ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at:www.ijdsir.com

Volume – 7, Issue – 4, August – 2024, Page No. : 78 - 91

Comparison of Recurrence after Surgery & Surgery with Radiation in Oral Squamous Cell Carcinoma Patients Having Perineural Invasion - A Systematic Review

[1]Dr. Rajan Arora, BDS, MDS, Resident, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida.

[2]Dr. Ashish Sharma, BDS, MDS, Professor and Head, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida.

[3]Dr. Himanshu Bhutani, BDS, MDS, Professor, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida

[4]Dr. Yashobanta Biswal, BDS, MDS, Resident, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida

[5]Dr. Sugandha Kaushik, BDS, MDS, Resident, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida

[6]Dr. Anisha Grover, BDS, MDS, Resident, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida

Corresponding Author: Dr. Rajan Arora, BDS, MDS, Resident, Department of Oral and Maxillofacial Surgery, ITS Dental College, Greater Noida.

Citation of this Article: Dr. Rajan Arora, Dr. Ashish Sharma, Dr. Himanshu Bhutani, Dr. Yashobanta Biswal, Dr. Sugandha Kaushik, Dr. Anisha Grover, "Comparison of Recurrence after Surgery & Surgery with Radiation in Oral Squamous Cell Carcinoma Patients Having Perineural Invasion - A Systematic Review", IJDSIR- August – 2024, Volume –7, Issue - 4, P. No. 78 – 91.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

This systematic review evaluates the recurrence rates of oral squamous cell carcinoma (OSCC) in patients with perineural invasion (PNI) who underwent either surgery alone or surgery with adjunctive radiation. By analysing multiple studies, we aimed to assess the impact of PNI on treatment outcomes and the effectiveness of additional radiation therapy. Our findings suggest that perineural invasion serves as a significant independent predictor for cervical lymph node involvement. Consequently, elective neck dissection appears to enhance neck control and improve disease-specific survival in PNI-positive patients. However, the data also indicate that radical surgical resection alone may be adequate for managing OSCC, even when PNI is present. These results advocate for individualised

treatment plans, considering PNI as a crucial factor in decision-making for OSCC management.

Keywords: Perineural Invasions, Oral Squamous Cell Carcinoma, Surgical Recurrence, Elective Neck Dissection, Radiation Therapy.

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most usual malignancy found globally and accounts for at least 90% of all oral malignant conditions.[1] OSCC is associated with severe disease and treatment-related morbidity, and despite cancer treatment improvement, patients have been reported at high risk of relapse and disease-free survival.

The incidence of oral squamous cellcarcinoma (OSCC) over the past few years has been 2.1% of all malignancies in men and 0.7% in women.[1]However, recent research shows that results are better after the initial surgery, depending on the location of the lesion and the use of more aggressive treatment (such as neck elective).[2]Although these patients are difficult to treat, they are usually due to local or distant infection. Like other epithelial malignancies, OSCC is a group of tumors that result from a combination of various genetic and epigenetic changes that occur as a result of exposure to cancer, usually resulting in activation of oncogenes and loss of surviving cancer cells.[1]

Surgical resection is the mainstay of treatment for oral squamous cell carcinoma (OSCC), depending on the presence or absence of surgical or invasive features such asperineural invasion (PNI), lymphovascular involvement (LVI), involvement of lymph nodes and lymphatic vessels designated to treat extra-capsular disease (ECD).[3] At the same time as clinical failure, various histopathological features are used to identify patients at risk of relapse in order to identify better treatment options.[4] Among these, perineural invasion is commonly considered a poor prognosis and is associated withtumor progression, disease recurrence, and increased morbidity and mortality in OSCC patients.

The occurrence of PNI in squamous cell carcinomas of the head and neck region is quite high, ranging from 6% to 30%, and thus could play an important role in treatment decisions.[1]Perineuralinvasion or perineural spread is a specific way in which cancer cells spread within and along nerve fascicles, also described in the literature, it is a better village invasion site.[2] It is characterised by some tumors with central nervous system tropism (known as “neurotropicmalignancy") and may occur in the absence of lymphatic or vascular invasion.[2]

Treatment for advanced head and neck pain of ten involves a combination of different modalities. Radiation therapy (RT) in patients who have undergone surgery can reduce the risk of tumor recurrence while showing advanced features. Evidence for the use of adjuvant radiotherapy in patients with oral squamous cell carcinoma after primary surgery comes from retrospective studies of patient outcomes.[3,4]

The decision to treat after surgery is based on a detailed clinical examination, which includes evaluation of the difference between the tumor (its grade), the intervention pattern, the incision, and lymph nodes (if neck surgery is part of the procedure). Radiation therapy is applied to patients who are at risk of recurrence after the first surgery. After primary surgery for oral squamous cell carcinoma (OSCC), there is reasonable consensus to identify 'high risk' patients; those with extra-capsular involvement or spread.[3,4]

Oral squamous cell carcinoma is associated with high morbidity, recurrence, and decreased survival.Its prognosis is affected by many clinicopathological factors, one of which is perineural. invasion (PNI).[5] It is

a common type of cancer characterised by aggressive behavior, recurrent disease, and neurotropic malignancies associated with increased morbidity and mortality. PNI results from the tropism of tumor cells to blood vessels in the surrounding stroma. PNI occurs in up to 80% of head and neck cancers.[5] Adjuvant radiotherapy has shown a significant survival benefit in such patients. Several clinical and pathological conditions have been described that allow patients to be stratified according to their risk of relapse (either in the first place or in the neck), so those most likely to benefit from it may receive additional treatment.[6]

There is no standard protocol for treatment of oral squamous cell carcinoma patients with PNI and the controversy exists in the management of these type of cases. So, it was decided to conduct a systematic review to come to a more definitive treatment protocol for OSCC patients with PNI.

