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Review

Surgical Management of Endolymphatic Sac Tumor: A Systematic Review and Meta-Analysis

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The aim of our study was to report rates of facial nerve palsy and residual tumor following surgical intervention and subsequent tumor recurrence in patients with endolymphatic sac tumors. A systematic literature review of preoperative assessment and surgical management is also included.

Studies including patient/s affected by sporadic or von Hippel-Lindau disease related endolymphatic sac tumors, reporting levels of facial nerve function, residual and recurrence pathology following a surgical procedure, were considered. Data were combined for proportional meta-analysis, and the selected studies' methodological quality was also evaluated.

Overall 34 papers, including 202 subjects (209 cases of endolymphatic sac tumors) were analyzed. Pooled proportion rate (95% CI) of overall facial nerve palsy was 39.7% (28.2-51.9) and residual tumor was 16.5% (10.3-23.7) after surgical procedure. Pooled proportion rate (95% CI) of tumor recurrence was 14.0% (9.7-19.3) during a mean follow-up period of 49.7 months (8-136).

Our results showed that preoperative facial nerve function is impaired in almost 30% of patients with endolymphatic sac tumors. Surgical management of endolymphatic sac tumor may cause a worsening of facial nerve function in a low percentage of treated subjects. Residual and/or recurrence of endolymphatic sac tumors are not rare events, and follow-up strategies should be designed accordingly.

KEYWORDS: Ear surgery, endolymphatic sac tumor, facial nerve, middle ear surgery, otology

INTRODUCTION

Endolymphatic sac tumors (ELSTs) are slow-growing, locally aggressive, low-grade malignancies that originate from the epithelium of the endolymphatic duct and sac.[1] Embryologically, the endolymphatic sac derives from the neuroectoderm and consists of proximal and distal segments.[2] Both histological and radiological investigations suggest that the origin of ELSTs occurs in the proximal portion of the sac.[3] Endolymphatic sac tumors develop either sporadically or as part of the autosomal dominant von Hippel–Lindau (VHL) disease. von Hippel–Lindau disease is caused by a mutation of the synonymous tumor suppressor transcribing gene. Among VHL patients, 3.6%-16% develop an ELST, and overall, 1/3 of ELSTs are related to VHL disease.[4] The clinical manifestations of ELST are nonspecific and can include hearing loss or episodes of vertigo.[5] Differential diagnosis for ELST includes all intrinsic temporal bone neoplasms (most commonly paraganglioma).[6] Surgical resection is the treatment of choice, and although currently controversial, some tumors may require pre-/postoperative radiation therapy.[5] Endolymphatic sac tumors often invade adjacent structures located within all 4 vectors, including lateral, medial, superior, and anterior. Laterally, tumor growth toward the middle ear usually travels *via* the transmastoid route, eroding the vestibule, the posterior semicircular canal, and the mastoid cavity. Subsequently, the tumor can involve the jugular bulb and facial nerve.[3] Medial tumor extension to the cerebellopontine angle region or the posterior fossa is another common growth pathway.[7] Superior extension occurs through the semicircular canals and into the middle fossa, whereas anterior extension along the petrous ridge may invade the clivus, cavernous sinus, or sphenoid sinus.[1] Smaller tumors

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localized to the endolymphatic sac area and adjoining the posterior fossa can be treated with a retrolabyrinthine or retrosigmoid approach.[3] For larger tumors extending through the labyrinth and/or intradurally in the posterior fossa, in patients with poor hearing, the translabyrinthine approach is usually employed. Tumors including involvement of the middle ear are best managed with a petrosectomy[2] while for extensive tumors with complete exenteration of the otic capsule requiring exposure of the petrous carotid artery, the transcochlear approach is recommended.[3] Furthermore, various combined skull-based approaches have been described in literature, according to tumor extension and surgeons' experience.

Total tumor resection from the endolymphatic duct and the vestibular aqueduct can help to reduce the risk of recurrence. However, 2 combined factors can complicate surgical excision, including (i) the elevated level of vascularization (that may be reduced by preoperative embolization) and (ii) infiltration of posterior fossa dura.[8]

The purpose of our study was to systematically review rates of facial nerve palsy and residual tumor following surgical intervention and subsequent tumor recurrence in patients with endolymphatic sac tumors managed surgically and to report pooled proportions. A secondary aim is to perform a systematic literature review of preoperative and surgical management of ELSTs.

