## 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 metanalysis.

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, metanalysis, 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 metanalisi.

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, metanalisi, revisione sistematica

## Introduction

Among head and neck tumours, lesions of the upper aerodigestive tract stand out, of which 40% are oral cavity tumours <sup>1,2</sup>. Approximately 95% of these are squamous cell carcinoma (SCC)<sup>3,4</sup>. SEER <sup>5</sup> 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. Received: April 30, 2021 Accepted: November 21, 2021

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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 Cruveiheir<sup>9</sup> 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 circumference <sup>10</sup>. 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 PNI <sup>11</sup>.

The growth patterns of PNI are diverse, and can occur as: intraneural invasion, increasing formation, circular formation and onion-peel formation <sup>12</sup>. 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 lesions <sup>13</sup>. 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 rupture <sup>14</sup>; 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 Websco, 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. Analyzes 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

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Myer     South     0.16     0.0398     1.8%     0.16     0.08.0.241     2000       Sparano 2004     0.343     0.0694     1.5%     0.29     0.20.63     2004       Sparano 2004     0.343     0.0694     1.5%     0.29     0.20.63     2004       Sparano 2004     0.343     0.0694     1.5%     0.29     0.20.6     1.9%     0.25     0.02.0     1.9%     0.25     0.02.0     1.9%     0.26     0.21.0.29     2006     1.9%     0.26     0.21.0.21     2010     0.25     0.25     0.25     0.21.0     1.20     0.25     0.21     0.21     0.21     0.21     0.21     0.21     0.21     0.21     0.20     0.26     0.22     0.21     0.21     0.21     0.21     0.22     0.21     0.22     0.21     0.21     0.21     0.22     0.21     0.22     0.21     0.22     0.21     0.22     0.21     0.22     0.21     0.22     0.21     0.22     0.22     0.22     0.21     0.22     0.22 <td>Yuen 1998</td> <td>0.12</td> <td>0.046</td> <td>1.7%</td> <td>0.12 [0.03, 0.21]</td> <td>1998</td> <td></td>	Yuen 1998	0.12	0.046	1.7%	0.12 [0.03, 0.21]	1998	
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Sparano 2004 0.343 0.0694 1.5% 0.34 (0.21, 0.48) 2004 Kutz 2005 0.253 0.0776 1.4% 0.52 (0.37, 0.68) 2005 Bandwein-Gensler 2005 0.1655 0.0227 1.9% 0.17 (0.12, 0.21) 2005 Garzino-Demo 2006 0.253 0.0205 1.9% 0.25 (0.21, 0.23) 2010 Liao 2010 0.28 0.0253 1.9% 0.26 (0.21, 0.31) 2010 Liao 2010 0.29 0.0153 1.9% 0.29 (0.26, 0.32) 2010 Camisasca 2011 0.455 0.0673 1.5% 0.46 (0.32, 0.59) 2011 Chaises 2011 0.455 0.0673 1.5% 0.46 (0.32, 0.59) 2011 Chaises 2012 0.315 0.0582 1.8% 0.22 (0.20, 0.32) 2011 Chaises 2012 0.315 0.0582 1.8% 0.22 (0.20, 0.32) 2012 Mates 2012 0.315 0.0582 1.8% 0.22 (0.20, 0.32) 2012 Mates 2012 0.315 0.0582 1.8% 0.22 (0.20, 0.32) 2012 Montebugnoli 2013 0.217 0.031 1.8% 0.28 (0.23, 0.22) 2012 Montebugnoli 2013 0.217 0.031 1.8% 0.28 (0.23, 0.22) 2012 Montebugnoli 2013 0.217 0.031 1.8% 0.22 (0.16, 0.28) 2014 Mates 2014 0.244 0.0254 1.9% 0.22 (0.16, 0.28) 2014 Mates 2014 0.245 0.0661 1.8% 0.50 (0.39, 0.61] 2014 Mates 2014 0.245 0.0661 1.8% 0.50 (0.39, 0.61] 2014 Mates 2014 0.254 0.0255 1.9% 0.22 (0.16, 0.27) 2014 Mates 2014 0.255 0.0464 1.7% 0.27 (0.16, 0.27) 2015 Tarsitano 2015 0.2436 0.0566 1.5% 0.42 (0.11, 0.37) 2015 Matsushita 2015 0.2436 0.0566 1.5% 0.42 (0.11, 0.37) 2015 Tarsitano 2015 0.2435 0.0464 1.7% 0.24 (0.11, 0.37) 2015 Tarsitano 2015 0.2436 0.0566 1.5% 0.42 (0.11, 0.37) 2015 Tarsitano 2015 0.2438 0.0656 1.5% 0.42 (0.11, 0.37) 2015 Tarsitano 2016 0.011 0.0133 1.9% 0.01 (0.06, 0.14) 2016 Tarsitano 2016 0.011 0.02 1.9% 0.011 (0.06, 0.14) 2016 Tarsitano 2016 0.011 0.022 1.9% 0.011 (0.06, 0.14) 2016 Tarsitano 2016 0.014 0.052 0.0048 1.9% 0.028 (0.33) 2017 Tarsitano 2015 0.2438 0.0452 1.7% 0.23 (0.16, 0.32] 2017 Tarsitano 2016 0.013 1.9% 0.020 (0.20, 0.14) 2016 Tarsitano 2016 0.013 1.9% 0.020 (0.20, 0.14) 2016 Tarsitano 2017 0.067 0.0055 1.9% 0.007 (0.06, 0.02 2018 Tarsitano 2018 0.076 0.0024 1.9% 0.03 (0.22, 0.75) 2017 Tarsitano 2016 0.013 0.9% 0.20 (0.10, 0.12) 2018 Tarsitano 2018 0.076 0.0221 1.9% 0.11 (0.06, 0.14) 2016 Tarsitano 2017 0.037 1.8% 0.040 (0.03, 0.1	Myers 2000	0.16	0.0398	1.8%	0.16 [0.08, 0.24]	2000	
Kutz 2005   0.523   0.0776   1.4%   0.52   0.37, 0.66   2005     Bandwein-Gensler 2005   0.1655   0.0227   1.9%   0.17   [0.12, 0.21]   2005     Fan 2010   0.2635   0.0253   1.9%   0.26   0.21, 0.31   2010     Lice 2010   0.2535   0.059   1.6%   0.54   0.42, 0.65   2010     Mendelsohn 2010   0.555   0.059   1.6%   0.54   0.42, 0.65   2010     Camisasca 2011   0.455   0.0571   1.6%   0.42   0.62   2011     Chiazot 21   0.275   0.0552   1.9%   0.22   0.21   2011     Chiazot 21   0.277   0.025   1.9%   0.22   0.20   2011	Rahima 2004	0.292	0.0469	1.7%	0.29 [0.20, 0.38]	2004	
Kutz 2005   0.523   0.0776   1.4%   0.52 (0.37, 0.66)   2005     Garzino-Demo 2006   0.2635   0.0205   1.9%   0.17 (0.12, 0.21)   2006     Garzino-Demo 2006   0.2635   0.0205   1.9%   0.26 (0.21, 0.31)   2010     Liao 2010   0.2635   0.029   0.1153   1.9%   0.26 (0.21, 0.31)   2010     Mendelsohn 2010   0.535   0.059   1.6%   0.54 (0.42, 0.65)   2010     Camisaca 2011   0.455   0.652   1.9%   0.42 (0.65)   2011     Camisaca 2012   0.315   0.0582   1.6%   0.32 (0.20, 0.43)   2012     Matos 2012   0.315   0.0582   1.6%   0.32 (0.20, 0.43)   2012     Matos 2014   0.6245   0.063   1.6%   0.26 (0.50, 75)   2014     Matos 2014   0.6245   0.063   1.6%   0.50 (0.34, 0.61)   2014     Avazian 2014   0.240   0.250 (0.27, 72)   2014   4     Avazian 2015   0.2416   0.270 (0.24, 0.34)   2014   4     Avazian 2014   0.250 (0.560   1.9%   0.260 (0.26, 0.	Sparano 2004	0.343	0.0694	1.5%	0.34 [0.21, 0.48]	2004	
