Prevalence of occult nodal metastases in squamous cell carcinoma of the temporal bone: A systematic review and meta-analysis

Daniele Borsetto[1], Ananth Vijendren[2], Gianni Franchin[3], Neil Donnelly[4], Patrick Axon[5], Liam Masterson[6], Manohar Bance[1], Athanasios Saratziotis[7], Jerry Polesel[8], Paolo Boscolo-Rizzo[9], and James Tysome[5]

[1]Addenbrooke's Hospital
[2]Colchester Hospital University NHS Foundation Trust
[3]Aviano AB, Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS Pordenone, Friuli Venezia Giulia, IT
[4]Cambridge University Hospital NHS Foundation Trust
[5]Cambridge University Hospitals
[6]Addenbrookes Hospital
[7]University Hospital of Larissa
[8]Aviano AB
[9]University of Padua

November 15, 2021

Abstract

Objectives : Primary : To determine the rate of occult cervical metastasis in primary temporal bone squamous cell carcinomas (TBSSC). Secondary : to perform a subgroup meta-analysis of the risk of occult metastasis based on the clinical stage of the tumour and its risk based on corresponding levels of the neck Design : A systematic review and meta-analysis of papers searched through Medline, Cochrane, Embase, Scopus and Web of Science up to January 2021 to determine the pooled rate of occult lymph node/parotid metastases. Quality assessment of the included studies was assessed through the Newcastle-Ottawa scale. Setting : Centres around the world that perform surgery for TBSCC Participants : Patients with TBSCC Results : Overall, 9 out of 1034 screened studies met the inclusion criteria, for a total of 907 patients of which 388 had TBSCC. Out of the 191 patients who underwent a neck dissection, 21 had positive lymph nodes giving a pooled rate of occult metastases of 11% (95% CI: 7%-17%). When analysed using the Modified Pittsburg staging system, 21 pT2 cases had a pooled occult metastases rate of 3% (95% CI: 0%-21%), 27 pT3 cases had a pooled occult metastases rate of 12% (95% CI: 1%-60%), and 65 pT4 cases had a pooled occult metastases rate of 14% (95% CI: 7%-25%). Data available showed that most of the positive nodes were in Level II. Conclusion: The rate of occult cervical metastases in TBSCC increases based on the tumour (T) staging of the disease with majority of nodal disease found in level 2 of the neck.

Abstract

Objectives : Primary : To determine the rate of occult cervical metastasis in primary temporal bone squamous cell carcinomas (TBSSC). Secondary : to perform a subgroup meta-analysis of the risk of occult metastasis based on the clinical stage of the tumour and its risk based on corresponding levels of the neck

Design : A systematic review and meta-analysis of papers searched through Medline, Cochrane, Embase, Scopus and Web of Science up to January 2021 to determine the pooled rate of occult lymph node/parotid metastases. Quality assessment of the included studies was assessed through the Newcastle-Ottawa scale.

Setting : Centres around the world that perform surgery for TBSCC

Participants : Patients with TBSCC

Results : Overall, 9 out of 1034 screened studies met the inclusion criteria, for a total of 907 patients of which 388 had TBSCC. Out of the 191 patients who underwent a neck dissection, 21 had positive lymph nodes giving a pooled rate of occult metastases of 11% (95% CI: 7%-17%). When analysed using the Modified Pittsburg staging system, 21 pT2 cases had a pooled occult metastases rate of 3% (95% CI: 0%-21%), 27 pT3 cases had a pooled occult metastases rate of 12% (95% CI: 1%-60%), and 65 pT4 cases had a pooled occult metastases rate of 14% (95% CI: 7%-25%). Data available showed that most of the positive nodes were in Level II.

Conclusion: The rate of occult cervical metastases in TBSCC increases based on the tumour (T) staging of the disease with majority of nodal disease found in level 2 of the neck.

Key Words: lymph node metastases, squamous cell carcinoma, elective neck dissection, meta-analysis, temporal bone carcinoma.

