



Review

Prognostic importance of the lymphovascular invasion in head and neck adenoid cystic carcinoma: A systematic review and meta-analysis



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ABSTRACT

The presence of lymphovascular invasion is considered a prognostic determinant for different human neoplasms and is frequently taken into account by surgeons and oncologists to determine patients' treatment. However, the exact frequency of this microscopic event and its prognostic impact for patients affected by adenoid cystic carcinoma (AdCC) remains unclear. Therefore, the aim of this study was to carry out a systematic review and meta-analysis to address the prevalence and the prognostic potential of lymphovascular invasion in head and neck AdCC. A literature search on PubMed, Scopus, ClinicalTrials.gov, Web of Science and ProQuest databases was undertaken in January 2019. The primary outcomes of interest were overall survival (OS) and disease-free survival (DFS). The relative frequency of lymphovascular invasion and its possible association with other clinicopathological parameters were addressed. A total of 22 studies and 2117 patients were included in this study. The frequency of lymphovascular invasion ranged from 5.2% to 72.5%. Lymphovascular invasion was associated with an increased likelihood of lymph node metastasis (OR = 2.58; 95% CI 1.61–4.12; $p = 0.0001$) and death (OR = 3.09; 95% CI 1.82–5.26; $p = 0.0001$), solid/higher-grade AdCC were more likely to present lymphovascular invasion (OR = 5.51; 95% CI 1.87–16.21; $p = 0.002$) and patients with this microscopic finding had a significantly lower OS (HR = 8.30; 95% CI 1.68–40.91; $p = 0.009$) and DFS (HR = 3.76; 95% CI 1.13–12.53; $p = 0.03$). In conclusion, lymphovascular invasion seems to be a significant predictor of poor prognosis for head and neck AdCC patients.

Introduction

Salivary gland tumors are a heterogeneous group of benign and malignant neoplasms, with variable clinical behavior which account for approximately 5% of all head and neck tumors [1]. Adenoid cystic carcinoma (AdCC) is one of the most frequent malignant subtypes and predominantly affects minor salivary glands of the oral cavity and the parotid glands. It has a relentless growth pattern associated with local recurrences and late distant metastases, significantly decreasing patients' long-term survival [2].

Persson et al. [3] described the importance of the translocation of

chromosomes 6 and 9 involving MYB and NFIB genes for the pathogenesis of the tumor. Thereafter, other studies confirmed these findings and subsequently demonstrated other molecular alterations that also contribute to the neoplasm development [4,5]. Although new insights were obtained regarding the pathogenesis of AdCC, limited information concerning prognostic factors for this disease exists, with some clinical parameters representing the most frequently reported prognostic determinants. We have recently demonstrated through a systematic review and meta-analysis that t(6;9)(MYB-NFIB) does not seem to represent a prognostic factor for these patients, although methodological drawbacks were found in the available studies [6]. Other molecular

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markers have also been investigated, but additional prognostic validation remains necessary.

The microscopic subtype of AdCC has long been considered a useful parameter to determine the survival rates of affected patients [7], although variability of the classification criteria has made the comparison of the results obtained by different authors more difficult. The presence of positive surgical margins has also been advocated as a prognostic factor [8], as well as the presence of neural involvement, which is considered a highly frequent microscopic finding of AdCC [9]. On the other side, the importance of the lymphovascular invasion for the prognosis of the affected patients has not been fully established and no study was identified that attempted to investigate lymphovascular invasion as its main objective, with several studies describing the lymphovascular invasion as a secondary finding [10,11]. Meanwhile, the description of the lymphovascular invasion in pathological reports is commonly performed and it may influence the therapeutic management of the patients [12,13]. Therefore, this systematic review and meta-analysis aims to determine whether patients affected by head and neck AdCC with lymphovascular invasion have a worse prognosis than those not presenting lymphovascular invasion.

Material and methods

This systematic review and meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) checklist [14] and was registered at the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD 42019115387).

Study design

This systematic review and meta-analysis investigated whether the presence of lymphovascular invasion predicts the prognosis of patients with head and neck AdCC by means of the survival rate and the clinicopathological features of the affected individuals. In addition, we also determined the frequency of lymphovascular invasion in individuals with head and neck AdCC.

Eligibility criteria

Inclusion criteria

Articles that evaluated the presence of lymphovascular invasion and/or its prognostic potential in patients affected by head and neck AdCC.

Exclusion criteria

Studies were excluded due to the following reasons: (1) studies that investigated the lymphovascular invasion in AdCC from other anatomical regions different than the head and neck. Cutaneous head and neck AdCC were also excluded; (2) studies that investigated the lymphovascular invasion in other SGTs different from AdCC; (3) studies that investigated peri-lymphovascular invasion; (4) studies developed in animal models or laboratorial cell cultures; (5) case reports, literature reviews, letters, personal opinions, book chapters, and conference abstracts; and (6) articles not published in the English, Spanish or Portuguese languages.

