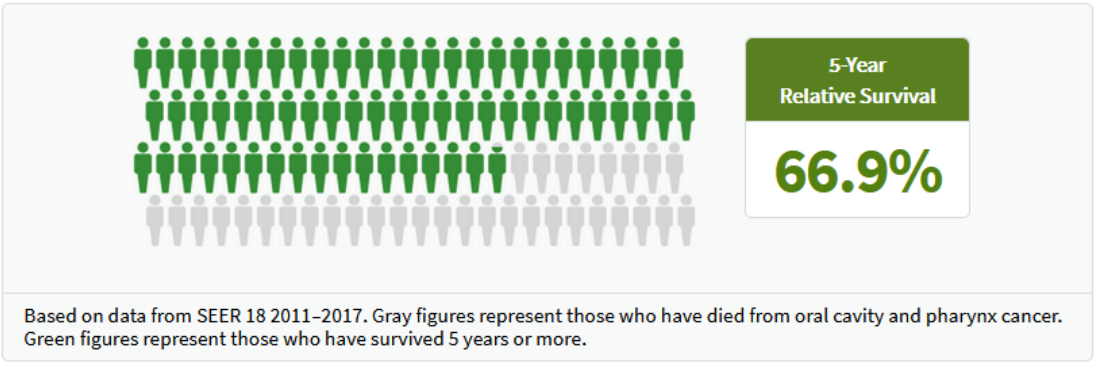

Figure 6. 5-year relative survival rate of patients with oral cavity and pharynx cancers in the USA, according to data from 2011 to 2018 [26].

The earlier oral cavity and pharynx cancer is detected, the better chance a person has of surviving five years after being diagnosed (Figure 7) [26].

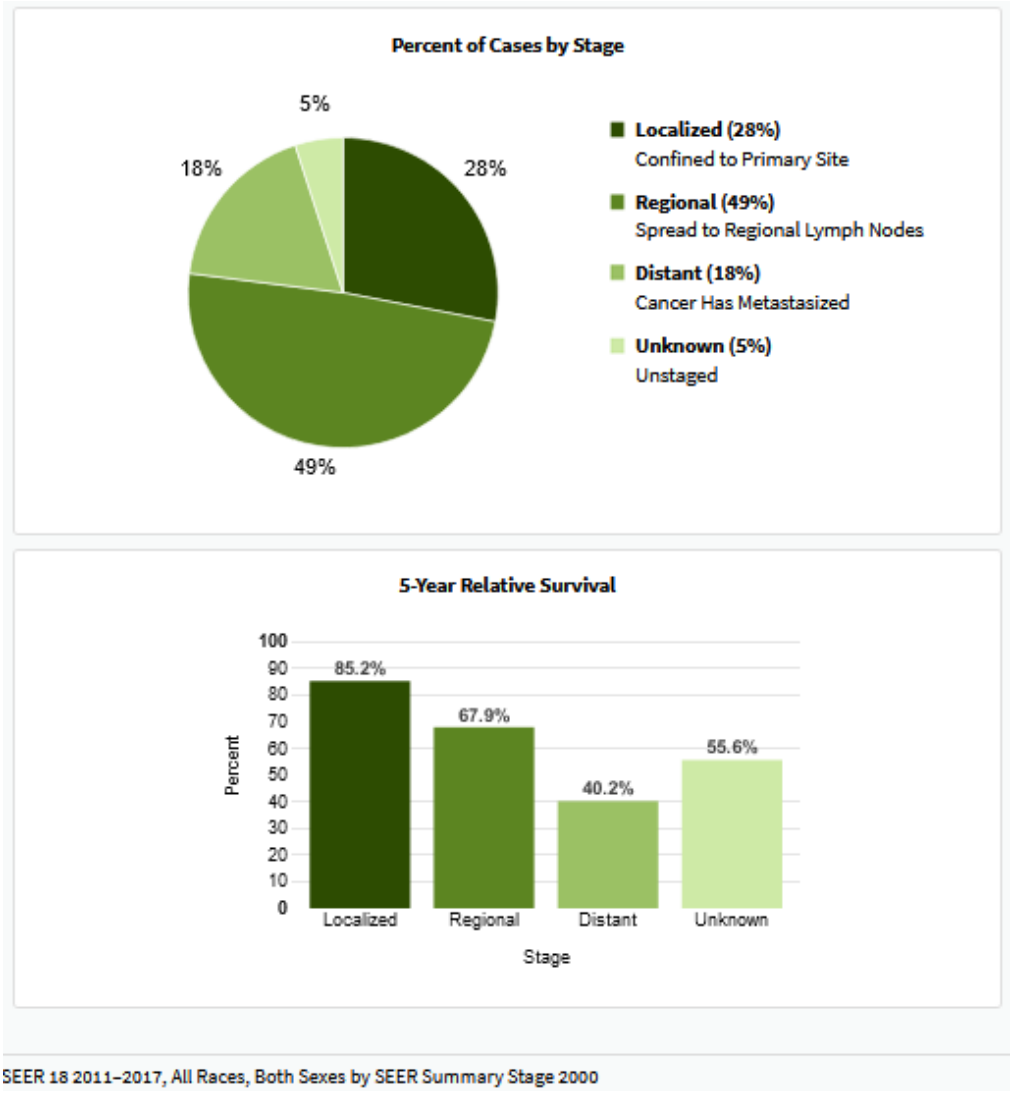

Figure 7. Percent of cancer cases by stage and 5-year stage-specific relative survival rate of patients with oral cavity and pharynx cancers in the USA, according to data from 2011 to 2018 [26].

Estimates of new cases and deaths for 2021 are projections made by the American Cancer Society (ACS), based on earlier reported data. In 2021, it was estimated that there would be 54,010 new cases of oral cavity and pharynx cancer and an estimated 10,850 people would die of this disease (Figure 8) [27].

	Common Types of Cancer	Estimated New Cases 2021	Estimated Deaths 2021
1.	Breast Cancer (Female)	281,550	43,600
2.	Prostate Cancer	248,530	34,130
3.	Lung and Bronchus Cancer	235,760	131,880
4.	Colorectal Cancer	149,500	52,980
5.	Melanoma of the Skin	106,110	7,180
6.	Bladder Cancer	83,730	17,200
7.	Non-Hodgkin Lymphoma	81,560	20,720
8.	Kidney and Renal Pelvis Cancer	76,080	13,780
9.	Uterine Cancer	66,570	12,940
10.	Leukemia	61,090	23,660
	-	-	-
	Oral Cavity and Pharynx Cancer	**54,010**	**10,850**

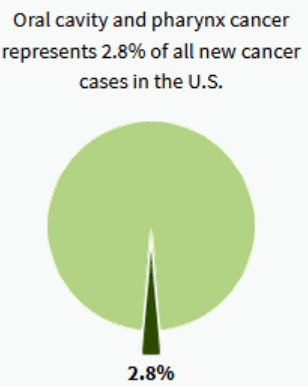

Figure 8. Estimates of new cancer cases and deaths for 2021 by the American Cancer Society (ACS), based on earlier reported data [26].

The Global Cancer Observatory (GCO) is an interactive web-based platform presenting global cancer statistics to inform cancer control and cancer research [28]. CANCER TODAY enables a comprehensive assessment of the cancer burden worldwide in 2020, based on the GLOBOCAN estimates of incidence, mortality and prevalence for year 2020 in 185 countries or territories for 36 cancer types by sex and age group [29]. Lip and oral cavity cancer is the 16th most common type of cancer globally across all age groups of both sexes, with 377,713 new cases recorded in 2020 (Figure 9). 65.8% of the new cases are located in Asia, followed by Europe (17.3%), as seen in Figure 10. Over the last 5 years, 959,248 patients have been diagnosed with lip and oral cavity cancer, 60.9% of those living in Asia (Figure 10). Age-standardized world incidence rates are higher in men comparing to women (Figure 11).

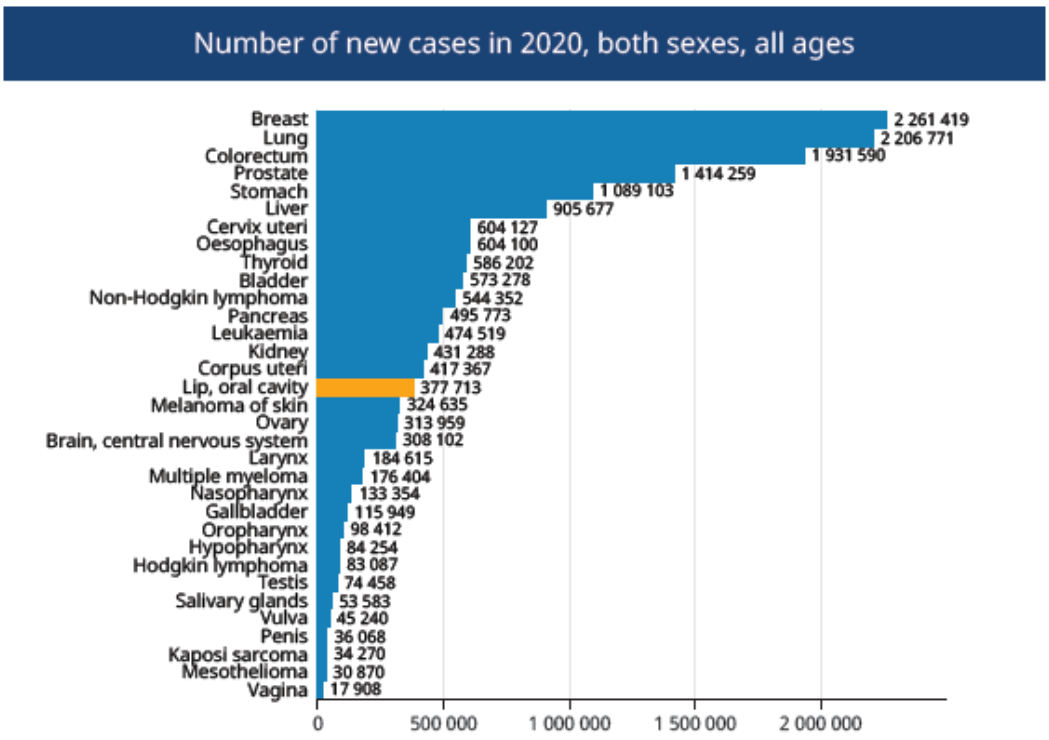

Figure 9. Number of new cancer cases in year 2020 globally, for both sexes and all ages [29].

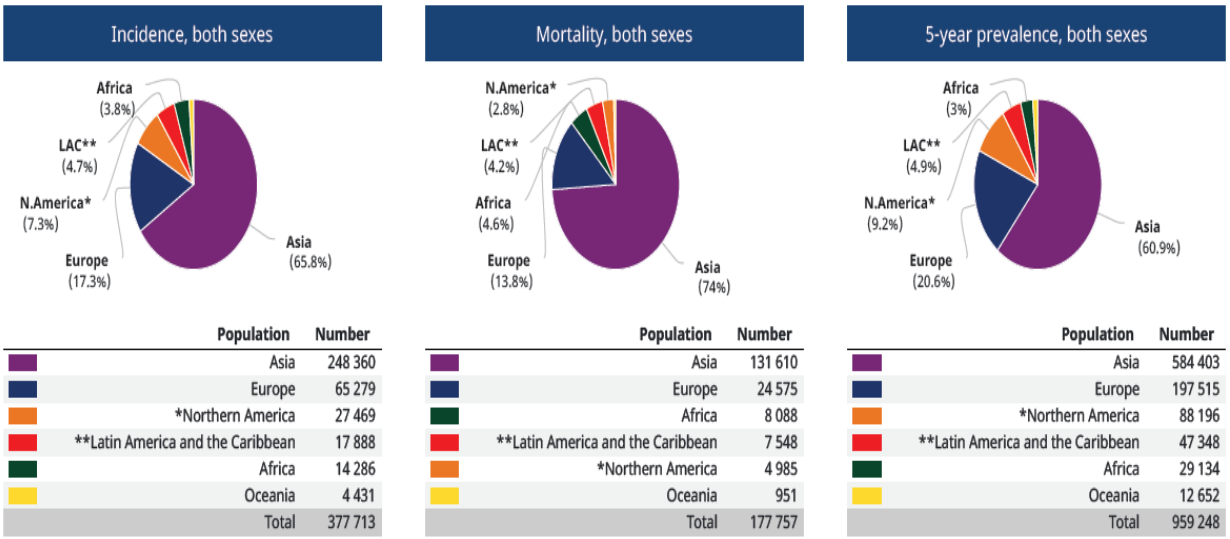

Figure 10. Incidence, mortality and 5-year prevalence of lip and oral cavity cancers globally, for both sexes [29].

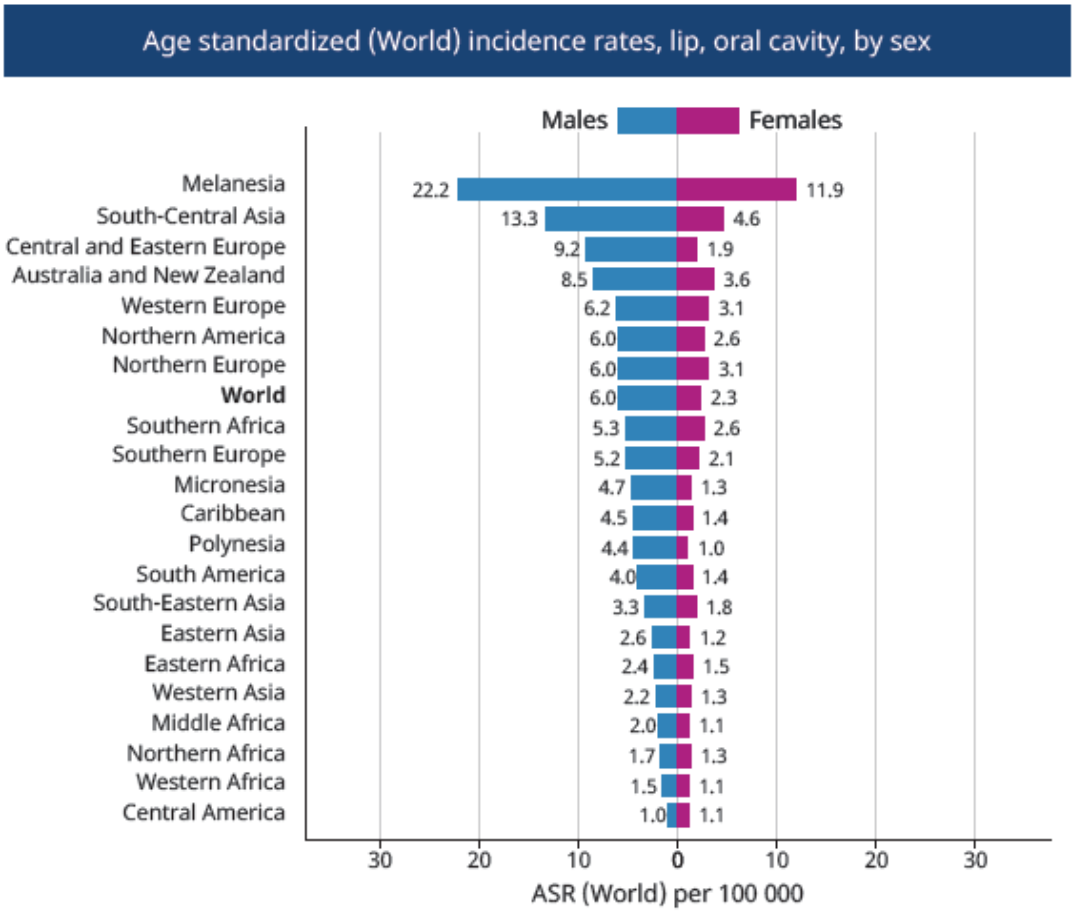

Figure 11. Age-standardized world incidence rates of lip and oral cavity cancers, for women (purple) and men (blue) [29].

CANCER TOMORROW provides a suite of data visualization tools to predict the future incidence and mortality for a given country or region up until 2040 [30]. In the following bar charts showing the predicted percentage change of lip and oral cavity cancer incidence and mortality from year 2020 to 2040 across all continents, Europe seems to present the slightest increase, followed by North America (Figures 12,13). The COVID-19 pandemic effect on population screening for the diagnosis of early-stage cancer remains to be researched in the years to come. It will be interesting to see how this effect will be numerically reflected in the differences between the observed rates and the tendencies predicted by the model.

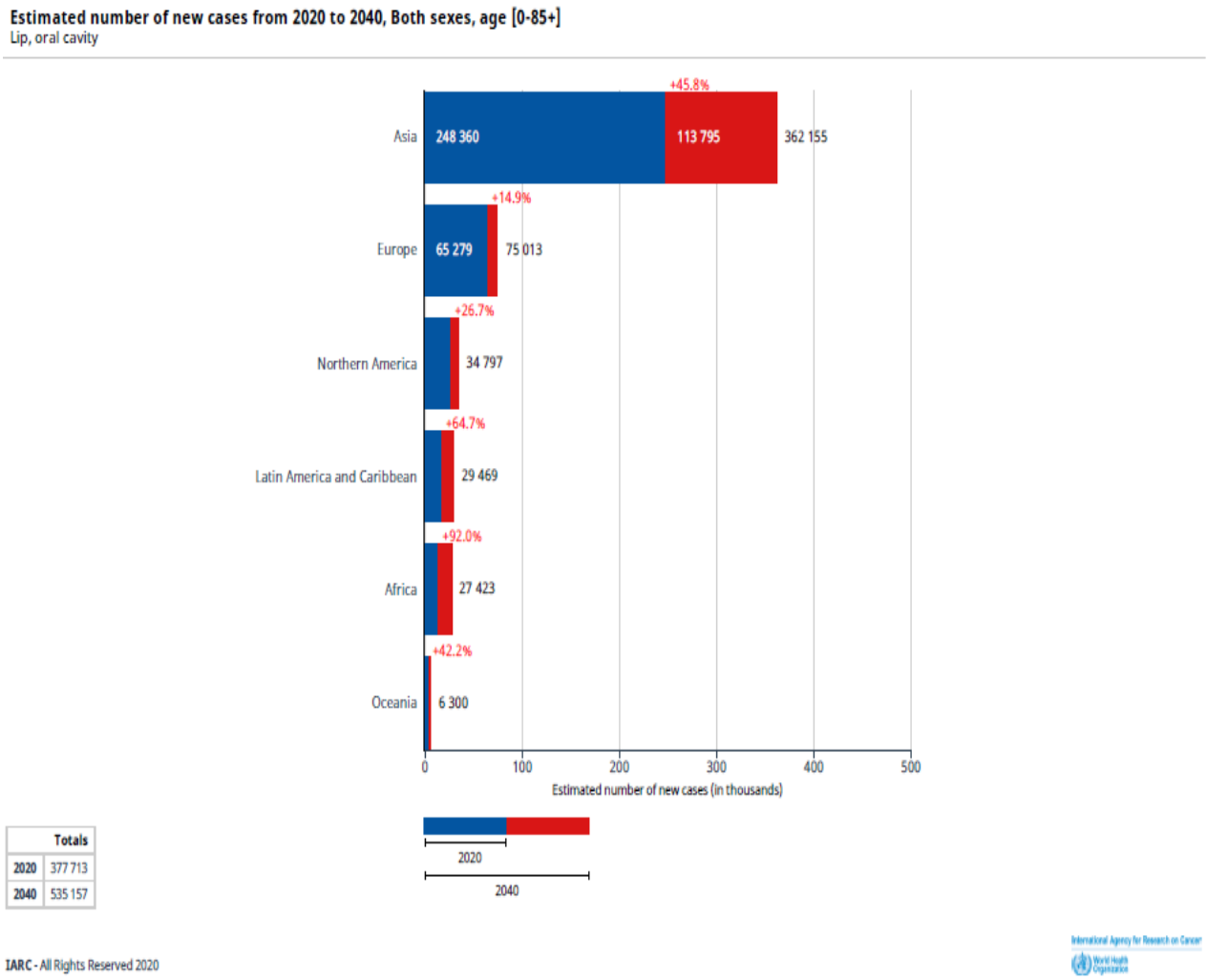

Figure 12. Estimated number of new lip and oral cavity cancer cases from year 2020 to 2040, for both sexes and all ages.