Bandwein-Gensier 2005 0.0627 1.9% 0.77 [0.12, 0.21] 2005 Garzino-Demo 2006 0.263 0.0205 1.9% 0.25 [0.21, 0.29] 2006 Garzino-Demo 2006 0.263 0.0253 1.9% 0.26 [0.21, 0.31] 2010 Liao 2010 0.263 0.0253 1.9% 0.26 [0.21, 0.31] 2010 Liao 2010 0.29 0.0153 1.9% 0.29 [0.22, 0.32] 2011 Tai 2011 0.274 0.0254 1.9% 0.27 [0.22, 0.32] 2011 Choi 2011 0.455 0.0673 1.5% 0.46 [0.32, 0.52] 2011 Choi 2011 0.274 0.0254 1.9% 0.27 [0.22, 0.32] 2011 Choi 2011 0.275 0.0255 1.9% 0.28 [0.23, 0.32] 2012 Matos 2012 0.315 0.0562 1.6% 0.32 [0.20, 0.43] 2012 Montebugnoli 2013 0.277 0.031 1.8% 0.22 [0.16, 0.28] 2013 Montebugnoli 2013 0.217 0.031 1.8% 0.22 [0.16, 0.28] 2014 Matos 2014 0.224 0.0256 1.9% 0.29 [0.24, 0.34] 2014 Aivazian 2014 0.294 0.0256 1.9% 0.29 [0.24, 0.34] 2014 Aivazian 2014 0.5245 0.0663 1.6% 0.62 [0.50, 0.75] 2014 Aivazian 2014 0.5245 0.0661 1.6% 0.50 [0.30, 0.61] 2014 Aivazian 2015 0.276 0.0256 1.9% 0.29 [0.24, 0.34] 2015 Taristano 2015 0.2435 0.0446 1.7% 0.22 [0.16, 0.27] 2015 Taristano 2015 0.2435 0.0656 1.5% 0.24 [0.11, 0.37] 2015 D'Alessandro 2015 0.2435 0.0656 1.5% 0.24 [0.11, 0.37] 2015 D'Alessandro 2015 0.2435 0.0656 1.5% 0.24 [0.11, 0.37] 2015 Taristano 2015 0.2435 0.0656 1.5% 0.24 [0.11, 0.37] 2015 D'Alessandro 2015 0.2435 0.0656 1.5% 0.24 [0.11, 0.37] 2015 Taristano 2015 0.2435 0.0656 1.5% 0.24 [0.11, 0.27] 2015 Taristano 2016 0.11 0.021 1.9% 0.010 [0.06, 0.08] 2017 Taristano 2016 0.110 0.021 1.9% 0.010 [0.06, 0.08] 2017 Taristano 2016 0.100 0.211 1.9% 0.010 [0.06, 0.08] 2017 Taristano 2016 0.110 0.021 1.9% 0.020 [0.16, 0.22] 2018 Taristano 2017 0.110 0.022 1.9% 0.030 [0.23, 0.73] 2018 Taristano 2018 0.030 1.9% 0.20 [0.16, 0.22] 2018 Taristano 2016 0.130 1.9% 0.21 [0.16, 0.22] 2018 Taristano 2017 0.131 0.024 1.9% 0.28 [0.23, 0.23] 2018 Taristano 2018 0.037		0.523	0.0776	1.4%			
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Fan 2010   0.2833   0.0253   1.9%   0.26 [0.21, 0.31]   2010     Liao 2010   0.29   0.29   0.26, 0.32]   2010     Mendelsohn 2010   0.535   0.059   1.6%   0.29 [0.22, 0.32]   2011     Camisasca 2011   0.245   0.673   1.5%   0.26 [0.21, 0.34]   2011     Choi 2011   0.231   0.0571   1.6%   0.23 [0.20, 0.43]   2011     Tai 2012   0.315   0.0582   1.6%   0.32 [0.20, 0.43]   2012     Tai 2012   0.275   0.0255   1.9%   0.28 [0.23, 0.32]   2012     Matos 2012   0.275   0.0255   1.9%   0.28 [0.23, 0.32]   2014     Matos 2014   0.6245   0.063   1.6%   0.29 [0.24, 0.34]   2014     Matos 2014   0.6245   0.963   0.6% [0.39, 0.61]   2014     Matos 2014   0.6245   0.963   0.6% [0.39, 0.61]   2014     Matsushia 2015   0.27   0.461   1.7%   0.27 [0.16, 0.27]   2014     Jardim 2015   0.2435   0.0464   1.7%   0.27 [0.16, 0.27]   2015 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>							
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Tai 2011   0.224   0.0254   1.9%   0.27 [0.22, 0.32]   2011     Camisasca 2011   0.455   0.0671   1.5%   0.46 [0.32, 0.59]   2011     Matos 2012   0.315   0.0571   1.6%   0.32 [0.2, 0.34]   2012     Matos 2012   0.315   0.0525   1.9%   0.28 [0.23, 0.32]   2012     Montebugnoli 2013   0.217   0.031   1.8%   0.22 [0.16, 0.28]   2013     Matos 2014   0.6245   0.0631   1.6%   0.50 [0.50, 0.75]   2014     Alvazian 2014   0.6245   0.0661   1.6%   0.50 [0.39, 0.61]   2014     Jardim 2015   0.4995   0.0416   1.8%   0.50 [0.42, 0.58]   2015     Matus 2015   0.216   0.270 [0.16, 0.27]   2015							
Camisasca 2011 0,455 0,0673 1,5% 0,46 0,32,0,59 2011 Choi 2011 0,231 0,0571 1,6% 0,23 (0,20, 0,43) 2011 Tai 2012 0,275 0,0255 1,9% 0,28 (0,23, 0,32) 2012 Tai 2012 0,275 0,0255 1,9% 0,28 (0,28, 0,28) 2012 Montebugnoli 2013 0,217 0,031 1,8% 0,22 (0,14, 0,28) 2014 Matos 2014 0,244 0,0255 1,9% 0,29 (0,24, 0,34) 2014 Matos 2014 0,244 0,0255 1,9% 0,29 (0,24, 0,34) 2014 Avazian 2014 0,294 0,0255 1,9% 0,29 (0,24, 0,34) 2014 Aradim 2015 0,4995 0,0416 1,8% 0,50 (0,32, 0,58) 2015 Tarsitano 2015 0,216 0,0268 1,9% 0,22 (0,16, 0,32) 2015 D'Alessandro 2015 0,245 0,0656 1,5% 0,24 (0,11, 0,37) 2015 D'Alessandro 2015 0,2435 0,0656 1,5% 0,24 (0,11, 0,37) 2015 D'Alessandro 2015 0,0220 0,018 1,9% 0,05 (0,02, 0,09) 2016 Chen 2016 0,0522 0,018 1,9% 0,010 (0,6, 0,14) 2016 Tarsitano 2017 0,11 0,021 1,9% 0,01 (0,6, 0,04) 2016 Tarsitano 2017 0,11 0,021 1,9% 0,01 (0,6, 0,08) 2017 Matsuura 2017 0,11 0,022 1,19% 0,018 (0,6, 0,14) 2016 Targ 2017 0,629 0,0365 1,8% 0,08 (0,20, 0,75) 2017 Jana 2017 0,629 0,0365 1,8% 0,038 (0,27, 0,75) 2017 Jana 2017 0,226 50 0,452 1,7% 0,23 (0,14, 0,32) 2017 Anard 2017 0,226 50 0,452 1,7% 0,23 (0,14, 0,32) 2017 Targ 2018 0,059 0,134 1,9% 0,05 (0,02, 0,75) 2017 Targ 2018 0,059 0,134 1,9% 0,05 (0,02, 0,75) 2017 Targ 2018 0,059 0,18% 0,38 (0,37) 2018 Targ 2018 0,059 0,18% 0,37 (0,30, 0,44) 2019 Targ 2018 0,059 0,18% 0,38 (0,37) 2018 Targ 2018 0,059 0,18% 0,37 (0,30, 0,44) 2019 Targ 2018 0,154 0,023 1,18% 0,30 (0,20, 0,37] 2018 Targ 2018 0,154 0,033 1,8% 0,37 (0,30, 0,44) 2019 Targ 2018 0,154 0,037 1,8% 0,37 (0,30, 0,44) 2019 Targ 2019 0,371 0,371 1,8% 0,37 (0,31, 0,44) 2019 Targ 2019 0,371 0,371 1,8% 0,37 (0,31, 0,44) 2019 Targ 2019 0,366 0,0196 1,19% 0,37 (0,24, 2,057) 2019 Targapa 2019 0,445 0,0371 1,8% 0,49 (0,42, 0,57) 2019 Tarderige 201							
Choi 2011 0.231 0.0571 1.6% 0.32 [0.12, 0.34] 2011 Matos 2012 0.315 0.0562 1.6% 0.32 [0.20, 0.43] 2012 Montebugnoli 2013 0.217 0.031 1.8% 0.22 [0.16, 0.28] 2013 Lok 2014 0.247 0.032 1.8% 0.21 [0.14, 0.28] 2014 Matos 2014 0.6245 0.063 1.6% 0.62 [0.50, 0.75] 2014 Aivazian 2014 0.249 0.0255 1.9% 0.29 [0.24, 0.34] 2014 Lot 2014 0.50 561 1.6% 0.50 [0.50, 0.61] 2014 Jardim 2015 0.4995 0.0416 1.8% 0.50 [0.42, 0.58] 2015 Tarsitano 2015 0.277 0.047 1.7% 0.27 [0.16, 0.28] 2015 Chaizisefanou 2014 0.5265 0.0466 1.7% 0.24 [0.16, 0.27] 2015 Chaizisefanou 2015 0.2435 0.0566 1.5% 0.24 [0.16, 0.27] 2015 Chaiz 105 0.277 0.047 1.7% 0.24 [0.16, 0.27] 2015 Chinn 2015 0.2365 0.0446 1.7% 0.24 [0.16, 0.32] 2015 Chinn 2015 0.2435 0.0566 1.5% 0.24 [0.11, 0.37] 2015 Chinn 2015 0.2435 0.0566 1.5% 0.24 [0.11, 0.37] 2015 Chinn 2015 0.2435 0.0566 1.5% 0.24 [0.11, 0.37] 2015 Chinn 2016 0.0522 0.0188 1.9% 0.05 [0.02, 0.9] 2016 							