Information sources and search strategy

Studies were retrieved from the following databases: PubMed, Scopus, ClinicalTrials.gov and Web of Science. A partial grey literature search was performed using the ProQuest Dissertations & Theses Global database (Supplementary Table 1). The initial search across the databases included all articles published up to 27th October 2017. The search was updated on 14th January 2019. No time restriction was imposed. Duplicated references were removed by reference manager

software (EndNote®, Thomson Reuters, Philadelphia, USA). The reference list of selected articles was manually screened for potentially relevant studies that could have been missed during the electronic database searches.

Study selection

The study selection was performed in two steps. First, two authors independently reviewed titles/abstracts, and they selected articles that appeared to meet the inclusion criteria. The agreement between both authors was evaluated using the Kappa test when the first 10% of abstracts were evaluated and were repeated until a satisfactory result (> 0.7) was obtained to demonstrate an acceptable concordance between authors. Second, the same two authors independently read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. Disagreements in both steps were jointly settled to make the final decision.

Data collection process

One author collected key information from each selected article. A second author cross-checked the collected information and confirmed its accuracy. The following information was recorded: year of publication, author(s), country, total number of head and neck AdCC cases reported in the study, anatomical site affected, sample features (sex and mean age), microscopic subtype, frequency of lymphovascular invasion observed in each study, follow-up time obtained for the sample investigated, association of lymphovascular invasion with pathological features (i.e., microscopic aspect, surgical margin status, neural invasion, etc.), association of lymphovascular invasion with clinical parameters (sex, age, site, distant metastases, recurrences, etc.), association with lymph node metastases, association with patients' status (dead/alive), association with survival rates, and the endpoint (disease-free survival/progression-free survival, disease specific survival and overall survival) used by each study.

Risk of bias in individual studies

The risk of bias of selected studies was evaluated using a standardized critical appraisal instrument. Only for those articles that investigated the potential of the lymphovascular invasion to determine the survival rates of the patients, the Newcastle-Ottawa Scale (NOS), which is recommended by the Cochrane Collaboration for use in non-randomized studies was applied [15]. For each study, a quality score was calculated based on three major categories: group selection (four items), comparability between groups (one item), and outcome and exposure assessment (three items). A maximum of 1 point was awarded for each item in the group selection and outcome and exposure assessment categories. A maximum of two points was awarded for comparability. Therefore, the maximum score was nine points and represented the highest methodological quality [16]. A study was categorized as high quality if the total score was 7 or higher [17]. The quality appraisal of the studies was performed by one author and cross-checked by a second author independently.

Summary measures

The primary outcome for this systematic review and meta-analysis was the capacity of the presence of lymphovascular invasion to determine the survival rate of the patients affected by head and neck AdCC. Moreover, a secondary outcome was the frequency in which the lymphovascular invasion was observed in each study and its association with other clinicopathological parameters.

Statistical analysis (synthesis of results)

Lymphovascular invasion was categorized as “positive” vs “negative”. Odds ratio (OR) with 95% confidence interval (CI) was calculated to determine the association between lymphovascular invasion and clinicopathological variables (tumor grade/microscopy, lymph node metastasis and death) in patients with head and neck AdCC. The hazard ratio (HR) with 95% CI was used to estimate the impact of lymphovascular invasion on time-to-event variables (OS and DFS). The HRs and 95% CIs were directly extracted from the original articles and only the multivariate HRs values were used in our meta-analysis. Forest plots were created to graphically represent the general effect of lymphovascular invasion. Heterogeneity was calculated by the inconsistency index (I^2), and a value higher than 40% was considered an indicator of substantial heterogeneity among studies [15]. The fixed effect model (Mantel-Haenszel methods and inverse variance) would be used if I^2 was lower than 40%. The random effect model (DerSimonian and Laird method) would be used if the I^2 was higher than 40%. The MedCalc statistical software, version 14.8.1 (MedCalc Software, Ostend, Belgium) and the Review Manager statistical software, version 5.3.5 (RevMan, Cochrane community) were used. The significance level was set at 5% or a p -value < 0.05.

Risk of bias across studies

Methodological heterogeneity was considered by comparing the variability in study design and risk of bias. Statistical heterogeneity (I^2) was also considered.

Results

Study selection

In the first phase of the study selection, 2004 references were identified, followed by an additional reference manually obtained. The duplicated references were removed and 1435 citations remained (Supplementary Table 2). Comprehensive evaluation of the titles/abstracts of each article was carried out and another 1298 articles were excluded and 137 articles remaining in the first phase. All manuscripts retrieved in the first phase were fully reviewed and 115 articles were excluded (Supplementary Table 3). At the end, 22 articles were selected for descriptive analysis (Supplementary Table 4), of which 15 investigated the prognostic importance of lymphovascular invasion in head and neck AdCC (Fig. 1).

Study characteristics

The 22 studies included in the descriptive analysis were conducted across six different countries (China, Republic of Korea, USA, Mexico, Brazil and Denmark) and were published between 1986 and 2019. The total sample of these 22 studies included 2117 individuals affected by head and neck AdCC, whereas the 15 studies that investigated the prognosis of lymphovascular invasion comprised 1272 patients. Sample sizes ranged from eight to 616 patients to investigate the presence of lymphovascular invasion and from 23 to 228 to determine its prognostic importance. As regards the studies that evaluated the prognostic potential of lymphovascular invasion, the time of follow-up was provided by all studies and varied from two to 354 months. Multivariate analysis was applied in 10 studies (Supplementary Tables 5 and 6).