METHODS

Search Methods for Identification of Studies

We report a systematic review according to the recommendations suggested by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[9]

A computerized search of "Ovid MEDLINE," "Web of Science," and "Scopus" was made using the following string: "Endolymphatic Sac" AND "Neoplasms," OR "Adenocarcinoma" OR "Adenoma." The final search was run in February 2022. Abstracts and titles were screened independently by 2 authors (FMG and MR), according to a predefined criteria.

Prime study inclusion criteria were (i) at least 1 patient affected by sporadic or VHL-related ELSTs; (ii) no restriction for patient age; (iii) studies reported in English. Review articles have not been considered together with any other studies reporting pathological conditions unrelated to ELST.

Among the identified manuscripts, those meeting the initial inclusion criteria were then selected for full-text review. The review was performed by the same 2 authors (FMG and MR) independently.

Full-text inclusion criteria specified the reporting of at least one of the following: reported data (i) about postoperative facial nerve alterations (levels of facial nerve function reported according to House–Brackmann grading system); (ii) postoperative residual tumor; and (iii) tumor recurrence or clearance during follow-up. Studies with duplicate data were excluded. A manual check of reference lists of included studies was made to identify any further study meeting inclusion criteria.

Extracted data were (i) clinical symptoms, (ii) tumor size reported based on radiological imaging, (iii) pre- and postoperative pathological side facial nerve condition, (iv) presence or absence of any postoperative residual mass, and (v) tumor recurrence or complications identified during follow-up.

Statistical Assessment

We performed proportional meta-analysis with MedCalc, MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014). MedCalc uses a Freeman-Tukey transformation (arcsine square root transformation; Freeman and Tukey, 1950) to calculate the weighted summary Proportion under the fixed and random effects model (DerSimonian and Laird, 1986). The program lists the proportions (expressed as a percentage),

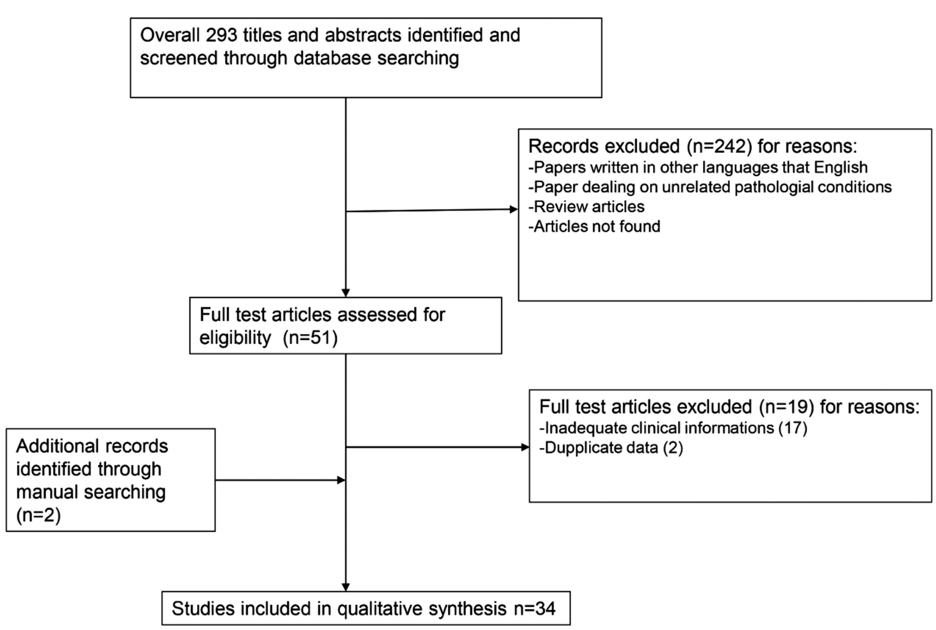

Figure 1. Workflow diagram describing the systematic selection of studies for meta-analysis inclusion.

with their 95% CI, found in the individual studies included in the meta-analysis.

Pooled proportions (with 95% CI) were calculated with both the fixed and random effects models. The summary effect derived from the fixed-effects model assumes that studies share a common true effect, producing an estimate of a common effect size, while the random effects model assumes that true effects vary between studies and reports the summary effect as a weighted average of those reported in the different studies. An overall effect (95% CI) was calculated with forest plots for each symptom, with the marker size relative to the individual study weight. Pooled effects of all clinical complications are represented by diamond shapes: the effect size is represented by its location and precision by its width.