Key points

- Temporal bone squamous cell carcinomas (TBSCCs) are rare cancers of the head and neck with overall poor prognosis.
- As they tend to spread locally, there is a dilemma if prophylactic neck dissections should be performed in clinically staged N0 necks.
- We identified 9 studies containing 907 patients of which 388 had TBSCC
- 21 out of 191 patients who underwent elective neck dissection were found to have positive lymph nodes giving a pooled occult metastases rate of 11%
- As the rate of occult metastases increased with T- staging of the tumour (pT2: 3%, pT3: 12%, pT4: 14%) and were most commonly found in level 2 of the neck, we would recommend dissecting a minimum of level II of the neck in pT3 and pT4 TBSCC.

Introduction

Temporal bone cancers account for around 0.2% of head and neck malignancies and squamous cell carcinoma (SCC) represents the commonest histopathological subtype (1).

Despite its low incidence, temporal bone squamous cell carcinomas (TBSCC) are aggressive with poor survival outcomes and high morbidity. Patients usually present with a troublesome discharging ear, hearing loss, pain, head and neck lumps and not infrequently a facial palsy(2). A combination of biopsies and CT as well as MRI imaging is essential to investigate, diagnose and stage the disease for treatment options. Although there is no Union for International Cancer Control (UICC) or American Joint Committee on Cancer Control (AJCC) on TBSCC, the modified Pittsburgh staging is commonly employed(3).

TBSCC tend to spread locally rather than metastasize to regional lymph nodes or distant sites, making radical resection of the primary lesion the mainstay of treatment. Therefore, while neck dissections (ND) are generally advocated in the presence of nodal disease, although survival of patients with neck metastases is very poor(4), its role in a clinically N0 neck (cN0) has been a subject of debate, mainly due to the lack of evidence and because many units will routinely treat at least the upper neck as well as the primary site with adjuvant radiotherapy. The UK national multidisciplinary guidelines on the management of head and neck cancer(5, 6) have recommended that all TBSCC with cN0 undergo neck dissection of levels 2-5 based on Rinaldo et al.'s narrative review, which estimated that the risk of occult metastases lies between 17-25%.(7) Others may decide on the extent of neck dissection based on the clinical staging, or on performing no neck dissection given that radiotherapy may be planned post-operatively to the neck.

With these discrepancies in mind, the aim of this systematic review and meta-analysis is to estimate the rate of occult cervical metastasis in primary TBSSC and to analyse the evidence on the indication and extent of elective neck dissection in these tumours.

Methods

Ethical consideration

As the meta-analyses did not involve any direct patient care within or outside the NHS, Research Ethics Committee approval was not necessary. The project did not constitute a form of audit nor research and hence local audit and research department approval were not required either.

Outcome measures

The primary outcome of this meta-analysis is the prevalence of occult cervical metastases in primary TBSSC. The secondary outcome is a) to perform a subgroup meta-analysis of the risk of occult metastasis based on the clinical stage of the tumour and b) the rate of occult metastasis in each level in the neck.

Search strategy

This systematic review and meta-analysis were conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist(8). Medline (via Ovid), Cochrane, Embase (via Ovid), Web of Science (Core Collection) and Scopus were searched from inception through to January 2021 (Appendix 1). The research was conducted according to PRISMA criteria. A combination of MeSH terms and free-text words were utilized to search for "temporal bone squamous cell carcinoma" or "temporal bone" or "squamous cell carcinoma" AND "Neck dissection" OR "Elective" OR "Node" OR "Lymphnode" OR "Lymph node" OR "N0".

The reference lists of articles included in this review as well as narrative reviews published in the last 10 years were also manually searched to minimize the risk of missing data. Two authors (DB and AV) independently screened all titles and abstracts generated by the search and then evaluated the full texts of all the relevant articles identified against the inclusion criteria (Figure 1); a third author (PBR) settled discordances when present.