Review of Literature

Johannes J. Fagan, Bobby Collins (1998) stated in their study to determine if perineural invasion (PNI) of small nerves affects the outcome of patients with squamous cell carcinoma (SCC) of the upper aero digestive tract concluded with perineuralinvasion of small nerves is associated with an increased risk of local recurrence and cervical metastasis and is, independent of extra-capsular spread, a predictor of survival for patients with SCC of the upper aero digestive tract.[7]

Samuel W. Beenken, et.al., (1998) did a retrospective analysis in which they analysed all patients undergoing definitive surgical treatment of T1 and T2 SCC of the oral tongue between 1956 and 1994 at the University of Alabama at Birmingham was performed, which concluded with the presence of poorly differentiated disease gave the worst prognosis in this population of patients with T1 and T2 SCC of the oral tongue. A high incidence of nodal micro metastatic disease and the absence of recurrent disease after END suggest that END is appropriate therapy for these patients.[8]

Sefa Kaya, et.al., (2001) stated in their study that the files of 58 N0 patients with tongue cancer were evaluated retrospectively. In every patient, partial glossectomy continuous with neck dissection was the mainstay of the treatment. TNM staging, intraoperative Nstaging, pathologically con- firmed cervical lymph node metastases and their levels, and clinical outcomes (local and regional recurrences) were recorded. The sensitivity and specificity of intraoperative staging was determined, in which they resulted with fifty-four percent (31/58) of the patients presented as T1, and 26% (15/58) as T2. The overall occult metastasis rate was 29.3% (17/58). The occult metastasis rate for T1 and T2 lesions was 19.4% (6/31) and 26.7% (4/15), respectively. The sensitivity of intraoperative staging was 76.5%, and the specificity was 51.2% and they concluded with the rate of occult metastasis to the neck is too high in all tongue cancer cases to take the risk of regional recurrence, and the surgeon cannot solely depend on neck palpation for determination of neck metastasis. Radiologic investigations and fine-needle aspiration decrease, but never reduce to zero the rate of false-negative examination. There is an obvious indication for neck dissection, even in early cases.[9]

Shyh-Kuan Tai, et. al. (2002) stated in their study that perineural invasion (PNI) has been a poor prognostic factor for head and neck cancers, few studies have focused on oral squamous cell carcinoma (OSCC). The independent significance of PNI in early T1-2 OSCC and the benefit of treatment modification based on PNI status have not been assessed. This study investigated the role of PNI in T1-2 OSCC patients, with focus on the controversial issues of neck management and

postoperative adjuvant therapy. PNI status was re-reviewed under hematoxylin and eosin staining in tumours of 307 consecutive T1-2 OSCC patients. Oncologic and survival outcomes were analyzed by univariate and multivariate analyses. In their study, they concluded that elective neck dissection is indicated for cN0 patients with PNI-positive tumours for the efficacy of improving disease-specific survival as well as neck control. However, low-risk PNI-positive patients who undergo neck dissection do not need postoperative adjuvant therapy, because the residual risk from PNI is minimal.[10]

Bibi Rahima, et.al., (2004) stated a study in their study to evaluate the occurrence and prognostic significance of perineural invasion (PNI) in squamous cell carcinomas (SCC) of the oral cavity and oropharynx and they did a retrospective study of 101 patients with previously untreated SCC of the oral cavity and oropharynx was undertaken to evaluate the occurrence and prognostic significance of PNI in relation to local recurrence, regional recurrence, distant metastasis and survival. The logistic regression test was used for univariate and multivariate analyses. Actuarial survival curves were determined using the Kaplan-Meier method and concluded with PNI was present in 26 (25.7%) of 101 patients and was significantly associated with tumor differentiation, lymph node metastasis, and depth of invasion.[10] Univariate analyses showed PNI was associated with local recurrence (P = .005), regional recurrence (P = .007), and distant metastasis (P = .013). In multivariate analysis, PNI was significantly associated with regional recurrence (P = .033) and distant metastasis (P = .021), but not with local recurrence (P = .109). The 5-year disease-specific survival for patients with and without PNI was 56.6% and 94.6%, respectively (P = .0001). Also they concluded that PNI is an important predictor for outcome of patients with SCC of the oral cavity and oropharynx.[11]

Jacques Bernier, MD, PhD,1 Jay S. Cooper, MD, (2005) compared the addition of concomitant relatively high doses of cisplatin (on days 1, 22, and 43) to radiotherapy vs radiotherapy alone given after surgery in patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypo-pharynx. A comparative analysis of the selection criteria, clinical and pathologic risk factors, and treatment outcomes was carried out using data pooled from these two trials. And they concluded with Subject to the usual caveats of retrospective subgroup analysis, our data suggest that in locally advanced head and neck cancer, microscopically involved resection margins and extra-capsular spread of tumor from neck nodes are the most significant prognostic factors for poor outcome. The addition of concomitant cisplatin to postoperative radiotherapy improves outcome in patients with one or both of these risk factors who are medically fit to receive chemotherapy.[12]