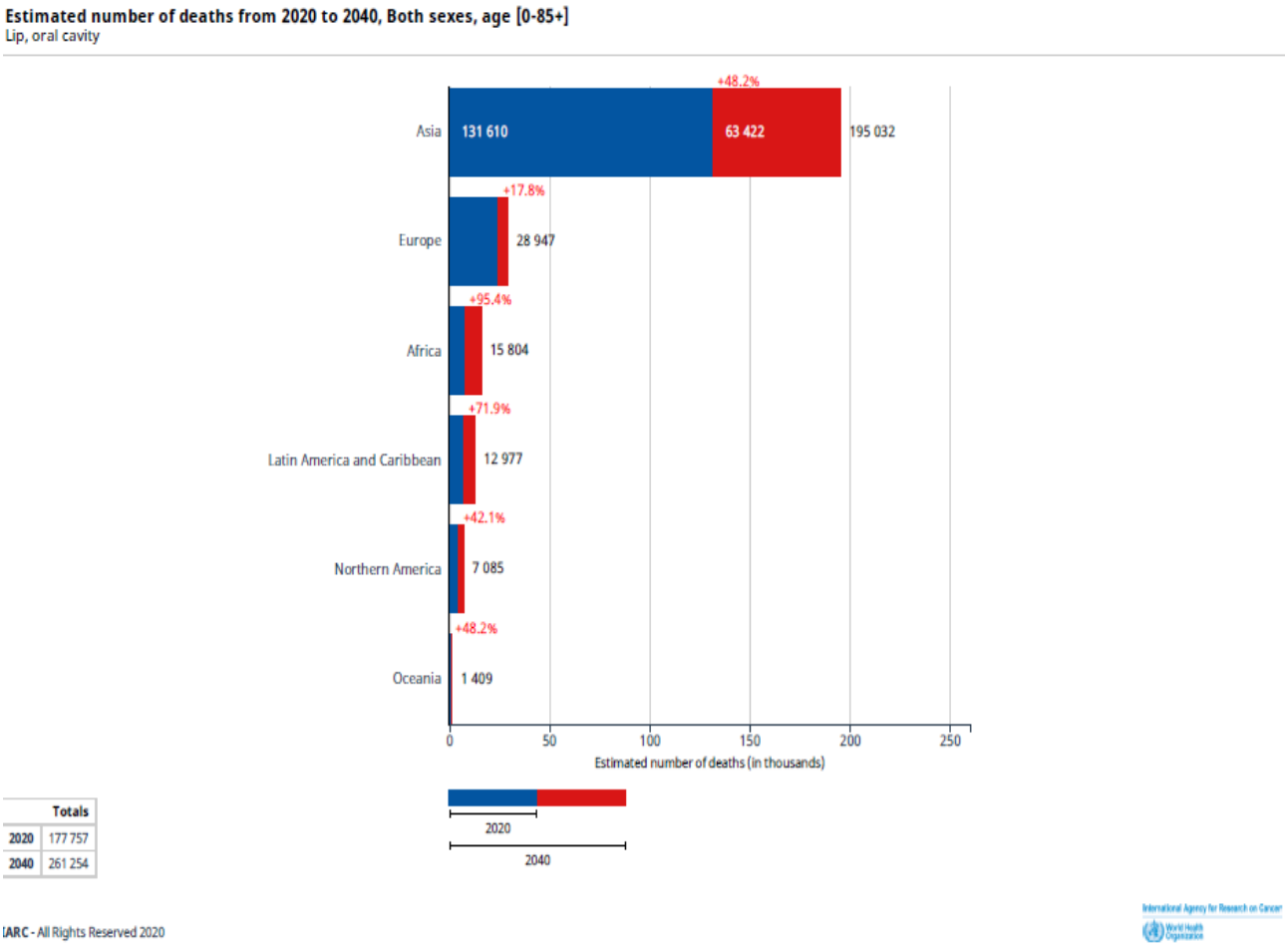

Figure 13. Estimated number of deaths from lip and oral cavity cancers from year 2020 to 2040, for both sexes and all ages.

1.3. Diagnostic process

The diagnostic process usually begins with physical examination. Through palpation, any lumps around the head and neck area are easy to detect. In some cases, endoscopy may be required. Biopsy and laboratory tests are run to determine the nature of the tumor and identify specific biomarkers or causal factors, such as an HPV infection [31].

Initial imaging of the primary site to evaluate the malignancy is done with computed tomography (CT) of the soft tissues of the neck, or magnetic resonance imaging (MRI) of the neck. Unless contraindicated, the use of a contrast medium is required for both techniques. To ensure complete evaluation of the primary and detection of any nodal disease, imaging should be expanding from the skull base to the thoracic inlet. MRI is generally preferred over CT in patients with cranial nerve involvement or tumors that encroach upon the skull base, and oral cavity cancer patients with bone involvement, where it contributes to the evaluation of bone marrow invasion. CT on the other hand, is complementary to MRI in cases where evaluation of bony erosion or cartilage invasion exist [32]. Panoramic X-rays are part of the pre-radiation dental evaluation, assessing the health of the affected dentition and determining the necessity of pre-treatment dental procedures or extractions, in OSCC tumors with adjuvant radiotherapy planned.

Both CT and MRI are valuable techniques for the evaluation of nodal metastases, but FDG positron emission tomography (PET/CT scan) achieves the greatest acccuracy [32]. For tumors approaching the midline, the higher sensitivity of FDG PET/CT helps determine the contralateral neck dissection procedure. FDG PET/CT is also more sensitive to nodal involvement, especially in cases of locoregional or distant metastases. A meta-analysis of 18 studies, showed that the positive predictive value (PPV) and negative predictive value (NPV) of FDG PET/CT for detection of cervical lymph node involvement, in patients with clinically node-negative squamous cell carcinoma, was 0.62 (95% CI: 0.55 -0.69) and 0.83 (95% CI, 0.79–0.86), respectively, based on a patient-based analysis [33]. Its usage in evaluating distant disease and metastases for patients with locoregionally advanced cancer (e.g. T3–T4 primary or ≥N1 nodal staging) is conclusively established. If there is concern about metastasis to a specific anatomic area, then directed CT or MRI may also be done.

1.4. The AJCC TNM Staging Classification System for the Oral Cavity

The American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system is the simplest and most widely accepted system, introduced in 1987. It is based on tumor characteristics (T), nodal spread (N) and distant metastasis (M) and stages cancer prior treatment (cTNM), after surgery (pTNM) and at recurrence (rTNM). It helps clinicians stratify patients into prognostic groups, select the appropriate treatment strategy and evaluate the results of the treatment [34].

The 8th Edition of the AJCC Staging Manual, Head and Neck Section has been implemented since 2017, with changes targeting improved predictability. First of all, lip has been divided into cutaneous and mucosal and only mucosal lip is included in the oral cavity [34]. Changes in the oral cavity cancer staging lie in the T- and N- categories. For the T-stage of oral cancer, tumor size used to be the most important characteristic associated with worse survival as a predictor of neck recurrence. Depth of invasion (DOI), is a pathologic term defined as the distance from an adjacent normal mucosal line to the deepest point of cancer cells invasion [35], newly introduced into the T-category of the staging system as a better predictor of risk of nodal metastases, due to its ability of separating superficial tumors from smaller, deeply invasive ones with a worse prognostic profile. Extranodal extension (ENE), or extracapsular spread (ECS), defined as the lymph node metastasis which is extended beyond the capsule, infiltrating the surrounding stromal tissue with or without stromal reaction [36], was embodied into the N-category for its prognostic value [34,37].

The TNM Staging Classification for the Oral Cavity according to the 8th edition is followed in the international literature. Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included [38].

1.5. Treatment strategies

1.5.1. General guidelines

The management of patients with head and neck cancers is complex and multidisciplinary. Due to the nature of the disease and the plethora of therapeutic options, which more than often need to be combined, the collaboration of medical practitioners expertised in various areas is required [39]. Histological examinations need to be evaluated by a pathologist who reports to the head and neck surgeon and the radiation/medical oncologist. The major surgery is likely to be followed by a plastic/reconstructive surgery. For the management and prevention of complications after surgery, radiotherapy and systemic therapy (e.g. pain, lymphedema, xerostomia, dysphagia, severe weight loss, speech and swallowing problems, depression) the presence of professionals familiar with the disease is vital [40,41]. Dental care to prevent and treat radiotherapy effects should be offered, as well as fertility/reproductive counseling for the younger patients. The patient is taken under the care of dentists, nurses and dietitians, physiotherapists, speech and swallowing therapists and

psychiatrists to help control potential stress and depressive disorders, particularly during the process of smoking and alcohol cessation in case of history [42–46].

Symptoms affecting the most basic physiologic functions (breathing, chewing, swallowing etc.) as well as the external appearance, are expected to stand as an obstacle in the patient's struggle to maintain a good quality of life. Patients should always be asked to evaluate their health status, ability to function daily, and the effect such symptoms have on their psychological state [44,47]. All these factors should be considered thoroughly after diagnosis and during the course of treatment. Patients should be kept well-informed of the risks, benefits, and potential outcomes of treatment options and should be actively participating in the shared decision- making process [42].

All patients should be evaluated by a head and neck surgical oncologist prior treatment, to ensure that the biopsy material is adequate, to review staging and imaging to determine the extent of disease, to exclude the presence of a synchronous primary tumor, to assess current functional status and evaluate for surgical options available. Pre-treatment evaluation should always include consultations with a medical oncologist, radiation oncologist, dental oncologist, speech/language therapist, and reconstructive surgeon. This multidisciplinary team is obliged to discuss treatment options with the goal of maximizing survival. A prospective surveillance plan including adequate dental, nutritional, health behavioral evaluation and intervention, is necessary [39]. Combined modality therapy is generally recommended for approximately 60% of patients presented with locally or regionally advanced disease at diagnosis [39].

1.5.2. Neck dissection surgery

The resection of advanced tumors of the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinus will vary in extent depending on the structures involved. Resection should be planned based on the extent of the primary tumor [32].

Cervical (i.e. neck) lymph node dissections are classified as *radical* or *modified radical* procedures, with the less radical procedures preserving the sternocleidomastoid muscle, jugular vein, spinal accessory nerve, or selective lymph node levels. A radical neck dissection usually requires removal of 31 to 42 nodes, while a modified radical 6 to 13 less [48,49]. Nowadays, the surgical procedures are alternatively named *comprehensive* or *selective* respectively [50]. A *comprehensive* neck dissection is one that removes all lymph node groups that would be included in a radical neck dissection, justifying its recommendation as a therapeutic option for N3 disease, regardless of the preservation of the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve. *Selective* neck dissections have been designed based on the head and neck tumors metastasis pattern to regional nodes, often recommended for N0 disease depending on the site [51,52]. A selective neck dissection that includes the nodes found above the omohyoid muscle (levels I–III and sometimes superior parts of level IV), is recommended when the nodal metastases are attributed to primary tumors of the oral cavity (Figure 14) [2], [50,53]. Average nodal yield from level I to level V has been reported to be 6, 11, 12, 10, 12, respectively [48]. Squamous cell carcinoma without clinical nodal involvement, rarely presents with nodal metastasis beyond the confines of an appropriate selective neck dissection (<10% of the time) [54].

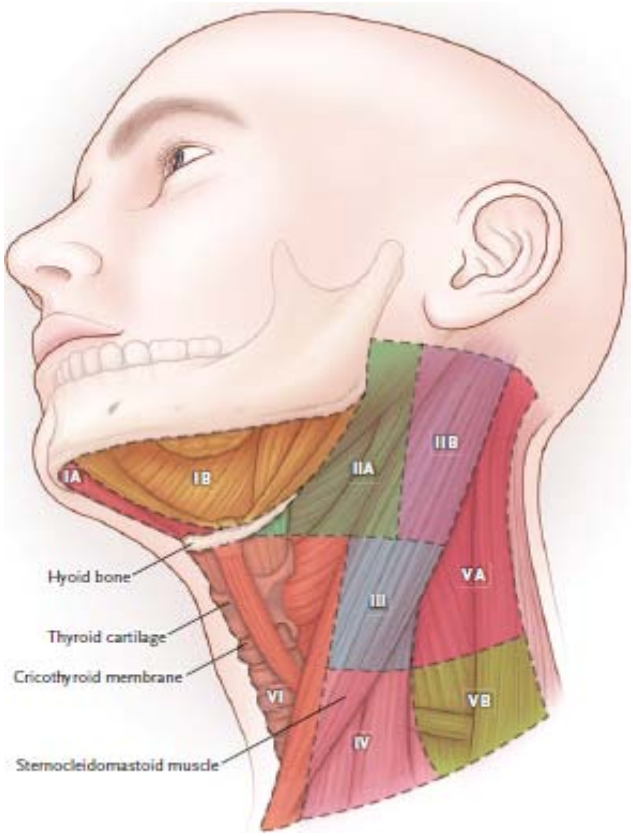

Figure 14. Lymph node levels of the neck [2].

When tumor burden is low, for instance in patients with N1 to N2 disease, selective neck dissection may prevent morbidity as opposed to comprehensive neck dissection and considered a treatment option [55–57]. Patients with cervical node metastases who undergo therapeutic surgery, are generally treated with cervical lymphadenectomy to remove all clinically positive nodes, other levels of the neck that may be at high risk for harboring metastasis, and non-lymphatic structures that are directly involved with cancer [58]. Patients undergoing surgery for resectionof the primary tumor will most probably undergo dissection of the ipsilateral side of the neck bearing serious risk for metastases. Tumor sites that frequently have bilateral lymphatic drainage (e.g. base of tongue, palate, supraglottic larynx, hypopharynx, nasopharynx) often should have both sides of the neck dissected. For patients with tumors approaching the midline, both sides of the neck are at risk for metastases, and bilateral neck dissections should be performed as well. Patients with advanced lesions involving the anterior tongue, floor of the mouth, or alveolus that approximate or cross the midline, should undergo contralateral selective/modified neck dissection to achieve adequate tumor resection [59].

The type of neck dissection (comprehensive or selective) is determined according to preoperative clinical staging (N0, N1, N2a-c, N3). Oncologic surgery aims at complete tumor resection with histologic verification of tumor-free margins, crucial for diminishing risk for local tumor recurrence [60].

1.5.3. Principles of radiotherapy

Radiation, either as primary or adjuvant treatment, despite its complexity, is a therapeutic approach often demanded by the disease profile. Modern techniques such as intensity-modulated radiotherapy (IMRT) or intensity-modulated proton therapy (IMPT) are constantly gaining the clinicians' appreciation for their precision.

Optimal radiation dose is dependent on the primary tumor, neck node size and clinical circumstances, e.g. potential use of concurrent systemic therapy. The dose may need to be decreased in areas putting adjacent organs at risk (e.g. brain, cochlea, optic chiasm and nerves, spinal cord). In these cases, precise target definition is vital, and on-treatment imaging should be used to ensure accurate radiation delivery. Anatomical changes (e.g. rapidly shrinking tumors, changes in air cavities, significant weight loss) may require repeated imaging and changes in the course of treatment [61].

Postoperative irradiation is recommended according to tumor features (e.g. stage, histology, and surgical-pathologic findings) for risk factors such as advanced T-stage, depth of invasion, multiple positive nodes, or perineural/lymphatic/vascular invasion. High doses of postoperative radiotherapy (e.g. 66 Gy) with or without addition of systemic therapy are generally recommended for high-risk features such as extranodal extension and positive margins, with a maximum time lapse between surgery and beginning of postoperative radiotherapy of 6 weeks. Postoperative radiation fractionation is usually set to 60–66 Gy at 2 Gy per fraction whether or not systemic therapy is added in the scheme [62–64].

However, no single fractionation schedule shows the same effectiveness on each tumor type. Squamous cell carcinoma can develop its own mechanisms of compensating for radiation-induced cell loss, promoting accelerated repopulation [65,66], requiring dosing of at least 1,000 cGy per week [67,68]. Conventionally fractionated radiation combined with concurrent systemic therapies is the most common treatment strategy followed. Most published studies have used conventional fractionation (at 2.0 Gy/fraction to a typical dose of 70 Gy in 7 weeks) with single-agent high-dose cisplatin (given every 3 weeks at 100 mg/m^2) [69]. Compared to radiation alone, addition of systemic therapy increases acute toxicity. The issue of long-term toxicity increase beyond that caused by radiotherapy alone is still under research [70–72]. Toxicity may be further increased by altered fractionation and/or multiagent systemic therapy. Chemoradiation should be performed by an experienced team providing every form of supportive care [73], keeping an accurate schedule of administration of a specific chemotherapy agent with a strictly defined dosage.

There is a need of modulating the intensity of the radiation beam in order to decrease doses received by normal structures, without compromising the doses targeted to the tumor site, addressed by modern technology using contemporary computer-based planning and radiation delivery [74,75]. Over the last 15 years, IMRT, a highly advanced form of CRT permitting more precise cancer targeting while reducing dose to normal tissues, has displaced older techniques in the treatment of most head and neck malignancies [76,77]. Overall survival may be similar between patients treated with IMRT and those receiving conventional 3D-RT [76], but both are superior to older 2D techniques, as shown by a prospective Korean study for survival outcomes. IMRT was associated with improved survival in multivariate analysis, particularly in T3–T4 tumors [78].

Another benefit from the use of IMRT stems from its long-term toxicity reducing properties. Xerostomia is a common long-term side effect of RT, which can be diminished with use of IMRT, drug therapy (e.g. pilocarpine, cevimeline), salivary substitutes, and other novel approaches (e.g. surgical relocation of submandibular gland) [79–82]. IMRT also reduces other long-term toxicities due to decreased radiation doses sent to structures such as pharyngeal constrictors, larynx, temporal lobes, mandible, auditory structures (including cochlea), and optic structures [83–86]. Patients who received IMRT had a shorter duration of feeding tube placement, compared to those who received 3D-RT ($p = 0.03$) [87].

Proton therapy has been also used in challenging conditions for which other radiotherapy options were not considered safe or beneficial enough [88,89], currently established as the number one particle therapy under research in the United States.

Data considering proton beam therapy (PBT) comes mainly from non-randomized institutional reports and a small number of systematic reviews [90,91]. However, occasional fatal outcomes have been reported with proton therapy from time to time, including a number of deaths occurring after episodes of brainstem injury [92,93]. Without high-quality prospective comparative data and controlled randomized clinical trials with large sample sizes, it is premature to underline the PBT's superiority to other modern radiation techniques such as IMRT.

For patients whose cancer has been treated with radiotherapy of any kind, the recommended follow-up should include assessment of thyroid function, physical examination, symptom assessment and supportive care, and/or imaging. Thyroid-stimulating hormone (TSH) levels should be determined every 6–12 months. Changes in TSH may be an indicator of thyroid gland dysfunction, or hypopituitarism, if the skull base was irradiated [94–96].

1.5.4. Principles of systemic therapy

Treatment that includes systemic therapy is recommended for locoregionally advanced and metastatic disease of the head and neck. Randomized trials and meta-analyses have shown significantly improved overall survival, disease free survival and locoregional control when a systemic therapy and radiotherapy regimen (concomitant or sequential) is compared to radiotherapy alone, in cases of locally advanced disease.

A combination of high-dose cisplatin plus radiotherapy, with conventional fractionation at 2.0 Gy per fraction to 70 Gy, administered over 7 weeks with concurrent cisplatin 100 mg/m^2 given every three weeks for up to 3 doses, is the most studied effective scheme [64,97]. Low-dose once-a-week administration of cisplatin has been studied, because in this way toxicity levels are kept low. A randomized phase III trial, with locoregional control as the primary outcome, compared adjuvant treatment of cisplatin 30 mg/m^2 given once weekly, to high-dose cisplatin, with concurrent radiotherapy, to patients with locally advanced squamous cell carcinoma of the head and neck. The 2-year locoregional control rate was 58.5% in the weekly cisplatin arm and 73.1% in the high-dose cisplatin arm ($p = 0.014$). Acute toxicities of grade 3 or greater were less common in the weekly arm compared to the high-dose cisplatin arm (71.6% vs. 84.6%, $p = 0.006$) [98].

Epidermal growth factor receptor (EGFR) overexpression, as in many malignancies, is a common feature of squamous cell carcinoma of the head and neck, and a causal factor of poor prognosis [99]. EGFR inhibitors have been evaluated [100].

