• Meta-Analysis •

Treatment of lacrimal gland adenoid cystic carcinoma: a systematic review and Meta-analysis

Hai-Han Yan, Rui Liu, Nan Wang, Liang-Yuan Xu, Qi-Han Guo, Jing Li, Jian-Min Ma

Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University; Beijing Ophthalmology & Visual Sciences Key Laboratory, Beijing 100730, China

Correspondence to: Jian-Min Ma. Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University; Beijing Ophthalmology & Visual Sciences Key Laboratory, Beijing 100730, China. jmma@sina.com; yanhaihan@mail.ccmu.edu.cn

Received: 2022-11-07 Accepted: 2023-11-17

Abstract

● **AIM:** To evaluate lacrimal gland adenoid cystic carcinoma (LGACC) of prognosis in patients who underwent different treatment regimens.

● **METHODS:** We searched PubMed, EMBASE, and the Cochrane Library for studies done on the treatment of LGACC, between January 1987 and April 2022. A Meta-analysis was conducted to pool the 5-year overall survival rate (OR), and the 5-year recurrence rate (RR) and 5-year metastasis rate (MR) were assessed.

● **RESULTS:** The 30 studies involved 585 patients were included in the Meta-analysis. The pooled 5-year OR with surgery alone was 50%, the 5-year RR was 63%, and the 5-year MR was 34%. The pooled 5-year OR with surgery and adjuvant radiotherapy combined was 67% (95%CI 61%,73%), the 5-year RR was 41%, and the 5-year MR was 35%. The pooled 5-year OR with surgery and adjuvant chemoradiotherapy combined was 72% (95%CI 59%, 84%), the 5-year RR was 48%, and the 5-year MR was 36%. The pooled 5-year OR with surgery, intra-arterial cytoreductive chemotherapy, and adjuvant chemoradiotherapy combined was 78% (95%CI 68%, 89%), the 5-year RR was 15%, and the 5-year MR was 27%.

● **CONCLUSION:** Comprehensive treatment is more effective than surgery alone. Surgery combined with intra-arterial chemotherapy and adjuvant chemoradiotherapy seems to add value to the therapeutic effect of comprehensive treatment of LGACC but further high-quality research is required to validate this.

● **KEYWORDS:** adenoid cystic carcinoma; lacrimal gland; Meta-analysis

DOI:10.18240/ijo.2024.01.22

Citation: Yan HH, Liu R, Wang N, Xu LY, Guo QH, Li J, Ma JM. Treatment of lacrimal gland adenoid cystic carcinoma: a systematic review and Meta-analysis. *Int J Ophthalmol* 2024;17(1):164-172

INTRODUCTION

Adenoid cystic carcinoma (ACC) is the most common malignant epithelial tumor of the lacrimal gland, accounting for 11% of cystic epithelial tumors and 1.6% of all orbital tumors[1-2]. ACC may involve extensive local infiltration, significant bone metastasis, and peripheral nerve infiltration[3]. Thus, the prognosis with ACC is poor as it is characterized by high rates of recurrence, invasiveness, metastasis, and mortality[4].

Currently, the most commonly used surgical method is expanded local resection. The bone wall is a natural barrier; however, since ACC easily invades the bone wall, it is the most vulnerable site for tumor invasion and recurrence. It is difficult to completely remove tumor cells that have invaded the bone wall with surgery, and a small number of residual tumor cells can easily cause a recurrence of disease[5-6]. Therefore, postoperative radiotherapy, chemotherapy, and/or other comprehensive treatment measures are necessary; however, there are no standard adjuvant therapy protocols due to the rarity of lacrimal gland adenoid cystic carcinoma (LGACC). At present, surgery and postoperative radiotherapy is the main treatment method. Near distance local particles implantation radiotherapy (IR) and external beam radiotherapy (EBRT) are commonly used postoperative adjuvant radiotherapies[7]. Adjuvant radiotherapy, combined with chemotherapy, is another treatment option[8-9]. Cisplatin and doxorubicin-based concurrent chemoradiotherapy is the most commonly used chemotherapy drug, apatinib and nedaplatin were also successful applications in some cases[10]. In addition, some studies have advocated the application of intra-arterial cytoreductive chemotherapy as a multi-modal approach, suggesting that this approach can improve the rates of local control and disease-free survival[11]. Some studies proved the therapeutic effect of intra-arterial cytoreductive chemotherapy to LGACC and advanced LGACC in a histologically level[12]. Based on existing studies, we analyzed the efficacy of different treatment methods for LGACC to find the most appropriate treatment.