J.S. Brown, et. al. (2006) described their study by reviewing computerised database and medical records for 462 consecutive patients at the Regional Maxillofacial Unit in Liverpool who were treated with primary surgery with or without post-operative radiotherapy was carried out.[12] They classified 29% (134) of patients as being at ‘low’ risk of disease recurrence (pT1-2, N0 with clear margins), 29% (135) at ‘high’ risk (involved margins or lymph node extra-capsular spread) and the remaining 42% (193) at ‘intermediate’ risk. Of those at intermediate risk, 41% (80/193) received adjuvant radiotherapy and their 5 year survival was 54% (6%) compared to 71% (5%) for those with primary surgery alone (P = 0.002). A higher

proportion of patients having radiotherapy had loco-regional recurrence (19/80 24%) compared to those treated by surgery alone (17/113 15%). The improved salvage rate for recurrent disease in the surgery alone group (8/17 53%), compared to those receiving radiotherapy (2/19 13%, P = 0.05), indicates an advantage in withholding radiotherapy for patients at intermediate risk of recurrence. This study indicates a potential disadvantage associated with the use of postoperative radiotherapy for patients at intermediate risk of recurrence.[1]

Chun-Ta Liao, et. al. (2008) in their study they have a purpose that The criteria for administration of adjuvant radiation therapy (RT) in oral cavity squamous cell carcinoma (OSCC) remain controversial, and it is unclear whether patients with pT1-3N0 disease benefit from adjuvant radiation in the presence of free margins and perineural invasion. The goal of this report was to determine whether this group would benefit from adjuvant radiation therapy in terms of5-year local control rate and overall survival rate. In all, 460 pT1-3N0 OSCC patients had tumor-free margins, of whom 68 had perineural invasion. Postoperative adjuvant RT was performed in patients with pT4 tumours, positive lymph nodes, or close margins (#4 mm). In addition, selected OSCC patients with large pT3 tumours or perineural invasion received postoperative adjuvant RT. Local control and overall survival rates were plotted by Kaplan-Meier analysis. They concluded that these data seem to indicate that radical surgical resection alone should be considered a sufficient treatment for OSCC patients with pT1-3N0 disease, even in the presence of perineural invasion.[2]

Crispian Scully , Jose V. Bagan (2008) stated in their paper provides a synopsis of the main papers on diagnosis, imaging, treatment, prognostication and treatment outcomes in patients with oral and oropharyngeal squamous cell carcinoma (OSCC) and head and neck SCC (HNSCC) published in 2008 in Oral Oncology – an international interdisciplinary journal which publishes high quality original research, clinical trials and review articles, and all other scientific articles relating to the atiopathogenesis, epidemiology, prevention, clinical features, diagnosis, treatment and management of patients with neoplasms in the head and neck, and orofacial disease in patients with malignant disease.[3]

J.W. Moor a, S. Wills b (2009) stated Histological analysis of tumour resection for squamous cell carcinoma (SCC) of the tongue yields prognostic information. They analysed histological slides of biopsy and tumour resection specimens using an adapted malignancy grading score and analysed variables of neck dissections. There was moderate correlation between biopsy and tumour resection using malignancy grading scores (correlation coefficient 0.45); good agreement of tumour grade (79%), tumour depth (76%), and type of invasive front (80%), but correlation was only fair to moderate ($\kappa = 0.38$, $\kappa = 0.51$, and $\kappa = 0.41$, respectively). Correlation of the biopsy grading score and invaded nodes in the neck, extra capsular spread, and soft tissue disease was not significant.[13]

Su Jung Shim, et.al. (2010) finalised their study with the aim of this study was to assess the results of curative surgery with and without radiotherapy in patients with T1-2N0-1 oral tongue squamous cell carcinoma (OSCC) and to evaluate survival and prognostic factors and conducted a retrospective analysis of 86 patients with T1-2N0-1 OSCC who received surgery between January 2000 and December 2006. Fourteen patients (16.3%) received postoperative radiotherapy (PORT). Patient characteristics, tumor characteristics, treatment modality,

failure patterns, and survival rates were analyzed, which concluded in T1-2N0-1 OSCC, factors that affected prognosis after primary surgery were higher tumor grade and deep invasion depth over 0.5 cm. Postoperative radiotherapy should be considered in early oral tongue cancer patients with these high-risk pathologic features.[14]

Shyh-Kuan Tai, MD,1, Wing-Yin Li, MD, (2011) stated risks of perineural invasion (PNI) in T1-2 oral tongue squamous cell carcinoma (SCC) have not been specifically elucidated and concluded with PNI is a crucial pathological feature for T1-2 oral tongue SCC. Elective neck dissection should be performed in patients who were cN0 with PNI. Careful evaluation for PNI should be advocated in regular pathological diagnosis.[15]