Induction chemotherapy, administration of chemotherapy prior definitive surgery or radiotherapy, has gained interest regarding the management of locally advanced squamous cell carcinoma of the head and neck, for various reasons. Induction chemotherapy permits greater drug delivery to fight distant metastases, a major cause of treatment failure [101], and in contrary to concurrent systemic therapy/radiotherapy, the long-term safety profile seems to be better [102]. Docetaxel, a taxane, with cisplatin/5-FU is a category one preferred recommendation for induction chemotherapy [103]. Other induction chemotherapy regimens have been evaluated as well, mainly in phase II trials, without encouraging results [104], [105]. Induction chemotherapy with subsequent radiotherapy could provide an alternative against morbid surgery, preserving organs and patients' quality of life. The Veterans Affairs (VA) Laryngeal Cancer Study Group trial [106] in advanced larynx cancer, established the role of induction cisplatin/5-FU followed by definitive radiotherapy in responding patients as an alternative treatment to total laryngectomy and postoperative radiotherapy.

However, research continues to highlight concurrent systemic therapy/radiotherapy (mainly high-dose cisplatin), as the gold standard, by offering superior locoregional control and overall survival compared to radiotherapy alone and shorter duration of therapy compared to induction therapy followed by radiation. The Intergroup 91-11 trial compared three treatment arms (radiotherapy alone, concurrent cisplatin/radiotherapy, and induction cisplatin/5-FU followed by radiotherapy) in patients operated for locally relapsed/refractory laryngeal cancer. The concurrent cisplatin/radiotherapy arm had the highest larynx preservation rate [107]. Long-term follow-up of this trial confirmed that concomitant systemic therapy/radiotherapy improved the larynx preservation rate and induction chemotherapy was not superior to radiotherapy alone. Overall survival remained similar among the three treatment arms [108]. Conclusions are expected to be further established after more and larger clinical trials are conducted.

1.5.5. Principles of supportive care

Nutritional management is vital to improve outcomes and to minimize significant treatment-related complications in head and neck cancer patients [109]. All patients should receive nutritional evaluation before and after treatment to assess the need for interventions , such as enteral support via feeding nasogastric (NG) tubes, percutaneous endoscopic gastrostomy (PEG) tubes, or intravenous nutrition support [110]. High-risk patients are expected to benefit significantly from prophylactic tube placement [110,111]. Reactive feeding tube placement, in which patients are first given oral nutrition supplements followed by enteral feeding, should be considered for patients with a weight loss of 5% or more in 1 month, for those with severe dysphagia (grade 3+) and those older than 60 years of age [112,113]. All patients should receive dietary counseling with the initiation of treatment and regular follow-up should continue until nutritional stability is achieved [109].

Oral mucositis is an inflammation common in patients treated with radiotherapy or concurrent systemic therapy/radiotherapy. It negatively affects quality of life by causing pain in the mouth while eating or drinking and during swallowing, also associated with absence from treatment schedules, as well as hospitalization [114]. As clinically indicated, the administration of doxepin, diphenhydramine-lidocaine-antacid mouthwash, or gabapentin is recommended for pain related to oral mucositis [115].

Treatment and disease progression often cause deterioration in speaking and swallowing, justifying the necessity of a formal speech and swallowing evaluation at baseline, including assessment for any changes in speech and communication, taste, assessment for xerostomia, pain and trismus. Patients with ongoing abnormal function should be seen regularly by speech-language pathologists and follow-up should continue at least until the patient has achieved a stable baseline following treatment [116–118].

Head and neck cancer patients are at risk of oral and dental complications after surgery or radiotherapy, because of treatment-induced xerostomia and salivary gland dysfunction [114,119]. Radiotherapy to the salivary and oral soft tissues is also associated with bone demineralization and trismus of the masticatory muscles. IMRT, dose limitation to the salivary glands and oral cavity, are measures associated with gradual recovery of salivary function over time and with reduced risk for dental caries [120,121]. Dental and oral evaluation can help decrease dental caries and arising problems such as dentoalveolar infection and osteoradionecrosis [114,121].

Dental and oral evaluation, including a complete oral and head and neck examination, considering past dental history, existing periodontal and dental conditions, with radiographs of all teeth, is a prerequisite for the beginning of radiotherapy. Patients should be informed regarding complications of radiotherapy upon teeth and the oral cavity and be motivated to comply with preventive protocols [122]. The plan that needs to be implemented before radiotherapy should include: 1) eliminating potential sources of infection; 2) if performing dental extractions, allowing adequate time (at least 2 weeks) for healing before treatment [123]; 3) treating active dental caries and periodontal disease; 4) treating oral candidiasis with antifungal agents; and 5) if patients have metal restorations, the use of silicone guards to minimize radiation backscatter is mandatory [124].

Some of the general strategies to decrease oral and dental complications include: 1) decrease dry mouth by increasing hydration, avoiding ingestion of caffeinated products, using salivary substitutes (e.g. gels containing lysozyme, peroxidase), stimulating saliva production by administering xylitol chewing gum/lozenges or cholinergic agonists (e.g. pilocarpine, cevimeline) when indicated [125,126]; 2) reduce risk of dental caries with diet counseling, recommendation for a meticulous oral hygiene (e.g. brushing teeth twice daily, using interdental cleaner, alcohol-free mouthwash and high potency topical fluoride) [127,128]; 3) decrease dentoalveolar infection with frequent evaluations; 4) prevent and address osteoradionecrosis; 5) prevent and control candidiasis with topical or systemic antifungal therapy [124]; 6) decrease trismus of the masticatory muscles (e.g. by using custom mouth-opening devices to maintain range of motion) [129,130]; and 7) have patient undergo evaluations during and after treatment to help minimize complications [131].

1.6. Lymph node ratio (LNR) and scope of study

Research has shown that during clinical examination, almost half of OSCC patients are diagnosed with nodal metastasis [132,133]. Lymph node metastasis is the strongest prognostic factor in oral cancer, since neck involvement is typically associated with drastically reduced survival. The size, number and distribution of metastatic nodes have been reasonably incorporated in the AJCC Staging System [38].

The probability of identifying metastases though, relies on the expertise of surgeons and pathologists, since identification itself is based on the quality of neck dissection and sampling procedure. The total number of lymph nodes retrieved from a neck dissection surgery, important for staging and disease eradication, is referred as lymph node yield (LNY), which grossly depends on the adequacy of the neck dissection [132]. LNY is higher in cases of modified radical or radical dissections, where mostly LNY is greater than 30 [134]. However, there is no consensus on the actual threshold of nodal yield for each type of neck dissection and among institutions, practice can vary [135]. There are also cases, mainly concerning patients with N3 status, where during pathological examination of the surgical specimens, sometimes it can't be precisely specified if there is one large infiltered lymph node or multiple lymph nodes involved [133]. The number of positive nodes identified reflects the extent and burden of disease spread. Since pathological nodal involvement derives from total nodal yield, and as a consequence depends on the surgical procedure, a low value of positive nodes, especially after a selective neck dissection, might give a false estimation of the actual extent of disease and the likelihood of residual micrometastases increases [136]. Determination of the size of metastatic nodes and presence of extranodal extension rely on the quality of pathological specimens procession.

The factors mentioned above probably explain why N-stage was not a significant predictor of disease progression in a number of studies, including an international, multicenter one [132]. The need to improve the current staging system by proposing integration of alternative prognostic factors, set researchers' attention on lymph node ratio (LNR), or lymph node density (LND), an already well described prognostic factor for colorectal [137,138] and breast cancer [139]. This factor equals the ratio of positive lymph nodes to the total number of nodes excised [133] and thus takes into account the parameters of both disease regional spread and surgical procedure, eliminating the risk of bias introduced by sampling method.

This ratio is of interest when investigated as a dichotomous categorical variable, according to a cut-off value determined through ROC-curve analysis or calculated from individual patient data measurements [135]. The purpose is to stratify patients into high and low risk groups based on the distance of individual LNR values from the specified cut-off and design the appropriate treatment scheme accordingly. Numerous LNR cut-offs have been investigated for their association with survival outcomes. A study combining data from 11 centers worldwide [132] proposed a cut-off point of 0.07, meaning that 14 nodes would have to be retrieved from a patient for one node to be pathologically confirmed as positive. Multivariate analysis showed that patients with LNR values exceeding 0.07 were faced with a 70% greater risk of worse overall survival compared to patients with lower values. Furthermore, in multivariate analysis LNR was proven a more potent prognostic factor than the conventional N-staging system, for all survival outcomes.

The present study is a systematic review of the literature researching the impact of lymph node ratio on the survival of node-positive and node-negative oral squamous cell

carcinoma patients, and a statistical synthesis of the results for meta-analysis. The scope is to help establish LNR as an independent prognostic factor, eliminating any confounding relationships, for its future incorporation into staging systems. Hopefully, patients' risk stratification will gain more accuracy and a proposed cut-off will effectively guide surgical and adjuvant treatment plans to ensure a better survival.

2. Materials and Methods

2.1. Study protocol and eligibility of individual studies

The present systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [140]. The PRISMA Statement consists of a 27-item checklist, presented in Supplementary Table 1, that includes items essential for transparent reporting of a systematic review. The objectives and methods were prespecified in a study protocol, that was discussed and agreed upon in advance by all authors, to eliminate the likelihood of biased *post hoc* decisions. The study protocol was designed and agreed upon from all authors and submitted to PROSPERO International Prospective Register of Systematic Reviews.

To ensure that studies are selected in a systematic and unbiased manner, study eligibility criteria including the populations, interventions, comparators, outcomes, and study designs of interest (PICOS) were formulated *a priori*, in the protocol. The chosen population consisted of patients with oral cancer who had undergone neck dissection. Neck dissection, either selective, modified radical, radical or bilateral, was the intervention. The comparison of interest was high versus low lymph node ratio, and the outcome the survival of patients (overall survival, disease-specific survival, disease-free survival, recurrence-free survival, locoregional disease-free survival, local recurrence-free survival, distant metastasis-free survival). Research was focused on observational studies (cohort, retrospective cohort, case-control) and experimental studies (RCTs, non RCTs). Case reports, case series, reviews and meta-analyses were excluded. All studies should report that the entire patient cohort has oral cancer and a neck dissection surgery is performed and the survival data should be presented by measurements of the lymph node ratio as a dichotomous categorical variable. No evidence of pre-operative radiation or chemotherapy administered should be found. In case of overlapping study populations, only the larger study was included. The selection of studies was performed by two reviewers (ZG, AK), working independently, and any disagreements were resolved following consultation with a senior author (TNS) and team consensus.

2.2. Search strategy

A systematic search was conducted in PubMed, Google Scholar, Cochrane, EMBASE and ClinicalTrials.gov for identification of potentially missing studies, and other sources (OpenGrey) for the tracing of unpublished material (unpublished dissertations, conference presentations). As far as publication language is concerned, no restriction was implemented. End-of-search date was the 20th of December 2020. The search strategy of eligible studies in PubMed, without any language restriction, included the following keywords:

((node OR nodal) AND (ratio OR density)) AND oral AND (carcinoma OR carcinomas OR cancer OR cancers OR neoplasm OR neoplasms OR malignant OR malignancy) AND (Prognosis OR Prognostic OR Outcome OR fatal OR OS OR mortality OR fatality OR death OR survival OR PFS OR DFS OR DSS OR progression OR TTP OR EFS OR recurrence OR LRF)

There were no limits applied to the search. The search algorithm was rather broad, so as to maximize the number of articles to be scrutinized, aiming to uncover any hidden (i.e. not apparent in the abstract) information in the full text and tables of articles.

2.3. Data abstraction and effect estimates

The abstraction of data included general information (first author's name, study year, PMID), study characteristics (study design, time period, geographical region, median follow-up period, cohort size), categorization of exposure (oral cancer subsite and LNR cut-off determination) and intervention (type of neck dissection), characteristics of participants [age of participants (mean, range), ethnicity, percentage of males, percentage of patients under each TNM-classification (metastasis was defined as a binary categorical variable under yes or no), classification into treatment groups (surgery alone, surgery plus radiotherapy and surgery plus chemoradiotherapy)], definition of endpoints as well as adjusting factors regarding multivariate analyses. If the required data for the meta-analysis was not readily available in the published article, the corresponding authors were to be contacted twice (a reminder e-mail following the first one after seven days). It was necessary to contact the authors in one case [141], where the number of patients with high and low LNR values was required and not provided in the published article. Unfortunately, no response was received and the study was excluded from the analysis. Data was extracted, analyzed and recorded in duplicate in a pre-developed data extraction sheet by two independent reviewers (ZG and AK), using Excel software. Disagreements were resolved and final decision was reached after consultation with a senior author (TNS) and team consensus. If multiple publications by the same authors existed, the articles were checked for overlapping patient pools among studies to avoid introduction of bias by multiple data entry. In such cases, the largest sample size was chosen.

The maximally adjusted types of effect estimate, hazard ratios (HRs) with their 95% confidence intervals (95% CIs), were extracted from each cohort study by category of lymph node ratio (high versus low LNR). If the 95% CI did not overlap the value 1, a HR of >1 would indicate a worse prognosis. When more than two LNR cut-off categories were present, the lowest cut-off was chosen for that study. When the adjusted hazard ratio was not available, by provision of the number of patients under each LNR category and survival data,

crude effect estimates, relative risks (RRs) and 95% CIs were calculated by means of 2x2 tables.

2.4. Statistical analyses

Statistical analyses included pooling of studies as well as *a priori* meta-regression. Separate analyses were performed based on type of survival outcome and statistical synthesis was performed in case of two or more eligible study arms. *A priori* subgroup analyses according to the different LNR cut-offs used, were also performed. The category of high lymph node ratio was compared with the one corresponding to the low lymph node ratio, node-negative patients not excluded. Random-effects (DerSimonian–Laird approach) models were appropriately used to calculate pooled effect estimates and the corresponding 95% CIs. The random-effects model assumes that there is no common treatment effect for all included studies but rather that the variation of the effects across studies follows a particular distribution. It is believed that the included studies represent a random sample from a larger population of studies addressing the question of interest [140]. Heterogeneity is expected due to differences between subgroups of studies, as definition of endpoints vary and different LNR cut-offs are used. Between-study heterogeneity was assessed by estimating I^2 , that represents the percentage of the total variation in estimated effects across studies that is due to heterogeneity rather than to chance, and the *p*-value from the Mantel-Haenszel Q-test [140]. A value of I^2 greater than 50% and a *p*-value <0.05 point out significant heterogeneity .

Meta-regression examines the quantitative influence of study characteristics on the effect size and allows authors to examine the contribution of different variables to the heterogeneity in study findings [140]. Meta-regression analysis was performed in cases of 10 or more pooled study arms and aimed to assess whether gender (expressed as a 10% increase of percentage of males in the individual studies), age (expressed as a 10-year increase of the mean age in the individual studies), percentage of each cancer subsite (expressed as a 10% increase in the individual studies), percentage of radical dissection (expressed as a 10% increase in the individual studies), percentage of extracapsular spread (expressed as a 10% increase in the individual studies), percentage of positive margins (expressed as a 10% increase in the individual studies), percentage of administered radiotherapy (expressed as a 10% increase in the individual studies), percentage of administered chemotherapy (expressed as a 10% increase in the individual studies), median number of nodes removed (expressed as 1 node increase in the individual studies), median number of positive nodes removed (expressed as 1 positive node increase in the individual studies) and publication year (expressed as 1-year increase in the individual studies) modified the association between higher lymph node ratio values and worse prognosis.

To determine whether LNR can be characterized as an independent prognostic factor, subanalyses by degree of adjustment (multivariate versus univariate analysis) under each survival outcome were also performed. Statistical analysis and meta-regression analysis were performed using STATA/SE version 13 (Stata Corp, College Station, TX, USA).

2.5. Assessment of within-study quality and publication bias

As far as the risk of bias is concerned, the Newcastle-Ottawa Quality scale was used to evaluate the quality of the included non-randomized studies [142]. Regarding the items assessing the completeness (adequacy) of follow-up of cohorts and whether the follow-up period was long enough for outcomes to occur, the cut-off values were set *a priori* at 90% response rate and 2 years, respectively. Study quality was considered "low" when the Newcastle-Ottawa score (NOS) ranged between 1-3, "intermediate" for studies with NOS between 4-6 and "high" for those with a score between 7-9. Two independently working reviewers (ZG, AK) rated the studies and, in case of disagreement, final decision was reached after consultation with a senior author (TNS) and team consensus.

Publication bias was evaluated in the analyses that included 10 or more study arms. Egger's statistical test was implemented as well as a visual inspection of the funnel plot for asymmetry, which can result from the non-publication of small studies with negative results or small studies that tend to show larger estimates of the effects of the intervention [140]. For the interpretation of Egger's test to see if the effect decreased with increasing sample size, statistical significance was defined as $p<0.1$. The evaluation of publication bias was performed using STATA/SE version 13 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Description of study selection process

A total of 2,155 records were identified (806 from Pubmed, 74 from EMBASE, 185 from Cochrane Library and 90 from ClinicalTrials.gov), using the search algorithm, with the first 1,000 hits of Google Scholar also screened. No records of unpublished literature were identified through OpenGrey. After duplicates were removed, out of 1,081 records, 796 titles were considered irrelevant and finally 285 abstracts were screened. Reference lists of reviews and eligible articles were also systematically searched for relevant articles in a "snowball" procedure. 233 were excluded as irrelevant to the topic or because of absence of full-text. 52 full-text articles were retrieved and assessed for eligibility, with the justified exclusion, after critical appraisal of the full-text publications, of 20 articles for not meeting the eligibility criteria, data overlap or missing data and insufficient analysis. The studies excluded are analytically presented alongside with the reasons for exclusion in Table 1. 32 studies were finally included in the qualitative synthesis, with the 20 of those analyzing both node-positive and node-negative oral cancer patients eligible for meta-analysis. The whole study selection process is graphically presented in the flow chart (Figure 15).

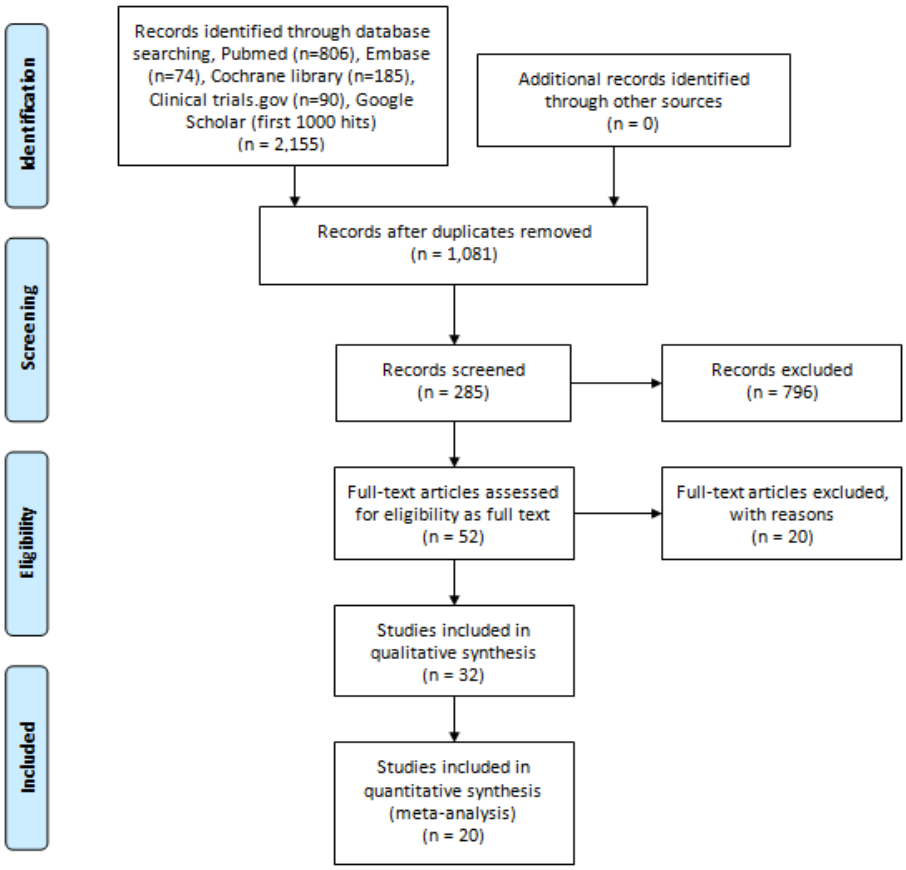

Figure 15. PRISMA Flow Diagram.

