

REVIEW

Prognostic impact of perineural invasion in oral cancer: a systematic review

Impatto prognostico dell'invasione perineurale nel cancro orale: una revisione sistematica

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SUMMARY

Introduction. Numerous studies have evaluated the prognostic significance of perineural invasion (PNI) in oral cancer; however, the results are inconclusive.

Purpose. To identify the prognostic value of PNI in oral cancer through a metaanalysis.

Methods. A literature review was carried out, searching the MedLine databases via Pubmed, Scielo, Lilacs, Cochrane and Websco.

Results. A total of 56 studies were included. The results indicate that PNI in oral cancer has an incidence of 28% (95% confidence interval (CI) 24-31%); 5-year survival with relative risk (RR) 0.67 (0.59-0.75); 5-year disease-free survival RR 0.71 (0.68-0.75); locoregional recurrence with RR 2.09 (1.86-2.35).

Conclusions. PNI is a negative prognostic factor in oral cancer.

KEY WORDS: oral cancer, carcinoma, squamous cell, perineural invasion, prognosis, risk factors, metaanalysis, systematic review

RIASSUNTO

Introduzione. Numerosi studi hanno valutato il significato prognostico dell'invasione perineurale (PNI) nel cancro orale; tuttavia, i risultati sono inconcludenti.

Scopo. Identificare il valore prognostico della PNI nel cancro orale attraverso una metaanalisi.

Metodi. È stata effettuata una revisione della letteratura, sfruttando MedLine Pubmed, Scielo, Lilacs, Cochrane e Websco.

Risultati. Sono stati inclusi un totale di 56 studi sul cancro orale. I risultati indicano che la PNI nel cancro orale ha un'incidenza del 28% (95% Confidence Interval (CI) 24-31%); Sopravvivenza a 5 anni con rischio relativo (RR) 0,67 (0,59-0,75); sopravvivenza libera da malattia a 5 anni RR 0,71 (0,68-0,75); recidiva locoregionale con RR 2,09 (1,86-2,35).

Conclusioni. La PNI è un fattore prognostico negativo nel cancro orale.

PAROLE CHIAVE: cancro orale, carcinoma, cellule squamose, invasione perineurale, prognosi, fattori di rischio, metaanalisi, revisione sistematica

Introduction

Among head and neck tumours, lesions of the upper aerodigestive tract stand out, of which 40% are oral cavity tumours^{1,2}. Approximately 95% of these are squamous cell carcinoma (SCC)^{3,4}. SEER⁵ data (Surveillance, Epidemiology and End Results Program) indicate that the estimated incidence of oral cancer for 2020 is 53,260 new cases in the USA (2.9%), with 10750 estimated deaths (1.8%). Its mortality in the period from 2013 to 2017 was 2.5/100,000. Over the past 20 years it has remained stable in terms of incidence and mortality.

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The prognosis of oral cavity cancer patients depends mainly on the size of the lesion, level of local invasion, regional lymphatic dissemination and presence of distant metastases⁶; other predictive factors are race, sex, vascular embolisation, perineural invasion (PNI) and histological grade⁷. However, SCC is not the most marked tendency to PNI, such as, for example, adenoid cystic carcinoma. Assessment of prognostic factors acts as a guide for treatment and follow-up decisions⁸.

PNI is a process predominantly characterised by neoplasm invasion of the nerves, which can occur in the absence of lymphatic or vascular invasion. Its propagation does not occur through lymphatic dissemination, but through molecular mediators that guide these cells through neural invasion. PNI was first described in head and neck cancer by Cruveiheur⁹ in 1835, being defined more than a century later as the invasion of one of the three nerve layers or the involvement of at least one third of its circumference¹⁰. Its incidence varies from 2 to 30%, with some reports of 82%. Such variation occurs when there are studies that specifically study PNI and studies where PNI is an evaluated cofactor, as well as discrepancies when there is a slide review with an active search for PNI¹¹.

The growth patterns of PNI are diverse, and can occur as: intraneural invasion, increasing formation, circular formation and onion-peel formation¹². Neoplastic cells tend to be concentrated in the perineurium, which is hypovascularised, and can extend up to 12 cm beyond the surgical margin through skip lesions¹³. Tumour growth via the neural pathway can occur in two ways: i) perineural invasion, usually in the small nerves, identified under microscopy; invasion of minor nerves is associated with an increased risk of local recurrence and cervical metastases, and is a predictor of survival, regardless of the risk of capsular rupture¹⁴; ii) perineural dissemination, where there is gross invasion of the nerve.