Selection criteria

Studies were included in the analysis if they met the following criteria:

(a) population study including previously untreated primary squamous cell carcinoma involving the temporal bone

(b) neck staging carried out by performing ultrasound (US) and/or computerized tomography (CT) and/or magnetic resonance imaging (MRI) and/or positron emission tomography (PET)

(c) studies reporting complete or extractable data on the number of patients with cN0 parotid tumours, number of elective neck dissections and cases of occult metastases.

The exclusion criteria were

(a) studies that did not declare precisely how they staged the neck (palpation or imaging) before elective dissection

(b) studies with fewer than 5 patients

(c) non-English language studies

(d) reviews, editorials and letters.

(e) studies containing aggregated and non-extractable data, or duplicated data from previously published work

e) non-squamous cell carcinoma or metastasis

f) recurrent disease.

We defined occult metastases (pN+/cN0) as lateral cervical lymph node metastases identified upon elective neck dissection of patients with clinically uninvolved cervical lymph nodes (cN0) at preoperative staging.

Data extraction and statistical analysis

An electronic data-collection form was used to extract the following data from each of the included studies: author, year of publication, study design, country and period of conduction, number of patients, demographic characteristics, staging, grading of the tumours, type of imaging used to stage the neck, criteria used for elective neck dissection and dissected levels if specified, number of cN0 patients who underwent elective neck dissection and cases of occult metastases identified (pN+/cN0). The authors of the selected studies were contacted in order to gather missing information about individual patient data and attempt to perform subgroup meta-analysis. Two authors (DB, AV) independently assessed the quality of the included studies with the Newcastle-Ottawa Scale(9).

The pooled proportion of occult metastases and corresponding 95% confidence interval (CI) were calculated according to random-effects models of DerSimonian and Laird(10), using the logit transformation and weighting through the inverse variance method. Statistical heterogeneity among studies was evaluated using the $\mathbf{I^2}$ and t^2statistics. Influence analysis was performed when pooled proportions were estimated from five or more studies: pooled proportion was calculated by omitting one study at a time. Publication bias was assessed through a funnel plot(11).

The results of the meta-analysis were presented graphically using forest plots, plotting the individual paper, pooled proportions and corresponding 95% CI. Analyses were conducted using R 3.6, and statistical significance was claimed for $p < 0.05$ (two sided).

Results

Literature search

The literature review yielded 1034 articles. From the review of the titles and abstracts, 1008 articles were excluded for being irrelevant to the topic, non-English language, non-original, case reports, editorials or duplicated studies (Figure 1). Twenty-six full-text articles were examined reporting elective neck dissection in the therapeutic management of cN0 in squamous cell carcinoma of the temporal bone. Of these, 17 were excluded as they did not meet the inclusion criteria, or because there were no available data on clinically N0 patients, the data were secondary, or because the authors were contacted but were unable to provide the data requested (authors of the studies were contacted where required for information about individual patient data to ensure a subgroup meta-analysis could be performed for specific tumour histology of squamous cell carcinoma). From the articles included in the systematic review, it was determined that nine studies fully satisfied the inclusion criteria.

Demographics

The nine articles(4, 12-19) that satisfied the criteria for inclusion in the systematic review and meta-analysis were retrospective case series published between 2009 and 2018. All the studies focused on management of squamous cell carcinoma of the temporal bone. Patient demographics were only available in six studies(4, 12-15, 18). The total population of the included studies was 907 patients, 388 of whom had squamous cell carcinoma. Studies ranged from 6 to 125 patients with an overall median of 43.1 patients. The median age was 65.08 years (range, 3.8-92 years). Gender was reported in six articles, with 140 (57.8%) male and 102 (42.14%) female.