Table 1. Excluded studies, with reasons (continued).

Author	Year	PMID	Reasons for exclusion
Adel et al. [143]	2016	27057838	Data overlap with paper including similar analysis from ICOR database (Patel et al., 2013)
Amar et al. [144]	2012	22714852	Insufficient data analysis with no hazard ratios (HRs) provided as effect estimate
Chen et al. [145]	2015	26302761	No separate analysis for oral cancer
Faisal et al. [146]	2020	33236214	Insufficient data, multivariate analysis with LNR=0 as reference and the number of patients under each LNR category was not provided
Feng et al. [147]	2017	28751709	No separate analysis for oral cancer

Hingsammer et al. [148]	2019	30738712	Multivariate analysis with insufficient survival data and no HRs
Iocca et al. [149]	2020	32380357	Oral cancer as reference group in multivariate analysis and no association investigated between LNR and survival
Kim KY et al. [150]	2012	22193423	Data overlap with more recent paper by the same author (2017)
Kim KY et al. [141]	2017	27588367	Insufficient data, multivariate analysis with LNR=0 as reference and the number of patients under each LNR category was not provided - Unsuccessful attempts to contact the authors
Liao et al. [151]	2012	22104249	Data overlap with paper including similar analysis from ICOR database (Patel et al., 2013) and use of multiple LNR cut-off points according to neck dissection levels
Mascitti et al. [152]	2018	30217459	Insufficient data analysis with no HRs and 95% CIs provided
Noble et al. [153]	2016	26851040	Insufficient data analysis with no 95% CIs provided in the multivariate analysis and absence of Kaplan - Meier curves for LNR
Roberts et al. [154]	2016	26969807	No separate analysis for oral cancer
Safi et al. [155]	2017	28981183	Patient data included in a larger cohort investigated around the same time (Safi et al., 2017)
Safi et al. [156]	2017	28529103	Patient data included in a larger cohort investigated around the same time (Safi et al., 2017)
Safi et al. [157]	2018	29709331	Patient data included in a larger cohort investigated around the same time (Safi et al., 2017)
Sayed et al. [158]	2013	23893514	Data overlap with paper including similar

			analysis from ICOR database (Patel et al., 2013)
Shrime et al. [159]	2009	19340867	Includes patients who received preoperative radiation
Troeltzsch et al. [160]	2018	30098956	LNR is investigated as a continuous variable
Zirk et al. [161]	2018	29249633	Data overlap with study investigating a larger cohort (Safi et al., 2017)

3.2. Characteristics of the eligible studies

The abstraction of data is presented in Supplementary Tables 2 and 3. Data concerning more general information about the included studies is shown in Supplementary Table 2, while treatment-, tumor- and LNR-related information is presented in Supplementary Table 3. Studies in bold analyzed both node-positive and node-negative patients and were eligible for meta-analysis.

The included articles were published between 2009 and 2020. Most studies followed the retrospective cohort design, with the exception of three prospective ones [162–164]. There was only one multicontinental study, with 11 centers worldwide, conducted by Patel et al. [132]. 17 studies took place in Asia and the rest in Europe, USA or Canada and Australia. The patients' pool ranged between 35 and 4,254, with a total patient pool of 20,994. The mean age ranged between 47 and 70 years and more than half of the sample size of each study consisted of male patients. A median follow-up of around 2 years or greater, long enough for outcomes to occur, was seen in every study. The most frequent outcome measured was overall survival (OS), followed by disease-specific survival (DSS), disease-free survival (DFS), locoregional disease-free survival (LRDFS), distant metastasis-free survival (DMFS), local recurrence-free survival (LRFS) and recurrence-free survival (RFS).

The majority included tumors from all sites of OSCC, with tongue being the most common subsite. Four studies focused solely on tongue [162,165–167] and one on buccal mucosa [168]. The LNR cut-off points used in the studies ranged from 0.012 to 0.2 and the values were mainly determined via ROC-curve analysis or according to previously published literature. The median total lymph node yield ranged from 19 to 42.5 and the median number of positive nodes from 0 to 3.4 (Supplementary Table 4). Extracapsular spread and close or involved margins were reported in the majority of studies (Supplementary Table 4).

3.3. Meta-analysis

Since the prognostic value of LNR was to be investigated in patients with and without nodal involvement, 12 out of the 32 studies comprising the qualitative synthesis that limited their analyses to node-positive patient pools [132,133,136,162,164,166,168–173], were excluded from meta-analysis. Research focused on comparing the survival of a group of patients with LNR values greater than the specified cut-off (high LNR group) versus a group formed by the sum of patients with LNR values lower than the specified cut-off and those with LNR=0 (low LNR group) in each study. The effect estimate was preferred to be reported as adjusted hazard ratio (HR) with 95% confidence interval (95% CI), resulting from multivariate analysis. In several studies [167,174–181] the results of the multivariate analysis referred to a comparison of high- and low-LNR patients versus node-negative ones (LNR=0). In such cases, when the number of patients under each category was provided, data was synthesized to form the groups of interest. Time-specific survival data resulting from univariate analysis helped define the surviving and non-surviving populations of the high- and low-LNR groups at the time-point given. Data was organized in 2x2 tables and crude effect estimates, relative risks (RRs) with 95% CIs, were calculated.

Overall, 20 studies were eligible for meta-analysis, with a total of 11,701 patients [163,165,167,174–190]. The identified endpoints were overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), locoregional disease-free survival (LRDFS), distant metastasis-free survival (DMFS), local recurrence-free survival (LRFS) and recurrence-free survival (RFS). Distant failure (DF), referred by Hosni et al. [176], was considered a nominal variation of DMFS, by the definition provided by the authors (Table). Similarly, locoregional recurrence (LRR) referred by Safi et al. [187], is of the same clinical interpretation as LRDFS (Table). LRFS was reported by a single study only, Zhao et al. ($HR_{high\ vs\ low}$: 2.02; 95% CI: 1.4-2.92) [190]. As a result, it was excluded from the quantitative synthesis. RFS, reported by Son et al. ($HR_{high\ vs\ low}$: 5.79; 95% CI: 3.11-10.79) [163], was excluded too for the same reason. Both studies pointed out the increased risk of patients with higher LNR values, with statistical significance.

18 studies were included in the statistical synthesis for the outcome of overall survival (Figure 16). Patients with high LNR values have double likelihood of worse prognosis compared to patients with low LNR values (Table 2), with statistical significance (pooled RR:2.38; 95%CI: 1.99-2.85). Considerable heterogeneity existed among the studies for OS (I^2 : 82.6%, $p<0.001$).

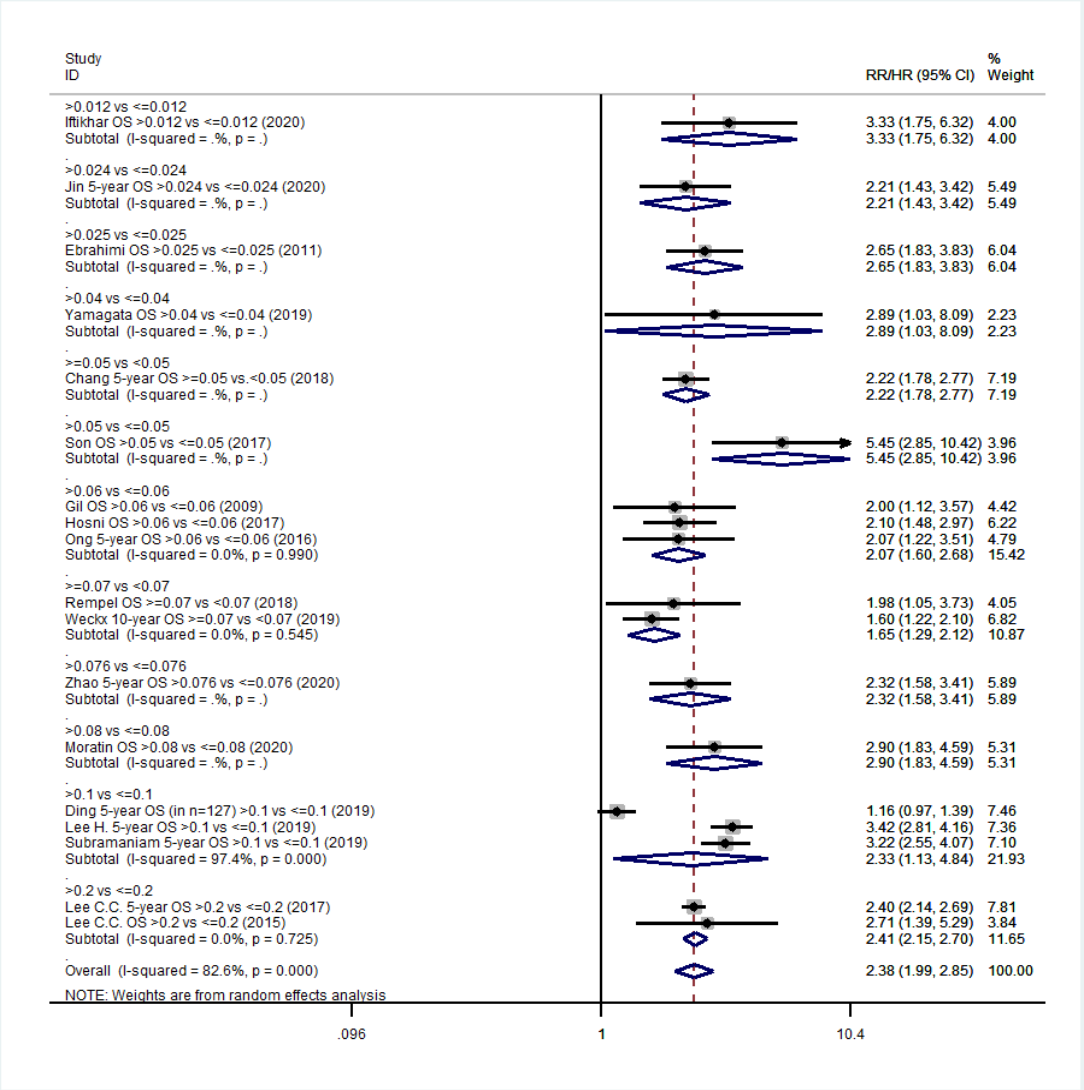

Figure 16. Forest plot describing the association between lymph node ratio (LNR) and overall survival. Apart from the overall analysis, the subanalyses by LNR cut-off values are presented.

Pooling of 7 studies (Figure 17) also exhibited a burdening effect of higher LNR values on disease-free survival (Table 2), again achieving statistical significance (pooled RR:2.04; 95%CI: 1.48-2.81). Heterogeneity was considerable in this case as well (I^2 : 93.2%, p<0.001).

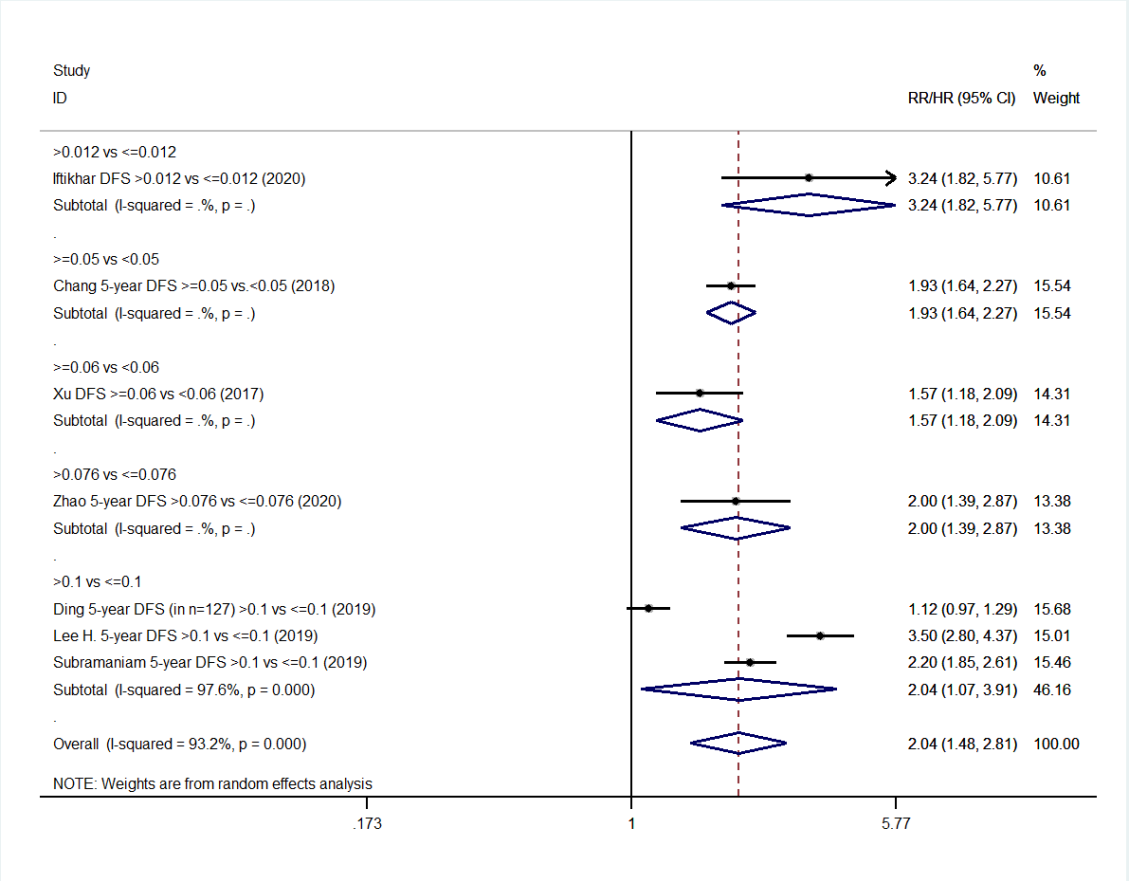

Figure 17. Forest plot describing the association between lymph node ratio (LNR) and disease-free survival. Apart from the overall analysis, the subanalyses by LNR cut-off values are presented.

Pooled analysis of 8 studies (Figure 18) on disease-specific survival indicated a relative risk of 2.90 (95%CI: 2.35-3.57) when comparing patients with high LNR values to those under the low LNR category (Table 2), with substantial heterogeneity (I^2 : 61.2%, p=0.012).

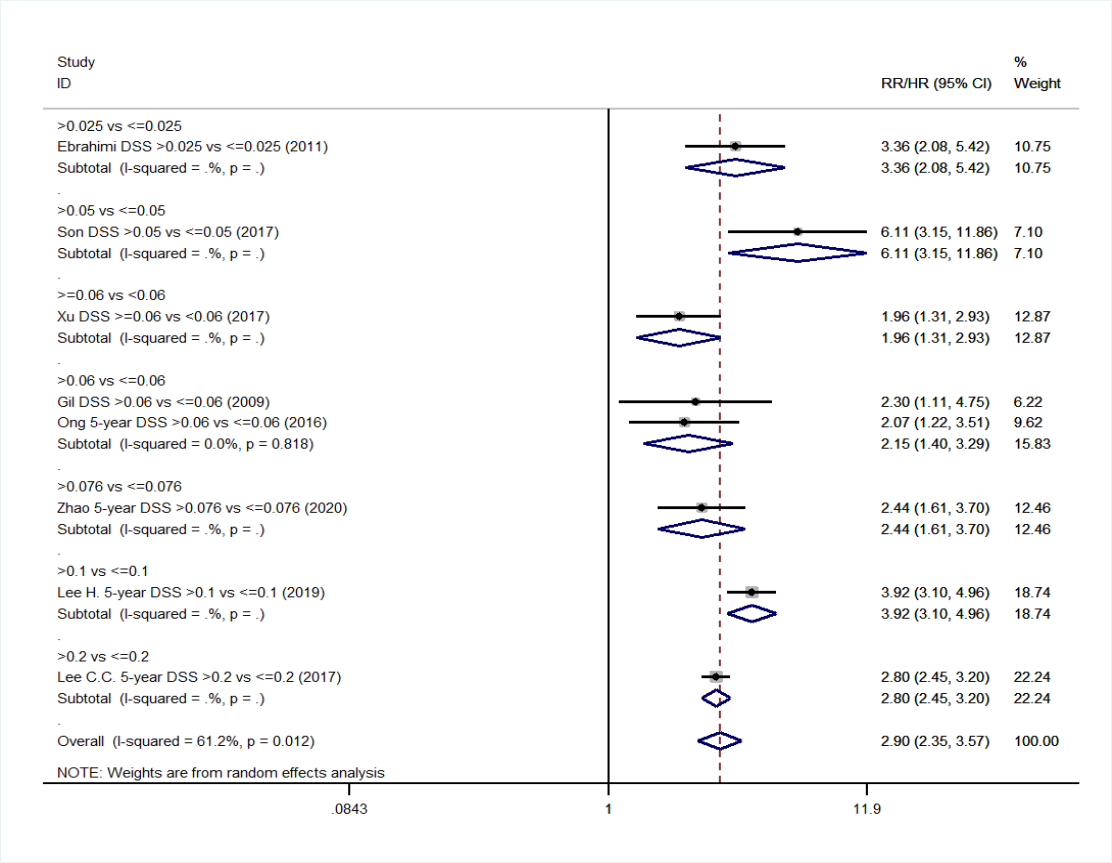

Figure 18. Forest plot describing the association between lymph node ratio (LNR) and disease-specific survival. Apart from the overall analysis, the subanalyses by LNR cut-off values are presented.

As far as locoregional disease-free survival and distant metastasis-free survival are concerned (Figures 19, 20), synthesis of 3 study arms for each outcome resulted again in a relative risk greater than 1 (pooled RR_{LRDFS}:1.88 and pooled RR_{DMFS}:2.11), but without statistically significant associations (95%CI: 0.83-4.25 for LRDFS and 95%CI: 0.97-4.63 for DMFS). Substantial heterogeneity was observed (Table 2) regarding LRDFS and considerable regarding DMFS (I^2 : 72.4%, p=0.027 and I^2 : 94%, p<0.001, respectively).

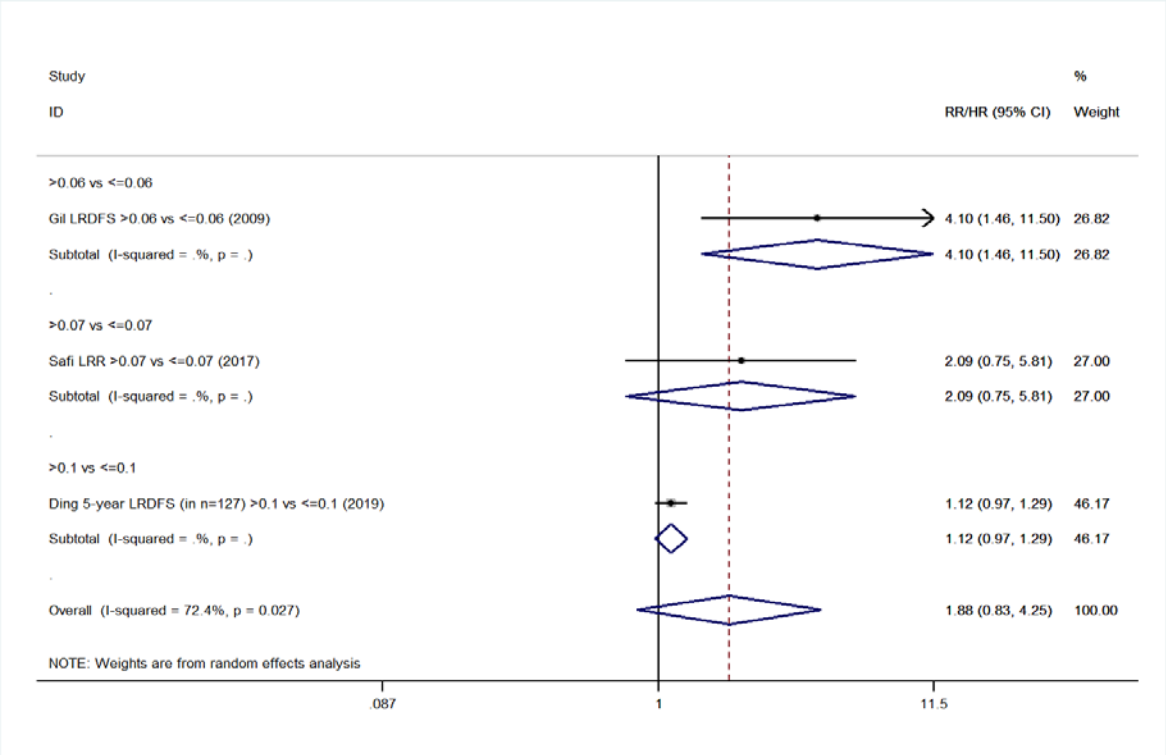

Figure 19. Forest plot describing the association between lymph node ratio (LNR) and locoregional disease-free survival. Apart from the overall analysis, the subanalyses by LNR cut-off values are presented.