Between studies, heterogeneity according to study outcomes was assessed with χ^2-based Cochran's Q statistic test and I^2 metric. Heterogeneity was considered significant at $P < .01$ for Q statistic (to assess whether observed variance exceeds expected variance), whereas the I^2 metric ($I^2 = 100\% \times (Q - df)/Q$) has cut-offs: $I^2 = 0\%$-25%, homogeneous; $I^2 = 25\%$-50%, moderate heterogeneity; $I^2 = 50\%$-75%, large heterogeneity; $I^2 = 75\%$-100%, extreme heterogeneity.

Table 1. Main Features and Data of the Selected Studies

Authors	Year	Number of Patients	Number of ELSTs	Middle Age (Years)	Number of Facial Nerve Palsies		Number of Residuals	Mean Follow-Up (Months)	Number of Recurrences
					Before Surgery	After Surgery			
Panchwagh[13]	1999	1	2	22	1	1	1	8	0
Megerian[14]	2002	4	5	27.5	0	0	0	49.2	0
Cohen[15]	2003	1	1	35	0	0	0	n/a	n/a
Hansen[16]	2004	14	14	42.4	6	7	1	59.6	3
Rodrigues[17]	2004	7	7	48.3	5	6	n/a	70.2	1
Kupferman[18]	2004	1	1	4	1	1	0	18	0
Schipper[12]	2006	7	7	44.5	0	0	0	n/a	0
Wada[19]	2006	1	1	48	0	0	0	36	0
Doherty[20]	2007	3	3	35.3	2	3	2	32	0
Diaz[6]	2007	3	3	31.7	1	2	0	73.7	1
Jagannathan[21]	2007	1	1	33	0	0	0	n/a	n/a
Bae[22]	2008	4	4	48	2	2	0	23.5	1
Ni[23]	2008	3	3	31	0	1	0	11.6	0
Timmer[24]	2011	9	10	36.5	2	n/a	2	136	0
Poletti[3]	2011	7	7	48.8	n/a	3	n/a	66.8	2
Bastier[25]	2012	3	3	33.6	1	0	0	n/a	1
Kim[26]	2012	31	33	38.2	4	2	3	49.9	1
Carlson[27]	2013	11	12	n/a	3	4	0	65.4	1
Friedman[28]	2013	18	18	46	6	8	n/a	67	2
Virk[29]	2013	2	2	66	0	0	0	n/a	n/a
Ferri[30]	2014	1	1	37	0	0	0	36	0
Kunzel[31]	2014	1	1	39	0	0	1	120	0
Schnack[32]	2017	1	1	65	0	0	0	30	0
Zanoletti[2]	2017	4	4	44.2	0	1	0	41.5	0
Riggs[33]	2017	1	1	38	0	0	0	n/a	n/a
Alkhotani[34]	2018	1	1	25	1	1	1	n/a	n/a
Sykopetrites[4]	2020	13	13	37	2	4	2	61.3	1
Guo[35]	2020	14	14	38	10	13	1	58	1
Li[36]	2020	16	17	37	6	7	1	35.1	3
Bae[37]	2020	5	5	41	4	4	2	85.2	2
Longoni[38]	2020	1	1	48	1	1	0	12	0
Tahir[39]	2021	1	1	74	0	0	1	24	1
Lodi[40]	2021	1	1	17	0	0	1	12	1
Hou[41]	2021	11	11	43	2	4	1	61.5	1

ELSTs,

RESULTS

The first search found 293 studies, of which 54 papers had required features for review. A total of 32 studies met definitive inclusion criteria. Subsequent check of the bibliography identified 2 additional studies, resulting in a total of 34 final articles, comprising 202 subjects and 209 ELSTs (Figure 1).

The main characteristics of selected studies are reported in Table 1. Among studies reporting this information (including overall 191 patients), the percentage of subjects suffering from VHL syndrome represented 34% (n = 65). Mean ELSTs dimension was 25.2 mm, reported in 18 papers. Among the 209 ELSTs reported in included studies, 10 cases were not surgically treated for various reasons: a total of 199 ELSTs received surgical treatment.