The purpose of this study is to analyse the prognostic impact of PNI in oral cancer patients through a systematic review, regarding locoregional recurrence, disease-free survival and mortality.

Methods

Studies that evaluated PNI in patients with oral cavity SCC were included. There was no restriction on the study design, year of publication; all articles in English, Spanish and Portuguese were reviewed. Overall survival, disease-free survival, and locoregional recurrence were evaluated. The MedLine databases were consulted via Pubmed, Scielo, Lilacs, Cochrane and Webco, with the keywords: “mouth cancer” OR “oral cancer” AND “perineural invasion” AND “prognosis”.

Studies where there was no analytical distinction among the multiple sites of primary disease, non-surgical treatment, studies that primarily evaluated surgical technique, studies evaluating a specific head and neck cancer population, duplicate studies or studies with replicated series, in vitro studies, and those that primarily assessed toxicity or quality of life were excluded.

Outcomes were treated as categorical and analysed with relative risk (RR) including 95% confidence interval (95% CI). Significant heterogeneity (occurs when different studies have different designs, for example) was defined as $I^2 > 50\%$. A random effect model was used, except when statistical heterogeneity was not significant. The funnel plot was used to assess heterogeneity. Analyses developed in RevMan 5.4 and R software, in the “Meta-Analysis” package.

Results

A total of 112 studies were retrieved; after reading all the articles, 56 studies potentially eligible for inclusion in the review were selected.

The incidence of PNI ranged between 3.35 and 63.15%. The risk of bias was assessed using the Cochrane scale, which highly value blinding. Through this scale, we identified a high potential for bias. In our study, the combined incidence of PNI in oral cavity SCC, using the random effect, was 28% (Fig. 1).

Of the total 5969 patients evaluated for overall 5-year survival, the RR was 0.67 (95% CI 0.64-0.74), with a high rate of heterogeneity when assessing the fixed model, so that the random evaluation model was used, with RR 0.67 (95% CI 0.59-0.75) (Fig. 2). The funnel plot shows publication bias regarding overall survival (Fig. 3).

Regarding disease-free survival at 5 years, the outcome was binary (recurrence/total number of subjects observed in the study). A total of 5508 patients were evaluated; the RR was 0.71 (95% CI 0.68-0.75), with low heterogeneity (Fig. 4). Publication bias was also identified (Fig. 5).

As for locoregional recurrence, a total of 2593 patients were evaluated; the RR was 2.09 (95% CI 1.86-2.35), with a high heterogeneity rate when assessing the fixed model. For evaluation of the random model, the RR was 2.2 (95% CI 1.6-3.01) (Fig. 6). Publication bias was identified (Fig. 7).

Discussion

The search for prognostic factors serves the purpose of better understanding the natural history of cancer, prediction of therapeutic interventions, identification of homogeneous