Nada O. Binmadi, John R. Basile (2011) stated in their study that the perineural invasion (PNI) is a tropism of tumor cells for nerve bundles in the surrounding stroma. It is a form of tumor spread exhibited by neurotropic malignancies that correlates with aggressive behavior, disease recurrence and increased morbidity and mortality. Oral squamous cell carcinoma (OSCC) is a neurotropic malignancy that traditionally has been difficult to treat and manage. Evidence suggests that demonstration of PNI in OSCC should impact adjuvant treatment decisions and surgical management of this disease. Despite its importance as a prognostic indicator, experimental studies to explore the molecular mechanisms responsible for PNI are limited. The aim of this review is to discuss the difficulties in evaluating for PNI, review the literature regarding the relationship of PNI with patient outcomes in OSCC, and summarise the recent studies describing the molecular agents associated with this pathological phenomenon.[5]

Tseng Cheng Chen, et.al. (2013) stated in their study that for early stage oral squamous cell carcinoma (OSCC) patients, the impact of perineural invasion (PNI) and lymphovascular invasion (LVI) on disease control and survival has not been clarified. In their study, there are a total of 442 early stage patients were included in this study. There were 360 patients in group A (without PNI or LVI) and 82 patients in group B (with PNI and/or LVI). Between groups A and B patients, there were no significant differences in the 5-year disease-free survival (73.8 vs 68.7 %, p = 0.48) and overall survival (90.9 vs 86.1 %, p = 0.25). Between groups A and B patients without postoperative radiotherapy (PORT), there were no significant differences in the 5-year disease free survival (73.8 vs 70.2 %, p = 0.51) and overall survival (90.9 vs 85.2 %, p = 0.18). Between group B patients with and without PORT, there was no significant difference in either the disease free survival (61.1 vs 70.2 %, p = 0.98) and overall survival (88.9 vs 85.2 %, p = 0.64).Multivariate analyses revealed that PNI, LVI, and PORT could not provide significant effect on treatment outcome. They concluded that PNI and LVI were not significant risk factors for the disease control and overall survival for early stage OSCC patients. Furthermore, PORT could not provide an additional benefit for the disease control and overall survival for stages I and II OSCC patients with PNI and/or LVI.[16]

Ioannis Chatzistefanou, et. al. (2014) stated that loco-regional recurrence is one of the main causes of treatment failure in patients with oral squamous cell carcinoma (OSCC). Perineural invasion (PNI) is widely accepted as an oncologic feature strongly associated with aggressive behavior, disease recurrence and poorer prognosis. Their study investigated the role of PNI in OSCC patients, regarding the controversial issues of its impact on loco-regional recurrence, neck management and postoperative adjuvant treatment decisions. Also they concluded that the perineural invasion should be

considered as an independent predictor for cervical lymph node involvement.[20] Elective neck dissection could therefore be an indicator in improving neck control and subsequently disease-specific survival in cN0 patients with PNI-positive SCC.[17]

Andres M. Bur, et.al. (2015) in their study stated perineural invasion (PNI) is widely regarded as a negative prognostic factor in head and neck squamous cell carcinoma (HNSCC). Treatment guidelines recommend adjuvant radiotherapy (RT) for patients with adverse pathologic features, including PNI. The purpose of this study was to systematically review the literature to determine if patients with PNI as their only indication for adjuvant therapy benefit from adjuvant RT. In total, 339 abstracts were reviewed for relevance leaving 85 articles, which were evaluated in detail. Thirteen retrospective studies addressed the role of adjuvant RT for patients with PNI. Evidence is lacking to recommend adjuvant RT for all patients with HNSCC with PNI. However, the literature suggests that large nerve or multifocal PNI may predict worse outcome and may be a more appropriate indication for adjuvant therapy. We advocate that patients decide whether to undergo adjuvant therapy after a discussion of the limitations of current evidence.[18]

J.F. Jardim, A.L.N. Francisco (2015) stated in their study Perineural invasion (PNI) and lymphovascular invasion (LVI) have been associated with the risk of local recurrences and lymph node metastasis. The aim of this study was to evaluate the prognostic impact of PNI and LVI in patients with advanced stage squamous cell carcinoma of the tongue and floor of the mouth. One hundred and forty-two patients without previous treatment were selected. These patients underwent radical surgery with neck dissection and adjuvant treatment. Clinicopathological data were retrieved from the medical charts, including histopathology and surgery reports. Univariate analysis was performed to assess the impact of studied variables on survival. Overall survival was negatively influenced by six tumour-related factors: increasing T stage ($P = 0.003$), more than two clinically positive nodes ($P = 0.002$), extra-capsular spread of lymph node metastasis ($P < 0.001$), tumour thickness ($P = 0.04$), PNI ($P < 0.001$), and LVI ($P = 0.012$). Disease-free survival was influenced by PNI ($P = 0.04$), extra-capsular spread of lymph node metastasis ($P = 0.008$), and N stage ($P = 0.006$). Multivariate analysis showed PNI to be an independent predictor for overall survival ($P = 0.01$) and disease-free survival ($P = 0.03$). Thus the presence of PNI in oral carcinoma surgical specimens has a significant impact on survival outcomes in patients with advanced stage tumours submitted to radical surgery and adjuvant radiotherapy/**radio - chemotherapy.** [19]