Risk of bias within studies

Using the NOS scale for the 15 studies that attempted to investigate the prognostic potential of lymphovascular invasion, three studies were classified as high-quality studies, whereas 12 were graded as low-quality studies (Supplementary Table 7).

Results of individual studies

The analysis of the 22 articles in which the presence of lymphovascular invasion in head and neck AdCC was investigated revealed a relative frequency that ranged from 5.2% to 72.5% (Fig. 2). In only three of these studies, there was no significant association between lymphovascular invasion and either DFS, OS or DSS, whereas all other studies demonstrated some statistical significance with survival rates, which are detailed in Supplementary Table 6. Few studies attempted to determine the association of lymphovascular invasion with clinicopathological parameters, being significantly associated with distant metastases [11], lymph node metastases [18], recurrences [19] and death [19,20].

Synthesis of results

Demographic features

Major salivary glands were affected in 756 cases, of which parotid glands were affected in 325, submandibular glands in 321 and sublingual glands in 99 cases, while minor salivary glands were affected in 853 cases. Other non-salivary glands like sinonasal (nasal cavity, paranasal sinuses and nasopharynx), larynx, auditory canal and lacrimal glands, were also investigated in the studies included and accounted for 265 cases.

Seventeen studies demonstrated a female predilection, whereas in only two studies males predominated. In aggregate, female individuals (1094) outnumbered male individuals (875), leading to a F:M ratio of 1.25:1. The mean age of the patients described in different studies ranged from 13.9 to 54.4 years old.

Microscopic features

All 22 studies included provided the microscopic classification of their samples. However, the criteria used by the authors varied, with 15 studies using the WHO criteria, five studies classifying tumours as grade I, grade II and grade III, one classifying tumors as low-grade and high-grade and one study classifying tumors as low-grade, intermediate-grade and high-grade. Moreover, authors also grouped tumors in different ways (e.g.: Stage I vs Stage II/III, Stage I/II vs Stage III, Cribriform vs Tubular/Solid, Cribriform/Tubular vs Solid).

Quantitative analysis of the presence of lymphovascular invasion

Meta-analysis was applied to determine the association of lymphovascular invasion with different clinicopathological parameters, including tumor microscopy/grade, cervical metastasis, death and survival rates, both overall and disease-free. Fig. 3A demonstrates that solid/higher-grade tumors were significantly more likely to present lymphovascular invasion than lower-grade tumors (OR = 5.51; 95% CI, 1.87–16.21; p = 0.002). Moreover, cases presenting lymphovascular invasion were significantly more likely to develop cervical metastases than cases without lymphovascular invasion (OR = 2.58; 95% CI, 1.61–4.12; p = 0.0001) (Fig. 3B). Similarly, those patients affected by head and neck AdCC with lymphovascular invasion were significantly more likely to die than patients affected by head and neck AdCC without lymphovascular invasion (OR = 3.09; 95% CI 1.82–5.26; p = 0.0001) (Fig. 3C).

The presence of lymphovascular invasion negatively impacted the DFS of patients affected by head and neck AdCC (HR = 3.76; 95% CI, 1.13–12.53; p = 0.03) (Fig. 4A), and the presence of lymphovascular invasion was significantly associated with a worse OS (HR = 8.30; 95% CI, 1.68–40.91; p = 0.009) (Fig. 4B).

Risk of bias across studies

Among the 15 studies that investigated the prognosis of lymphovascular invasion, in seven of them it is unclear how the lymphovascular invasion was assessed by the authors or whether they have used