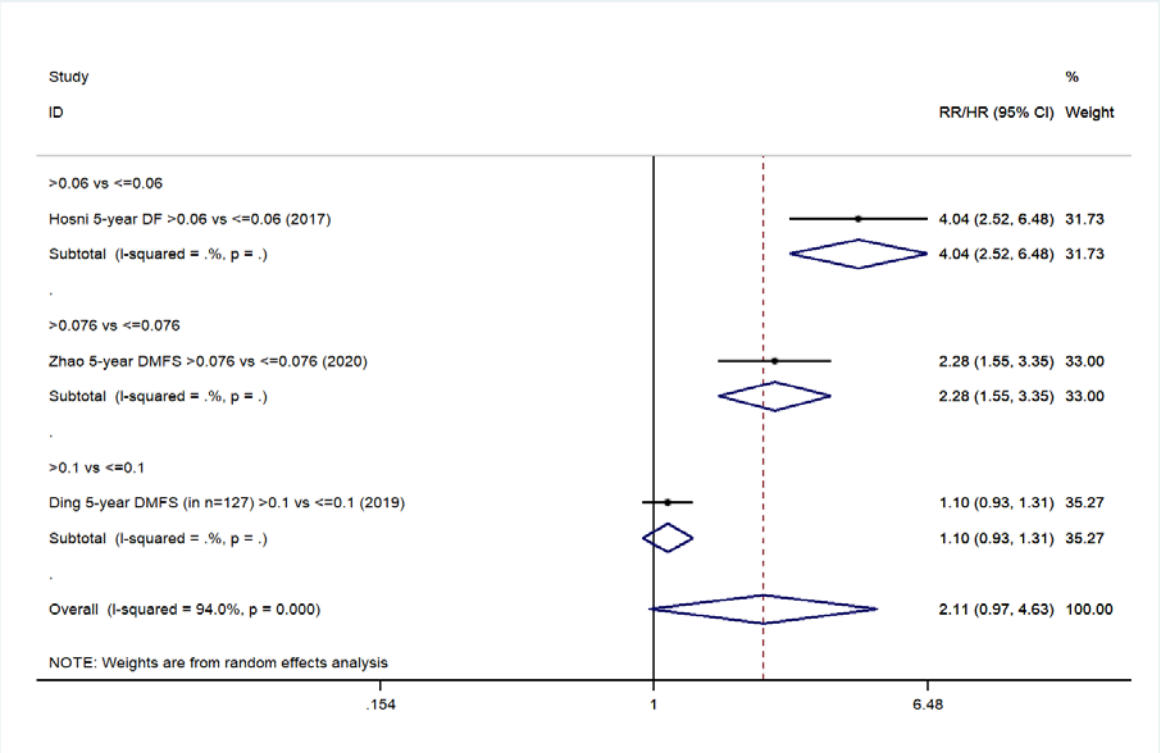

Figure 20. Forest plot describing the association between lymph node ratio (LNR) and distant metastasis-free survival. Apart from the overall analysis, the subanalyses by LNR cut-off values are presented.

Table 2. Results of the meta-analyses examining the association between lymph node ratio (LNR) and survival outcomes; subgroup analyses by LNR cut-off values are presented. Bold cells denote statistically significant associations.

	Studies analyzing patients with positive and negative lymph nodes		
	n§	RR (95% CI)	Heterogeneity I^2, p
Overall survival (OS)	18	**2.38 (1.99-2.85)**	82.6%, <0.001
Disease-free survival (DFS)	7	**2.04 (1.48-2.81)**	93.2%, <0.001
Disease-specific survival (DSS)	8	**2.90 (2.35-3.57)**	61.2%, 0.012
Recurrence-free survival (RFS)	1	Only 1 study	NC
Locoregional disease-free survival (LRDFS)	3	1.88 (0.83-4.25)	72.4%, 0.027
Distant metastasis-free survival (DMFS)	3	2.11 (0.97-4.63)	94%, <0.001
Local recurrence-free survival (LRFS)	1	Only 1 study	NC

§number of studies; RR: relative risk

3.4. Meta-regression analysis

Meta-regression analysis was planned in case of 10 or more pooled study arms, criterion met by the analysis of overall survival alone. The results of the meta-regression analysis for the outcome of overall survival are presented in Table 3. Percentages of lip, alveolus, retromolar trigone, gingiva and hard palate tumors were reported as variables in an amount of less than 10 studies, so their role as potential modifiers in the association between LNR and overall survival could not be investigated. Increasing percentage of males, mean age of study, percentage of buccal mucosa and floor of mouth tumors, percentage of radical dissection, extracapsular spread, positive margins, administered radiotherapy, administered chemotherapy, increasing median number of total and positive nodes removed and year of publication exhibited a null effect on the worse prognostic potential of increasing LNR. Increasing number of tumors located in the tongue was the only factor identified that could modify the association between LNR and survival of patients (exponentiated coefficient: 1.08; 95% CI: 1.01-1.16). The bubble plot (Figure 21) depicts the burdening effect mediated by high LNR values in terms of overall survival more pronounced in high percentages of tongue tumors.

Table 3. Meta-regression analysis examining the role of potential modifiers in the association between lymph node ratio (LNR) and survival outcomes.

Variables	Category or increment	OS - Studies analyzing patients with positive and negative lymph nodes		
		n[§]	Exponentiated coefficient (95% CI)	p
Percentage of males	10% increase	18	1.01 (0.85-1.21)	0.858
Mean age of study	10 year increase	16	0.79 (0.54-1.15)	0.204
Percentage of lip	10% increase	4	Less than ten studies	
Percentage of upper gum	10% increase		Insufficient data	
Percentage of lower gum	10% increase		Insufficient data	
Percentage of gum	10% increase		Insufficient data	
Percentage of buccal mucosa	10% increase	13	0.98 (0.84-1.15)	0.784
Percentage of tongue	10% increase	**18**	**1.08 (1.01-1.16)**	**0.032**
Percentage of alveolus	10% increase	3	Less than ten studies	
Percentage of retromolar trigone	10% increase	7	Less than ten studies	
Percentage of gingiva	10% increase	3	Less than ten studies	
Percentage of hard palate	10% increase	8	Less than ten studies	
Percentage of floor of mouth	10% increase	13	0.85 (0.72-1.00)	0.056
Percentage of radical dissection	10% increase	10	0.97 (0.88-1.07)	0.504
Median number of nodes removed	One node increase	13	1.00 (0.95-1.05)	0.911
Median number of positive nodes removed	One positive node increase	11	0.93 (0.65-1.34)	0.683
Percentage of extracapsular spread	10% increase	10	1.11 (0.87-1.42)	0.341
Percentage of positive margins	10% increase	15	0.82 (0.67-1.01)	0.060
Percentage of administered chemotherapy	10% increase	13	0.93 (0.85-1.02)	0.126
Percentage of administered radiotherapy	10% increase	14	0.93 (0.83-1.04)	0.187
Publication year	1 year increase	18	1.00 (0.94-1.07)	0.998

[§]number of studies

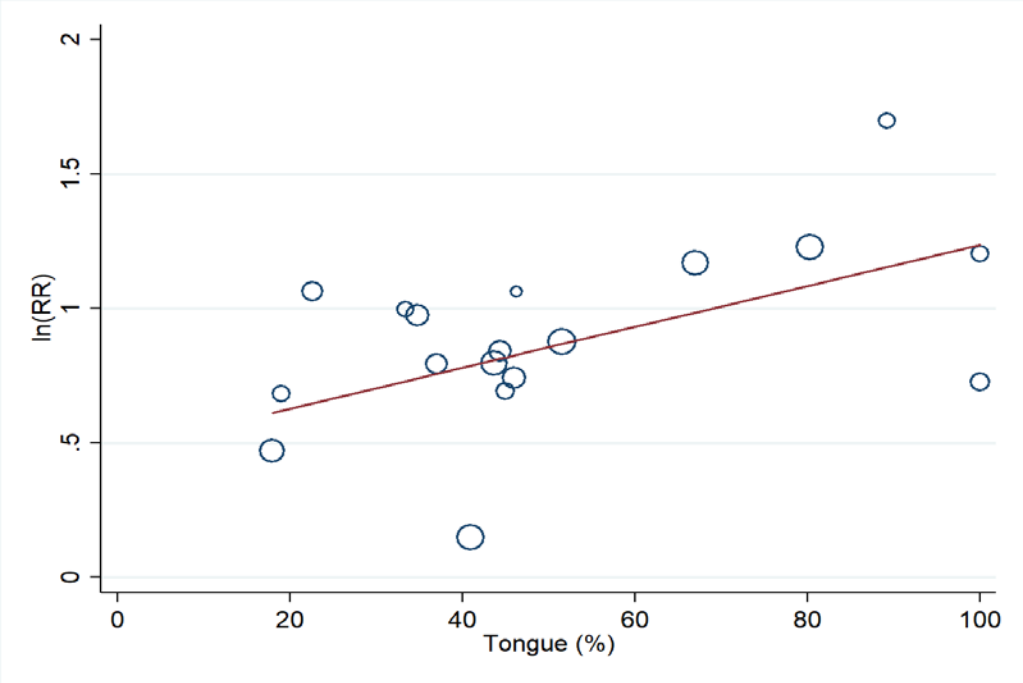

Figure 21. Plot depicting the modifying effect mediated by percentage of tumors affecting the tongue upon the association between high lymph node ratio (LNR) values and overall survival. The circle sizes represent the inverse of each within-study variance.

3.5. LNR as an independent prognostic factor

A hypothesis was formed as to whether LNR can be established as an independent prognostic factor. To address this question, subanalyses by degree of adjustment under each survival outcome of interest were performed (Figures 22-26). When adjusting for potential confounders, patients with high LNR values were faced with a twofold risk of worse prognosis, at a minimum, with statistical significance (pooled RR_{OS}: 2.82; 95% CI: 2.36-3.37, pooled RR_{DFS}: 2.58; 95% CI: 1.44-4.64, pooled RR_{DSS}: 3.23; 95% CI: 2.25-4.64, pooled RR_{LRDFS}: 2.92; 95% CI: 1.41-6.03). Regarding studies that didn't adjust for potential confounding factors, the results from the analysis were the following; pooled RR_{OS}: 2.06; 95% CI: 1.59-2.67, pooled RR_{DFS}: 1.74; 95% CI: 1.22-2.48, pooled RR_{DSS}: 2.72; 95% CI: 2.40-3.08. Results regarding univariate analysis in LRDFS and DMFS lacked statistical significance (pooled RR_{LRDFS}: 1.12; 95% CI: 0.97-1.29, pooled RR_{DMFS}: 2.11; 95% CI: 0.97-4.63).

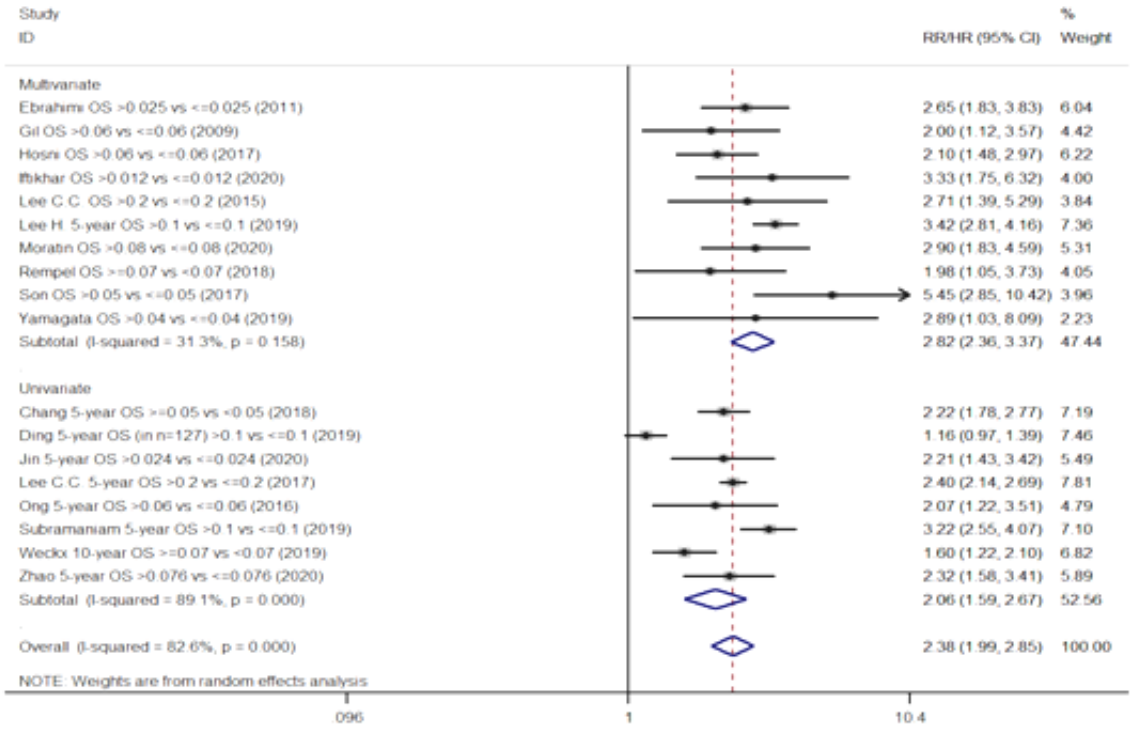

Figure 22. Forest plot describing the association between lymph node ratio (LNR) and overall survival. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.

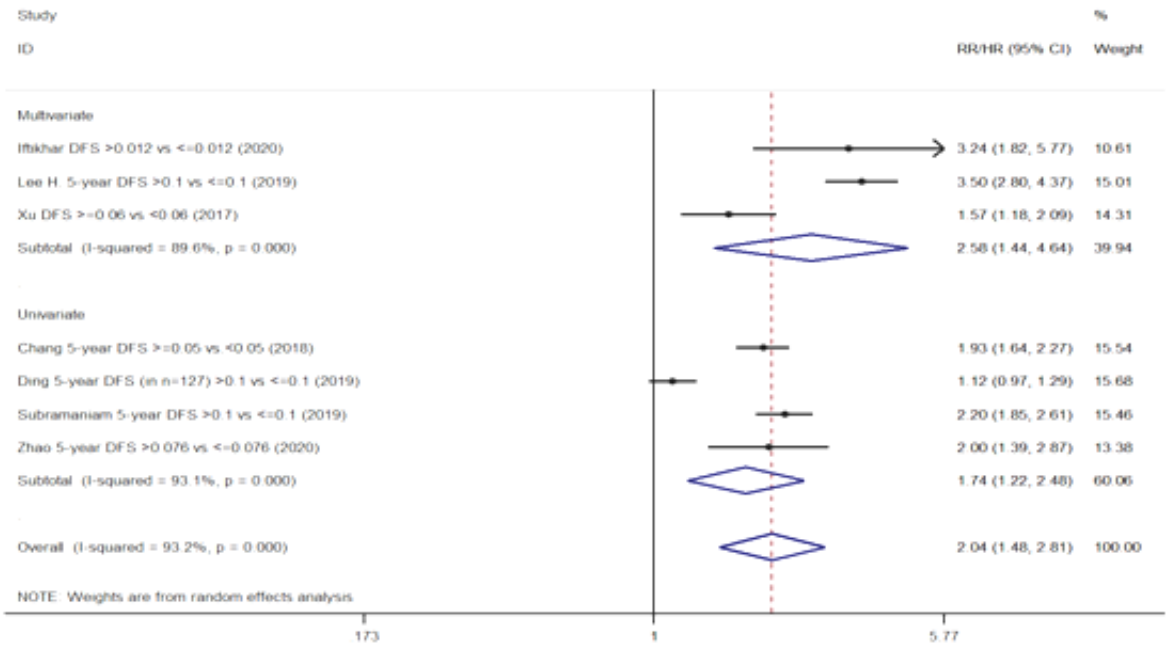

Figure 23. Forest plot describing the association between lymph node ratio (LNR) and disease-free survival. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.

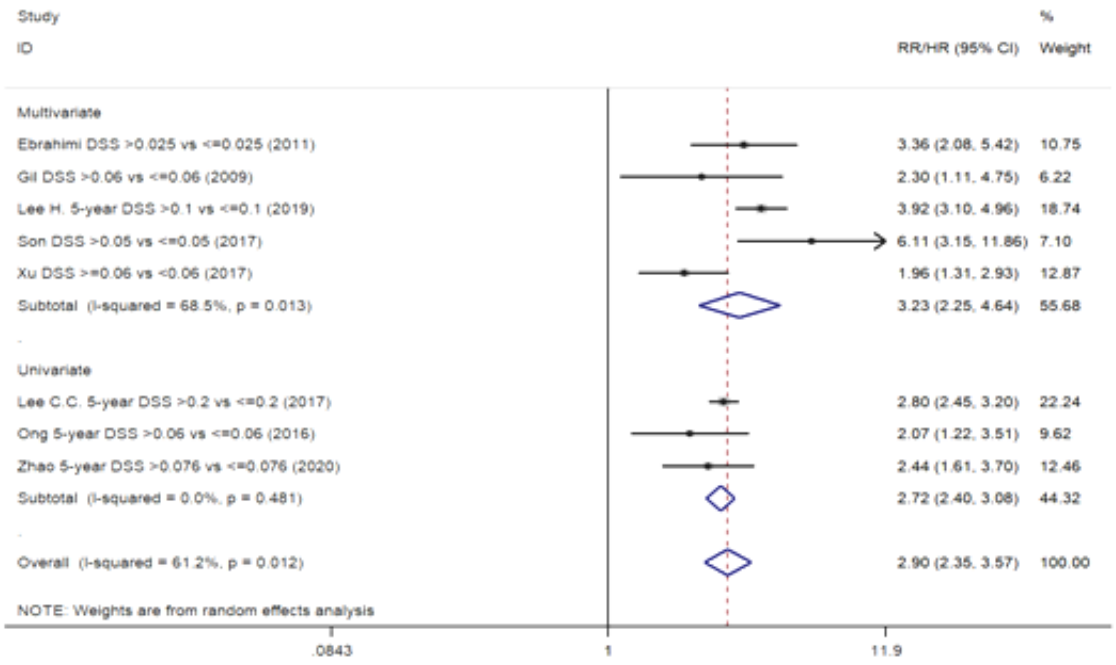

Figure 24. Forest plot describing the association between lymph node ratio (LNR) and disease-specific survival. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.