MATERIALS AND METHODS

Hypothesis This systematic review was conducted following the principles of the Preferred Reporting Items for Systematic Reviews and Meta Analyses statement[13]. The protocol was registered in PROSPERO (CRD42022313798). The clinical question was as follows: How do various treatment options compare with each other based on the overall survival rate (OR) of patients with LGACC.

Study Selection Eligibility was assessed by title and abstract screening. Full-text assessment was then done by two independent researchers. Duplicates were removed using the software EndNote (Version 9.3.3 Bld13966, Clarivate Analytics US LLC). The inclusion criteria of the study were as follows: 1) ACC was confirmed by histopathology of the eye and orbit according to the Third Edition of the International Classification of Diseases for Oncology; 2) study included at least one oncological outcome [OR, recurrence rate (RR) or metastatic rate (MR)]; 3) study type was a randomized controlled study, retrospective and/or prospective cohort study, case series, or case report. The exclusion criteria were as follows: 1) studies with shorter follow-up times if two studies included the same cases; 2) studies with follow-up times <5y.

Data Extraction and Quality Assessment Two reviewers independently reviewed the retrieved articles and extracted the data. The data were extracted using Excel. Any discrepancies between reviewers were resolved by discussion and consensus with a third reviewer. The main items extracted included study title, year, design, demographic data, follow-up time, histology outcomes, The 8th Edition of the American Joint Committee on Cancer stage, type of treatment, and oncological outcome.

Each study was assessed for study quality and level of evidence according to the Oxford Center for Evidence-based medicine guidelines (OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine; 2020).

Statistical Analysis Meta-analysis was performed using StataMP 14 (64-bit) software. The pooled estimates and 95% confidence intervals (CI) of 5-year OR, 5-year RR, and 5-year MR were determined. Heterogeneity was assessed using I2 statistics, and significant heterogeneity was confirmed when I^2>50% or P<0.1. Results are presented based on a random-effects model when the test for heterogeneity was significant; otherwise, results are presented based on a fixed-effects model.

RESULTS

Search Strategy Results A total of 753 records were identified by our search strategy (PubMed, *n*=239; Embase, *n*=389; Cochrane Library, *n*=125). After articles from reference lists were added and duplicates were removed, 541 potential articles were remained and were screened by reading titles and abstracts. Of these, 164 articles were examined for more details. After the full texts were reviewed, 39 studies were included in the systematic review, and 29 studies were excluded with reasons. Of the excluded studies, 19 lacked sufficient follow-up time, 8 did not have the required data, and 2 reported a shorter follow-up time of the same cases. Thirty studies were included in the Meta-analysis (Figure 1). The 30 studies involved 585 patients (Table 1)[1,11,14-41]. There were 16 retrospective cohort studies and 14 case series. No randomized controlled trials (RCT) were found. Multiple groups of patients that underwent different treatment regimens were included in 5 articles and were re-integrated into the current study according to the treatment methods. Nineteen patients in three studies were treated with surgery alone, 449 patients in 24 studies were treated with surgery and radiotherapy, 72 patients in five studies were treated with surgery and chemoradiotherapy, and 45 patients in six studies were treated with surgery, intra-arterial cytoreductive chemotherapy, and adjuvant chemoradiotherapy.