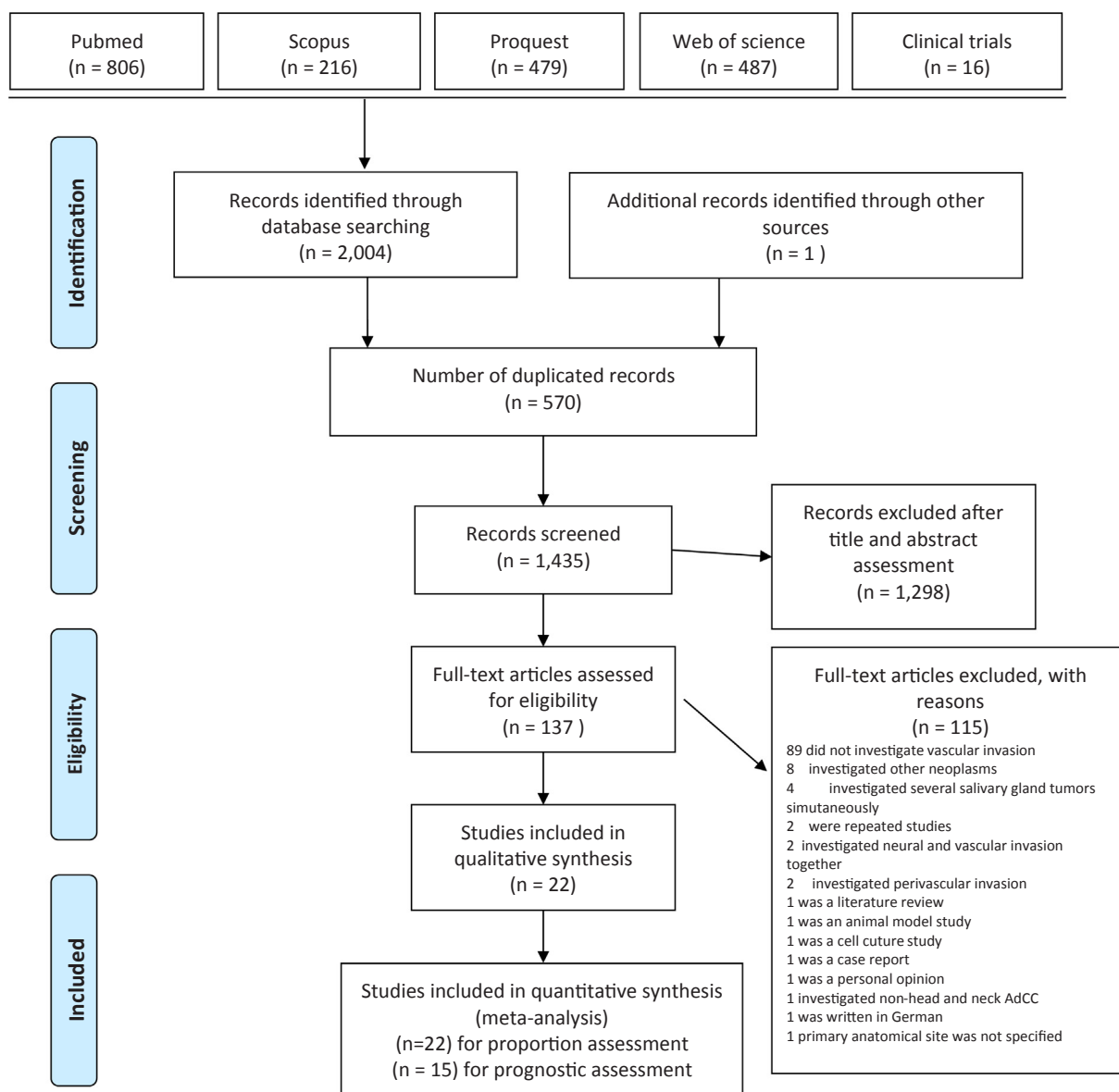


Fig. 1. Flow diagram of literature search and selection criteria adapted from PRISMA.

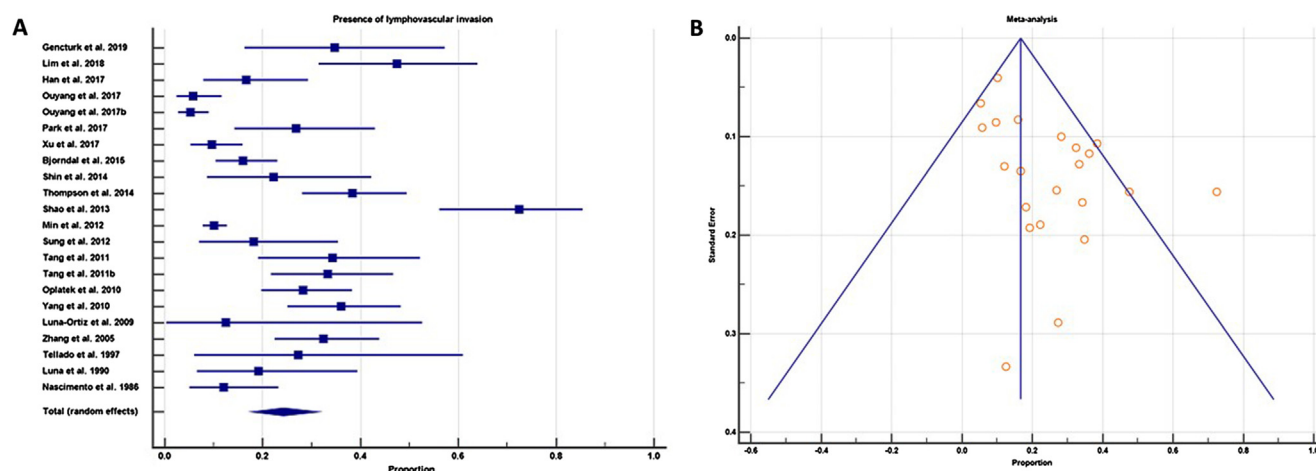


Fig. 2. Frequency of lymphovascular invasion. (A) Distribution of lymphovascular invasion in the 22 studies included. (B) Funnel-plot of the studies describing the frequency of lymphovascular invasion in AdCC.