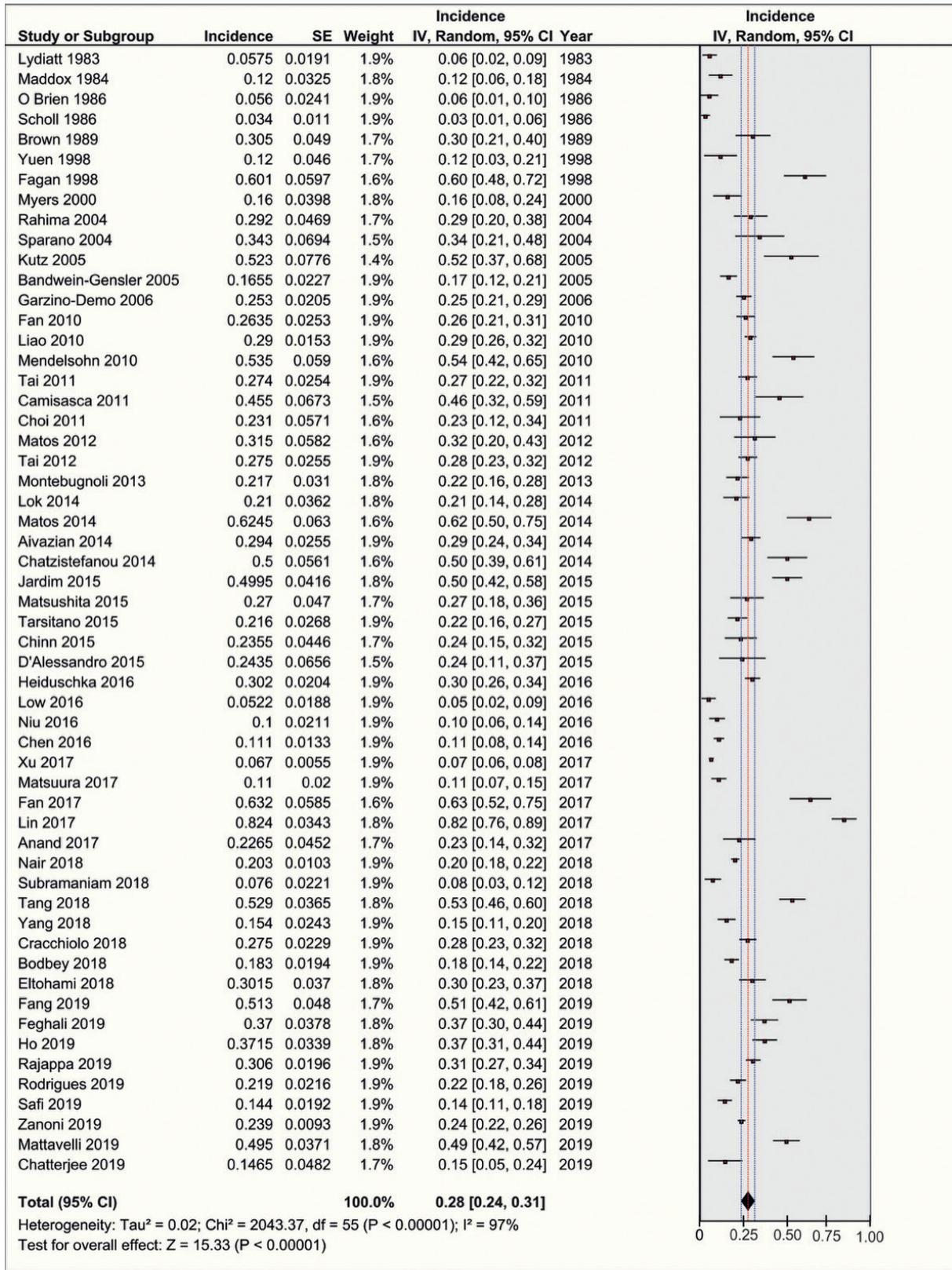


Figure 1. Combined incidence of PNI using a random effect model. An incidence of 28% was identified.