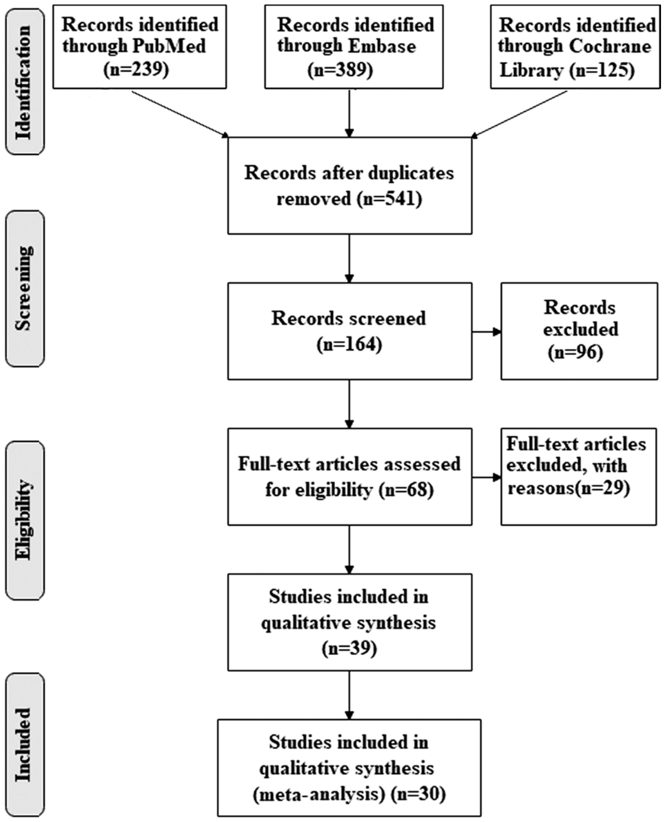

Figure 1 Flow chart of study selection.

Quality and Validity Assessment According to the Oxford Center for Evidence Based Medicine 2011 guidelines, the levels of evidence were III (16 studies) and IV (14 studies)[42].

Meta-analysis Eight patients in 3 studies were treated with surgery alone, 484 patients in 30 studies were treated