BK Varsha, et. al. (2016) stated that oral cancer constitutes 3% of all neoplasms and is the eighth most frequent cancer in the world. Oral squamous cell carcinoma (OSCC) corresponds to around 95% of all oral cancers. It is associated with severe morbidity, recurrence and reduced survival rates. Its prognosis is affected by several clinicopathologic factors, one of which is perineuralinvasion (PNI). It is the third most common form of tumor spread exhibited by neuro tropic malignancies that correlate with aggressive behavior, disease recurrence and increased morbidity and mortality. In the study, they concluded that PNI is present in both primary and recurrent tumours, irrespective of its histologic grading. The presence of PNI should be checked in every surgical specimen with OSCC as it gives significant prognostic value and influences recurrence and distant metastasis. The presence of PNI necessitates more aggressive resection,

coincident management of neck lymph nodes and the addition of adjuvant therapy.[20]

Ioannis Chatzistefanou, et. al. (2017) stated that the role of perineural invasion (PNI) in the management of patients with oral squamous cell carcinoma (OSSC) is still controversial, and there is no consensus regarding the most appropriate therapeutic approach. The purpose of this study is to review the findings in the literature describing OSCC as a neurotropic malignancy, with the aim of correlating perineural invasion with treatment decisions and disease prognosis. Perineural invasion (PNI) is a widely recognised indicator of poor prognosis in oral cancer patients, strongly correlating with aggressive tumor behavior, disease recurrence, and increased morbidity and mortality. Elective neck dissection could be an indicator in improving neck control in PNI-positive patients, while the addition of adjuvant postoperative radiotherapy may not significantly improve survival rates. Various molecular markers have been correlated with perineural tumor spread, but further investigations are required before targeting PNI as part of advanced cancer therapies.[20]

Kang-Hsing Fan, et.al, (2017) proposed their study to investigate the advantage of concurrent chemotherapy with postoperative radiotherapy (RT) of oral squamous cell carcinoma (OSCC) in patients with three or more minor risk factors. In study, Minor risk factors included pT4 disease, pN1 disease, margin $\leq$ 4 mm, poor differentiation, perineural invasion, vessel or lymphatic invasion, and tumor invasion depth $\geq$ 11 mm. Surgery was the primary treatment, followed by radiotherapy or concurrent chemoradiation (CCRT). After propensity score matching, 34 patients in each treatment group were selected for comparison. And after that they concluded with postoperative CCRT for patients with three or more minor risk factors increased recurrence-free and overall survival.[21]

Deepa Nair, Manish Mair (2017) stated a retrospective study of 1524 treatment naive patients with oral cavity SCC who underwent surgery from January 2012 to March 2015 was conducted. Survival analysis was performed using Cox regression model and concluded with aggressive treatment of the primary cancer with the coincident management of the neck is important in the presence of PNI. The PNI worsens survival and warrants intensification of adjuvant treatment.[6]

Jennifer Cracchiolo, Bin Xu (2018) stated Patients with oral tongue SCC who received primary surgical treatment were identified. Specimens were reviewed by head and neck pathologists. Disease-specific survival (DSS) and loco-regional recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant recurrence-free survival (DRFS) were calculated. The PNI and PNI characteristics were analyzed as predictors of outcome. The utility of grading the extent of PNI was assessed by quantifying the number of PNI foci per slide reviewed, nerve caliber, and percent circumference involved and concluded The presence of PNI in oral tongue SCC predicts worse DSS, with distant recurrence as the most common pattern of failure. High PNI foci density is associated with worse DRFS.[22]

Methodology

A systematic literature search of PubMed, Google Scholar, Medline, and Cochrane databases was performed from 1998 to 2022 using specific mesh words. Mesh words used are oral squamous cell carcinoma, treatment modalities for perineural invasion in oral cancer. Duplicates were excluded and abstracts were screened based on predetermined selection criteria. Relevant full text articles were retrieved and reference lists manually screened for additional articles.

Subsequently, the full texts of these articles were critically analysed.

Studies consisting of a mixed group of patients, in whose diagnosed with Oral Squamous Cell Carcinoma having perineural invasion could not be extracted from the whole study group to analyse the outcomes separately, were excluded. If there was double reporting of patients from the same centre in different publications, the article describing the largest group was included.

Inclusion criteria

1. Studies related with oral squamous cell carcinoma.
2. Studies related with perineural invasion.
3. Studies involving treatment modalities for oral squamous cell carcinoma.
4. Studies involving neck dissection as treatment protocol for cancer.
5. Studies involving radiotherapy and chemo-radiotherapy.

Exclusion Criteria

1. Studies involving malignancies of other region.
2. Studies on oral cancer patients without perineural invasion.
3. Studies with no involvement of treatment modalities.

Articles that did not meet the selection criteria were excluded. The data extraction was done using the PICO analysis. PICO analysis includes population that we are covering the patients diagnosed with oral squamous cell carcinoma, intervention including the patients with perineural invasion in which the comparison is done in between treatment modalities, that are surgery and surgery with radiation, and the outcome for our study will be opting out the better treatment modality with less recurrence rate, and better 5 year survival rate.