Matos 2012   0.316   0.0682   1.6%   0.32   0.20   0.43   2012     Tai 2012   0.275   0.0255   1.9%   0.28   0.23   0.32   2012     Montebugnoli 2013   0.217   0.0362   1.8%   0.22   1016   0.28   2013     Lok 2014   0.21   0.0362   1.8%   0.22   1016   0.28   2014     Matos 2014   0.6245   0.0663   1.6%   0.50   0.75   2014     Avazian 2014   0.25   0.1%   0.29   0.24, 0.58   2015     Jardim 2015   0.495   0.046   1.7%   0.27   10.16, 0.32   2015     Matsushita 2015   0.237   0.047   1.7%   0.24   10.16, 0.32   2015     Tarsitano 2015   0.2435   0.0666   1.5%   0.24   10.16, 0.32   2016     Low 2016   0.0302   0.0204   1.9%   0.30   10.26, 0.34   2016     Low 2016   0.111   0.021   1.9%   0.07   10.06, 0.08   2017   •     Fan 2017   0.632   <							
Tai 2012   0.275   0.0255   1.9%   0.28 [0.23, 0.32]   2012     Montebugnoli 2013   0.217   0.031   1.8%   0.22 [0.16, 0.28]   2013     Lok 2014   0.6245   0.063   1.8%   0.21 [0.14, 0.28]   2014     Alvazian 2014   0.6245   0.0661   1.8%   0.52 [0.50, 0.75]   2014     Alvazian 2014   0.294   0.0255   1.9%   0.29 [0.24, 0.34]   2014     Alvazian 2015   0.0561   1.8%   0.50 [0.30, 0.61]   2014     Jardim 2015   0.27   0.047   1.7%   0.27 [0.18, 0.36]   2015     Tarsitano 2015   0.2435   0.0446   1.7%   0.22 [0.16, 0.27]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.22 [0.16, 0.27]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30 [0.26, 0.34]   2016     Low 2016   0.11   0.011   0.05 [0.02, 0.09]   2016							
Montebugnoli 2013   0.217   0.031   1.8%   0.22 [0.16, 0.28]   2013     Lok 2014   0.21   0.0362   1.8%   0.21 [0.14, 0.28]   2014     Aivazian 2014   0.6245   0.063   1.6%   0.620 [0.50, 0.75]   2014     Aivazian 2014   0.29   0.0255   1.9%   0.29 [0.24, 0.34]   2014     Aivazian 2014   0.5   0.50 [0.39, 0.61]   2014							
Lok 2014 0.21 0.0362 1.8% 0.21 (0.14, 0.28) 2014 Matos 2014 0.6245 0.063 1.6% 0.62 (0.50, 0.75) 2014 Avazian 2014 0.294 0.0255 1.9% 0.29 (0.24, 0.34) 2014 Chatzistefanou 2014 0.5 0.0561 1.6% 0.50 (0.39, 0.61) 2014 Jardim 2015 0.4995 0.0416 1.8% 0.50 (0.42, 0.58) 2015 Matsushita 2015 0.27 0.047 1.7% 0.27 (0.18, 0.36) 2015 Tarsitano 2015 0.216 0.0268 1.9% 0.22 (0.16, 0.27) 2015 Chim 2015 0.2355 0.0446 1.7% 0.24 (0.15, 0.32) 2015 Chim 2015 0.2355 0.0446 1.7% 0.24 (0.11, 0.37) 2015 Heiduschka 2016 0.302 0.2024 1.9% 0.30 (0.26, 0.34) 2016 Low 2016 0.0552 0.0188 1.9% 0.05 [0.02, 0.09] 2016 Nu 2016 0.0552 0.0188 1.9% 0.01 (0.06, 0.14) 2016 Vu 2016 0.0552 0.0188 1.9% 0.01 (0.06, 0.14) 2016 Vu 2017 0.067 0.055 1.9% 0.07 [0.06, 0.08] 2017 Hatsuura 2017 0.11 0.02 1.9% 0.11 (0.07, 0.15) 2017 Fan 2017 0.632 0.0585 1.6% 0.63 [0.52, 0.75] 2017 Anand 2017 0.2265 0.0452 1.7% 0.23 [0.14, 0.32] 2017 Targ 2018 0.076 0.0221 1.9% 0.01 [0.03, 0.14] 2018 Vang 2018 0.0529 0.0365 1.8% 0.53 [0.46, 0.60] 2018 Tang 2018 0.0529 0.0365 1.8% 0.53 [0.46, 0.60] 2018 Tang 2018 0.0515 0.037 1.8% 0.35 [0.46, 0.60] 2018 Tang 2018 0.0515 0.037 1.8% 0.37 [0.30, 0.44] 2019 Feghali 2019 0.513 0.048 1.7% 0.51 [0.41, 0.22] 2018 Tang 2018 0.0154 0.0229 1.9% 0.16 [0.23, 0.32] 2018 Tang 2018 0.0154 0.0239 1.9% 0.36 [0.23, 0.37] 2018 Tang 2018 0.0154 0.037 1.8% 0.37 [0.30, 0.44] 2019 Feghali 2019 0.513 0.048 1.7% 0.51 [0.42, 0.61] 2019 Feghali 2019 0.513 0.048 1.7% 0.51 [0.42, 0.61] 2019 Feghali 2019 0.513 0.048 1.7% 0.51 [0.42, 0.61] 2019 Tang 2019 0.513 0.048 1.7% 0.51 [0.42, 0.61] 2019 Tang 2019 0.514 0.0393 1.8% 0.37 [0.30, 0.44] 2019 Tang 2019 0.514 0.0393 1.8% 0.37 [0.30, 0.44] 2019 Tang 2019 0.514 0.0482 1.7% 0.51 [0.27, 0.34] 2019 Tang 2019 0.514 0.0482 1.7% 0.51 [0.27, 0.34] 2019 Tang 2019 0.5145 0.0482 1.7% 0.49 [0.42, 0.57] 2019 Tang 2019 0.5146 0.0482 1							
Matos 2014   0.6245   0.063   1.6%   0.62 [0.50, 0.75]   2014     Aivazian 2014   0.2294   0.0255   1.9%   0.29 [0.24, 0.34]   2014     Chatzistefanou 2014   0.50 0.0561   1.6%   0.50 [0.39, 0.61]   2015     Chatzistefanou 2015   0.4995   0.0416   1.8%   0.50 [0.42, 0.58]   2015     Matsushita 2015   0.27   0.047   1.7%   0.27 [0.16, 0.37]   2015     Chinn 2015   0.2355   0.0446   1.7%   0.24 [0.15, 0.32]   2015     D'Alessandro 2015   0.2435   0.0204   1.9%   0.30 [0.26, 0.34]   2016     Low 2016   0.0522   0.0188   1.9%   0.05 [0.02, 0.09]   2016     Nu 2016   0.11   0.021   1.9%   0.01 [0.06, 0.14]   2016     Xu 2017   0.067   0.055   1.9%   0.07 [0.06, 0.8]   2017     Matsura 2017   0.11   0.02   1.9%   0.21 [0.27, 0.52]   2017     Fan 2017   0.632   0.6585   1.6%   0.63 [0.52, 0.75]   2017     Variationaliam 2018   0.076   0.022 [0.18, 0.22] <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
Aivazian 2014   0.294   0.0255   1.9%   0.29   0.24   0.34   2014     Chatzistefanou 2014   0.5   0.0661   1.6%   0.50   0.39   0.61   2014     Jardim 2015   0.4945   0.0416   1.8%   0.50   0.215   0.11     Chinn 2015   0.216   0.0268   1.9%   0.22   0.16   0.27   2015     D'Alessandro 2015   0.2435   0.0656   1.5%   0.24   (0.1, 0.37)   2015     D'Alessandro 2016   0.302   0.0204   1.9%   0.30   0.26, 0.34   2016     Low 2016   0.0522   0.0188   1.9%   0.05   0.02, 0.09   2016     Niu 2016   0.1   0.0211   1.9%   0.10   0.06, 0.14   2016     Vau 2017   0.067   0.055   1.9%   0.07   0.06, 0.08   2017     Matsuura 2017   0.11   0.022   0.018   2017   -     Matsura 2017   0.224   0.343   1.8%   0.82   2017   -     Nair 2018   0.0203   0.0103   1.9%							