Table 1 Characteristic of included study

Study, y	Country and region	Study design	Level of evidence	No. of patients	Treatment	Dose/drugs	Mean follow-up time (mo)	Age, y	Sex (female/male)	OR	RR	MR
Tse *et al*[11], 2022	USA	Retrospective cohort study	3	10	IACC+S+R+C	Cisplatin and doxorubicin	300	40.6	4/6	60%	10%	40.0%
Liu *et al*[14], 2022	USA	Retrospective cohort study	3	82/27	S+R/S+R+C	-	200	-	-	74%	-	-
Manjandavida *et al*[15], 2021	USA	Retrospective cohort study	3	12/8/20	S+R/S+R+C/ IACC+S+R+C	50 Gy/cisplatin and doxorubicin	58	36	14/26	85%/58%/87%	42%/25%/15%	67%/13%/5%
Liu *et al*[16], 2021	China	Retrospective cohort study	3	35	S+R	50-60 Gy	36	42	13/22	96%	44%	31%
Lesueur *et al*[17], 2020	France	Case series	4	15	S+R	75.6 Gy	67.4	43	12/3	78%	40%	22%
Yang *et al*[18], 2019	China	Retrospective cohort study	3	10/10/4	S+R/S+R+C/S	-	60	64.3/50.6/50	11/13	70%/60%	50%/70%	22%/40%
Rose *et al*[19], 2019	UK	Case series	4	53	S+R	50-60 Gy	56.4	48	-	77%	34%	36%
Hung *et al*[20], 2019	Taiwan, China	Case series	4	11	S+R	60-70 Gy	86.4	40	4/7	82%	55%	-
Akbaba *et al*[21], 2019	Germany	Retrospective cohort study	3	18	S+R	50 Gy	20	51	10/8	68%	44%	58%
Wolkow *et al*[22], 2018	USA	Retrospective cohort study	3	18	S+R	72 Gy	154.8	40	14/4	89%	11%	11%
Hayashi *et al* [23],2018	Japan	Retrospective cohort study	3	16	S+R	57.6-64 Gy	53.7	58	-	65%	44%	31%
Han *et al*[24], 2018	USA	Case series	4	10	S+R	50-66 Gy	89.5	42.4	4/6	90%	10%	0
Tunc *et al*[25], 2016	Turkey	Case series	4	5	S+R	-	60	-	-	100%	80%	-
Sanders *et al*[26], 2016	USA	Case series	4	8	S+R	74.4 Gy	39.6	-	6/2	25%	50%	38%
Noh *et al*[27], 2016	Korea	Retrospective cohort study	3	19	S+R	59.4-70 Gy	57.5	-	9/10	63%	21%	5%
Esmaeli *et al*[28], 2016	USA	Case series	4	7	S+R+C	52-64 Gy	33	49.7	-	100%	0	0
Roshan *et al*[29], 2015	India	Retrospective cohort study	3	10	S+R	60 Gy	23	32	5/5	71%	20%	10%
Ueda *et al*[30], 2014	Japan	Retrospective cohort study	3	10	S+R	-	60	49.5	4/6	56%	50%	40%
Ghonsikar *et al*[31], 2014	India	Retrospective cohort study	3	20	S+R+C	-	36	15-75	11/9	90%	10%	-
Fellman *et al*[32], 2013	USA	Case series	4	2	IACC+S+R+C	45-61 Gy/cisplatin and doxorubicin	60	34	2/0	100%	0%	100%
Gensheimer *et al*[33], 2013	USA	Case series	4	11	S+R	16.9-18.4 Gy	75	43.4	8/3	91%	18%	9%
Wang *et al*[34], 2012	China	Retrospective cohort study	3	6	S+R	-	48	47	4/2	50%	-	100%
Wilson *et al*[35], 2011	USA	Case series	4	7	S+R	-	39	46	-	71%	0	29%
Meel *et al*[36], 2009	USA	Case series	4	2	IACC+S+R+C	60 Gy/cisplatin and doxorubicin	60	17.5	2/0	100%	0	0
Ahmad *et al*[1], 2009	USA	Retrospective cohort study	3	42/11	S+R/S	57 Gy	94	40.4	22/31	-	-	10%/100%
Esmeali *et al*[37], 2006	USA	Retrospective cohort study	3	7	S+R	45-66 Gy	24	44	4/3	29%	0	0
Tse[38], 2005	USA	Case series	4	9/7	IACC+S+R+C/ S+R	Cisplatin and doxorubicin	60	44.3/49	7/9	89%/14%	22%/86%	22%/86%
Esmeali *et al*[39], 2004	USA	Case series	4	16/4	S+R/S	-	34	40.3/31.5	14/6	63%/25%	31%/50%	69%/50%
Tang *et al*[40], 2002	China	Retrospective cohort study	3	21	S+R	60 Gy	60	37.5	-	29%	-	-
Meldrum[41], 1998	USA	Case series	4	2	IACC+S+R+C	55-60 Gy	120	30	2/0	0%	-	100%

IACC: Intra-arterial cytoreductive chemotherapy; S: Protocols-surgery; R: Adjuvant radiotherapy; C: Adjuvant chemotherapy; OR: 5-year overall survival rate; RR: 5-year recurrence rate; MR: 5-year metastasis rate.

by comprehensive treatment. Among patients treated by comprehensive treatment, 380 patients in 18 studies were treated with adjuvant radiotherapy, 65 patients in 4 studies were treated with adjuvant chemoradiotherapy, and 39 patients in 5 studies were treated with intra-arterial cytoreductive chemotherapy and adjuvant chemoradiotherapy. Overall, studies in which patients were treated with intra-arterial cytoreductive chemotherapy and adjuvant chemoradiotherapy had the highest 5-year OR (78%, 95%CI 68%, 89%), followed by studies in which patients were treated with adjuvant chemoradiotherapy (72%, 95%CI 59%, 84%), and studies in which patients were treated with adjuvant radiotherapy (67%, 95%CI 61%,73%). Patients treated with surgery alone had a 50% OR. The I^2 values for each of these studies were 98.2%, 99.8%, 99.4%, and 98.3%, indicating significant heterogeneity (Figure 2); hence, a random-effects model was used.