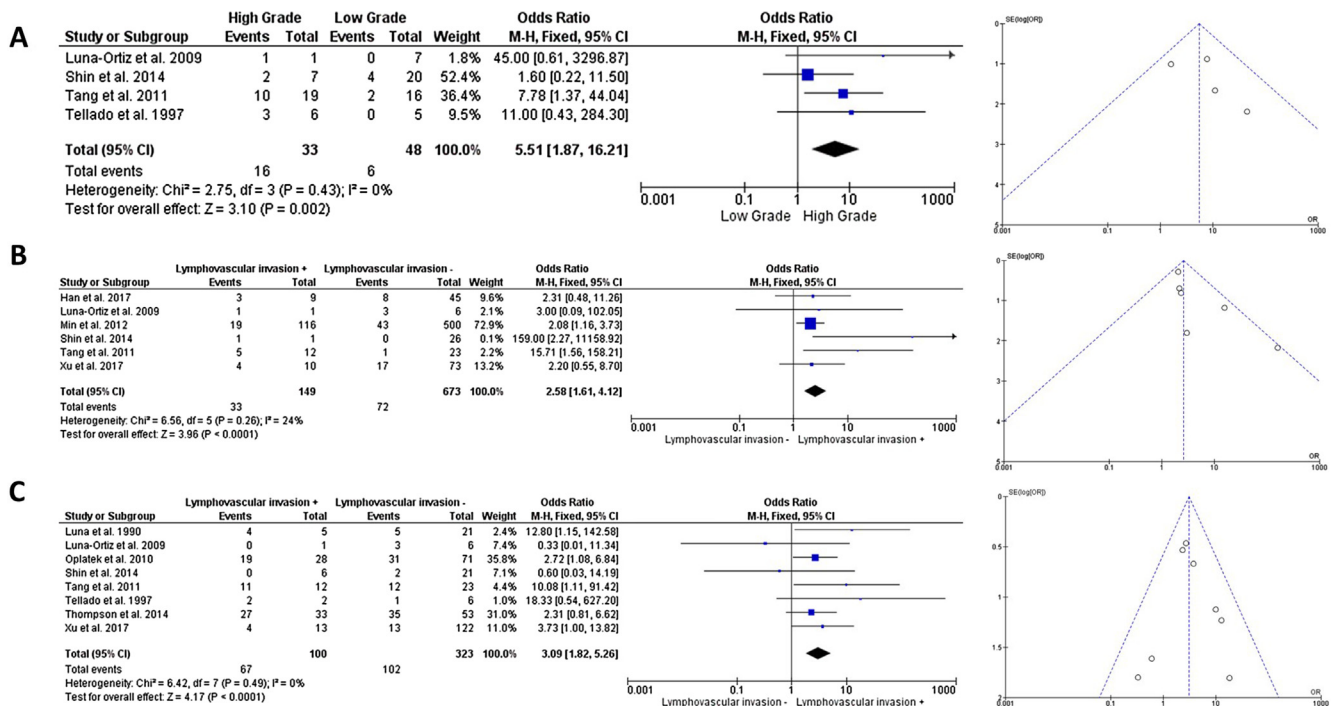


Fig. 3. Forest-plot and funnel-plot graphics for microscopic grade, lymph node metastasis and death. (A) It was observed that solid/higher-grade tumors had a significantly increased chance of presenting lymphovascular invasion with an odds-ratio of 5.51 (95% CI, 1.87–16.21). (B) Tumors presenting lymphovascular invasion showed a higher likelihood of developing lymph node metastases (OR = 2.58; 95% CI, 1.61–4.12). (C) Similarly, the presence of lymphovascular invasion also increased significantly the chances of death (OR = 3.09; 95% CI, 1.82–5.26).

information available in the original pathological reports, with no microscopic review of the histological sections. In the remaining studies, though, the lymphovascular invasion was confirmed microscopically. Lymphovascular invasion may be a difficult microscopic finding, and the use of laboratorial tools like immunohistochemistry or special histological staining may show an increased frequency of lymphovascular invasions, but none of the studies available used immunomarkers. However, despite these potential risks of bias, we obtained low heterogeneity among studies, making the results obtained more reliable.

Discussion

Adenoid cystic carcinoma is one of the most common malignant salivary gland tumors and is associated with an unsatisfactory long-term survival due to frequent local recurrences and late distant metastases [1,10]. Despite recent improvements in the understanding of the molecular pathogenesis of this neoplasm, few known prognostic parameters are available to determine clinical behavior of affected

patients and the search for more reliable determinants is still necessary. In this systematic review and meta-analysis, we have demonstrated that lymphovascular invasion represents a significant prognostic parameter for head and neck AdCC, associated to a shorter overall survival rate and a higher chance of lymph node metastases and death.

A number of studies has demonstrated that lymphovascular invasion is a microscopic finding associated with a worse clinical behavior of different human neoplasms, including prostate [21], bladder [22], lung [23] and kidney [24] cancers, as well as with other salivary gland malignant disorders, such as myoepithelial carcinoma [25] and carcinoma ex-pleomorphic adenoma [26]. In the context of AdCC, Tang et al. [27] revealed that lymphovascular invasion is an independent prognostic determinant, while Oplatek et al. [19] showed a significant association with recurrences. Although these results point towards a more aggressive condition associated with lymphovascular invasions, none of the available studies describing the lymphovascular invasion in AdCC attempted to determine its importance as their main objective, always representing secondary findings. Therefore, very few authors