Chatzistefanou 2014   0.5   0.0561   1.6%   0.50   0.39, 0.61   2014     Jardim 2015   0.4995   0.0416   1.8%   0.50   0.42, 0.58   2015     Tarsitano 2015   0.216   0.0268   1.9%   0.22   0.16, 0.27   2015     Chin 2015   0.2355   0.0446   1.7%   0.24   0.15, 0.32   2015     D'Alessandro 2015   0.2355   0.0656   1.5%   0.24   0.15, 0.32   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30   0.26, 0.34   2016     Low 2016   0.111   0.0211   1.9%   0.05   0.02, 0.09   2016     Viu 2016   0.11   0.021   1.9%   0.11   0.06, 0.04   2016	Matos 2014	0.6245	0.063	1.6%			
Jardim 2015   0.4995   0.0416   1.8%   0.50   0.42, 0.58   2015     Matsushita 2015   0.27   0.047   1.7%   0.27   0.18, 0.36   2015     Tarsitano 2015   0.216   0.0268   1.9%   0.22   [0.16, 0.27]   2015     Chinn 2015   0.2355   0.0446   1.7%   0.24   [0.16, 0.27]   2015     D'Alessandro 2015   0.2435   0.0656   1.5%   0.24   [0.11, 0.37]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30   [0.26, 0.34]   2016     Low 2016   0.0522   0.0188   1.9%   0.05   [0.20, 0.09]   2016     Niu 2016   0.11   0.0211   1.9%   0.10   [0.06, 0.14]   2016     Vu 2017   0.0652   0.0585   1.6%   0.63   [0.52, 0.7]   2017     Matsuura 2017   0.11   0.02   1.9%   0.21   [0.76, 0.89]   2017     Nair 2018   0.221   1.9%   0.20   [0.18, 0.22]   2018      Subramaniam 2018   0.076   0.0452	Aivazian 2014	0.294	0.0255	1.9%	0.29 [0.24, 0.34]	2014	
Matsushita 2015   0.27   0.047   1.7%   0.27   0.18, 0.36   2015     Tarsitano 2015   0.216   0.0268   1.9%   0.22   [0.16, 0.27]   2015     Chinn 2015   0.2355   0.0466   1.7%   0.24   [0.15, 0.32]   2015     D'Alessandro 2015   0.2435   0.0656   1.5%   0.24   [0.17, 0.37]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30   [0.26, 0.34]   2016     Low 2016   0.01522   0.0188   1.9%   0.05   [0.02, 0.09]   2016     Niu 2016   0.11   0.0211   1.9%   0.10   [0.06, 0.14]   2016     Chen 2016   0.11   0.021   1.9%   0.01   [0.06, 0.08]   2017     Matsuura 2017   0.11   0.02   1.9%   0.11   [0.07, 0.15]   2017     Fan 2017   0.632   0.0585   1.6%   0.633   [0.52, 0.75]   2017     Lin 2017   0.824   0.033   1.8%   0.82   [0.76, 0.89]   2017     Anard 2017   0.2265   0.4452	Chatzistefanou 2014	0.5	0.0561	1.6%	0.50 [0.39, 0.61]	2014	
Tarsitano 2015   0.216   0.0268   1.9%   0.22 [0.16, 0.27]   2015     Chinn 2015   0.2355   0.0446   1.7%   0.24 [0.15, 0.32]   2015     D'Alessandro 2015   0.2435   0.0656   1.5%   0.24 [0.11, 0.37]   2015     Heiduschka 2016   0.0302   0.0204   1.9%   0.30 [0.26, 0.34]   2016     Low 2016   0.0522   0.0188   1.9%   0.05 [0.02, 0.09]   2016     Nu 2016   0.11   0.013   1.9%   0.01 [0.06, 0.14]   2016     Xu 2017   0.067   0.0055   1.9%   0.07 [0.06, 0.08]   2017     Fan 2017   0.632   0.0585   1.6%   0.63 [0.52, 0.75]   2017     Fan 2017   0.632   0.0585   1.6%   0.63 [0.52, 0.75]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2017     Nair 2018   0.020   0.0103   1.9%   0.20 [0.18, 0.22]   2018     Tang 2018   0.0229   1.9%   0.21 [0.14, 0.22]   2018	Jardim 2015	0.4995	0.0416	1.8%	0.50 [0.42, 0.58]	2015	
Chinn 2015   0.2355   0.0446   1.7%   0.24 [0.15, 0.32]   2015     D'Alessandro 2015   0.2435   0.0666   1.5%   0.24 [0.11, 0.37]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30 [0.26, 0.34]   2016     Low 2016   0.055   0.045   0.09   2016     Niu 2016   0.11   0.0133   1.9%   0.11 [0.08, 0.14]   2016     Xu 2017   0.067   0.0055   1.9%   0.01 [0.06, 0.14]   2016     Xu 2017   0.011   0.02   1.9%   0.11 [0.07, 0.15]   2017     Fan 2017   0.632   0.0585   1.6%   0.63 [0.52, 0.75]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2017     Anand 2018   0.076   0.0221   1.9%   0.08 [0.03, 0.12]   2018	Matsushita 2015	0.27	0.047	1.7%	0.27 [0.18, 0.36]	2015	
D'Alessandro 2015   0.2435   0.0656   1.5%   0.24 [0.11, 0.37]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30 [0.26, 0.34]   2016     Low 2016   0.0522   0.0188   1.9%   0.05 [0.02, 0.09]   2016     Niu 2016   0.1   0.0211   1.9%   0.10 [0.06, 0.14]   2016     Chen 2016   0.111   0.0133   1.9%   0.11 [0.08, 0.14]   2016     Xu 2017   0.067   0.0055   1.9%   0.07 [0.06, 0.08]   2017     Fan 2017   0.632   0.0585   1.6%   0.63 [0.52, 0.75]   2017     In 2017   0.824   0.0343   1.8%   0.82 [0.76, 0.89]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2018     Subramaniam 2018   0.076   0.0221   1.9%   0.08 [0.03, 0.12]   2018     Yang 2018   0.154   0.0243   1.9%   0.28 [0.23, 0.37]   2018     Grachiolo 2018   0.275   0.0229   1.9%   0.38 [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7% <td>Tarsitano 2015</td> <td>0.216</td> <td>0.0268</td> <td>1.9%</td> <td>0.22 [0.16, 0.27]</td> <td>2015</td> <td></td>	Tarsitano 2015	0.216	0.0268	1.9%	0.22 [0.16, 0.27]	2015	
D'Alessandro 2015   0.2435   0.0656   1.5%   0.24 [0.11, 0.37]   2015     Heiduschka 2016   0.302   0.0204   1.9%   0.30 [0.26, 0.34]   2016     Low 2016   0.0522   0.0188   1.9%   0.05 [0.02, 0.09]   2016     Niu 2016   0.1   0.0211   1.9%   0.016 [0.6, 0.14]   2016     Chen 2016   0.111   0.0133   1.9%   0.11 [0.07, 0.15]   2017     Matsuura 2017   0.11   0.02   1.9%   0.017 [0.06, 0.88]   2017     Fan 2017   0.632   0.0585   1.6%   0.63 [0.52, 0.75]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2018     Subramaniam 2018   0.200   0.0103   1.9%   0.28 [0.23, 0.32]   2018     Yang 2018   0.154   0.0221   1.9%   0.28 [0.23, 0.37]   2018     Yang 2018   0.154   0.037   1.8%   0.30 [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7%<	Chinn 2015	0.2355	0.0446	1.7%	0.24 [0.15, 0.32]	2015	<b>→</b>
Heiduschka 2016   0.302   0.0204   1.9%   0.30   0.26, 0.34   2016     Low 2016   0.0522   0.0188   1.9%   0.05   [0.02, 0.09]   2016     Niu 2016   0.1   0.0211   1.9%   0.10   [0.06, 0.14]   2016     Chen 2016   0.111   0.013   1.9%   0.07   [0.06, 0.08]   2017     Matsuura 2017   0.11   0.02   1.9%   0.11   [0.07, 0.15]   2017     Fan 2017   0.632   0.0585   1.6%   0.63   [0.22, 0.75]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23   [0.14, 0.32]   2017     Nair 2018   0.203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Subramaniam 2018   0.529   0.0365   1.8%   0.53   [0.40, 0.32]   2017     Nair 2018   0.154   0.0221   1.9%   0.28   [0.23, 0.32]   2018     Gracchiolo 2018   0.529   0.3065   1.8%   0.53   [0.41, 0.22]   2018     Fang 2019   0.513   0.044   1.9% <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