Table 2. Meta-analysis of the Proportions of Facial Palsy After Surgery

Study	Number of Ear Surgeries	Facial Palsy	Proportion (%)	95% CI
Panchwagh et al (1999)	1	1	100.0	2.5 to 100.0
Megerian et al (2002)	5	0	0.0	0.0 to 52.2
Cohen et al (2003)	1	0	0.0	0.0 to 97.5
Hansen et al (2004)	14	7	50.0	23.0 to 76.9
Rodrigues et al (2004)	7	6	85.7	42.1 to 99.6
Kupferman et al (2004)	1	1	100.0	2.5 to 100.0
Schipper et al (2006)	7	0	0.0	0.0 to 40.9
Wada et al (2006)	1	0	0.0	0.0 to 97.5
Diaz et al (2007)	3	2	66.7	9.4 to 99.1
Jagannathan et al (2007)	1	0	0.0	0.0 to 97.5
Doherty et al (2007)	3	3	100.0	29.2 to 100.0
Bae et al (2008)	4	2	50.0	6.7 to 93.2
Ni et al (2008)	3	1	33.3	0.8 to 90.6
Poletti et al (2011)	7	3	42.9	9.9 to 81.6
Kim et al (2012)	33	2	6.1	0.7 to 20.2
Bastier et al (2012)	2	0	0.0	0.0 to 84.2
Carlson et al (2013)	11	4	36.4	10.9 to 69.2
Friedman et al (2013)	18	8	44.4	21.5 to 69.2
Virk et al (2013)	2	0	0.0	0.0 to 84.2
Ferri et al (2014)	1	0	0.0	0.0 to 97.5
Kunzel et al (2014)	1	0	0.0	0.0 to 97.5
Zanoletti et al (2017)	4	1	25.0	0.6 to 80.6
Riggs et al (2017)	1	0	0.0	0.0 to 97.5
Schnack et al (2017)	1	0	0.0	0.0 to 97.5
Alkhotani et al (2018)	1	1	100.0	2.5 to 100.0
Sykopetrites et al (2020)	13	4	30.8	9.1 to 61.4
Li et al (2020)	14	7	50.0	23.0 to 76.9
Bae et al (2020)	5	4	80.0	28.3 to 99.5
Guo et al (2020)	14	13	92.9	66.1 to 99.8
Longoni et al (2020)	1	1	100.0	2.5 to 100.0
Hou et al (2021)	11	4	36.4	10.9 to 69.2
Lodi et al (2021)	1	0	0.0	0.0 to 97.5
Tahir et al (2021)	1	0	0.0	0.0 to 97.5
Total (fixed effects)	193	75	38.1	31.7 to 44.7
Total (random effects)	193	75	39.7	28.2 to 51.9

Preoperative facial nerve condition was reported in 33 studies comprising 202 pathological sides. Facial nerve impairment was observed in 29.7% (n = 60) of pathological sides. Overall, 33 studies reported that postoperative facial nerve condition was achieved after treatment of 193 pathological sides, with impairment rates rising to 38.8% (n = 75) of pathological sides. Postsurgical residual mass rate was calculated from data reported in 31 studies, resulting in a rate of 11.9% (n = 20). Tumor recurrence was reported in 29 studies, and calculated rates were 11.9% (n = 23). Follow-up was reported in 27 studies only, and the mean follow-up was 49.7 months (8-136).

Overall, postoperative facial nerve palsy was calculated based on 193 ELSTs reported in 33 studies; pooled proportion (95% CI) was 39.7% (28.2-51.9), with significantly large heterogeneity between studies ($Q = 919.3$, $df = 32$, $I^2 = 65.2\%$, $P < .001$), see Table 2 and Figure 2. Overall, postoperative residual mass was calculated based on 167 ELSTs reported in 31 studies; the pooled proportion was 16.5% (10.3-23.7), classified with insignificantly moderate heterogeneity between the studies ($Q = 422.8$, $df = 30$, $I^2 = 29.0\%$, $P = .067$), see Table 3 and Figure 3. Overall, tumor recurrence during follow-up was reported in 193 ELSTs in 29 studies; the pooled proportion was 14.0% (9.7-19.3), considered as insignificantly homogeneous ($Q = 279.3$, $df = 28$, $I^2 = 0.0\%$, $P = .468$), see Table 4 and Figure 4.