Core data

Data on positive SCC histology was available for all 388 patients; of which 191 patients had undergone a neck dissection. Positive metastatic lymph nodes were found in 21 of these 191 patients (Table 1). Only three studies reported the level of the positive lymph nodes(13, 14, 18). Ng et al, Gidley et al. and Cristalli et al. had reported a total of 33 cases undergoing prophylactic neck dissections of which 5 patients had positive nodal involvement. 3 of these patients were found to have nodes in level II of the neck with the levels not

reported in the remaining 2 patients(13, 14, 18). The data on tumour grading based on Modified Pittsburgh classification were available in 128 out of the 191 patients with the following percentages; T1 = 4.68%, T2 = 24.21 %, T3 = 20.31%, and T4 = 50.78%.

Meta-analysis pN+/cN0

In the nine studies, neck staging was determined by a combination of PET, MRI, US and/or CT. Of these 191 patients with TBSCC and cN0 necks, there were 21 cases were pN+/cN0, with a pooled rate of occult metastases of 11% (95% CI: 7%-17% – Figure 2); with corresponding levels of neck dissected known in 11 patients. No publication bias emerged by inspection of funnel plot (Supplementary Figure 1.A). Influence analysis did not report substantial modification when one study was omitted at a time, with pooled proportion ranging from 9% when McRackan was excluded to 14% when Masterson was excluded (Supplementary Figure 1.B). Of the 191 patients included in the meta-analysis, 121 patients had data available on the Tumour stage according to the Pittsburgh classification: 21 cases were pT2 with a pooled rate of occult metastases of 3% (95% CI: 0%-21%), 27 cases were pT3 with a pooled rate of occult metastases of 12% (95% CI: 1%-60%), and finally 65 cases were pT4 with a pooled rate of occult metastases of 14% (CI: 7%-25%) (Figure 3).

Quality of studies assessed and risks of biasness

Four out of the nine studies reported a Newcastle-Ottawa Scale (NOS) score [?]7, meaning they are high quality studies, but the NOS median of 6 establishes an overall high risk of bias in the meta-analysis. A detailed report on the quality of included studies according to the Newcastle-Ottawa Scale is reported in Supplementary Table 1.

Discussion

Summary of findings

Our meta-analyses of 191 cN0 TBSCC patients estimated an overall rate of occult lymph nodes metastases of 11% with level II being the only affected neck region, although the level was only known in 5 patients..

Comparison to other studies

The treatment of TBSCC remains a multidisciplinary challenge. The treatment of a clinical N0 neck has been fraught with controversies and differing opinions, particularly on the benefits of a prophylactic neck dissection, the extent of dissection and the role of postoperative radiotherapy. Regional lymph node involvement has negative impact on prognosis. Morris (17) reported a 5-year disease-specific survival (DSS) of 18.8% and 80.8% in node-positive and node-negative patients while Nakagawa (20) found a 5-year estimated survival rate of 70% in patients with negative regional lymph node involvement, but a significant decline in estimated survival to 19% in patients with positive lymph node involvement. Masterson et al(4) reported a 5-year overall survival of 0% in his cohort of TBSCC with positive lymph node involvement. The negative impact of nodal metastasis on survival supports the argument that complete surgical clearance of the tumour both at primary site and in the neck is required irrespective of the presence of nodal involvement.

.

Historically, elective neck dissections have been advocated for cN0 necks in patients with head and neck SCC thought to have a 20% risk of occult cervical metastases. This recommendation was based on risk-benefit analyses performed in the 1970s by authors such as Ogura et al.(21) and Lee et al.(22). It was commonly accepted then that radical neck dissections were the main surgical approaches of choice for total disease clearance, which in effect also carries a higher morbidity with the associated removal of the accessory nerve, internal jugular vein and/or the sternocleidomastoid muscle. It is understandable why a 20% cut off was a reasonable historic choice to balance the pros and cons of the surgery. Since then, the surgical procedures for cN0 have evolved from radical neck dissections to functional, selective and highly selective procedures with consequent reduction in morbidity. These more selective approaches have been shown to adequately remove pathology while minimising morbidity such as shoulder dysfunction and have become the more mainstay form of prophylactic treatment of cervical disease. With the change in surgical technique over the years, it

seems reasonable to re-evaluating the 20% cut off point and accept a lower risk of metastases as an indication for a selective neck dissection to achieve adequate disease removal and pathological neck staging.