Low 2016 0.0522 0.0188 1.9% 0.05 [0.02, 0.09] 2016 Niu 2016 0.1 0.0211 1.9% 0.10 [0.06, 0.14] 2016 Chen 2016 0.111 0.0133 1.9% 0.11 [0.08, 0.14] 2016 Xu 2017 0.067 0.0055 1.9% 0.07 [0.06, 0.08] 2017 Hatsuura 2017 0.11 0.02 1.9% 0.01 [0.07, 0.15] 2017 Fan 2017 0.632 0.0585 1.6% 0.63 [0.52, 0.75] 2017 Fan 2017 0.2265 0.0452 1.7% 0.23 [0.14, 0.32] 2017 Anand 2017 0.2265 0.0452 1.7% 0.23 [0.14, 0.32] 2017 Nair 2018 0.203 0.0103 1.9% 0.20 [0.18, 0.22] 2018 Subramaniam 2018 0.076 0.0221 1.9% 0.08 [0.03, 0.12] 2018 Tang 2018 0.529 0.0365 1.8% 0.53 [0.46, 0.60] 2018 Tang 2018 0.154 0.0243 1.9% 0.15 [0.11, 0.20] 2018 Cracchiolo 2018 0.275 0.0229 1.9% 0.28 [0.23, 0.37] 2018 Bodbey 2018 0.183 0.0194 1.9% 0.18 [0.14, 0.22] 2018 Fang 2019 0.513 0.048 1.7% 0.51 [0.42, 0.61] 2019 Feghali 2019 0.3715 0.0339 1.8% 0.37 [0.30, 0.44] 2019 Ho 2019 0.3715 0.0339 1.8% 0.37 [0.30, 0.44] 2019 Rodrigues 2019 0.316 0.0196 1.9% 0.22 [0.18, 0.26] 2019 Safi 2019 0.144 0.0192 1.9% 0.14 [0.11, 0.18] 2019 Safi 2019 0.144 0.0192 1.9% 0.24 [0.22, 0.26] 2019 Mattavelli 2019 0.230 0.0071 1.8% 0.49 [0.42, 0.57] 2019 Mattavelli 2019 0.445 0.0371 1.8% 0.49 [0.42, 0.57] 2019 Mattavelli 2019 0.445 0.0482 1.7% 0.15 [0.05, 0.24] 2019							
Niu 2016   0.1   0.0211   1.9%   0.10   [0.06, 0.14]   2016     Chen 2016   0.111   0.0133   1.9%   0.11   [0.08, 0.14]   2016     Xu 2017   0.067   0.0055   1.9%   0.07   [0.06, 0.08]   2017     Matsuura 2017   0.11   0.02   1.9%   0.11   [0.07, 0.15]   2017     Fan 2017   0.632   0.0585   1.6%   0.63   [0.52, 0.75]   2017     Anand 2017   0.2266   0.0452   1.7%   0.23   [0.14, 0.32]   2017     Nair 2018   0.203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Subaranniam 2018   0.076   0.0221   1.9%   0.08   [0.33, 0.12]   2018     Yang 2018   0.154   0.0243   1.9%   0.15   [0.14, 0.22]   2018     Subaranniam 2018   0.075   0.027   1.9%   0.28   [0.23, 0.37]   2018     Yang 2018   0.153   0.048   1.7%   0.51   [0.42, 0.61]   2019     Gracchiolo 2018   0.371   0.37   0.37							<b></b>
Chen 2016   0.111   0.0133   1.9%   0.111   0.08, 0.141   2016     Xu 2017   0.067   0.0055   1.9%   0.07   [0.06, 0.08]   2017     Matsuura 2017   0.11   0.02   1.9%   0.11   [0.07, 0.15]   2017     Fan 2017   0.632   0.0585   1.6%   0.63   [0.52, 0.75]   2017     Lin 2017   0.824   0.0343   1.8%   0.82   [0.76, 0.89]   2017     Nair 2018   0.203   0.0103   1.9%   0.23   [0.14, 0.32]   2017     Nair 2018   0.203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Subramaniam 2018   0.76   0.0221   1.9%   0.08   [0.03, 0.12]   2018     Yang 2018   0.154   0.0229   1.9%   0.28   [0.23, 0.32]   2018     Cracchiolo 2018   0.275   0.0229   1.9%   0.28   [0.23, 0.37]   2018     Cracchiolo 2018   0.371   1.8%   0.30   [0.23, 0.37]   2018							<b>—</b>
Xu 2017   0.067   0.0055   1.9%   0.07   [0.06, 0.08]   2017     Matsuura 2017   0.11   0.02   1.9%   0.11   [0.07, 0.15]   2017     Fan 2017   0.632   0.0585   1.6%   0.63   [0.52, 0.75]   2017     Lin 2017   0.824   0.0343   1.8%   0.82   [0.76, 0.89]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23   [0.14, 0.32]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23   [0.14, 0.32]   2017     Anand 2018   0.0203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Subramaniam 2018   0.0529   0.0365   1.8%   0.53   [0.46, 0.60]   2018     Yang 2018   0.154   0.0243   1.9%   0.28   [0.23, 0.32]   2018     Yang 2018   0.154   0.029   1.9%   0.28   [0.23, 0.32]   2018     Fang 2019   0.513   0.048   1.7%   0.51   [0.42, 0.61]   2019     Fang 2019   0.513   0.0378   1.8%							-
Matsuura 2017   0.11   0.02   1.9%   0.11   0.07, 0.15   2017     Fan 2017   0.632   0.0585   1.6%   0.63   [0.52, 0.75]   2017     Lin 2017   0.824   0.0343   1.8%   0.82   [0.76, 0.89]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23   [0.14, 0.32]   2017     Nair 2018   0.203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Tang 2018   0.529   0.0365   1.8%   0.53   [0.46, 0.60]   2018     Yang 2018   0.154   0.0243   1.9%   0.15   [0.11, 0.20]   2018     Cracchiolo 2018   0.275   0.029   1.9%   0.28   [0.23, 0.32]   2018     Bodbey 2018   0.183   0.0194   1.9%   0.18   [0.42, 0.61]   2019     Fang 2019   0.513   0.048   1.7%   0.51   [0.42, 0.61]   2019     Ho 2019   0.3715   0.039   1.8%   0.37   [0.30, 0.44]   2019     Ho 2019   0.3715   0.039   1.8%   0							-
Fan 2017   0.632   0.0585   1.6%   0.63   [0.52, 0.75]   2017     Lin 2017   0.824   0.0343   1.8%   0.82   [0.76, 0.89]   2017     Anand 2017   0.2265   0.0452   1.7%   0.23   [0.14, 0.32]   2017     Nair 2018   0.203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Subramaniam 2018   0.076   0.0221   1.9%   0.08   [0.03, 0.12]   2018     Tang 2018   0.529   0.365   1.8%   0.53   [0.46, 0.60]   2018     Yang 2018   0.154   0.0229   1.9%   0.28   [0.23, 0.32]   2018     Cracchiolo 2018   0.275   0.0229   1.9%   0.28   [0.23, 0.37]   2018     Eltohami 2018   0.3015   0.037   1.8%   0.30   [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7%   0.51   [0.42, 0.61]   2019     Ho 2019   0.3715   0.039   1.8%   0.37   [0.30, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9% </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
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Anand 2017   0.2265   0.0452   1.7%   0.23 [0.14, 0.32]   2017     Nair 2018   0.203   0.0103   1.9%   0.20 [0.18, 0.22]   2018     Subramaniam 2018   0.076   0.0221   1.9%   0.08 [0.03, 0.12]   2018     Tang 2018   0.529   0.0365   1.8%   0.53 [0.46, 0.60]   2018     Yang 2018   0.154   0.0243   1.9%   0.15 [0.11, 0.20]   2018     Cracchiolo 2018   0.275   0.0229   1.9%   0.28 [0.23, 0.32]   2018     Bodbey 2018   0.183   0.0194   1.9%   0.18 [0.14, 0.22]   2018     Fang 2019   0.513   0.048   1.7%   0.51 [0.42, 0.61]   2019     Feghali 2019   0.371   0.0378   1.8%   0.37 [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37 [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.21 [0.18, 0.26]   2019     Rajappa 2019   0.144   0.0192   1.9%   0.24 [0.22, 0.26]   2019							