DISCUSSION

Our analysis confirmed preoperative facial nerve weakness or paralysis among the upper limits of those reported in the literature; approximately 10%-30%.[10] Furthermore, our analysis reports only a moderate increase in overall postoperative facial nerve impairment. Further, postoperative residual mass and tumor recurrence throughout patient follow-up is not rare.

The recurrence of ELST occurs more frequently compared to other predominant petrous bone tumors, with the exception of petrous bone chondrosarcomas, to which our reported rates are similar.[4]

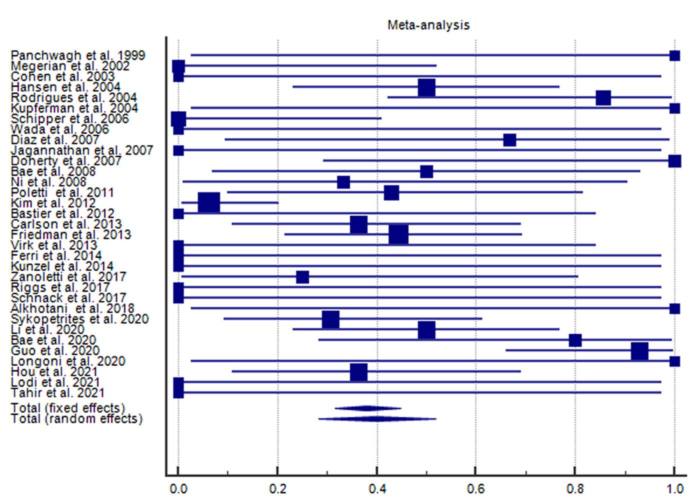

Figure 2. Meta-analysis of the proportions of facial palsy. Squares represent percentage point estimates and horizontal lines represent 95% CI.

Table 3. Meta-analysis of the Proportions of Residual After Surgery

Study	Approach	Residual	Proportion (%)	95% CI
Panchwagh et al (1999)	1	1	100.0	2.5 to 100.0
Megerian et al (2002)	5	0	0.0	0.0 to 52.2
Cohen et al (2003)	1	0	0.0	0.0 to 97.5
Hansen et al (2004)	14	1	7.1	0.2 to 33.9
Kupferman et al (2004)	1	0	0.0	0.0 to 97.5
Schipper et al (2006)	7	0	0.0	0.0 to 40.9
Wada et al (2006)	1	0	0.0	0.0 to 97.5
Diaz et al (2007)	3	0	0.0	0.0 to 70.7
Jagannathan et al (2007)	1	0	0.0	0.0 to 97.5
Doherty et al (2007)	3	2	66.7	9.4 to 99.2
Bae et al (2008)	4	0	0.0	0.0 to 60.2
Ni et al (2008)	3	0	0.0	0.0 to 70.7
Timmer et al (2011)	5	2	40.0	5.3 to 85.3
Kim et al (2012)	33	3	9.1	1.9 to 24.3
Bastier et al (2012)	2	0	0.0	0.0 to 84.2
Carlson et al (2013)	11	0	0.0	0.0 to 28.5
Virk et al (2013)	2	0	0.0	0.0 to 84.2
Ferri et al (2014)	1	0	0.0	0.0 to 97.5
Kunzel et al (2014)	1	1	100.0	2.5 to 100.0
Zanoletti et al (2017)	4	0	0.0	0.0 to 60.2
Riggs et al (2017)	1	0	0.0	0.0 to 97.5
Schnack et al (2017)	1	0	0.0	0.0 to 97.5
Alkhotani et al (2018)	1	1	100.0	2.5 to 100.0
Sykopetrites et al (2020)	13	2	15.4	1.9 to 45.4
Li et al (2020)	14	1	7.1	0.2 to 33.8
Bae et al (2020)	5	2	40.0	5.3 to 85.3
Guo et al (2020)	14	1	7.1	0.2 to 33.8
Longoni et al (2020)	1	0	0.0	0.0 to 97.5
Hou et al (2021)	11	1	9.1	0.2 to 41.3
Lodi et al (2021)	1	1	100.0	2.5 to 100.0
Tahir et al (2021)	1	1	100.0	2.5 to 100.0
Total (fixed effects)	166	20	14.4	9.787 to 20.1
Total (random effects)	166	20	16.5	10.3 to 23.7