Clinical applicability

While previous studies have included diffferent approaches to slelective neck dissection, the little data available has only showed occult metastases at level 2. As no level V found metastases were found and given the increased risk of damage to the accessory nerve, this data does not support inclusion of level V in a selective ND for a cN0 neck. While some authors have suggested a that frozen section samples are sent for Level 2 prior to proceeding to dissect other levels in the neck based on the results, it seems reasonable to perform a supra-omohyoid or level II and III neck dissection in cN0 necks given that this also facilitates vessel preparation for a microvascular free flap as is often required in these cases (23, 24).

Based on our meta-analysis's findings of an 11% occult risk of TBSCC cervical metastases, specifically 12% for T3 and 14% for T4 tumours predominantly confined to level II, we would advocate a selective level 2 and 3 neck dissection in T3 and T4 TBSCC patients after taking into account the low morbidity of the procedure and the aggressiveness of the cancer. This approach can be beneficial in a number of ways: by removing the cervical lymph nodes, one would be able to accurately stage the neck of and remove metastases not apparent on clinical staging, potentially avoiding adjuvant treatment completely if histological outcomes are favourable for this option. (24). Elective neck dissection has proved to improve the prognosis in head and neck cancers patient(25) as only a single modality treatment of the neck is required if pathologically N0, avoiding adjuvant radiotherapy of the regional lymph nodes and its related complications.(26) The low rate of occult metastases found in our pT2 (3%) analysis and relatively small rare occurrence of T1 and T2 TBSCC would suggest that an elective neck dissection is not required echoing the recommendations from Morris et al(17).

The role of adjuvant prophylactic radiotherapy as well as the total dose of radiation for elective neck treatment in TBSCC patients remains debatable. Although most clinicians would agree that radical surgery should be followed by postoperative radiation therapy (PORT) in cases with adverse histopathological features (eg. advanced tumours, multiple nodal involvement, extracapsular spread, perineural invasion, positive margins)(27, 28), the overall survival of patients with stage III-IV disease remains low despite dual modality of treatment(29, 30). Intensity-modulated radiotherapy (IMRT) has been shown to reduce the severity of toxicity and significantly improve quality of life in head and neck cancer patients (31). However, even treatment regimens incorporating doses of IMRT with 54-63 Gy of adjuvant radiotherapy, which is considered adequate in intermediate-risk disease management according to NCCN guidelines (32) may be excessive in clinical N0 necks of TBSCC patients. As there is a general consensus that single modality of treatment should be advocated for TBSCC patients where possible, we feel that surgical excision of the TBSCC should be accompanied by a selective neck dissection after a multidisciplinary decision has been made to treat the cN0 neck.

Strength and limitations of the study

The strength of this meta-analysis is represented by its systematic and quantitative assessment of the role of prophylactic neck dissections in TBSCC using a strict inclusion and exclusion criteria. Our limitations include the low number of cases reporting the level of metastasis in the neck and the fact that the rates of occult nodal metastasis reported in the literature could be underestimated as not all cN0 patients underwent a neck dissection. From a statistical point of view, this meta-analysis has the limitation of having only observational and retrospective studies included. Furthermore, there are a relative low number of cases in some of the studies predominantly as a result of the rarity of these malignancies. Further limitations of our study include:

(a) Insufficient of data for a statistical analysis on the prevalence of occult metastases in each of the different lymph node levels

b) Inability to determine whether selective neck dissection is better than radiotherapy.

c) The inclusion criteria for many studies were not specified. This resulted in the exclusion of 17 studies in the final phase of review.

It would be helpful to perform a prospective multicentre study to compare the effectiveness of elective neck dissection and radiotherapy in TBSCC cN0 necks as data from individual units are unlikely to be sufficiently powered to influence overall management.