Among studies that reported RR, 284 patients in 18 studies received adjuvant radiotherapy, 39 patients in 5 studies received intra-arterial cytoreductive chemotherapy and adjuvant chemoradiotherapy, 18 patients in 3 studies received adjuvant chemoradiotherapy, and 8 patients in 2 studies received surgery alone. These studies indicated significant heterogeneity; thus, a random-effects model was used (Figure 3). Overall, studies in which patients were treated with intra-arterial cytoreductive chemotherapy and adjuvant chemoradiotherapy had the lowest 5-year RR (15%), followed by studies in which patients were treated with adjuvant radiotherapy (41%), studies in which patients were treated with adjuvant chemoradiotherapy (48%), and studies in which patients were treated with surgery alone (63%). A quantitative random factor Meta-analysis was performed for 25 observational studies that reported absolute data on the 5-year MR (Figure 4). Overall, studies in which patients were treated with intra-arterial cytoreductive chemotherapy and adjuvant chemoradiotherapy had the lowest 5-year MR (27%, 8 of 41 patients), followed by studies in which patients were treated with surgery alone (34%, 3 of 8 patients), studies in which patients were treated with adjuvant radiotherapy (35%, 96 of 307 patients), and studies in which patients were treated with adjuvant chemoradiotherapy (36%, 9 of 18 patients).

Subgroup Analysis

External beam radiotherapy The external beam mean dose ranged from 50 to 70 Gy, and the EBRT mean follow-up time ranged from 20 to 89.5mo. Recurrence occurred in 39 patients and metastasis occurred in 34 patients. These studies had moderate heterogeneity; thus, the random-effects model was used. The 5-year OR was 62%, and the 5-year MR was 36%.

The 5-year RR was 36% per the fixed effects model (Figure 5).