Nair 2018   0.203   0.0103   1.9%   0.20   [0.18, 0.22]   2018     Subramaniam 2018   0.076   0.0221   1.9%   0.08   [0.03, 0.12]   2018     Tang 2018   0.529   0.0365   1.8%   0.53   [0.46, 0.60]   2018     Yang 2018   0.154   0.0229   1.9%   0.28   [0.23, 0.32]   2018     Cracchiolo 2018   0.275   0.0229   1.9%   0.28   [0.23, 0.32]   2018     Bodbey 2018   0.183   0.0194   1.9%   0.18   [0.14, 0.22]   2018     Fang 2019   0.513   0.048   1.7%   0.51   [0.42, 0.61]   2019     Feghali 2019   0.37   0.0378   1.8%   0.37   [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37   [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31   [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.216   1.9%   0.22   [0.18, 0.26]   2019      Safi 2019   0.144   0.0							
Subramaniam 2018   0.076   0.0221   1.9%   0.08 [0.03, 0.12]   2018     Tang 2018   0.529   0.0365   1.8%   0.53 [0.46, 0.60]   2018     Yang 2018   0.154   0.0243   1.9%   0.15 [0.11, 0.20]   2018     Cracchiolo 2018   0.275   0.0229   1.9%   0.28 [0.23, 0.32]   2018     Bodbey 2018   0.183   0.0194   1.9%   0.18 [0.14, 0.22]   2018     Eltohami 2018   0.3015   0.037   1.8%   0.30 [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7%   0.51 [0.42, 0.61]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37 [0.30, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.24 [0.22, 0.26]   2019      Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019      Chatterjee 2019							
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Cracchiolo 2018   0.275   0.0229   1.9%   0.28   [0.23, 0.32]   2018     Bodbey 2018   0.183   0.0194   1.9%   0.18   [0.14, 0.22]   2018     Eltohami 2018   0.3015   0.037   1.8%   0.30   [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7%   0.51   [0.42, 0.61]   2019     Feghali 2019   0.37   0.0378   1.8%   0.37   [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37   [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31   [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22   [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14   [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24   [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49   [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
Bodbey 2018   0.183   0.0194   1.9%   0.18 [0.14, 0.22]   2018     Eltohami 2018   0.3015   0.037   1.8%   0.30 [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7%   0.51 [0.42, 0.61]   2019     Feghali 2019   0.37   0.0378   1.8%   0.37 [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37 [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Mattavelli 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019							
Eltohami 2018   0.3015   0.037   1.8%   0.30 [0.23, 0.37]   2018     Fang 2019   0.513   0.048   1.7%   0.51 [0.42, 0.61]   2019     Feghali 2019   0.37   0.0378   1.8%   0.37 [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37 [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019							
Fang 2019   0.513   0.048   1.7%   0.51   0.42, 0.61   2019     Feghali 2019   0.37   0.0378   1.8%   0.37   [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37   [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31   [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22   [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14   [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24   [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49   [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15   [0.05, 0.24]   2019							
Feghali 2019   0.37   0.0378   1.8%   0.37 [0.30, 0.44]   2019     Ho 2019   0.3715   0.0339   1.8%   0.37 [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019	Eltohami 2018	0.3015	0.037	1.8%	0.30 [0.23, 0.37]	2018	
Ho 2019   0.3715   0.0339   1.8%   0.37 [0.31, 0.44]   2019     Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019	Fang 2019	0.513	0.048	1.7%	0.51 [0.42, 0.61]	2019	
Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019	Feghali 2019	0.37	0.0378	1.8%	0.37 [0.30, 0.44]	2019	
Rajappa 2019   0.306   0.0196   1.9%   0.31 [0.27, 0.34]   2019     Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019	Ho 2019	0.3715	0.0339	1.8%	0.37 [0.31, 0.44]	2019	
Rodrigues 2019   0.219   0.0216   1.9%   0.22 [0.18, 0.26]   2019     Safi 2019   0.144   0.0192   1.9%   0.14 [0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24 [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49 [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15 [0.05, 0.24]   2019	Rajappa 2019				0.31 [0.27, 0.34]	2019	
Safi 2019   0.144   0.0192   1.9%   0.14   0.11, 0.18]   2019     Zanoni 2019   0.239   0.0093   1.9%   0.24   [0.22, 0.26]   2019     Mattavelli 2019   0.495   0.0371   1.8%   0.49   [0.42, 0.57]   2019     Chatterjee 2019   0.1465   0.0482   1.7%   0.15   [0.05, 0.24]   2019							
Zanoni 2019     0.239     0.0093     1.9%     0.24     [0.22, 0.26]     2019       Mattavelli 2019     0.495     0.0371     1.8%     0.49 [0.42, 0.57]     2019       Chatterjee 2019     0.1465     0.0482     1.7%     0.15 [0.05, 0.24]     2019							-
Mattavelli 2019     0.495     0.0371     1.8%     0.49 [0.42, 0.57]     2019       Chatterjee 2019     0.1465     0.0482     1.7%     0.15 [0.05, 0.24]     2019							
Chatterjee 2019 0.1465 0.0482 1.7% 0.15 [0.05, 0.24] 2019							
Total (95% CI) 100.0% 0.28 [0.24, 0.31]	011010100 2013	0.1400	0.0402		0.10 [0.00, 0.24]	2010	
							•
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 2043.37, df = 55 (P < 0.00001); l <sup>2</sup> = 97% Test for overall effect: Z = 15.33 (P < 0.00001)				55 (P < 0	$.00001$ ; $l^2 = 97\%$		0 0.25 0.50 0.75 1.00