Conclusion

This meta-analysis estimated a pooled rate of occult lymph node metastases of 11% (99% CI: 0.07-0.17), with specific rates of 12% for pT3 tumours and 14% of pT4 tumours. Taking into account other pertinent factors such as the aim of single modality of treatment, the need to access the neck for reconstructive purposes, and the low morbidity for highly selective neck dissections, we would advocate that a selective neck dissection of at least level II should be considered in locally advanced (T3 and T4) TBSCC or radiotherapy to the upper neck.

References

1. Paleri V, Urbano T, Mehanna H, Repanos C, Lancaster J, Roques T, et al. Management of neck metastases in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Otology. 2016;130(S2):S161-S9.

2. Allanson BM, Low TH, Clark JR, Gupta R. Squamous Cell Carcinoma of the External Auditory Canal and Temporal Bone: An Update. Head Neck Pathol. 2018;12(3):407-18.

3. Moody SA, Hirsch BE, Myers EN. Squamous cell carcinoma of the external auditory canal: an evaluation of a staging system. Am J Otol. 2000;21(4):582-8.

4. Masterson L, Rouhani M, Donnelly NP, Tysome JR, Patel P, Jefferies SJ, et al. Squamous cell carcinoma of the temporal bone: clinical outcomes from radical surgery and postoperative radiotherapy. Otol Neurotol. 2014;35(3):501-8.

5. Roland N, Paleri V. Head and neck cancer: multidisciplinary management guidelines. Restorative Dentistry/Oral Rehabilitation London: ENT UK. 2011:56-62.

6. Paleri V, Roland N. Introduction to the United Kingdom national multidisciplinary guidelines for head and neck cancer. The Journal of Laryngology & Otology. 2016;130(S2):S3-S4.

7. Rinaldo A, Ferlito A, Suarez C, Kowalski LP. Nodal disease in temporal bone squamous carcinoma. Acta Otolaryngol. 2005;125(1):5-8.

8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

9. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa quality assessment scale cohort studies. University of Ottawa. 2014.

10. Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med. 1999;18(3):321-59.

11. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54(10):1046-55.

12. Chang CH, Shu MT, Lee JC, Leu YS, Chen YC, Lee KS. Treatments and outcomes of malignant tumors of external auditory canal. Am J Otolaryngol. 2009;30(1):44-8.

13. Cristalli G, Manciocco V, Pichi B, Marucci L, Arcangeli G, Telera S, et al. Treatment and outcome of advanced external auditory canal and middle ear squamous cell carcinoma. J Craniofac Surg. 2009;20(3):816-21.

14. Gidley PW, Roberts DB, Sturgis EM. Squamous cell carcinoma of the temporal bone. Laryngoscope. 2010;120(6):1144-51.

15. Matoba T, Hanai N, Suzuki H, Nishikawa D, Tachibana E, Okada T, et al. Treatment and Outcomes of Carcinoma of the External and Middle Ear: The Validity of En Bloc Resection for Advanced Tumor. Neurol Med Chir (Tokyo). 2018;58(1):32-8.

16. McRackan TR, Fang TY, Pelosi S, Rivas A, Dietrich MS, Wanna GB, et al. Factors associated with recurrence of squamous cell carcinoma involving the temporal bone. Ann Otol Rhinol Laryngol. 2014;123(4):235-9.

17. Morris LG, Mehra S, Shah JP, Bilsky MH, Selesnick SH, Kraus DH. Predictors of survival and recurrence after temporal bone resection for cancer. Head Neck. 2012;34(9):1231-9.

18. Ng SY, Pua KC, Zahirrudin Z. Temporal bone squamous cell carcinoma - Penang experience. Med J Malaysia. 2015;70(6):367-8.

19. Zanoletti E, Danesi G. The problem of nodal disease in squamous cell carcinoma of the temporal bone. Acta Otolaryngol. 2010;130(8):913-6.

20. Nakagawa T, Kumamoto Y, Natori Y, Shiratsuchi H, Toh S, Kakazu Y, et al. Squamous cell carcinoma of the external auditory canal and middle ear: an operation combined with preoperative chemoradiotherapy and a free surgical margin. Otol Neurotol. 2006;27(2):242-8; discussion 9.