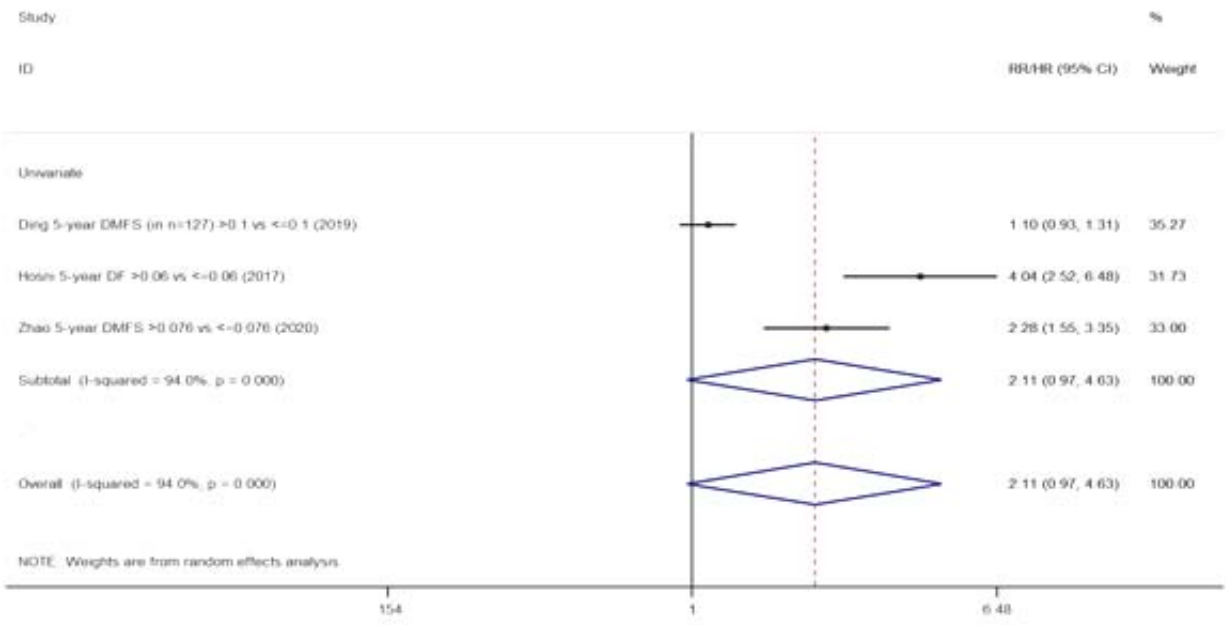

Figure 25. Forest plot describing the association between lymph node ratio (LNR) and distant metastasis-free survival. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.

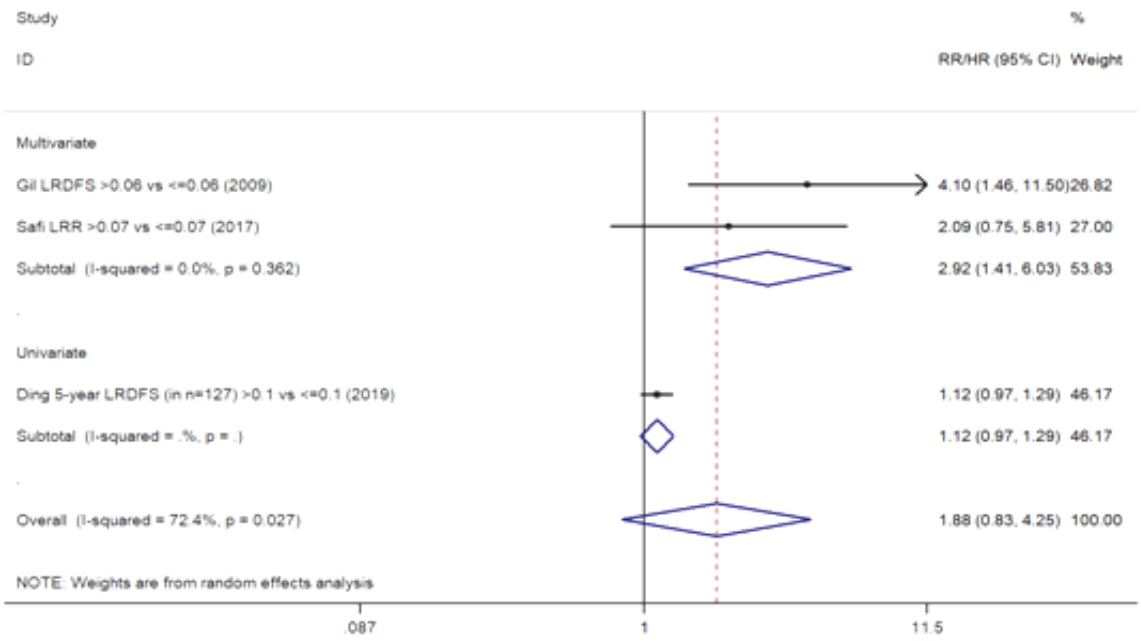

Figure 26. Forest plot describing the association between lymph node ratio (LNR) and locoregional disease-free survival. Apart from the overall analysis, the subanalyses on degree of adjustment are presented.

3.6. Evaluation of quality of studies and risk of bias

Within-study quality of all 32 studies included in the systematic review was evaluated with the Newcastle-Ottawa Scale [142], analytically presented in Supplementary Table 5. 24 studies were found to be of high quality, while the rest belonged in the "intermediate" range, the lowest graded one conducted by Subramaniam et al. [180]. All studies scored excellently in the selection process and follow-up was both long enough for outcomes to occur and adequate (≥90% response rate) in the majority of studies. In terms of comparability, pN-classification was considered the most significant confounding factor as it is directly associated with LNR. Only 6 studies were analyzed adjusted for pN-classification [132,171,179,183,186,190], and generally overall quality was compromised in the "comparability" section.

Regarding publication bias, non-significant publication bias was detected via Egger's test in the analysis on overall survival (p=0.572). The result is reflected in the respective funnel plot, as no obvious asymmetry is identified (Figure 27).

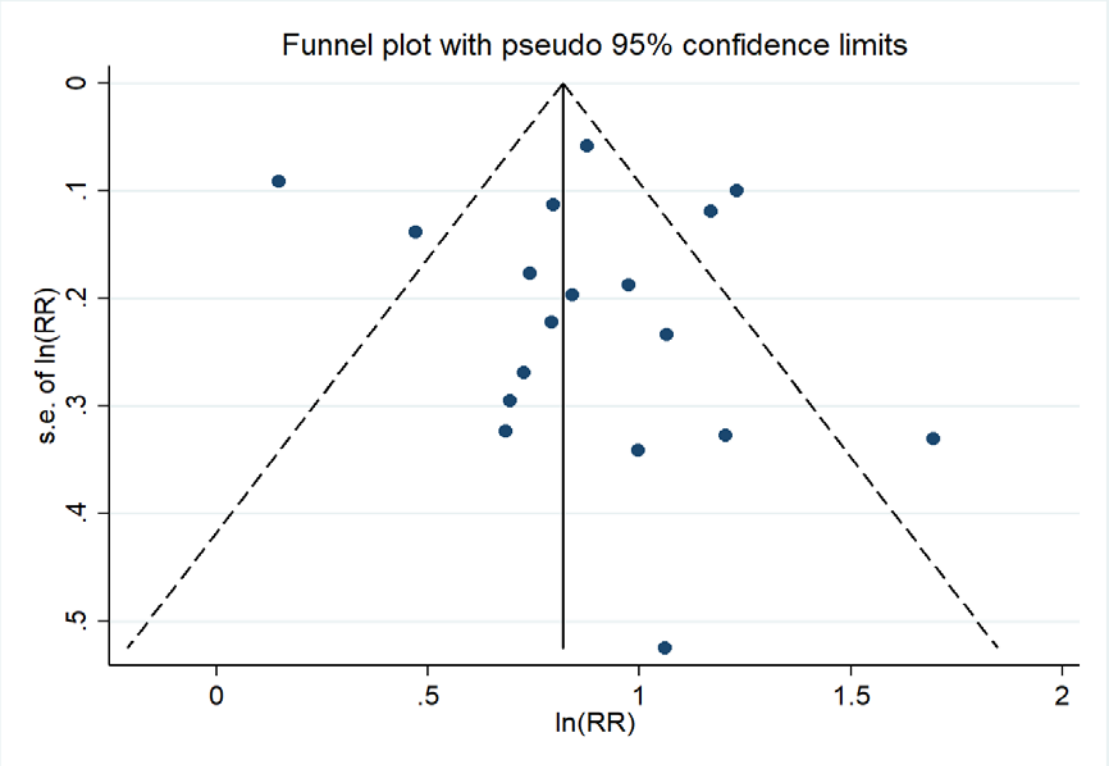

Figure 27. Funnel plot of the meta-analysis on overall survival without obvious asymmetry, i.e. no evidence of publication bias.

4. Discussion

4.1. Analysis of results

In the scope of the present systematic review, 32 studies examining the effect of LNR, as a categorical variable, on OSCC patients' survival after neck dissection, were identified and their data was extracted and presented. In 20 studies, the node-negative populations were not excluded from the group with low LNR values, and were eligible for meta-analysis. Overall, it was proven that high LNR values multiply the risk of worse prognosis at least by two, whether this occurs as all cause/tumor-related death or tumor recurrence of any kind. Similarities were observed even in the statistically non-significant, probably due to the small number of studies analyzed, results for LRDFS and DMFS.

The findings of the present study are in accordance with an earlier systematic review and meta-analysis, conducted by Huang et al. (2019) [135]. Their quantitative synthesis included 19 studies, focusing either on both node-positive and node-negative populations or on node-positive populations exclusively, classified into two groups. Group A consisted of the studies limited to node-positive patients, while group B of those analyzing both populations. Results regarding the overall, disease-free and disease-specific survival of patient pools under group B, pointed out the burdening effect of high LNR similarly to ours (pooled HR_{OS}: 2.76; 95%CI: 2.13–3.59, pooled HR_{DFS}: 2.01; 95%CI: 1.44–2.82, pooled HR_{DSS}: 2.83; 95%CI: 1.8–4.44). Heterogeneity though was significantly less pronounced in their study (I^2_{OS}:37.4%; p=0.12, I^2_{DFS}:50.7%; p=0.132, I^2_{DSS}:60.5%; p=0.038).

Considerable heterogeneity existed among the studies analyzed under each survival outcome in our research. Factors like varying study design, sample size, geographical region, study period and follow-up duration are expected to introduce heterogeneity [140]. Heterogeneity can also be attributed to differences between subgroups of studies, such as the multiple LNR cut-offs. In comparison to the previous publication, our search algorithm was broader, so as not to overlook any relative literature, and scan for eligible articles was expanded to every source possible. Furthermore, Huang et al. included only studies that reported HRs. In case all eligibility criteria were met, but HRs were unavailable or the comparison of interest was inadequately reported, we tried to synthesize data provided to build the correlation we were investigating and calculate crude effect estimates (RRs). Our extensive research and scrutiny resulted in a richer and more representative material for analysis, which explains the variety of LNR cut-off values. Methods of cut-off determination also varied significantly among studies. Many were based on ROC-curve analysis, some on previous literature and others set a cut-off equal to the median of the patients' individual data, a factor that obstructs our ability to express comparisons based on a single, fixed value. An effort to minimize the differences was made by choosing the lowest cut-off when more than one were provided. Subgroup analyses per LNR cut-off point were also performed in order to reduce heterogeneity. Heterogeneity could result from differences in the determination of survival outcomes as well. We tried to diminish the effect by paying close attention to the clinical interpretation researchers gave to their findings and designing our analyses based on that.

To further explore heterogeneity, we performed meta-regression on variables considered potential modifiers of the association between LNR and overall survival. Lymph node ratio is defined as the ratio of the positive lymph nodes to the total nodal yield. The number of positive nodes is a strong indicator of disease spread and simultaneously directly linked to the total number of nodes excised, which depends on the type of neck dissection performed according to the institution's practice, surgeon's expertise and patient's anatomical and pathological features. A radical or a modified radical neck dissection harvests a significantly greater number of nodes compared to a selective neck dissection, commonly contributing to low LNR cut-offs. Even when LNR is low, presence of extracapsular spread signals a poor prognosis. Positive margins also increase the risk for local relapse and if those are reported, adjuvant treatment with radiotherapy and/or chemotherapy should be considered for the eradication of any residual disease. Hence increase in the number of positive nodes, median nodal yield, percentage of radical dissection, extracapsular spread, positive margins and administered adjuvant treatment were examined as potential confounders without statistically significant influence on the prognostic impact of LNR. Null results were reported for percentage of males, age and publication year as well.

Since our research was not oriented to any particular OSCC subsite, the modifying effect of each subsite present was to be investigated. The oral cavity is rich in lymphatic supply and regional nodal dissemination to nodes from level I to III, but the risk of regional nodal metastasis differs among subsites involved. Patients with anterior tongue tumors are diagnosed with occult neck metastases in a percentage around 50%-60%, even in early T1/T2 stages [191]. Occult neck metastases can increase the risk of dying from cancer by 5 times [191]. Disease progression might be quicker compared to other sites, due to the complexity of tongue's lymphatic and vascular network [192]. We believe these particularities explain the relation found between increasing proportion of tongue tumors and worse overall survival mediated by high LNR.

By visual interpretation of the funnel plot and Egger's statistical test, no considerable publication bias could be traced, so this factor cannot be accounted for as contributing to the heterogeneity.

Authors' main goal in the previous meta-analysis was to highlight LNR as a strong independent prognostic factor. To achieve this, they performed additional analyses by pooling studies reporting adjusted HRs only, with statistically significant results. As mentioned above, LNR is a composite index. Number of positive nodes and total nodal yield depend on disease progression and surgical procedure. A patient's age and overall health status often determine the route of the disease. Type of treatment and follow-up are decided according to staging that takes into account clinical and pathological characteristics of the tumor (subsite, size, depth of invasion, extracapsular spread, margin status etc.). Therefore, LNR has potential of being incorporated as a meaningful prognostic factor in the AJCC Staging System, if its effect on survival is free from confounders. As an effort, we took a step forward and described the association between LNR and survival outcomes by performing additional subanalyses on degree of adjustment, with strong evidence of a worse prognosis in the presence of high LNR, when adjusting for significant confounding factors.

All cut-offs were deemed significant in the analyses. Focusing on overall survival the lowest cut-off identified was 0.012, proposed by Iftikhar et al. [165] through ROC-curve analysis, smaller than the one Huang et al. suggested (0.025). Analyzing this value, it means that at least 80 nodes need to be harvested for one node to be identified as positive with metastasis, and treat the patient accordingly to ensure a similar overall survival to a

pathologically negative one. A radical neck dissection usually requires yielding of around 40 nodes, if not less. Since the majority of our studies included node-negative populations comprising more than 50% of their sample size, selective neck dissection and modified radical were mostly the techniques of choice, in compliance with common practice. The removal of the entire cervical lymphatic system, jugular vein, sternocleidomastoid muscle and spinal accessory nerve through radical dissection is well known for the significant morbidity it accompanies, which set the basis for the introduction of modified radical dissection and later, selective, even for clinically node-positive patients. However, for subsites commonly associated with skip nodal metastases, with the previous node level free of metastatic disease, such as the tongue and floor of mouth, more radical procedures continue to be the preferred approach [193]. A low, significant LNR cut-off underlines the importance of eliminating residual disease to achieve better outcomes. In occasions where very extensive surgery is not feasible or desired, adjuvant treatment will play a most beneficial role. We believe that methods of LNR cut-off determination will be standardized in future research, and a universal value to guide therapeutic approach according to risk stratification will be established.

4.2. Limitations

It is quite clear that our study is not free of limitations. All but three studies followed a retrospective design which introduces some bias restrictions, since preliminary results or protocols of observational studies are not published before the final analysis [194], despite the generally good quality evaluation with the Newcastle-Ottawa scale. There was only one multicontinental study, excluded from the meta-analysis. In most cases, data concerned patients treated at a single institution, so potential bias is hard to eliminate. Studies lacked information regarding patients' history, so smoking, alcohol consumption etc. could not be evaluated for their association with LNR and survival. Detailed information regarding type of surgery and ethnicity was also absent in many cases. A factor that greatly contributed to heterogeneity was the varying methods of LNR cut-off determination, which may also introduce some bias in the individual study results.

4.3. Conclusions and future research directions

Despite the limitations, our study has a number of strengths. Literature was meticulously searched to lead to a rich material for analysis and every effort possible was made to explore and reduce heterogeneity. Even if not all effect estimates were adjusted, our subanalyses on degree of adjustment managed to underline LNR as an independent prognostic factor. It is now clear that low LNR cut-offs are capable of predicting significantly worse survival when surpassed and LNR can be incorporated to the future editions of the AJCC TNM Classification System for Oral Cavity tumors as well. More prospective studies with clearly defined endpoints and clinical trials with large sample sizes will help further validate these findings and hopefully establish a universal cut-off for each surgical procedure. Future research should focus on stratifying patients according to affected subsites and history. The role of adjuvant radiotherapy and chemotherapy in disease relapse, even for low-risk patients, is another object of investigation that will continuously be needing more light.

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Appendix

A. The present study is part of a systematic review and meta-analysis entitled: "Lymph node ratio as a prognostic factor in neck dissection in oral cancer patients: A systematic review and meta-analysis", the manuscript of which has been submitted for peer-review to *Cancers*, an open access journal of Oncology, published semimonthly online by MDPI, awaiting publication.

B. Supplementary Material

Table S1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist (continued) [140].

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p. 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p. 2-23
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p. 22-23
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p.23
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p. 23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p. 24
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p. 24
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p. 23.24
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p. 24-25
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p. 24
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p. 26

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p. 24-25
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p. 25

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p. 26
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p. 25
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p. 26-29, Figure 15, Table 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p. 29, Tables S2-S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p. 40, Table S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p. 30-35, Figures 16-20
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p. 30-35, Table 2, Figures 16-20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p. 41, Figure 27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p. 35-40, Table 3, Figures

			21-26
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p. 42-44
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p. 44
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p. 44
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

Table S2. Methodological characteristics of the included studies (continued).

Study	Year	PMID	Study period	Study design	End of study (0/1)	Number of patients	Number and percentage of males	Age, mean (range)	Country	Ethnicity	Median follow-up	Endpoints	Definition of endpoints
Agarwal et al. (2019) [169]	2019	30421434	2011	Retrospective cohort	1	94	70 (74%)	median 47 (24-80)	India/Pakistan	NR	66.5 mo (7-80)	OS, DFS	OS: date of treatment completion to date of death/last follow-up DFS: NR
Arun et al. (2020) [170]	2020	33021340	2011-2016	Retrospective cohort	1	212	153 (72.2%)	median 52 (21-85)	India/Pakistan	NR	23.2 mo	DFS, OS	DFS: time between the date of primary surgery and the date of clinicoradiological confirmation of disease recurrence (locoregional or distant metastasis)/last follow-up OS: time between the date of primary surgery for OSCC and the date of death of any cause/last follow-up
Bharath et al. (2018) [162]	2018	30344127	2012-2013	Prospective cohort	1	51	39 (78.6%)	NR	India/Pakistan	NR	mean 24 mo (24-36)	DFS, OS	NR
Chang et al. (2018) [174]	2018	29038963	2002-2015	Retrospective cohort	1	389	355 (91.3%)	51.8 (23-84)	East Asia	Eastern Asian	42 mo (0-152)	OS, DFS	OS: day of therapeutic surgery to date of death/last follow-up DFS: day of surgery to date of tumor recurrence (local/distant metastasis)
Chow et al. (2017) [168]	2017	28554580	2000-2016	Retrospective cohort	1	39	20 (51.3%)	median 70.0 (46-95)	East Asia	Eastern Asian	79 mo (5-167)	OS, DSS	NR
Ding et al.	2019	30452499	2000-	Retrospective	1	149	105	≤ 50:	USA/Canada	White: 117	20 mo (0	OS, DFS,	OS: date of