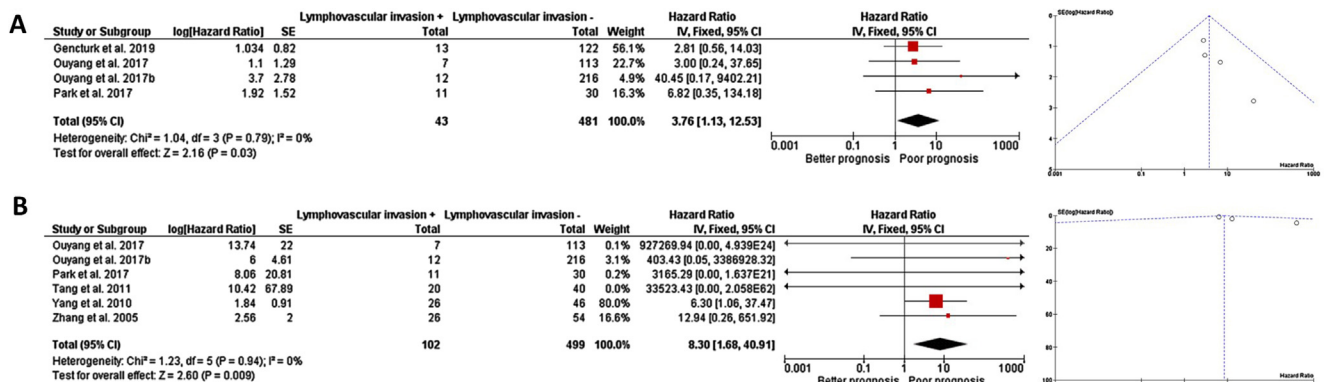


Fig. 4. Forest-plot and funnel-plot graphics for time-to-event variables. (A) The presence of lymphovascular invasion predicted a lower disease-free survival (HR = 3.76; 95% CI, 1.13–12.53; $p = 0.03$) and (B) a lower overall survival (HR = 8.30; 95% CI, 1.68–40.91; $p = 0.009$).

investigated the association of lymphovascular invasion with clinicopathological parameters, whereas some of them did not review the original slides, and none of them used ancillary techniques to better identify lymphovascular invasions, such as immunohistochemistry. Moreover, the profile of tumor emboli has been poorly described, since we don't know what kind of vessels are invaded, either blood or lymphatic vessels. The morphological characteristics of the vessel has not been described either. Hence, an original study aiming to investigate the prognostic potential of lymphovascular invasion to validate our results is necessary.

Other limitations of the available studies include the small sample size used and the short follow-up time described for most of them. Moreover, multivariate statistical analysis was not always performed, therefore, it remains unclear whether lymphovascular invasion is a significant prognostic factor once one controls for other important variables like tumor grade. Thus, the quality assessment of the studies included in this systematic review and meta-analysis demonstrated that most studies was classified as low quality. However, the heterogeneity value obtained for meta-analyses depicted a very low variability among studies, providing results with reliable estimates.

In addition to the significant association between the presence of lymphovascular invasion and the occurrence of patients' death with an odds ratio of 3.02 and with a significantly poorer disease-free and overall survivals of AdCC patients, we have also observed a strong association of lymphovascular invasion with the occurrence of lymph node metastases and with solid/higher-grade AdCC variants. Lymph node metastases and solid/higher-grade AdCC variant have been listed as two important determinants of a worse prognosis for the patients, as previously documented by Dubal et al. [28] and Han et al. [29], who showed that lymph node invasion predicted a lower survival for patients affected by tongue AdCC and van Weert et al. [7], who demonstrated that solid AdCC presented a poorer prognosis. Our results are also in accordance with other studies that observed a significant association of lymphovascular invasion with lymph node metastases and more aggressive microscopic subtype in some human cancers [30,31].

Translocation of chromosomes 6 and 9 affecting the transcription factors Myb and NFIB is a known and important molecular event driving the pathogenesis of a variable proportion of AdCC, being present in 30 to 100% of all cases [32]. We have recently demonstrated that despite its etiological importance, t(6;9)(MYB-NFIB) does not seem to carry a significant prognostic importance for the affected patients [6], although many variants of this genetic imbalance have been described including t(8;9)(MIBL1-NFIB) [5] and the t(8;14)(MYBL1-RAD51B) [33], and deserves to have their clinical relevance investigated. However, the importance of these mutations to different clinicopathological features of AdCC needs to be further investigated and, more specifically, the association with the tumor potential to cause lymphovascular invasion needs to be elucidated.

The current systematic review and meta-analysis in addition to demonstrate the prognostic importance of lymphovascular invasion for patients affected by head and neck AdCC also showed several methodological limitations of the available studies as already mentioned. Therefore, we understand that future studies need to determine the frequency and the prognostic potential of this feature using immunomarkers towards blood and lymphatic vessels, which will also contribute to determine whether the infiltration of both vessel types would carry the same importance, as well as to demonstrate how frequent lymphovascular invasion is misidentified when only regular H&E stained slides are used. Potential differences in the relative frequency of lymphovascular invasion observed in samples obtained from incisional biopsies and in surgical specimens could also be addressed. The use of larger and more representative samples with at least 5 years of follow-up is also recommended, and authors must be aware of the importance to carry out both univariate and multivariate analyses controlled for different potential prognostic factors.