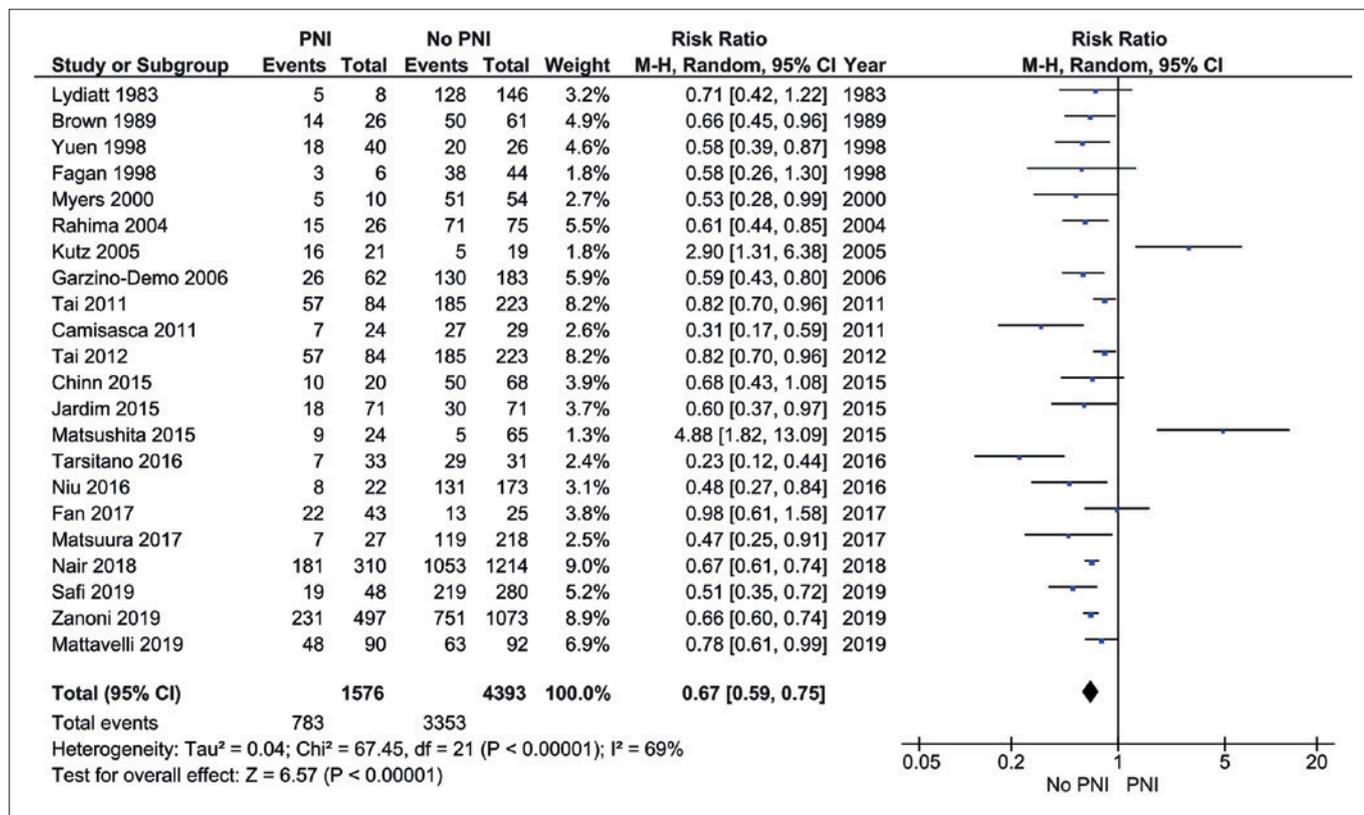


Figure 2. Meta-analysis of 5-year survival using a model with a random effect.

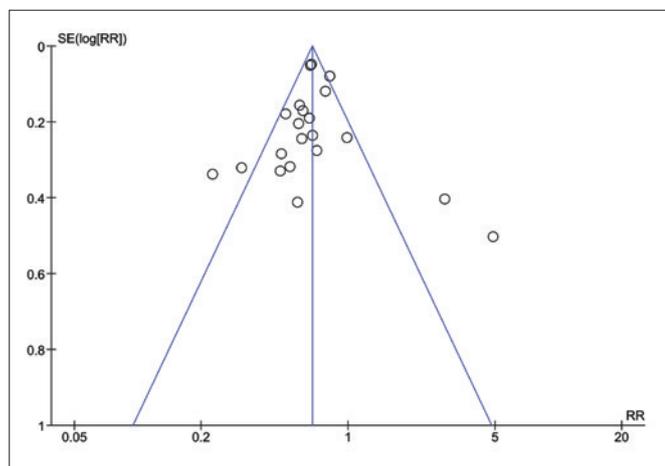


Figure 3. Funnel plot of the 5-year survival meta-analysis, indicating publication bias.

groups of patients, comparison of results of different treatments, identification of groups with unfavorable evolution and planning of follow-up strategies. It also allows for individualisation of treatment, with more aggressive strategies in groups with adverse variables and deintensification of treatment to those with more favourable variables ¹⁵.

One of the limitations in the literature about PNI is the lack of standardisation or method for its detection. Despite the definition disseminated by Liebig et al. ¹⁵, many authors use broader definitions, with PNI being contact of the nerve with neoplastic cells. Thus, studies of similar methodologies, with similar populations, tend to have different results, since they start from a different principle of PNI, justifying the combined incidence of PNI in oral cancer ranging from 3.35 to 63.15% in our study.

Furthermore, the technique used to detect PNI in studies is not standardised. Most pathologists report PNI as present or absent, without specifying the location, extent, or size of the nerve involved, which is not enough to identify characteristics that may actually cause a change in the impact of the disease (the simple contact of the nerve with tumour cells does not worsen prognosis; however, multiple foci of invasion lead to increased local recurrence) ¹⁶.