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

	PNI No PNI			NI		<b>Risk Ratio</b>		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
Lydiatt 1983	5	8	128	146	3.2%	0.71 [0.42, 1.22]	1983			
Brown 1989	14	26	50	61	4.9%	0.66 [0.45, 0.96]	1989			
Yuen 1998	18	40	20	26	4.6%	0.58 [0.39, 0.87]	1998			
Fagan 1998	3	6	38	44	1.8%	0.58 [0.26, 1.30]	1998			
Myers 2000	5	10	51	54	2.7%	0.53 [0.28, 0.99]	2000			
Rahima 2004	15	26	71	75	5.5%	0.61 [0.44, 0.85]	2004			
Kutz 2005	16	21	5	19	1.8%	2.90 [1.31, 6.38]	2005			
Garzino-Demo 2006	26	62	130	183	5.9%	0.59 [0.43, 0.80]	2006			
Tai 2011	57	84	185	223	8.2%	0.82 [0.70, 0.96]	2011	-		
Camisasca 2011	7	24	27	29	2.6%	0.31 [0.17, 0.59]	2011			
Tai 2012	57	84	185	223	8.2%	0.82 [0.70, 0.96]	2012	-		
Chinn 2015	10	20	50	68	3.9%	0.68 [0.43, 1.08]	2015			
Jardim 2015	18	71	30	71	3.7%	0.60 [0.37, 0.97]	2015			
Matsushita 2015	9	24	5	65	1.3%	4.88 [1.82, 13.09]	2015			
Tarsitano 2016	7	33	29	31	2.4%	0.23 [0.12, 0.44]	2016			
Niu 2016	8	22	131	173	3.1%	0.48 [0.27, 0.84]	2016			
Fan 2017	22	43	13	25	3.8%	0.98 [0.61, 1.58]	2017			
Matsuura 2017	7	27	119	218	2.5%	0.47 [0.25, 0.91]	2017			
Nair 2018	181	310	1053	1214	9.0%	0.67 [0.61, 0.74]	2018	× .		
Safi 2019	19	48	219	280	5.2%	0.51 [0.35, 0.72]	2019			
Zanoni 2019	231	497	751	1073	8.9%	0.66 [0.60, 0.74]	2019	-		
Mattavelli 2019	48	90	63	92	6.9%	0.78 [0.61, 0.99]	2019			
Total (95% CI)		1576		4393	100.0%	0.67 [0.59, 0.75]		•		
Total events	783		3353							
Heterogeneity: Tau <sup>2</sup> =	0.04; Chi <sup>2</sup>	= 67.4	5, df = 21	(P < 0	.00001); 12	2 = 69%		0.05 0.2 1 5 20		
Test for overall effect:	Z = 6.57 (	P < 0.0	0001)	1997 (SSG				0.05 0.2 1 5 20 No PNI PNI		

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

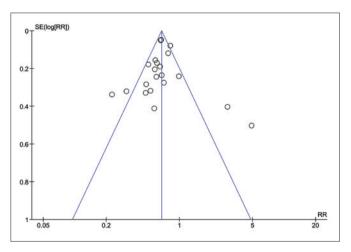


Figure 3. Funnel plot of the 5-year survival meta-analysis, indicating publication bias.