This may be due to the similarity of ELST and chondrosarcomas in bone infiltration, affecting the ability to effectively remove the entire tumor mass. Given the likelihood of residual mass and recurrent disease, some authors have recommended the follow-up approach to include a magnetic resonance imaging (MRI) examination every 6 months initially and annually thereafter for 10 years.[8]

Differential diagnosis of ELSTs from other neoplasms in the petrous bone and cerebellopontine angle and preoperative tumor evaluation requires radiological assessment. The first location of the mass can be important in obtaining differential diagnosis. The origin of ELSTs is usually observed in the retrolabyrinthine area, whereas temporal bone paragangliomas are often located in the jugular foramen region or on the promontory along the Jacobson nerve. Meningiomas and

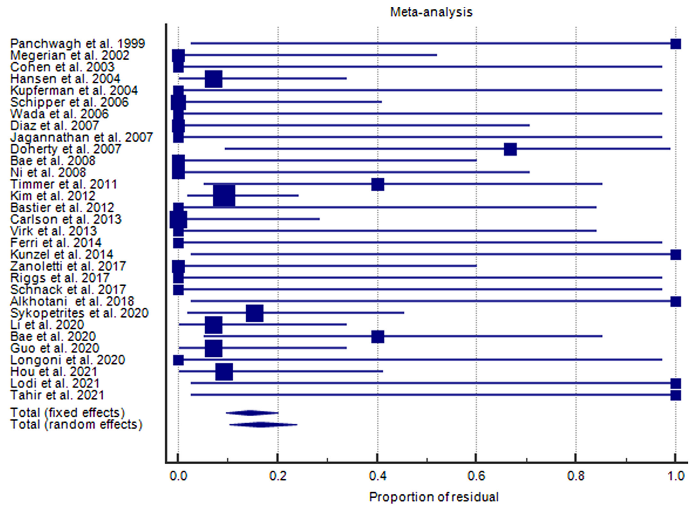

Figure 3. Meta-analysis of the proportions of residual. Squares represent percentage point estimates and horizontal lines represent 95% CI.

acoustic neuromas are most often positioned at the cerebellopontine angle. Middle ear carcinomas are typically located in the tympanum, tympanic sinus.[7]

High-resolution computed tomography allows to observe bone destruction produced by ELST, particularly the seventh cranial nerve passage, jugular vein cranial entrance, hypoglossal canal, and internal auditory compartment. Upon MRI, ELSTs show heterogonous foci of low and high signal intensity on T1-weighted and T2-weighted imaging. The hyperintense areas on noncontrast T1-weighted MRI is due to intraparenchymal hemorrhage. The hypointense areas may reflect residual bone or prominent calcification.[1]

Further investigations might be useful to rule out intracranial vessel involvement, essential for safe surgical planning. Arteriography may give information about carotid artery infiltration[2]

The best modality of ELST management is surgical. Therefore, the choice of the better surgical approach for each patient represents a crucial phase that every surgeon must face when planning ELST removal. Factors influencing the surgical planning approach should include tumor size, unilaterality or bilaterality of the tumor, sub-sites involvement, the patient's hearing function, and VHL status. To facilitate surgical approach selection, suggested guidelines have been developed. A retrospective analysis of 149 tumors assisted in an anatomic classification system, the Bambakidis and Megerian[11] grading system for ELST: (a) grade I tumors are confined to the temporal bone, the middle ear, and/or the external auditory canal; (b) grade II tumors extend into the posterior fossa; (c) grade III tumors extend to the posterior fossa and middle cranial fossa; (d) grade IV tumors extend to the clivus and/or to the sphenoid wings.

A classification, proposed by Schipper et al.[12] defined and classified ELSTs into 3 types (A, B, and C) with recommended surgical approaches.