Thus, there is difficulty in diagnosing PNI. A false-negative result can occur in biopsies ¹⁷, more frequently when pathologists are not specifically looking for PNI. Thus, molecular studies are being carried out in order to facilitate the detection of PNI ¹⁸; the expression of N-CAM demonstrates a relation with the presence of PNI ¹⁹, but it is not yet

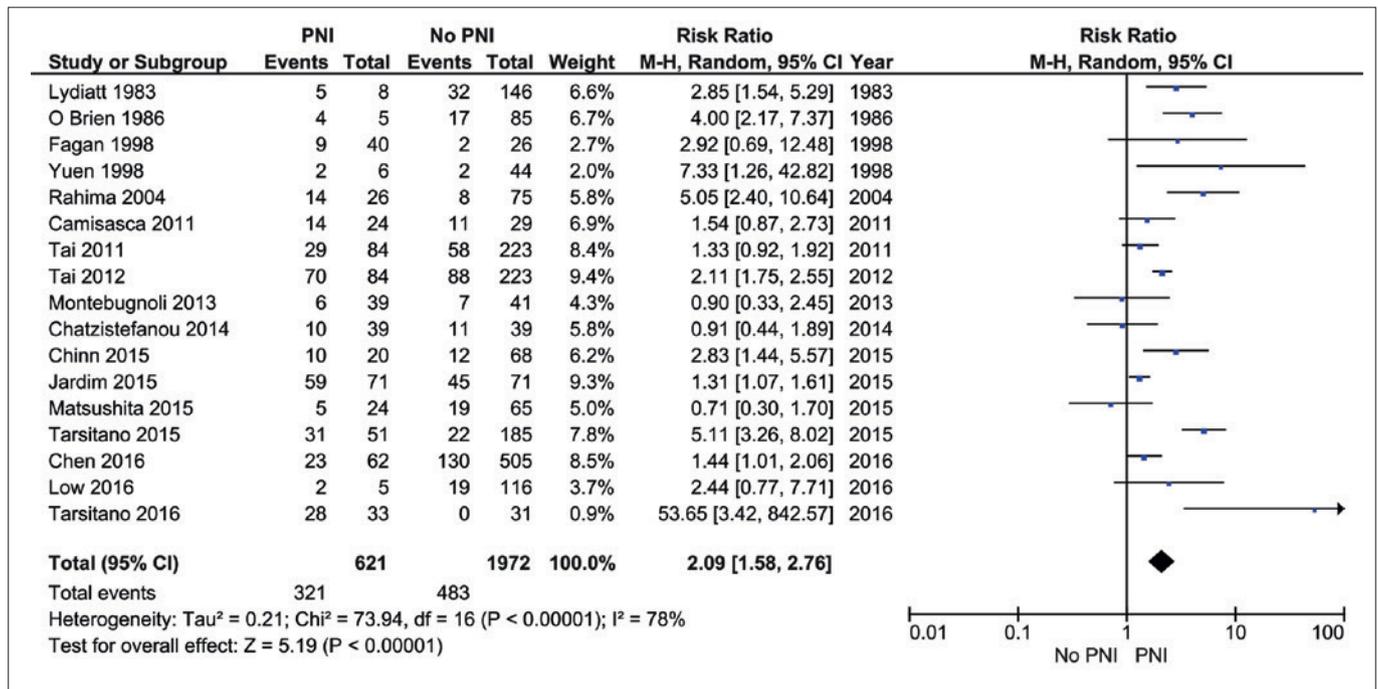


Figure 4. 5-year disease free-survival meta-analysis using a fixed effect model. Low heterogeneity.

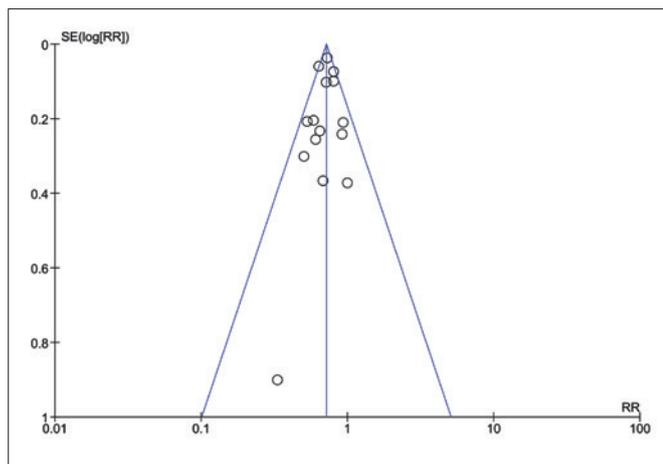


Figure 5. Funnel plot of the 5-year disease free-survival meta-analysis, indicating publication bias.

investigated in routine clinical practice. In studies where only PNI was evaluated, it has a higher incidence than in studies looking for multiple risk factors ¹¹.