The primary outcome was to figure out the better treatment modality in terms of recurrence rate and 5 year survival rate, after surgery and surgery with radiation therapy in OSCC patients having perineural invasion.

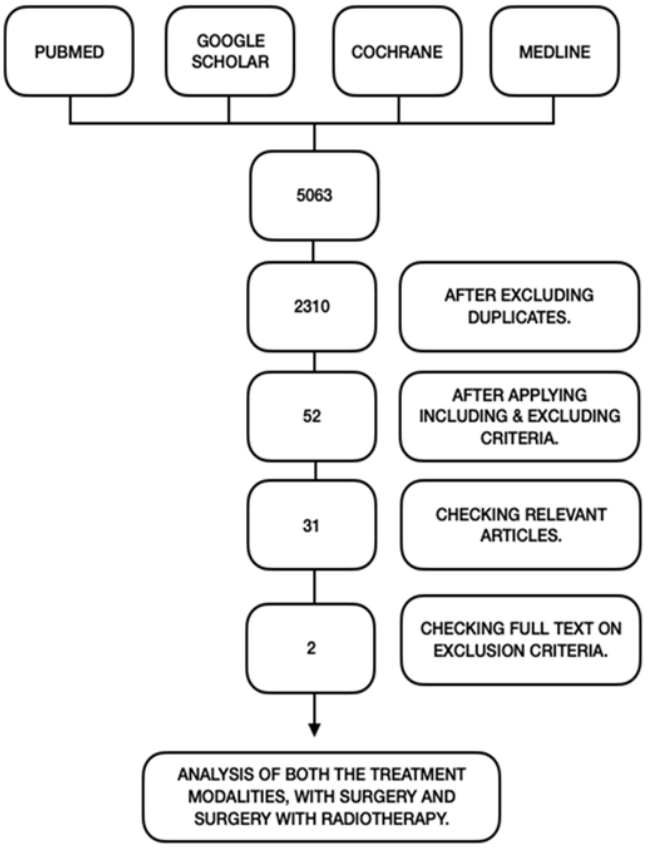

Table 1

P	I	C	O
Population	Intervention	Comparison	Outcome
Oral Squamous Cell Carcinoma Patients	With Perineural Invasion	In between treatment modalities : Surgery, Surgery with Radiation.	Less Recurrence Rate. Better 5-year Survival Rate.

Name of Article	The role of neck dissection and postoperative adjuvant radiotherapy in cN0 patients with PNI-positive squamous cell carcinoma of the oral cavity	DOES ADJUVANT RADIATION THERAPY IMPROVE OUTCOMES IN pT1-3N0 ORAL CAVITY CANCER WITH TUMOR-FREE MARGINS AND PERINEURAL INVASION?
Author	Ioannis Chatzistefanou	CHUN-TA LIAO
Inclusion of PICO	YES	YES
Review Method & Significant Deviation	YES	YES
Reason for selection of study design	YES	YES
Comprehensive Literature Search	YES	YES
Study selection in duplicate	YES	YES
Data extraction on duplicate	YES	YES
Exclusion Criteria & it's justification	NO	NO
Detailed description of PICO in study	NO	NO
Exclusion of risks of bias	YES	YES
Source of funding	NO	NO
Stat Analysis done if meta analysis included	YES	YES
Impact of ROB if meta analysis is performed.	NO	NO
Effect of ROB in data interpretation.	NO	NO
Explanation of heterogencity.	NO	NO
Investigation on publication bias on quantitative synthesis (if performed) and it's impact on result	YES	YES
Report on conflict of interest including funding.	NO	NO

Results

The initial search returned 5063 studies reported from January 1984 through July 2022. Abstracts and full text reports were acquired for 31 studies. After reviewing the full text reports on the basis of inclusion / exclusion criteria and Robis, only 2 studies were deemed eligible for the present preview.

Primary data was extracted from 2 included studies. The total sample size was 827 patients with oral squamous cell carcinoma, out of which on examination, concluded with 107 patients with perineural invasion.

Recurrence Rate: Elective neck dissection of the cervical lymph nodal levels I to III was found to significantly reduce the risk of regional recurrence in cN0 patients with PNI positive OSCC while neck observation demonstrated as an independent predictor of regional recurrence. Half of PNI positive patients, who had no END, developed regional recurrence within 3 years after initial treatment, while the relative percentage for those underwent END was only 8.5%. Postoperative adjuvant radiotherapy (RT) was found not to significantly alter the incidence of local or regional recurrence in patients with PNI positive OSCC. Among patients who did not receive postoperative RT, there was no statistical significant difference between patients with or without PNI, regarding local (26.3% vs. 27.5%) or regional (10.5% vs. 5.2%) recurrence.

Survival Rate: There were no significant differences in 5-year local control rates and overall survival rate between patients with perineural invasion (Group B) and patients without perineural invasion (Group A). Among patients with perineural invasion (Group B), the addition of adjuvant RT did not significantly alter the 5-yearlocal control rate or the overall survival rate. Among patients who did not receive postoperative RT (n = 343 in Group A, and n = 44 in Group B), no significant differences in 5-year local control (90.7% vs. 97.6%) and overall survival (82.8% vs. 86.2%) rates were evident between patients without (Group A) or with (Group B) perineural invasion.