21. Ogura JH, Biller HF, Wette R. Elective neck dissection for pharyngeal and laryngeal cancers. An evaluation. Ann Otol Rhinol Laryngol. 1971;80(5):646-50.

22. Lee JG, Krause CJ. Radical neck dissection: Elective, therapeutic, and secondary. Arch Otolaryngol. 1975;101(11):656-9.

23. Prasad SC, D'Orazio F, Medina M, Bacciu A, Sanna M. State of the art in temporal bone malignancies. Curr Opin Otolaryngol Head Neck Surg. 2014;22(2):154-65.

24. Mehta GU, Muelleman TJ, Brackmann DE, Gidley PW. Temporal bone resection for lateral skull-base malignancies. J Neurooncol. 2020;150(3):437-44.

25. Ferlito A, Rinaldo A, Silver CE, Gourin CG, Shah JP, Clayman GL, et al. Elective and therapeutic selective neck dissection. Oral Oncol. 2006;42(1):14-25.

26. Gujral DM, Chahal N, Senior R, Harrington KJ, Nutting CM. Radiation-induced carotid artery atherosclerosis. Radiother Oncol. 2014;110(1):31-8.

27. Bacciu A, Clemente IA, Piccirillo E, Ferrari S, Sanna M. Guidelines for treating temporal bone carcinoma based on long-term outcomes. Otol Neurotol. 2013;34(5):898-907.

28. Zhang T, Li W, Dai C, Chi F, Wang S, Wang Z. Evidence-based surgical management of T1 or T2 temporal bone malignancies. Laryngoscope. 2013;123(1):244-8.

29. Seligman KL, Sun DQ, Ten Eyck PP, Schularick NM, Hansen MR. Temporal bone carcinoma: Treatment patterns and survival. Laryngoscope. 2020;130(1):E11-E20.

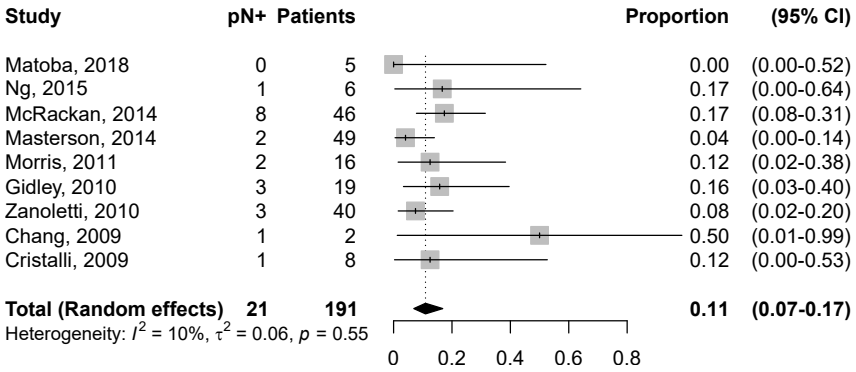
30. Xie B, Zhang T, Dai C. Survival outcomes of patients with temporal bone squamous cell carcinoma with different invasion patterns. Head Neck. 2015;37(2):188-96.

31. Ge X, Liao Z, Yuan J, Mao D, Li Y, Yu E, et al. Radiotherapy-related quality of life in patients with head and neck cancers: a meta-analysis. Support Care Cancer. 2020;28(6):2701-12.

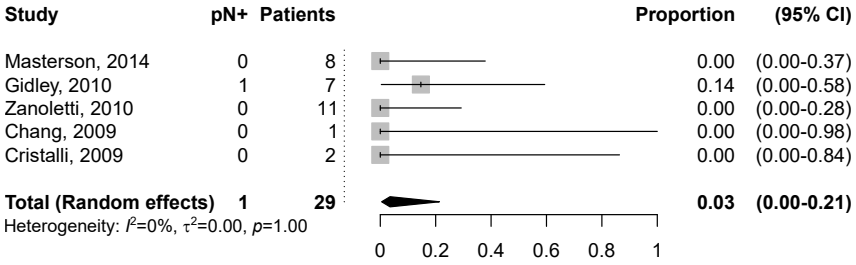
32. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(7):873-98.