As for clinical diagnosis, between 30 and 40% of patients are symptomatic, and 20% present neurological symptoms when, histologically, the tumour invades the nerve and interferes with its blood supply, causing local oedema, demyelination and segmental infarction ¹⁵. In addition, diagnosis by imaging (MRI) is only performed when PNI occurs in

large calibre nerves, when it is possible to identify bone erosion, enlargement of the foramina of the skull base, loss of fat in the pterygopalatine fossa and oedema in the nerve ²⁰.

Neural involvement usually starts with branches smaller than 1 mm, progressing to larger ones. When PNI is present, the surgical margins are no longer controlled by surgery, since tumour progression can occur up to 10 cm beyond its point of origin. Tumour cells tend to be concentrated in the perineurium, a poorly vascularised and relatively hypoxic environment, which leads to a relative radio resistance, corroborating the worst prognosis ¹⁴ of PNI.

PNI is associated with an increased risk of lymph node metastases. The presence of PNI is related to the expression of cortactin (a protein that has been suggested that affects the overall aggressiveness of head and neck carcinomas), as well as the presence of lymph node metastasis; it is inferred that their hyperexpression promotes cell migration ²¹, with the presence of both being related to reduced survival ²². It also contributes to worse prognosis as PNI is more prevalent in advanced tumours, which in itself is already a negative prognostic factor.

There are studies that associate PNI with increased risk of recurrence and reduced survival ¹⁵, while others fail to detect such a relationship ²³. This discrepancy probably results from the way in which the studies are conducted (studies that focus only on detecting PNI, without evaluat-