(2019) [175]			2015	cohort			(70.5%)	37(24.8%), 51-60: 44 (29.5%), >60: 68 (45.6%) Median 59 (28-88)		(78.5%), Non-white: 32 (21.5%)	-137), 34.5 for surviving patients	LRDFS,DMFS	diagnosis to date of death/last follow-up DFS: date of diagnosis to date of local recurrence/regional lymph node metastasis/distant metastasis LRDFS: date of diagnosis to date of local recurrence/regional lymph node metastasis DMFS: date of diagnosis to date of distant metastasis
Ebrahimi et al. (2011) [182]	2011	20967874	1987-2009	Retrospective cohort	1	313	204 (65.2%)	median 63.4 (28.5 - 91.5)	Australia	NR	32.3 mo	OS, DSS	OS: date of surgery to date of death/last follow-up DSS: date of surgery to date of OSCC death
Gil et al. (2009) [183]	2009	19691095	1986-1996	Retrospective cohort	1	386	227 (59%)	mean 58 (14-88)	USA/Canada	NR	67 mo (4-184)	OS, DSS, LRDFS	OS: date of surgery to date of death/last follow-up DSS: date of surgery to date of death from OSCC LRDFS: NR
Hosni et al. (2017) [176]	2017	28838425	1994-2012	Retrospective cohort	1	914	577 (63%)	median 61 (18-92)	USA/Canada	NR	51 mo (1-189)	RF, DF, OS	OS: date of surgery to death/last follow-up RF: date of surgery to regional failure with no evidence of local failure/distant metastases DF: date of surgery to distant metastases with no

													evidence of local/regional failure
Iftikhar et al. (2020) [165]	2020	32808800	2000-2018	Retrospective cohort	1	130	87 (66%)	High ratio: mean 48.3 Low ratio: mean 50.2	India/Pakistan	NR	NR	OS, DFS	OS: deceased or alive after 5 years from primary treatment (surgery) DFS: recurrence or no recurrence after 5 years from the start of treatment
Jin et al. (2020) [177]	2020	32535340	2009-2013	Retrospective cohort	1	233	127 (55%)	59.24	East Asia	NR	68 mo (1-122)	OS	OS: time from initial diagnosis to all-cause death
Kim et al. (2011) [133]	2011	21336511	1994-2006	Retrospective cohort	1	211	134 (64%)	55 (21-88)	East Asia	NR	58 mo (4-180)	DSS, OS	First day of treatment to date of event or last follow-up
Künzel et al. (2014) [171]	2014	24842444	1980-2010	Retrospective cohort	1	374	297 (79.4%)	median 55 (26-85)	Europe	NR	3.99 y (0.01-24.04) 2.93 y (0.01-23.17) LNR group	DSS, OS, LRC, LC, RC	OS: date of initial diagnosis to death/last follow-up DSS: date of initial diagnosis to tumor- or treatment related death/time of patient's last admission LRC: time of initial diagnosis/patient's last admission to the first locoregional recurrence LC: time of initial diagnosis/patient's last admission to the first local recurrence RC: time of initial diagnosis/patient's last admission to the first regional recurrence
Lee C.C. et al. (2015) [184]	2015	26166079	2004-2013	Retrospective cohort	1	347	322 (92.8%)	56	East Asia	NR	mean 33 mo	OS	NR

Lee C.C. et al. (2017) [178]	2017	29074847	2007-2013	Retrospective cohort	1	3958	2528 (63.9%)	mean 59	USA/Canada	White: 3316 (83.8%), Black/Other: 642 (16.2%)	NR	DSS, OS	OS: time of initial diagnosis to death from all causes DSS: time of initial diagnosis to death from cancer
Lee H. et al. (2019) [179]	2019	30672597	2006-2015	Retrospective cohort	1	345	214 (62%)	median 55 IQR (45-66)	East Asia	NR	58 mo IQR (38-88)	DFS, OS, DSS	DFS: time from initial surgery to recurrence/last follow-up OS: time from initial surgery to all-cause death/last follow-up DSS: time from initial surgery to disease-specific death/last follow-up
Lieng et al.(2016) [166]	2016	27261269	1980-2011	Retrospective cohort	1	72	48 (67%)	mean 59 (24-89) median 60	Australia	NR	55 mo (2.1-177)	DFS, OS	DFS: time from diagnosis to time of recurrence, death or development of a second malignancy OS: NR
Moratin et al. (2020) [185]	2020	31740138	2010-2017	Retrospective cohort	1	430	273 (63.5%)	63.9 (18-92)	Europe	NR	NR	OS, PFS	NR
Ong et al. (2016) [167]	2016	25917601	2002-2010	Retrospective cohort	1	99	56 (56.6%)	median 62 (23-94)	East Asia	NR	48.5 mo (2-156)	OS, DSS	OS: date of surgery to date of death/last follow-up DSS: date of surgery to death of tongue cancer
Patel et al. (2013) [132]	2013	24064974	NR	Retrospective cohort	1	4254	2815 (60.1%)	52.63 (14-99)	Multicontinental (11 centers worldwide)	NR	41 mo (2-322), N+: 46 mo (4-322)	OS, DSS, DFS, LRFS, LRDFS, DMFS	OS: date of surgery to date of death/last follow-up DSS: time of diagnosis to death resulting from OSCC DFS: NR LRFS: NR LRDFS: NR DMFS: NR
Rempel et al.	2018	30196863	1994-	Retrospective	1	171	129 (75%)	56.6	Europe	NR	80.5 mo	OS	OS: time from the

(2018) [186]			2013	cohort				(24-81)					beginning of primary therapy to death from any cause
Safi et al. (2017) [187]	2017	28797461	2004-2014	Retrospective cohort	1	499	290 (58.1%)	62.51 (28-98)	Europe	NR	35 mo (3-117)	LRR	LRR: tumor of similar histology appearing after 6 weeks of treatment and within the first 3 years after therapy of the primary tumor locally/within the lymph neck nodes
Shrime et al. (2009) [136]	2009	19441094	1994-2004	Retrospective cohort	1	143	94 (65.7%)	58.7 (14.8-89.4)	USA/Canada	NR	mean 32.4 mo (1.2-140.4)	OS	Date of diagnosis to date of death/last follow-up
Son et al. (2017) [163]	2017	28981214	2010-2015	Prospective cohort	1	157	101 (64.3%)	median 54 (24-87)	East Asia	NR	46 mo (14-74)	RFS, DSS, OS	RFS: date of surgery to date of first recurrence DSS: date of surgery to date of index-cancer death OS: date of surgery to date of all-cause death/last follow-up
Spoerl et al. (2020) [172]	2020	32754787	2004-2017	Retrospective cohort	1	717	515 (71.8%)	60.8 (28-91)	Europe	NR	89 mo	OS, RFS	OS: date of resection to date of death/last follow-up RFS: date of resection to date of first recurrence/last follow-up
Subramaniam et al. (2019) [180]	2019	31465931	2004-2014	Retrospective cohort	1	643	498 (77%)	55.1 (18-82)	India/Pakistan	NR	2.9 years (0.5-11)	DFS, OS	OS: time from initial surgery to date of death/last follow-up DFS: time from initial surgery to date of recurrence (local, regional or distant)
Suzuki et al. (2016) [164]	2016	26655796	2008-2013	Prospective cohort	1	35	22 (62.9%)	NR	East Asia	Eastern Asian	mean 20.9 mo	OS, DMFS, Lung MFS	OS: period from resection to death/last contact

													DMFS: period from resection to date of distant metastases/last contact Lung MFS: period from resection to date of lung metastases/last contact
Urban et al. (2013) [173]	2013	23157979	1988-2007	Retrospective cohort	1	3091	2021 (65%)	median 60 (14-99)	USA/Canada	White: 2515 (81%), Black: 320 (10%), Other: 256 (8%)	21 mo	OS, CSS	OS: time of initial diagnosis to date of death/last follow-up CSS: NR
Weckx et al. (2019) [181]	2019	31178216	2002-2015	Retrospective cohort	1	159	87 (55%)	mean 63.11 median 62	Europe	NR	mean 60.7 mo (3-408) median 43 mo	OS	OS: period of time from the beginning of the primary therapy to all-cause death, in months
Xu et al. (2017) [188]	2017	28787551	1999-2011	Retrospective cohort	1	2036	1151 (56.5%)	59	East Asia	NR	65 mo (1-178)	DFS, DSS	DFS: time from diagnosis until first documented recurrence/death DSS: time from the first operation to death/last follow-up
Yamagata et al. (2019) [189]	2019	30822404	2008-2015	Retrospective cohort	1	95	52 (54.7%)	median 65.5 (35-88)	East Asia	NR	NR	OS	OS: date of first diagnosis to death from any cause
Zhao et al. (2020) [190]	2020	32449223	2008-2010	Retrospective analysis from phase III RCT	1	248	172 (69.4%)	55.4 (26-75)	East Asia	NR	80 mo (3.2-93)	OS, DFS, DSS, LRFS, DMFS	OS: date of random assignment to occurrence of all-cause death DFS: date of random assignment to tumor recurrence/all-cause death DSS: date of random assignment to occurrence of

											OSCC death LRFS: date of random assignment to local tumor/neck recurrence/all-cause death DMFS: date of random assignment to tumor distant metastasis/all-cause death

Table S3. Tumor-related characteristics of the included studies and methods of analysis (continued).

Study	TNM stage (AJCC)	T stage	N stage	Metastasis (yes/no)	Oral cancer subsite	Number of patients per subsite	Type of neck dissection, patients per type	Treatment groups	LNR cut-off determination	Univariate/multivariate analysis	Adjustment factors
Agarwal et al. (2019) [169]	NR	T1: 6 (6%), T2: 7 (8%), T3: 13 (14%), T4: 68 (72%)	N1: 1 (1%), N2a: 28 (30%), N2b: 3 (3%), N2c: 1 (1%), N3b: 61 (65%)	No	lip, buccal mucosa, tongue, alveolus, retromolar trigone	3 (3%), 16 (17%), 39 (42%), 34 (36%), 2 (2%)	Unilateral Selective: 12 (13%), Bilateral Selective: 7 (7%), Unilateral Modified radical: 49 (52%), Unilateral Modified radical + Contralateral Selective: 15 (16%), Bilateral Modified radical: 11	Surgery + RT: 19 (20.2%), Surgery + CRT: 75 (79.8%)	Log-rank test	Multivariate	PNI, ENE >2, ENE grade 3-4

							(12%)				
Arun et al. (2020) [170]	NR	T1: 30 (14.2%), T2: 79 (37.3%), T3: 23 (10.8%), T4a: 63 (29.7%), T4b: 17 (8%)	N1: 83 (39.2%), N2a: 3 (1.4%), N2b: 102 (48.1%), N2c: 20 (9.4%), N3: 4 (1.9%)	No	NR	NR	Unilateral: 153 Bilateral: 59	Surgery alone: 19/205 (9.3%), Surgery + RT: 81/205 (39.5%), Surgery + CRT: 105 (51.2%)	Median	Univariate	N/A
Bharath et al. (2018) [162]	NR	T1: 14 (33.3%), T2: 29 (50.9%), T3: 6 (11.7%), T4: 2 (3.9%)	N1: 24 (47%), N2: 27 (53%)	No	tongue	51 (100%)	NR	Surgery alone: 2 (3.9%), Surgery + RT: 49 (96.1%), Surgery + CRT: 15 (29.4%)	Previous literature	Univariate	N/A
Chang et al. (2018) [174]	I: 99 (25.4%), II: 85 (21.9%), III: 64 (16.5%), IV: 141 (36.2%)	T1: 119 (30.6%), T2: 125 (32.1%), T3: 43 (11.1%), T4: 102 (26.2%)	N0: 256 (65.8%), N1: 55 (14.1%), N2a: 2 (0.5%), N2b: 64 (16.5%), N2c: 11 (2.8%), N3: 1 (0.3%)	No	lip, retromolar trigone, gingiva, tongue, hard palate, buccal mucosa, floor of mouth	2 (0.5%), 18 (4.6%), 52 (13.4%), 170 (43.7%), 9 (2.3%), 127 (32.6%), 11 (2.8%)	NR	Surgery alone: 106, Surgery + RT: 69, Surgery + CT: 56, Surgery + CCRT: 158	ROC curve	Univariate	N/A
Chow et al. (2017) [168]	I: 5(12.8%), II: 11 (28.2%), III: 10 (25.6%), IV: 13 (33.3%)	T1: 9 (23.1%), T2: 15 (38.5%), T3: 7 (17.9%), T4: 8 (20.5%)	N0: 20 (51.3%), N1: 10 (25.6%), N2: 9 (23.1%), N3: 0	No	buccal mucosa	39 (100%)	Selective 24 (61.5%), Modified radical 12 (30.8%), Radical 3 (7.7%)	Surgery alone: 21 (53.8%), surgery+ RT: 11 (28.2%), Surgery+ CT: 1 (2.6%), Surgery+ CRT: 6 (15.4%)	Previous literature	Univariate	N/A
Ding et al. (2019) [175]	NR	T1: 46 (30.9%), T2: 40 (26.8%), T3-T4: 63 (42.3%)	N0: 41 (27.5%), N1:24 (16.1%), N2-N3: 62 (41.6%)	No	tongue, floor of mouth, other	61 (40.9%), 43 (28.9%), 45 (30.2%)	NR	Surgery alone: 26 (17.4%), Surgery+ RT: 33 (22.1%), Surgery+ CRT: 90 (60.4%)	Median	Univariate	N/A
Ebrahimi et al.	NR	T1-T2:	N0: 148	No	tongue, floor	109	Level I-V: 61	NR	Log scale	Multivariate	age,

(2011) [182]		198 (63.3%) T3-T4: 115 (36.7%)	(47.3%), N1: 50 (16%), N2a: 6 (1.9%), N2b: 85 (27.2%), N2c: 24 (7.7%)		of mouth, alveolus, retromolar trigone, buccal, other	(34.8%), 116 (37.1%), 41 (13.1%), 28 (8.9%), 15 (4.8%), 4 (1.3%)	(15.2%), Level I-IV: 110 (27.4%), Level I-III: 220 (54.7%), Other: 11 (2.7%)				T-classification, ECS, involved margin
Gil et al. (2009) [183]	I: 44 (11%), II: 103 (27%), III: 90 (23%), IV: 149 (39%)	T1: 56 (15%), T2: 168 (44%), T3: 70 (18%), T4: 92 (24%)	N0: 219 (57%), N1: 72 (19%), N2a: 2 (1%), N2b: 83 (22%), N2c: 8 (2%), N3: 2 (1%)	No	tongue, floor of mouth, upper gum, lower gum, hard palate, retromolar trigone, buccal mucosa	175 (45%), 79 (20%), 4 (1%), 66 (17%), 2 (1%), 36 (9%), 24 (6%)	Selective 229 (59%), Modified radical 65 (17%), Radical 50 (13%), Bilateral 46 (12%)	Surgery alone: 162 (42%), Surgery + RT: 224 (58%)	Median	Multivariate	pT-, pN-classification, overall TNM stage, ECS, total no. of nodes, no. of positive nodes
Hosni et al. (2017) [176]	NR	T1-T2: 631 (69%), T3-T4: 283 (31%)	N0: 482 (52.7%), N1: 128 (14%), N2a: 6 (0.7%), N2b: 225 (24.6%), N2c: 73 (8%)	No	tongue, others	419 (46%), 495 (54%)	Ipsilateral (all) Selective 625 (68.4%), Modified Radical 239 (26.1%), Radical 21 (2.3%), Limited Upper 29 (3.2%) Contralateral (368) Selective 277 (75.3%), Modified Radical 38 (10.3%), Limited Upper 53	Surgery alone, Surgery + RT, Surgery + CRT	Maximally selected rank statistic	Univariate/ Multivariate	NR
Iftikhar et al. (2020) [165]	I: 34 (26.2%), II: 37 (28.5%), III: 21 (16.2%), IVA: 38 (29.2%)	T1: 44 (33.8%), T2: 69 (53.1%), T3: 11 (8.5%), T4: 6 (4.6%)	N0: 75 (57.7%), N1: 20 (15.4%), N2: 35 (26.9%)	No	tongue	130 (100%)	Ipsilateral Modified radical: 82 (68.3%), Selective: 20 (16.7%), Radical: 18 (15%) Contralateral Selective: 41 (75.9%), Modified radical: 12	Surgery alone: 53 (40.8%), Surgery + RT: 43 (33.1%), Surgery + CRT: 34 (26.2%)	ROC curve	Multivariate	Margin status

							(22.2%), Radical: 1 (1.85%)				
Jin et al. (2020) [177]	NR	T1-T2: 166 (71%), T3-T4: 67 (29%)	N0: 156 (67%), N1: 33 (14%), N2-N3: 44 (19%)	No	tongue, non-tongue	84 (37%), 149 (63%)	NR	NR	X-tile Software calculation	Univariate	N/A
Kim et al. (2011) [133]	I: 85 (40%), II: 33 (16%), III: 31 (15%), IV: 62 (29%)	T1: 101 (48%), T2: 71 (34%), T3: 11 (5%), T4: 28 (13%)	N0: 133 (63%), N1: 34 (16%), N2b: 37 (18%), N2c: 7 (3%)	No	tongue, floor of mouth, buccal mucosa, gingiva, hard palate, retromolar trigone	166 (79%), 17 (8%), 16 (8%), 5 (2%), 4 (2%), 3 (1%)	Elective: 151 (62%), Therapeutic: 60 (28%), Selective: 125 (59%), Modified Radical/Radical: 54 (26%), Bilateral: 32 (15%)	Surgery alone: 135 (64%), Surgery + RT: 69 (33%), Surgery + CRT: 7 (3%)	Previous literature	Multivariate/ Univariate	tumor thickness, T-classification, No. of positive nodes, size of metastatic deposits
Künzel et al. (2014) [171]	I: 105 (28.1%), II: 78 (20.9%), III: 73 (19.5%), IV: 118 (31.6%)	T1: 154 (41.2%), T2: 154 (41.2%), T3: 39 (10.4%), T4: 26 (7.2%), Tx: 1 (0.2%)	N0: 209 (55.9%), N1: 58 (15.5%), N2a: 6 (1.6%), N2b: 66 (17.6%), N2c: 18 (4.8%), N3: 17 (4.5%)	No	tongue, floor of mouth, cheek, gingiva	218 (58.3%), 137 (39.6%), 14 (3.7%), 5 (1.3%)	Bilateral: 182, Ipsilateral: 192	Surgery alone: 95 (25.4%), Surgery + RT: 235 (62.8%), Surgery + CRT: 43 (11.5%), Surgery + CT: 1 (0.3%)		Multivariate/ Univariate	pN (grouped), UICC
Lee C.C. et al. (2015) [184]	NR	T1: 95 (27.4%), T2: 112 (32.3%), T3: 30 (8.6%), T4: 110 (31.7%)	N0: 235 (67.7%), N1: 30 (8.6%), N2: 80 (23.1%), N3: 2 (0.6%)	No	buccal mucosa, tongue, other	158 (45.5%), 116 (33.4%), 73 (21%)	Elective: 195 Therapeutic: 152	NR	Previous literature	Multivariate	age, gender, comorbidity, pT, primary tumor site, margin status, differentiation
Lee C.C. et al. (2017) [178]	I: 938 (23.7%), II: 694 (17.5%), III: 849 (21.5%), IVA: 1393 (35.2%), IVB: 84 (2.1%)	T1 : 1398 (35.3%), T2: 1353 (34.2%), T3: 474 (12%), T4: 733 (18.5%)	N0: 2132 (53.9%), N1: 826 (20.9%), N2: 967 (24.4%), N3: 33 (0.8%)	No	tongue, lip, floor of mouth, gum and retromolar trigone, buccal mucosa, hard palate, other	2041 (51.6%), 160 (4%), 671 (17%), 680 (17.2%), 268 (6.8%), 55 (1.4%), 83 (2.1%)	NR	NR	Previous literature	Univariate	N/A

Lee H. et al. (2019) [179]	I: 134 (38.8%), II: 42 (12.2%), III: 48 (13.9%), IVA: 121 (35.1%)	T1: 170 (49.3%), T2: 89 (25.8%), T3: 6 (1.7%), T4a: 80 (23.2%)	N0: 196 (56.8%), N1: 61 (17.1%), N2b: 72 (20.9%), N2c: 16 (4.6%)	No	tongue, floor of mouth, buccal mucosa, gingiva, hard palate, retromolar trigone, lip	277 (80.3%), 31 (9%), 15 (4.3%), 13 (3.8%), 3 (0.9%), 4 (1.2%), 2 (0.6%)	Elective/ Therapeutic	Surgery alone: 190 (55.1%), Surgery + RT: 123 (35.7%), Surgery + CRT: 32 (9.3%)	ROC curve	Multivariate	KPS≤80, postoperative therapy, tumor site, tumor size, DOI, PNI, differentiation, involved margins, T-,N-classification, no. of positive nodes, >40 examined nodes, laterality of node involved, low neck node involvement, ENE
Lieng et al. (2016) [166]	NR	T1: 23 (32%), T2: 31 (43%), T3: 9 (12.5%), T4:9 (12.5%)	N1: 43 (60%), N2: 28 (39%), N3: 1 (1%)	No	tongue	72 (100%)	NR	Surgery alone: 19 (26%), Surgery + RT (+/- CT): 53 (74%	Log-rank test	Multivariate	NR
Moratin et al. (2020) [185]	I: 138 (32.1%), II: 73 (17%), III: 47 (10.9%), IV: 172 (40%)	T1: 165 (38.4%), T2: 122 (28.4%), T3: 28 (6.5%), T4: 115 (26.7%)	N0: 280 (65.1%), N1: 50 (11.6%), N2a: 3 (0.7%), N2b: 52 (12.1%), N2c: 31 (7.2%), N3a: 1 (0.2%), N3b: 10 (2.3%), Missing: 3 (0.7%)	Yes 0.2% (1 patient)	tongue, buccal mucosa, floor of mouth, alveolar process, maxilla, soft palate	97 (22.6%), 33 (7.7%), 120 (27.9%), 119 (27.7%), 29 (6.7%), 32 (7.4%)	NR	NR	ROC curve	Multivariate	T-stage, grading, age
Ong et al. (2016) [167]	I: 25 (25.3%), II: 26 (26.3%), III: 18 (18.2%), IV: 26 (26.3%), Unknown: 4 (4%)	T1: 39 (39.3%), T2: 44 (44.4%), T3: 8 (8.1%), T4: 6 (6.1%), Unknown : 2 (2%)	N0: 57 (57.6%), N1: 17 (17.2%), N2/N3: 25 (25.2%)	No	tongue	99 (100%)	Radical: 34 (34.3%), Comprehensi ve: 20 (20.2%), Selective (supraomohy oid): 39 (39.4%), Unknown: 6 (6.1%)	Surgery alone: 65 (65.7%), Surgery + RT: 25 (25.2%), Surgery + CRT : 9 (9.1%)	Previous literature	Univariate	N/A