In conclusion, the best evidence currently available demonstrates

that lymphovascular invasion is an important prognostic determinant for patients affected by head and neck AdCC, being also associated with a more aggressive microscopic variant, lymph node metastases and death. Therefore, our results suggest that more aggressive therapeutic approaches are recommended for those cases with lymphovascular infiltration and demand that pathologists are careful during microscopic analysis of this feature and during the description of this finding in pathology reports.

Conflict of interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.oraloncology.2019.04.014>.

References

- [1] Fonseca FP, Carvalho MV, Almeida OP, Rangel ALCA, Takizawa MCH, Bueno AG, et al. Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2012;114:230–9. <https://doi.org/10.1016/j.oooo.2012.04.008>.
- [2] Coca-Pelaz A, Rodrigo JP, Bradley PJ. Adenoid cystic carcinoma of the head and neck – an update. *Oral Oncol* 2015;51:652–61. <https://doi.org/10.1016/j.oraloncology.2015.04.005>.
- [3] Persson M, Andrén Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. *Proc Natl Acad Sci USA* 2009;106:18740–4. <https://doi.org/10.1073/pnas.0909114106>.
- [4] Rettig EM, Tan M, Ling S, Yonescu R, Bishop JA, Fakhry C, et al. MYB rearrangement and clinicopathologic characteristics in head and neck adenoid cystic carcinoma. *Laryngoscope* 2015;125:E292–9. <https://doi.org/10.1002/lary.25356>.
- [5] Mitani Y, Liu B, Rao PH, Borra VJ, Zafereo M, Weber RS, et al. Novel MYBL1 gene rearrangements with recurrent MYBL1-NFIB fusions in salivary adenoid cystic carcinomas lacking t(6;9) translocations. *Clin Cancer Res* 2016;22:725–33. <https://doi.org/10.1158/1078-0432.CCR-15-2867-T>.
- [6] Almeida-Pinto YD, Costa SFS, Andrade BAB, Altemani A, Vargas PA, Abreu LG, et al. t(6;9)(MYB-NFIB) in head and neck adenoid cystic carcinoma: a systematic review with meta-analysis. *Oral Dis* 2019. <https://doi.org/10.1111/odi.12984>. [in press].
- [7] van Weert S, van der Waal I, Witte BI, Leemans CR, Bloemena E. Histopathological grading of adenoid cystic carcinoma of the head and neck: analysis of currently used grading systems and proposal for a simplified grading scheme. *Oral Oncol* 2015;51:71–6. <https://doi.org/10.1016/j.oraloncology.2014.10.007>.
- [8] Amit M, Na'ara S, Trejo-Leider L, Ramer N, Burstein D, Yue M, et al. Defining the surgical margins of adenoid cystic carcinoma and their impact on outcome: an international collaborative study. *Head Neck* 2017;39:1008–14. <https://doi.org/10.1002/hed.24740>.
- [9] Ju J, Li Y, Chai J, Ma C, Ni Q, Shen Z, et al. The role of perineural invasion on head and neck adenoid cystic carcinoma prognosis: a systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016;122:691–701. <https://doi.org/10.1016/j.oooo.2016.08.008>.
- [10] Bjørndal K, Krogdahl A, Therkildsen MH, Charabi B, Kristensen CA, Andersen E, et al. Salivary adenoid cystic carcinoma in Denmark 1990–2005: Outcome and independent prognostic factors including the benefit of radiotherapy. Results of the Danish Head and Neck Cancer Group (DAHANCA). *Oral Oncol* 2015;51:1138–42. <https://doi.org/10.1016/j.oraloncology.2015.10.002>.
- [11] Ouyang D, Liang L, Zheng G, Ke Z, Weng D, Yang W, et al. Risk factors and prognosis for salivary gland adenoid cystic carcinoma in southern china. A 25-year retrospective study. *Medicine* 2017;96. <https://doi.org/10.1097/MD.0000000000005964>.
- [12] Lim WS, Oh JS, Roh JL, Kim JS, Kim SJ, Choi SH, et al. Prediction of distant metastasis and survival in adenoid cystic carcinoma using quantitative 18F-FDG PET/CT measurements. *Oral Oncol* 2018;77:98–104. <https://doi.org/10.1016/j.oraloncology.2017.12.013>.