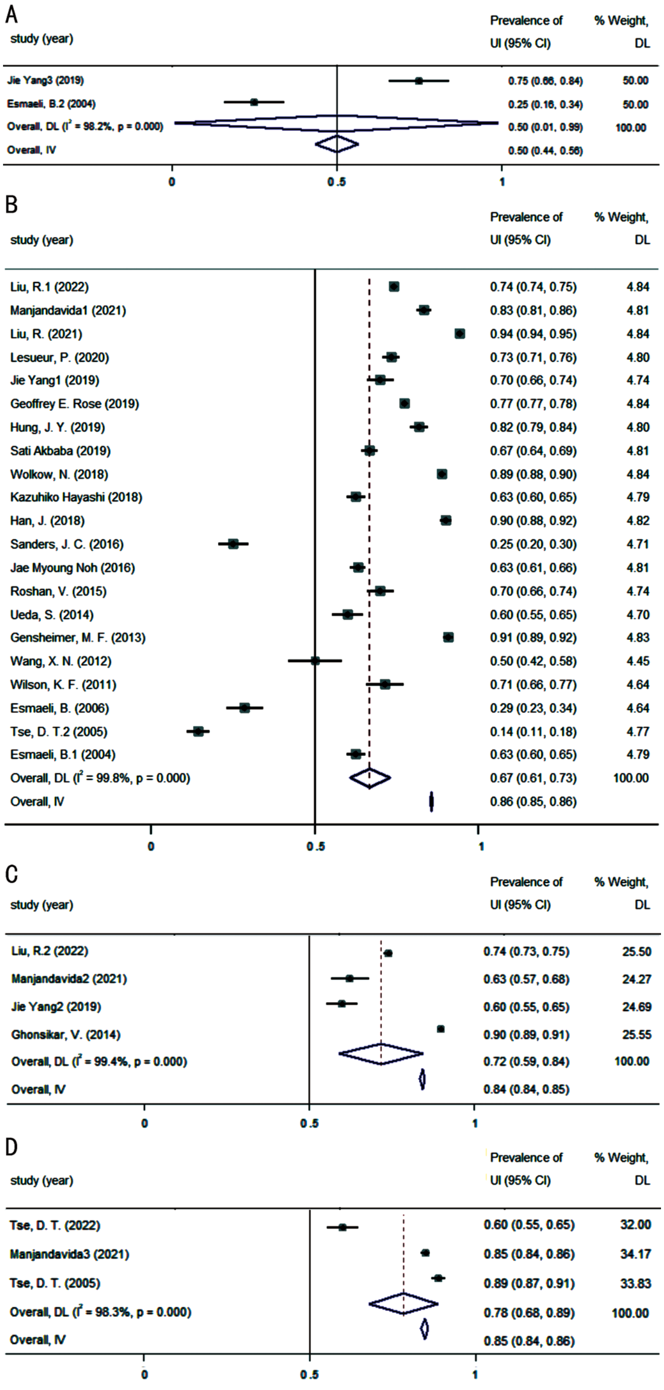

Figure 2 Pooled estimates of 5-year overall survival rate (OR) The random effect model was applied to minimize heterogeneity. A: Pooled 5-year OR of surgery; B: Pooled 5-year OR of surgery+adjuvant radiotherapy; C: Pooled 5-year OR of surgery+adjuvant radiotherapy+ chemotherapy; D: Pooled 5-year OR of intra-arterial cytoreductive chemotherapy+surgery+adjuvant chemoradiotherapy.

Implantation radiotherapy The IR mean dose ranged from 16.9 to 75.6 Gy. The mean follow-up time of studies in which patients were treated with IR ranged from 60 to 154.8mo. Recurrence occurred in 40 patients and metastasis occurred in 43 patients. The pooled 5-year OR was 82% (95%CI 0.71%–0.92%), 5-year RR was 32%, and 5-year MR was 27% with a moderate level of heterogeneity (Figure 5).

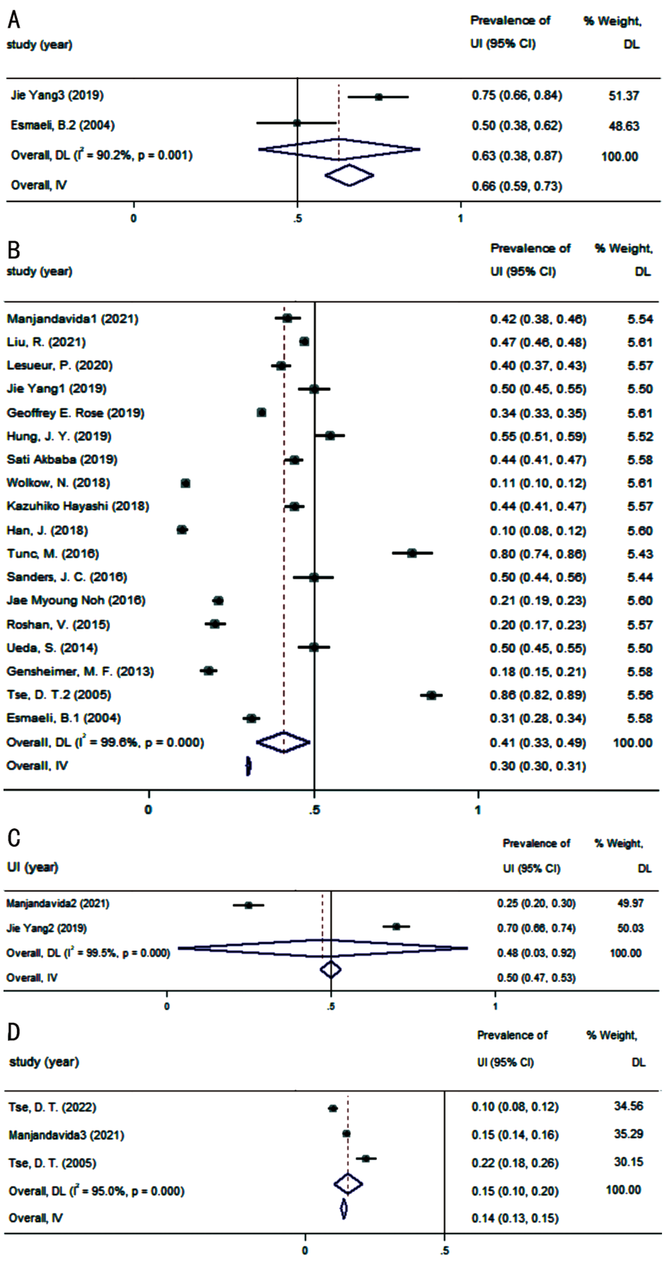

Figure 3 Pooled estimates of 5-year recurrence rate (RR) The random effect model was applied to minimize heterogeneity. A: Pooled 5-year RR of surgery; B: Pooled 5-year RR of surgery+ adjuvant radiotherapy; C: Pooled 5-year RR of surgery+ adjuvant radiotherapy+ chemotherapy; D: Pooled 5-year RR of intra-arterial cytoreductive chemotherapy+ surgery+adjuvant chemoradiotherapy.