Patel et al. (2013) [132]	I: 464 (9%), II: 799 (13%), III: 668 (16%), IV: 2323 (62%)	T1: 613 (13%), T2: 1374 (30%), T3: 623 (15%), T4: 1644 (42%)	N0: 2268 (43.3%), N1: 652 (15.3%), N2a: 88 (2%), N2b: 988 (23.2%), N2c: 246 (6%), N3: 12 (0.2%)	No	NR	NR	Elective: 2434 (52%), Therapeutic: 1820 (48%), I-III/IV: 2746 (60.7%), I-V: 525 (13.2%), Radical: 327 (9.9%), Bilateral: 656 (16%)	Surgery alone: 1297 (22%), Surgery + RT: 2245 (58%), Surgery + CRT: 553 (15%), Surgery + RT+ Erbitux: 159 (5%)	ROC curve	Multivariate	gender, age, DOI, ECS, margins, T-, N-classification, TNM stage, LND-based TNM stage, total no. of lymph nodes, treatment group
Rœmpel et al. (2018) [186]	II: 22 (13%), III: 24 (14%), IVA: 96 (56%), IVB: 29 (17%)	T2: 58 (34%), T3: 27 (16%), T4a: 57 (33%), T4b: 29 (17%)	N0: 34 (20%), N1: 29 (17%), N2: 106 (62%), N3: 2 (1%)	No	floor of mouth, tongue, mandibula/alveolar process, maxilla/hard palate, soft palate, buccal mucosa	71 (42%), 32 (19%), 32 (19%), 25 (15%),\ 5 (3%), 6 (4%)	Modified radical: 171 (100%)	Surgery + CRT: 171 (100%)	Previous literature	Multivariate	age, margin status, ypT-, ypN-classification
Safi et al. (2017) [187]	I: 166 (33.26%) II: 116 (23.24%) III: 64 (12.82%) IV: 153 (30.68%)	T1: 206 (41.28%) T2: 166 (33.26%) T3: 39 (7.8%) T4: 88 (17.66%)	N0: 342 (68.5%) N+: 157 (31.5%)	No	floor of mouth, tongue, lower jaw, palate, cheek	158 (31.66%), 119 (23.84%), 94 (18.83%), 54 (10.82%), 74 (14.85%)	Selective, Modified radical, Bilateral	Surgery alone: 258 (51.7%), Surgery + RT: 95 (19%), Surgery + CRT: 146 (29.3%)	ROC curve	Multivariate	grading, ECS, T-classification, treatment
Shrime et al. (2009) [136]	NR	T1-T2: 65 (45.8%), T3-T4: 77 (54.2%)	N1: 48 (33.6%), N2: 95 (66.4%)	No	tongue, upper and lower gingiva, floor of mouth, hard palate, buccal mucosa, retromolar trigone	NR	NR	Surgery alone: 50 (35%), Surgery + RT: 91 (63.6%), Surgery + CT: 2 (1.4%)	Maximally selected rank statistic	Multivariate	NR
Son et al. (2017) [163]	I: 59 (37.6%), II: 14 (8.9%), III: 19 (12.1%), IV: 65 (41.4%)	T1: 75 (47.8%), T2: 21 (13.4%), T3: 4 (2.5%), T4: 57 (36.3%)	N0: 92 (58.6%), N1: 22 (14%), N2: 43 (27.4%)	No	tongue, floor of mouth, buccal mucosa, gingiva, lip, hard palate, retromolar trigone	140 (89.2%), 4 (2.5%), 4 (2.5%), 3 (1.9%), 3 (1.9%), 2 (1.3%), 1 (0.6%)	Elective: 102, Therapeutic: 55	Surgery alone: 78 (49.7%), Surgery + RT: 56 (35.7%), Surgery + CRT: 23 (14.6%)	ROC curve	Multivariate	tumor size >2 cm, close/involved margins

Spoerl et al. (2020) [172]	I: 219 (30.5%), II: 117 (16.3%), III: 115 (16%), IV: 266 (37.1%)	T1: 290 (40.4%), T2: 236 (32.9%), T3: 56 (7.8%), T4: 135 (18.8%)	N0: 427 (59.5%), N1: 110 (15.3%), N2a: 8 (1.1%), N2b: 113 (15.8%), N2c: 50 (7%), N3: 9 (1.3%)	No	buccal mucosa, upper alveolus and gingiva, lower alveolus and gingiva, hard palate, tongue, floor of mouth	51 (7.1%), 22 (3.1%), 106 (14.8%), 48 (6.7%), 210 (29.3%), 280 (39.1%)	Unilateral: 72, Bilateral: 218	Surgery alone: 382 (53.3%), Surgery + RT: 232 (32.4%), Surgery + CRT: 103 (14.4%)	Median	Multivariate	NR
Subramaniam et al. (2019) [180]	NR	T1: 261 (41%), T2: 228 (35%), T3: 59 (9%), T4a: 95 (15%)	N0: 372 (58%), N1: 101 (15%), N2a: 10 (2%), N2b: 3 (1%), N2c: 22 (3%), N3b: 135 (21%)	No	tongue, floor of mouth, buccal cavity, alveolus/retro molar trigone	429 (67%), 37 (6%), 173 (26%), 4 (1%)	Ipsilateral selective, contralateral	Surgery alone: 301 (46%), Surgery + RT: 171 (27%), Surgery + CRT: 171 (27%)	Previous literature	Univariate	N/A
Suzuki et al. (2016) [164]	III: 4 (11.4%), IV: 31 (88.6%)	T1: 4 (11.4%), T2: 15 (42.9%), T3: 7 (20%), T4: 9 (25.7%)	N1: 5 (14.3%), N2: 29 (82.9%), N3: 1 (2.9%)	No	tongue, upper gum, lower gum, floor of mouth, cheek mucosa, hard palate	20 (57.1%), 4 (11.4%), 4 (11.4%), 3 (8.6%), 3 (8.6%), 1 (2.9%)	Unilateral: 26 (74.3%), Bilateral: 9 (25.7%)	Surgery alone: 14 (40%), Surgery + RT: 10 (28.6%), Surgery + CRT: 7 (20%), Surgery + CT: 4 (11.4%)	Previous literature	Multivariate	p stage (IV/III), positive surgical margin/ECS or both
Urban et al. (2013) [173]	NR	T1: 766 (27%), T2: 1217 (43%), T3: 857 (30%)	N1: 942 (32%), N2: 1798 (61%), N3: 227 (8%)	No	tongue, floor of mouth, gum and other	1338 (43%), 857 (28%), 896 (29%)	NR	Surgery alone: 747 (24%), Surgery + RT: 2344 (76%)	Previous literature	Univariate	N/A
Weckx et al. (2019) [181]	I: 36 (23%), II: 32 (20%), III: 18 (11%), IVA: 49 (31%), IVB: 24 (15%)	T1: 39 (25%), T2: 48 (30%), T3: 20 (13%), T4a: 44 (28%), T4b: 10 (6%)	N0: 96 (60%), N1: 21 (13%), N2a: 12 (8%), N2b: 9 (6%), N2c: 5 (3%), N3a: 0 (0%), N3b: 16	No	floor of mouth, tongue, lower jaw, upper jaw and hard palate, soft palate, cheek	55 (35%), 29 (18%), 38 (24%), 13 (8%), 8 (5%), 16 (10%)	Ipsilateral SND: 67 (42%), Ipsilateral MRND: 30 (19%), Ipsilateral RND: 6 (4%), Bilateral SND: 19 (12%), Ipsilateral	Surgery alone: 70 (44%), Surgery + RT: 31 (20%), Surgery + CRT: 58 (37%)	NR	Univariate	N/A

			(10%)				MRND + Contralateral SND: 24 (15%), Bilateral MRND: 11 (7%), Ipsilateral RND + Contralateral SND: 2 (1%)				
Xu et al. (2017) [188]	NR	T1: 497 (24.4%), T2: 793 (38.9%), T3: 211 (10.4%), T4a: 503 (24.7%), T4b: 32 (1.6%)	N0: 928 (45.6%), N1: 293 (14.4%), N2: 401 (19.7%), N3: 5 (0.2%), Unknown: 409 (20.1%)	No	tongue, lower gingiva, buccal mucosa, floor of mouth, upper gingiva, hard palate	842 (41.3%), 366 (18%), 331 (16.3%), 217 (10.7%), 213 (10.4%), 67 (3.3%)	Bilateral: 305, Ipsilateral selective: 889/1568	Surgery alone: 1076 (52.8%), Surgery + RT: 542 (26.6%), Surgery + CCRT: 149 (7.4%), Missing: 269 (13.2%)	Previous literature	Multivariate	PNI, ECS, pathologic grade, gender, clinical features, T-stage
Yamagata et al. (2019) [189]	I: 17 (17.9%), II: 23 (24.2%), III: 13 (13.7%), IVA: 40 (42.1%), IVB: 2 (2.1%)	T1: 23 (24.2%), T2: 40 (42.1%), T3: 7 (7.4%), T4a: 23 (24.3%), T4b: 2 (2.2%)	N0: 43 (45.3%), N1: 22 (23.2%), N2b: 24 (25.3%), N2c: 6 (6.3%)	No	tongue, lower gingiva, floor of mouth, buccal mucosa, hard palate, upper gingiva	44 (46.3%), 28 (29.5%), 8 (8.4%), 8 (8.5%), 2 (2.2%), 5 (5.3%)	RND: 47 (49.5%), SOHND: 37 (38.9%), RND + SOHND: 9 (9.5%), B/L SOHND: 2 (2.1%)	Surgery alone: 66 (69.5%), Surgery + RT: 4 (4.3%), Surgery + CRT: 25 (26.3%)	ROC curve	Multivariate	nodal disease area
Zhao et al. (2020) [190]	0: 11 (4.4%), I: 12 (4.8%), II: 21 (8.5%), III: 75 (30.2%), IV: 129 (52%	T0: 15 (6.1%), T1: 35 (14.1%), T2: 71 (28.6%), T3: 90 (36.3%), T4: 37 (14.9%)	N0: 103 (41.5%), N1: 41 (16.5%), N2a: 6 (2.5%), N2b: 77 (31%), N2c: 21 (8.5%)	No	tongue, gingiva, buccal mucosa, palate, floor of mouth, retromolar trigone	110 (44.4%), 39 (15.7%), 43 (17.3%), 16 (6.5%), 30 (12.1%), 10 (4%)	NR	Surgery + RT: 127 (51.2%), Surgery + CRT: 121 (48.8%)	ROC curve	Univariate/ Multivariate for pN+ =145	N/A/ T-, N-, TNM-classification, ENE for pN+ =145

Table S4. Node-related characteristics of the included studies (continued).

Study	Percentage of MRND, RND, B/L ND	Median/mean nodes removed (range)	Median/mean positive nodes removed (range)	Presence of extracapsular spread, n(%)	Close/involved margins, n(%)
Agarwal et al. (2019) [169]	U/L MND:49 (52%), U/L MND + C/L SND:15 (16%), B/L MND: 11 (12%)	NR	median 2 (1-25)	91 (97%)	Involved: 1 (1%)
Arun et al. (2020) [170]	NR	median 42.5 (14-168)	median 2 (1-42)	122 (57.5%)	Close/involved: 53 (25%)
Bharath et al. (2018) [162]	NR	mean 23.16	mean 1.98	22 (43.1%)	NR
Chang et al. (2018) [174]	NR	NR	NR	0 (0%)	0 (0%)
Chow et al. (2017) [168]	MRND: 12 (30.8%), RND: 3 (7.7%)	median 23 (8-93)	median 1 (1-17)	6 (15.4%)	Involved: 6 (15.4%)
Ding et al. (2019) [175]	NR	median 29 (1-110)	median 2	35 (23.5%)	Involved: 48 (32.2%)
Ebrahimi et al. (2011) [182]	Level I-V: 61 (15.2%)	mean 27.4	mean 3.4	62 (19.8%)	Involved: 18.2%
Gil et al. (2009) [183]	MRND: 65 (17%), RND: 50 (13%), B/L ND: 46 (12%)	mean 35 (6-114)	mean 2.7 (1-22)	24.6%	NR
Hosni et al. (2017) [176]	IPSILATERAL (all) MRND: 239 (26.1%), RND: 21 (2.3%) CONTRALATERAL (368) MRND: 38 (10.3%)	median 36 (6-125)	median 2 (1-49)	187 (20%)	Involved: 77 (8%)
Iftikhar et al. (2020) [165]	Ipsilateral MRND: 82 (68.3%), RND: 18 (15%) Contralateral MRND: 12 (22.2%), RND: 1 (1.85%)	NR	NR	NR	Involved: 12 (9.2%)
Jin et al. (2020) [177]	NR	mean 21.97	mean 0.74	NR	NR
Kim SY et al. (2011) [133]	MR/R: 54 (26%), Bilateral: 32 (15%)	median 25 (5-102)	median 2 (1-17)	19 (9%)	Involved: 12 (6%)
Künzel et al. (2014) [171]	B/L ND: 182	median 26 (10-71)	median 2 (1-15)	32 (9%)	Involved: 11 (3%)
Lee C.C. et al.(2015) [184]	NR	mean 23.2	mean 1.04	NR	Involved: 29 (8.4%)
Lee C.C. et al. (2017) [178]	NR	mean 33	mean 1.31	NR	NR
Lee H. et al. (2019) [179]	NR	median 35 IQR (25-52)	median 0 IQR (0-2)	149 (43.2%)	Involved: 20 (5.8%)
Lieng et al. (2016) [166]	NR	mean 22.8 (1-72) median 19	NR	33 (46%)	Involved: 7 (10%)
Moratin et al. (2020) [185]	NR	NR	NR	NR	Involved: 23 (5.3%)
Ong et al. (2016) [167]	RND: 34.3%	median 33 (2-88)	median 2 (0-13)	NR	Involved: 7 (7.1%)
Patel et al. (2013) [132]	RND: 327 (9.9%) B/L ND: 656 (16%)	mean 39 (2-104)	mean 3.1 (1-34)	1280 (30%)	NR
Rempel et al. (2018) [186]	MRND: 100%	mean 25.5 (6-87) median 22	mean 1.18 (0-18) median 0	NR	18 (10%)
Safi et al. (2017) [187]	NR	median 20 (1-112)	median 1 (1-11)	41 (8.2%)	0 (0%)

Shrime et al. (2009) [136]	NR	mean 41.6 (4-119) median 36	mean 3.3 (1-24)	56 (41.8%)	NR
Son et al. (2017) [163]	Therapeutic: 55 (41.4%)	NR	mean 1.4	NR	Involved: 6 (3.8%)
Spoerl et al. (2020) [172]	B/L ND: 218	mean 39.6 (1-104) median 38	mean 3.1 (1-41) median 2	78 (10.9%)	NR
Subramaniam et al. (2019) [180]	0%	median 23 (12-73)	NR	167 (26%)	Involved: 5 (1%)
Suzuki et al. (2016) [164]	B/L ND: 9 (25.7%)	NR	154	16 (45.7%)	7 (20%)
Urban et al. (2013) [173]	NR	median 27 (1-90)	median 2 (1-68)	287 (9.3%)	NR
Weckx et al. (2019) [181]	Ipsilateral MRND: 30 (19%), Ipsilateral RND: 6 (4%), Ipsilateral MRND + Contralateral SND: 24 (15%), Bilateral MRND: 11 (7%), Ipsilateral RND + Contralateral SND: 2 (1%)	NR	NR	21 (13%)	0 (0%)
Xu et al. (2017) [188]	B/L ND: 305	mean 23.5	mean 1.22 (0-55)	110 (26.3%)	0%
Yamagata et al. (2019) [189]	RND: 47 (49.5%), RND + SOHND: 9 (9.5%)	median 33 (10-118)	median 1 (0-33)	16 (16.8%)	Involved: 2 (2.2%) Close: 20 (20.1%)
Zhao et al. (2020) [190]	NR	mean 32.02 (1-100)	mean 1.9 (0-35)	37 (14.9%)	Involved: 0 (0%)

Table S5. Evaluation of within-study risk of bias with the Newcastle-Ottawa Scale (continued) [142].

Study	Selection				Comparability		Outcome			Total
	Representativeness	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start	Comparability on pN-classification	Comparability on other factors	Assessment of outcome	Long enough follow-up (median ≥2 years)	Adequacy (completeness) of follow-up (≥90% response rate)	
Agarwal et al. (2019)	1	1	1	1	0	1	1	1	1	8
Arun et al. (2020)	1	1	1	1	0	0	1	0	1	6
Bharath et al. (2018)	1	1	1	1	0	0	1	1	0	6
Chang et al. (2018)	1	1	1	1	0	0	1	1	1	7
Chow et al. (2017)	1	1	1	1	0	0	1	1	1	7
Ding et al. (2019)	1	1	1	1	0	0	1	0	1	6
Ebrahimi et al. (2011)	1	1	1	1	0	1	1	1	1	8
Gil et al. (2009)	1	1	1	1	1	1	1	1	1	9
Hosni et al. (2017)	1	1	1	1	0	0	1	1	1	7
Iftikhar et al. (2020)	1	1	1	1	0	1	0	0	1	6
Jin et al. (2020)	1	1	1	1	0	0	1	1	1	7
Kim SY et al. (2011)	1	1	1	1	0	1	1	1	1	8
Künzel et al. (2014)	1	1	1	1	1	1	1	1	1	9
Lee C.C. et al. (2015)	1	1	1	1	0	1	1	1	1	8

Lee C.C. et al. (2017)	1	1	1	1	0	0	1	0	1	6
Lee H. et al. (2019)	1	1	1	1	1	1	1	1	1	9
Lieng et al. (2016)	1	1	1	1	0	0	1	1	1	7
Moratin et al. (2020)	1	1	1	1	0	1	1	0	1	7
Ong et al. (2016)	1	1	1	1	0	0	1	1	1	7
Patel et al. (2013)	1	1	1	1	1	1	1	1	1	9
Rempel et al. (2018)	1	1	1	1	1	1	1	1	1	9
Safi et al. (2017)	1	1	1	1	0	1	1	1	1	8
Shrime et al. (2009)	1	1	1	1	0	0	1	1	1	7
Son et al. (2017)	1	1	1	1	0	1	1	1	1	8
Spoerl et al. (2020)	1	1	1	1	0	0	1	1	1	7
Subramaniam et al.(2019)	1	1	0	1	0	0	0	1	0	4
Suzuki et al. (2016)	1	1	1	1	0	1	1	0	1	7
Urban et al. (2013)	1	1	1	1	0	0	1	0	1	6
Weckx et al. (2019)	1	1	1	1	0	0	1	1	1	7
Xu et al. (2017)	1	1	1	1	0	1	1	1	0	7
Yamagata et al. (2019)	1	1	1	1	0	1	0	0	0	5
Zhao et al. (2020)	1	1	1	1	1	1	1	1	1	9