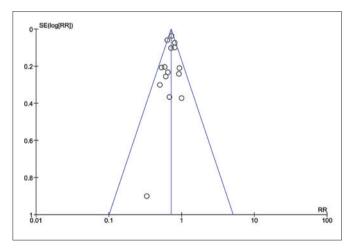
groups of patients, comparison of results of different treatments, identification of groups with unfavorable evolution and planning of follow-up strategies. It also allows for individualisation of treatment, with more aggressive strategies in groups with adverse variables and deintensification of treatment to those with more favourable variables <sup>15</sup>. 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.<sup>15</sup>, 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)<sup>16</sup>.

Thus, there is difficulty in diagnosing PNI. A false-negative result can occur in biopsies <sup>17</sup>, 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 <sup>18</sup>; the expression of N-CAM demonstrates a relation with the presence of PNI <sup>19</sup>, but it is not yet

	PNI No PNI					Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl		
Lydiatt 1983	5	8	32	146	6.6%	2.85 [1.54, 5.29]	1983			
O Brien 1986	4	5	17	85	6.7%	4.00 [2.17, 7.37]	1986			
Fagan 1998	9	40	2	26	2.7%	2.92 [0.69, 12.48]	1998	3		
Yuen 1998	2	6	2	44	2.0%	7.33 [1.26, 42.82]	1998			
Rahima 2004	14	26	8	75	5.8%	5.05 [2.40, 10.64]	2004			
Camisasca 2011	14	24	11	29	6.9%	1.54 [0.87, 2.73]	2011			
Tai 2011	29	84	58	223	8.4%	1.33 [0.92, 1.92]	2011			
Tai 2012	70	84	88	223	9.4%	2.11 [1.75, 2.55]	2012			
Montebugnoli 2013	6	39	7	41	4.3%	0.90 [0.33, 2.45]	2013			
Chatzistefanou 2014	10	39	11	39	5.8%	0.91 [0.44, 1.89]	2014			
Chinn 2015	10	20	12	68	6.2%	2.83 [1.44, 5.57]	2015			
Jardim 2015	59	71	45	71	9.3%	1.31 [1.07, 1.61]	2015	-		
Matsushita 2015	5	24	19	65	5.0%	0.71 [0.30, 1.70]	2015			
Tarsitano 2015	31	51	22	185	7.8%	5.11 [3.26, 8.02]	2015			
Chen 2016	23	62	130	505	8.5%	1.44 [1.01, 2.06]	2016			
Low 2016	2	5	19	116	3.7%	2.44 [0.77, 7.71]	2016			
Tarsitano 2016	28	33	0	31	0.9%	53.65 [3.42, 842.57]	2016			
Total (95% CI)		621		1972	100.0%	2.09 [1.58, 2.76]		•		
Total events	321		483					50 KO 50K		
Heterogeneity: Tau <sup>2</sup> =	0.21; Chi <sup>2</sup>	= 73.94	l, df = 16	(P < 0.	00001); l <sup>2</sup>	= 78%		0.01 0.1 1 10 10		
Test for overall effect:	Z = 5.19 (F	> < 0.00	0001)					0.01 0.1 1 10 10 No PNI PNI		

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 <sup>11</sup>.

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 <sup>15</sup>. 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 <sup>14</sup> 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 <sup>21</sup>, with the presence of both being related to reduced survival <sup>22</sup>. 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 <sup>15</sup>, while others fail to detect such a relationship <sup>23</sup>. This discrepancy probably results from the way in which the studies are conducted (studies that focus only on detecting PNI, without evaluat-

	PNI		No P	NI		<b>Risk Ratio</b>		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% CI
O Brien 1986	1	5	51	85	0.4%	0.33 [0.06, 1.94]	1986	;
Fan 2010	47	79	165	223	5.6%	0.80 [0.66, 0.98]	2010	) -
Tai 2011	59	84	196	223	7.0%	0.80 [0.69, 0.93]	2011	-
Tai 2012	59	84	196	223	7.0%	0.80 [0.69, 0.93]	2012	· · ·
Matos 2014	17	36	17	21	1.4%	0.58 [0.39, 0.87]	2014	
Chinn 2015	10	20	52	68	1.5%	0.65 [0.41, 1.03]	2015	;
Jardim 2015	17	71	28	71	1.8%	0.61 [0.37, 1.01]	2015	;
Matsushita 2015	9	24	9	24	0.6%	1.00 [0.48, 2.08]	2015	5 —
Tarsitano 2015	15	51	59	185	1.7%	0.92 [0.57, 1.48]	2015	; —
Low 2016	3	5	102	116	0.5%	0.68 [0.33, 1.40]	2016	s ————————————————————————————————————
Fan 2017	24	43	15	25	1.2%	0.93 [0.61, 1.41]	2017	· —
Matsuura 2017	8	27	127	218	1.8%	0.51 [0.28, 0.92]	2017	·
Nair 2018	150	310	914	1214	24.2%	0.64 [0.57, 0.72]	2018	3 •
Yang 2018	14	34	144	187	2.9%	0.53 [0.36, 0.81]	2018	
Mattavelli 2019	52	90	74	92	4.8%	0.72 [0.59, 0.88]	2019	, –
Zanoni 2019	310	497	913	1073	37.6%	0.73 [0.68, 0.79]	2019	• •
Total (95% CI)		1460		4048	100.0%	0.71 [0.68, 0.75]		1
Total events	795		3062					
Heterogeneity: Chi <sup>2</sup> =	18.29, df =	= 15 (P	= 0.25); 1	<sup>2</sup> = 18%	Ď			
Test for overall effect:	Z = 13.23	(P < 0.	00001)					0.01 0.1 1 10 100 No IPN IPN

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

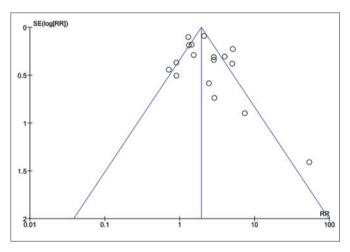


Figure 7. Funnel plot of the meta-analysis of locoregional recurrence, with publication bias.

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

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

metastases <sup>25</sup>; 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 furthers. The potential of artificial intelligence (AI) is improve workflow and derive novel insights into disease biology <sup>25</sup> (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 slow <sup>26</sup>.

## 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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