In accordance with the above stated results, it is determined that radical surgical resection alone should be considered a sufficient treatment for OSCC patients, even in the presence of perineuralinvasion and perineural invasion should be considered as an independent predictor for cervical lymph node involvement. Elective neck dissection could therefore be an indicator in improving neck control and subsequently disease-specific survival in cN0 patients with PNI-positive SCC.

Discussion

Oral cancer is the sixth most usual cancer found globally.[1]More than 90% of oral cancers are squamous

cell carcinomas (SCC).[1] The most important risk factors for oral SCC are smoking or regular consumption of nuts and alcohol.[2] However, recent exposure to high-risk human papillomavirus (HPV) genotypes and a diet low in fresh fruits and vegetables have also been associated with oral squamous cell carcinoma.[1]The region with the highest incidence and most cases of oral squamous cell carcinoma is the Indian subcontinent, the best chewing tobacco, quid and betel quid increase the risk of oral SCC.[3,12].The mutagenic effects of cigarettes, alcohol, betel quid or betel nut depend on dose, frequency of use, and duration of use, and become faster and more severe with the use of two or more of these substances.

Oral squamous cell carcinoma can have different types of treatment. Leukoplakia may appear asverrucous leukoplakia, erythrocytic leukoplakia, or erythema; one of these eventually develops into a necrotic ulcer with irregular, raised hard edges or may form a beautiful wart-like surface or create a beautiful surface such as a wart a broad-based exophytic mass can create a surface such as cobblestone. Oral squamous cell carcinomas bleed easily when injured and often become a secondary disease. Oral squamous cell carcinoma is usually not painful unless there is a secondary infection. Large lesions may interfere with normal speech, chewing, or swallowing.[14]

The course of oral SCC is uncertain, but the TNM stage of the primary tumor (T tumor size, N nodal metastasis, M distant metastasis) is closely related to survival.[12] A positive diagnosis is best when the tumor is small and there is no evidence of regional tumor involvement or distant metastasis. In fact, according to the TNM staging system, the5-year survival rate of patients with early oral SCC can reach 80–90%, while the 5-year survival rate of patients with oral SCC is about 40%.[16]

Perineural invasion is the tropism of tumor cells to the nerves of surrounding tissues.[18] PNI is a type of metastatic spread similar to, but different from, vascular or lymphatic invasion; this hinders the ability of tumor cells to maintain local control of malignancy, as they can travel through the vessels and away from the primary tumor with blood, and the process is often absent.[18] Therefore, these tumors show pain and sustained growth with long-term treatment and late onset of metastasis, a pattern observed in the neurotropic type of pain.[18]

Among the many parameters used to predict the outcome of malignant disease, PNI is widely used as an indicator of aggressive behavior. Cruveilheir was the first to describe PNI in head and neck cancer in 1835.[13]

Although PNI has been discovered for over 150 years, the mechanisms of PNI are still not fully understood and no treatment modalities have been developed for this pathological purpose to date. Different theories have been proposed to explain the reality of PNI. In the past, cancer cells were thought to extend mechanically along the negative plane, such as loose tissue from the perineurium or development of lymphatic vessels from theneurolemma.[13] with the advent of ultra-microscopy these considerations were abandoned analysis of nerve cells shows that the perineurium is very complex and very selective.

One thing that is very difficult is that doctors do not have an accepted or standardised definition of PNI. Dunn et al. described PNI as the presence of malignant cells in the perineural space with complete or near involvement of nerves on a tangential histopathological section.[18] Liebig et al. stated that the most widely accepted and relevant definitions of PNI are presented: (1) the tumor is close to the blood vessel with one-third of its circumference, and/or (2) the tumor cell sheath is located in one of the three layers of the brain.[27]However,

these concepts are not clearly distinguishable from the discovery of brain tumors in and around the perineural space without "perineural" spread or involvement of nerve fascicles, and "intraneural" spread or infiltration of tumor cells into nerve fascicles.[13] The nerves themselves are elements that may be difficult to histologically identify but may affect the tumor. In fact, a study of anterior, middle, and lateral skull base adenoid cystic carcinoma showed that 39% of tumors showed intraneural invasion with evidence of PNI.[2,13] In a study of cutaneous squamous cell carcinoma, Mendenhall et al. Because intraneural invasion is rare in structures, the term "PNI" is used to refer to any perineural invasion, including intraneural spread, but the significance of this phenomenon has not been explored in detail.[2,12]

Diagnostic and treatment decisions for OSCC are currently based on TNM staging as determined by neck selection and histopathological features assessed by clinical examination, imaging studies, and biopsies considered to be a risk factor for patient outcomes, including: Tumor aggressive pattern, presence of PNI, and quality of lymphocyte response have been shown to be important determinants of local recurrence and overall survival, independent of tumor structure.[17]