- [13] Gencturk M, Ozturk K, Koksel Y, Li F, Cayci Z. Pretreatment quantitative 18F-FDG PET/CT parameters as a predictor of survival in adenoid cystic carcinoma of the salivary glands. *Clin Imaging* 2019;53:17–24. <https://doi.org/10.1016/j.clinimag.2018.09.021>.
- [14] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. *Int J Surg* 2010;8:336–41. <https://doi.org/10.1016/j.ijssu.2010.02.007>.
- [15] Higgins JPT, Green S (editors). *Cochrane handbook for systematic reviews of interventions* version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.
- [16] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of non randomized studies in meta analysis. Available online: www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- [17] Abreu LG, Elyasi M, Badri P, Paiva SM, Flores-Mir C, Amin M. Factors associated with the development of dental caries in children and adolescents in studies employing the life course approach: a systematic review. *Eur J Oral Sci* 2015;123:305–11. <https://doi.org/10.1111/eos.12206>.
- [18] Min R, Siyi L, Wenjun Y, Ow A, Lizheng W, Minjun D, Chenping Z. Salivary gland adenoid cystic carcinoma with cervical lymph node metastasis: a preliminary study of 62 cases. *Int J Oral Maxillofac Surg* 2012;41:952–7. <https://doi.org/10.1016/j.ijom.2012.04.023>.
- [19] Oplatek A, Ozer E, Agrawal A, Bapna S, Schuller DE. Patterns of recurrence and survival of head and neck adenoid cystic carcinoma after definitive resection. *Laryngoscope* 2010;120:65–70. <https://doi.org/10.1002/lary.20684>.
- [20] Thompson LDR, Penner C, Ho NJ, Foss RD, Miettinen M, Wieneke JA, et al. Sinonasal tract and nasopharyngeal adenoid cystic carcinoma: a clinicopathologic and immunophenotypic study of 86 cases. *Head Neck Pathol* 2014;8:88–109. <https://doi.org/10.1007/s12105-013-0487-3>.
- [21] Galiabovitch E, Hovens CM, Peters JS, Costello AJ, Battye S, Norden S, et al. Routinely reported 'equivocal' lympholymphovascular invasion in prostatectomy specimens is associated with adverse outcomes. *BJU Int* 2017;119:567–72. <https://doi.org/10.1111/bju.13594>.
- [22] Li G, Song H, Wang J, Bao Y, Niu Y. Poor prognostic value of lympholymphovascular invasion for pT1 urothelial carcinoma with squamous differentiation in bladder cancer. *Sci Rep* 2016;9:27586. <https://doi.org/10.1038/srep27586>.
- [23] Ramnefjell M, Aamelfot C, Helgeland L, Akslen LA. Lymphovascular invasion is an adverse prognostic factor in resected non-small-cell lung cancer. *APMIS* 2017;125:197–206. <https://doi.org/10.1111/apm.12652>.
- [24] Van Poppel H, Vandendriessche H, Boel K, Mertens V, Goethuys H, Haustermans K, et al. Microscopic lymphovascular invasion is the most relevant prognosticator after radical nephrectomy for clinically nonmetastatic renal cell carcinoma. *J Urol* 1997;158:45–9. <https://doi.org/10.1097/00005392-199707000-00013>.
- [25] Kong M, Drill EN, Morris L, West L, Klimstra D, Gonen M, et al. Prognostic factors in myoepithelial carcinoma of salivary glands: a clinicopathologic study of 48 cases. *Am J Surg Pathol* 2015;39:931–8. <https://doi.org/10.1097/PAS.0000000000000452>.
- [26] Katabi N, Gomez D, Klimstra DS, Carlson DL, Lee N, Ghossein R. Prognostic factors of recurrence in salivary carcinoma ex pleomorphic adenoma, with emphasis on the carcinoma histologic subtype: a clinicopathologic study of 43 cases. *Hum Pathol* 2010;41:927–34. <https://doi.org/10.1016/j.humpath.2009.12.011>.
- [27] Tang Q, Fan S, Li H, Chen W, Shen X, Yuan X, et al. Expression of Cyr61 in primary salivary adenoid cystic carcinoma and its relation to Ki-67 and prognosis. *Oral Oncol* 2011;47:365–70. <https://doi.org/10.1016/j.oraloncology.2011.02.022>.
- [28] Dubal PM, Unsal AA, Chung SY, Patel AV, Park RCW, Baredes S. Population-based trends in outcomes in adenoid cystic carcinoma of the oral cavity. *Am J Otolaryngol* 2016. <https://doi.org/10.1016/j.amjoto.2016.06.001>.
- [29] Han N, Ong H, Liu Z, Ruan M, Yang W, Zhang C. Lymph node involvement predicts poor prognosis in primary tongue adenoid cystic carcinoma: a preliminary study of 54 cases. *J Craniomaxillofac Surg* 2017;45:589–94. <https://doi.org/10.1016/j.jcms.2017.01.012>.
- [30] Jardim JF, Francisco ALN, Gondak R, Damascena A, Kowalski LP. Prognostic impact of perineural invasion and lympholymphovascular invasion in advanced stage oral squamous cell carcinoma. *Int J Oral Maxillofac Surg* 2015;44:23–8. <https://doi.org/10.1016/j.ijom.2014.10.006>.
- [31] Chen B, Wang X, Yu X, Xia WJ, Zhao H, Li XF, et al. Lymph node metastasis in Chinese patients with clinical T1 non-small cell lung cancer: a multicenter real-world observational study. *Thorac Cancer* 2019. <https://doi.org/10.1111/1759-7714.12970>. [in press].
- [32] Fonseca FP, Sena Filho M, Altmani A, Speight PM, Vargas PA. Molecular signature of salivary gland tumors: potential use as diagnostic and prognostic marker. *J Oral Pathol Med* 2016;45:101–10. <https://doi.org/10.1111/jop.12329>.
- [33] Brayer KJ, Frerich CA, Kang H, Ness SA. Recurrent fusions in MYB and MYBL1 define a common, transcription factor-driven oncogenic pathway in salivary gland adenoid cystic carcinoma. *Cancer Discov* 2016;6:176–87. <https://doi.org/10.1158/2159-8290.CD-15-0859>.