Hosted file

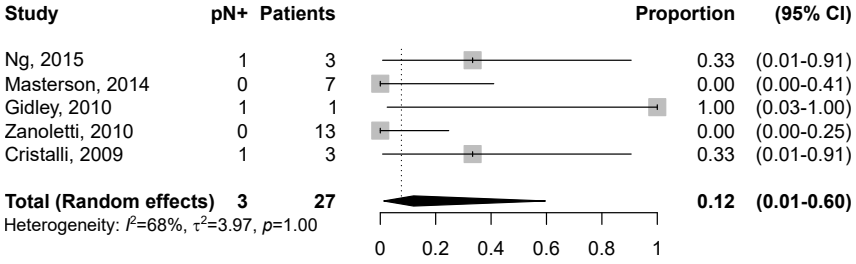
Figure 1.docx available at https://authorea.com/users/446299/articles/545581-prevalence-of-occult-nodal-metastases-in-squamous-cell-carcinoma-of-the-temporal-bone-a-systematic-review-and-meta-analysis



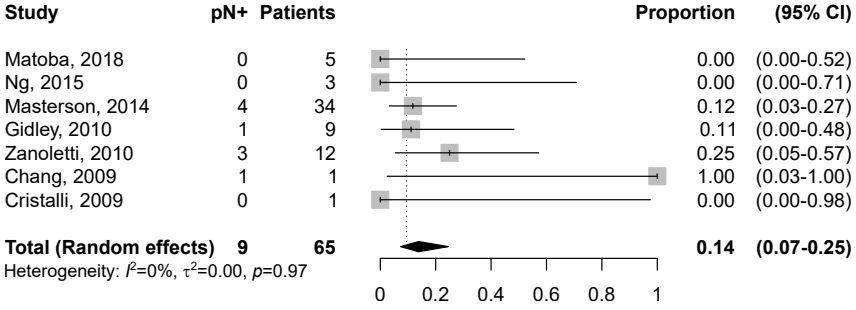
Pittsburgh T2



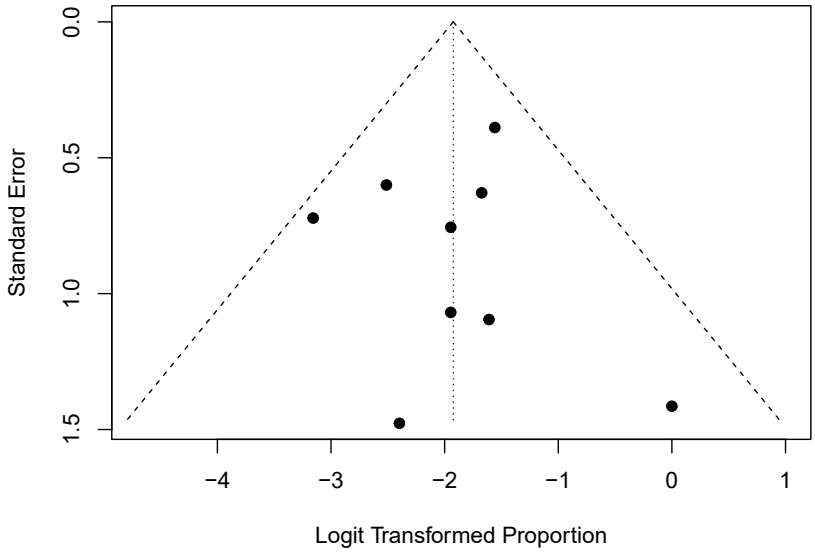
Pittsburgh T3



Pittsburgh T4



A. Funnel plot



B. Sensitivity analysis