The systematic review was done to compare in between the treatment modalities, that are surgery alone and surgery with radiation therapy to get to an conclusion with an outcome with less recurrence rate and better 5 year survival rate for OSCC patients with perineural invasion. Elective neck dissection of the cervical lymph nodal levels I to III was found to altogether decrease the chance of regional recurrence in cN0 patients with PNI-positive OSCC whereas neck observation illustrated as an free predictor of regional recurrence.[8] Half of PNI positive patients, who had no END, created regional recurrence after a time period of three years after starting treatment, whereas the relative rate for those experienced END was 8.5%. Postoperative adjuvant radiotherapy (RT) was found not to altogether change the rate of local or regional recurrence in patients with PNI- positive OSCC. Among patients who did not get postoperative RT, there was no statistical significant difference between patients with or without PNI, with respect to local (26.3% vs. 27.5%) or regional (10.5% vs. 5.2%) recurrence.[8]There were no significant differences in 5-year local control rates and overall survival rate between patients with perineural invasion (Group B) and patients without perineuralinvasion (Group A).[12] Among patients with perineural invasion (Group B), the addition of adjuvant RT did not significantly alter the 5-year local control rate or the overall survival rate. Among patients who did not get postoperative RT (n = 343 in Group A, and n = 44 in Group B), no significant differences in 5-year local control (90.7% vs. 97.6%) and overall survival (82.8% vs. 86.2%) rates were evident between patients without (Group A) or with (Group B) perineural invasion.[12]

The results of our current study clearly show that there is no significant difference in5-year local control and overall survival in patients with perineural invasion compared to those without. Adjuvant radiotherapy did not alter 5-year local control or overall survival, especially in patients with perineural invasion.

Conclusion

In conclusion, we can suggest that perineural invasion should be considered as an independent predictor for cervical lymph node involvement. Elective neck dissection could therefore be an indicator in improving neck control and subsequently disease specific survival in patients with PNI positive squamous cell carcinoma.

Altogether, the collected data seem to indicate that radical surgical resection alone should be considered a

sufficient treatment for OSCC patients, even in the presence of perineural invasion.

References

1. JS Brown, et al. A comparison of outcomes for patients with oral squamous cell carcinoma at intermediate risk of recurrence treated by surgery alone or with post-operative radiotherapy. J Oral Oncology2006:43, 764–773.
2. Chun ta Liao, et al. Does adjuvant radiation therapy improve outcomes in pT1-3N0 oral cavity cancer with tumor free margins and perineural invasion. Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 2, pp. 371–376, 2008
3. Crispian et al. Postoperative irradiation for squamous cell carcinoma of the oral cavity: 35-Year experience. Head Neck 2008;26:984–994.
4. Rahima B, Shingaki S, Nagata M, Saito C. Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:423–431.
5. Nada O. Binmadi, John R. Basile. Perineural invasion in oral squamous cell carcinoma: A discussion of significance and review of the literature. J Oral Oncology 2011 1005–1010.
6. Deepa Nair, et al. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2017:637–640.
7. Johannes J. Fagan et al. Higher distant failure in young age tongue cancer patients. Oral Oncol 1998: 718–725.
8. Samuel W. Beenken et al. Oral squamous cell carcinoma et al. Surgical outcome of T4a and resected T4b oral cavity cancer. Cancer 1998: 337–344.
9. Sefa Keya, et al. T4b oral cavity cancer below the mandibular notch is resectable with a favorable outcome. Oral Oncol 2001:570–579.
10. Shyh Kuan Tei, et al., Treatment for T1-2 Oral Squamous Cell Carcinoma with or Without Perineural Invasion: Neck Dissection and Postoperative Adjuvant Therapy, Ann Surg Oncol (2002).
11. Bibi Rehman, et al. Correlation of neural cell adhesion molecules with perineural spread of squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg 2004:717–720.
12. Jaques Bernier et al., editors. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag; 2005.
13. J.w. Moor et al. Biopsy examination of squamous cell carcinoma of the tongue: Source of significant prognostic information. BJOMS2009:984–994.
14. Su Jung Shim, et. al .Clinical outcomes for T1-2N0-1 oral tongue cancer patients underwent surgery with and without postoperative radiotherapy. J Radiation Oncology 2010:423–431.
15. Shyh Kun et al. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg 2011:224–231.
16. Tseng Cheng et al. The Impact of Perineural Invasion and/or Lymphovascular Invasion on the Survival of Early-Stage Oral Squamous Cell Carcinoma Patients. J. Ann Surg Oncol (2013) 20:2388–2395.
17. Ioannis V Chatzistefanou et al. The role of neck dissection and postoperative adjuvant radiotherapy in cN0 patients with PNI-positive squamous cell carcinoma of the oral cavity. J. Oral Oncol 2014 .05.005.

18. Andres M. Bur et al. Adjuvant radiotherapy for early head and neck squamous cell carcinoma with perineural invasion: A systematic review. J Head and Neck—DOI 10.1002/HED 2015.
19. JF Jardim et al. Prognostic impact of perineural invasion and lymphovascular invasion in advanced stage oral squamous cell carcinoma. Int J Oral Maxillofac Surg, 2015:570–579.
20. BK Varsha et al., editors. Perineural invasion in oral squamous cell carcinoma: Case series and review of literature; J Oral Maxillofac Pathol, 2016.
21. Ioannis Chatzistefanou et al., The role of perineural invasion in treatment decisions for oral cancer patients: A review of the literature, Journal of Cranio-Maxillo Facial Surgery, 2017.
22. Jennifer Crachiollo, et al. Patterns of recurrence in oral tongue cancer with perineural invasion J. Sciences and Specialities of Head and Neck2018:717–720.