Given the prominent hypervascularity of the area, preoperative embolization is very important to avoid intraoperative bleeding and reduce morbidities.[7]

Table 4. Meta-analysis of the Proportions of Recurrence After Surgery

Study	Approach	Number of Recurrences	Proportion (%)	95% CI
Panchwagh et al (1999)	1	0	0.0	0.0 to 97.5
Megerian et al (2002)	5	0	0.0	0.0 to 52.2
Hansen et al (2004)	14	3	21.4	4.6 to 50.8
Rodrigues et al (2004)	7	1	14.3	0.4 to 57.8
Schipper et al (2006)	7	0	0.0	0.0 to 40.9
Wada et al (2006)	1	0	0.0	0.0 to 97.5
Diaz et al (2007)	3	1	33.3	0.8 to 90.6
Doherty et al (2007)	3	0	0.0	0.0 to 70.7
Bae et al (2008)	4	1	25.0	0.6 to 80.6
Ni et al (2008)	3	0	0.0	0.0 to 70.7
Timmer et al (2011)	5	0	0.0	0.0 to 52.2
Poletti et al (2011)	7	2	28.6	3.7 to 70.9
Kim et al (2012)	33	1	3.0	0.1 to 15.7
Bastier et al (2012)	2	1	50.0	1.3 to 98.7
Carlson et al (2013)	11	1	9.1	0.2 to 41.3
Friedman et al (2013)	18	2	11.1	1.4 to 34.7
Ferri et al (2014)	1	0	0.0	0.0 to 97.5
Kunzel et al (2014)	1	0	0.0	0.0 to 97.5
Zanoletti et al (2017)	4	0	0.0	0.0 to 60.2
Schnack et al (2017)	1	0	0.0	0.0 to 97.5
Sykopetrites et al (2020)	13	1	7.7	0.2 to 36.0
Li et al (2020)	14	3	21.4	4.6 to 50.8
Bae et al (2020)	5	2	40.0	5.3 to 85.3
Guo et al (2020)	14	1	7.1	0.2 to 33.8
Longoni et al (2020)	1	0	0.0	0.0 to 97.5
Hou et al (2021)	11	1	9.1	0.2 to 41.3
Lodi et al (2021)	1	1	100.0	2.5 to 100.0
Tahir et al (2021)	1	1	100.0	2.5 to 100.0
Total (fixed effects)	192	23	14.043	9.7 to 19.3
Total (random effects)	192	23	14.043	9.8 to 18.9

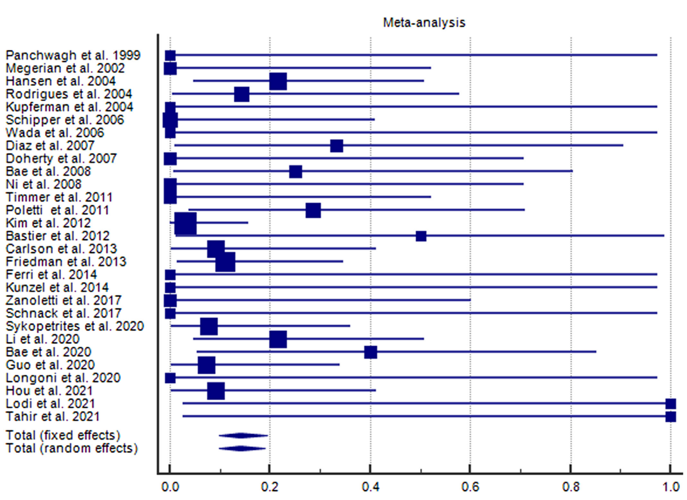

Figure 4. Meta-analysis of the proportions of recurrences. Squares represent percentage point estimates and horizontal lines represent 95% CI.

External-beam radiotherapy seems to have a limited role in long-term prognosis for patients and should only be considered for patients with close or positive margins, as well as those with gross disease, even after subtotal resection.[11]

Our study presents some important limitations. First, although it would have been interesting to investigate outcomes in terms of surgical approach, however, the wide variability of reported surgical approaches made a rigorous analysis of individual surgical approach effectiveness irrelevant. The current authors however suggest that the selection of the surgical approach should be tailored according to individual tumor cranial extent and size. Second, follow-up time was not reported in all included papers. Moreover, analysis of post-operative hearing function was not able to be performed due to the lack of information in the majority of analyzed studies. Further, tumor size was reported by most studies as the mean tumor diameter of the case series, with few studies accurately defining the individual ELST dimensions or this data were not reported at all. So we did not proceed to plan a statistical analysis of the connection between tumor dimension and recurrence rate.

CONCLUSION

Our study suggests that postoperative facial nerve function is impaired in less than 40% of ELST patients managed with a surgical approach, of whom almost 75% present with presurgical facial nerve damage. Residual and/or recurrence of ELST are not rare events, and follow-up strategies should be designed accordingly.

Peer-review: Externally peer-reviewed.

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