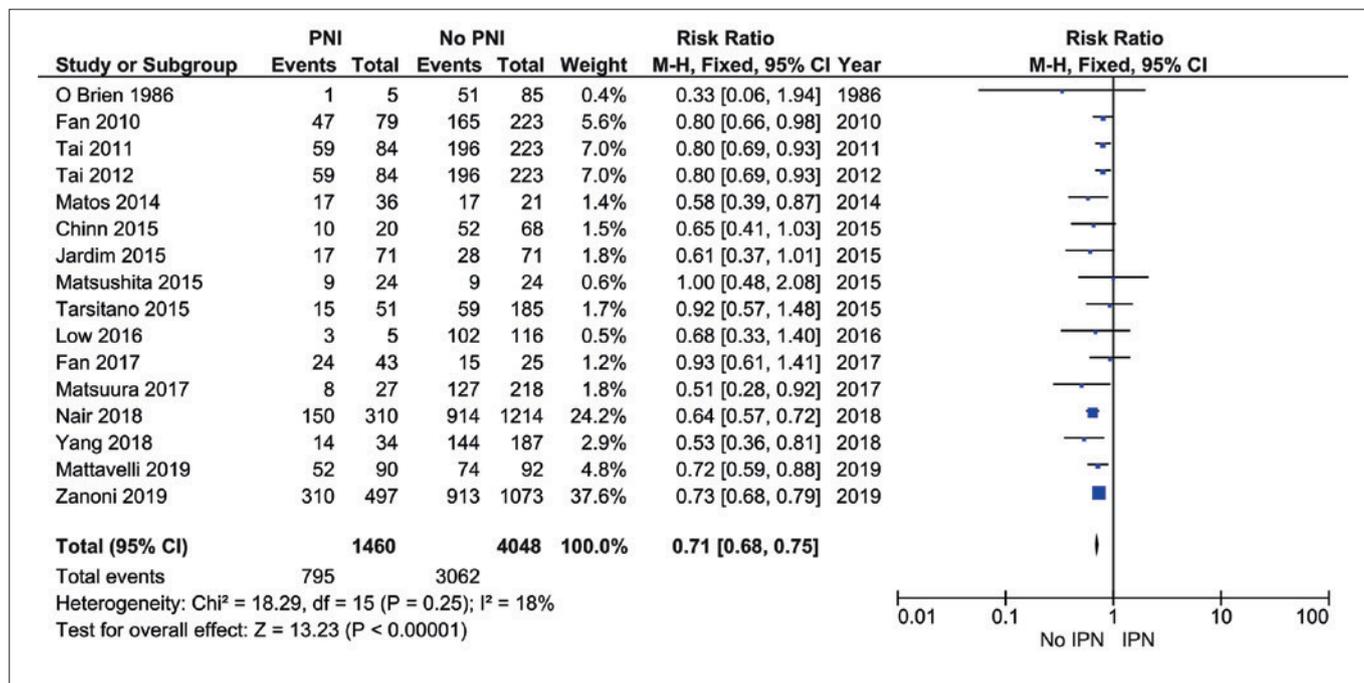


Figure 6. Meta-analysis of locoregional recurrence using a random effect model.

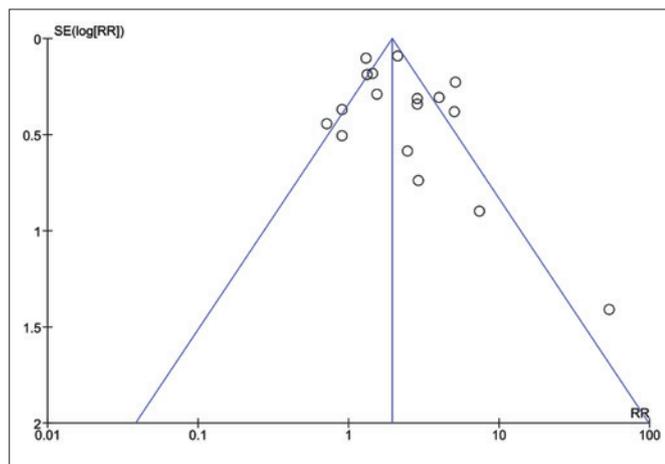


Figure 7. Funnel plot of the meta-analysis of locoregional recurrence, with publication bias.

ing other factors such as tumour margin or extension, are more positive)²⁴.

High analytical heterogeneity of the studies was identified, as well as publication bias. When conducting random evaluations of the sample, we observed that PNI represents a risk factor for lower overall survival, higher mortality, lower disease-free survival and greater risk of locoregional recurrence.

PNI should be considered a marker that indicates a more aggressive tumour behaviour, with a higher rate of cervical

metastases²⁵; therefore, its presence guides a more aggressive approach. In the absence of lymph node metastasis, PNI leads to greater locoregional recurrence and reduced disease-free survival, as an independent risk factor, despite studies with contradictory conclusions. The divergence in the conclusions of these studies is not due to low sampling, but rather to methodological differences in the studies, ranging from the definition of PNI to its measurement.

Considering that PNI has a negative impact on prognosis of patients with oral SCC, both in relation to overall survival and to disease-free survival, and is also a negative factor for locoregional recurrence, we have a perspective that should be regularly documented in all specimens (with description of both their presence and absence). This histopathological information must be performed in a standardised way, being reported the diameter of the affected nerve, as well as the presence of a single or multiple invasion focus.

Regarding the implications for clinical practice, characterisation of PNI is important for the development of personalised treatment strategies, and should be actively sought by the pathologist in the evaluation of oral cancer. However, including PNI in TNM staging system is not possible at present, due to the difficulty of standardising its identification by anatomopathological analyses. Machine learning methods in pathology may improve its detection on the future, as digital image analysis and the application of artificial intelligence develop further. The potential of artificial

intelligence (AI) is improve workflow and derive novel insights into disease biology²⁵ (survival and outcome prediction based on clinicopathological variables); this has been carried out on prostate cancer, breast cancer and cervical cancer with success. Despite the promise of AI models, the translational process to clinical application has been slow²⁶.

Conclusions

PNI is a negative prognostic factor in oral cancer in terms of overall survival, disease-free survival and locoregional recurrence.

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Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

DMVOQ: design of the work, data collection, data analysis and interpretation; drafting the article. RAD: design of the work; data analysis and interpretation; critical revision of the article. LPK: final approval of the version to be published.

Ethical consideration

This study was approved by the Institutional Ethics Committee of Faculdade de Medicina da Universidade de São Paulo (approval number/protocol number 367/17).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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