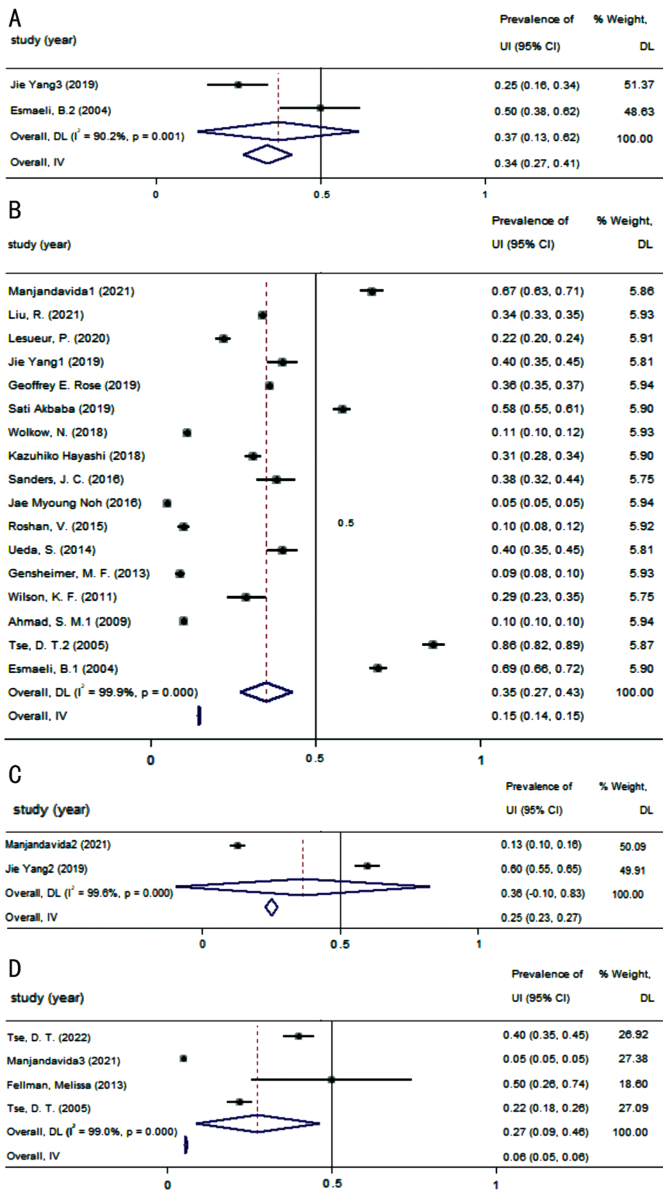

Figure 4 Pooled estimates of 5-year metastasis rate (MR) The random effect model was applied to minimize heterogeneity. A: Pooled 5-year MR of surgery; B: Pooled 5-year MR of surgery+ adjuvant radiotherapy; C: Pooled 5-year MR of surgery+adjuvant radiotherapy+ chemotherapy; D: Pooled 5-year MR of intra-arterial cytoreductive chemotherapy+surgery+adjuvant chemoradiotherapy.

DISCUSSION

LGACC is the most common tumor in lacrimal gland and occurred in all age groups[43]. The average age of onset was 40y, and most cases affected females. The typical clinical manifestations were unilateral lacrimal fossa masses, which may be flat in shape, and were painful. The main clinical symptoms were ocular protrusion and displacement, orbital mass, and local pain, seriously affects the appearance and life of patients. Currently, surgery is the main treatment method, incompletely removal of the tumor and unsatisfactory treatment of surrounding bone are related to the recurrence of ACC. Study showed that postoperative radiotherapy helps reduce recurrence[44]. Our study found that surgery combined with radiotherapy, surgery combined with chemoradiotherapy, and surgery combined with intra-arterial chemotherapy and chemoradiotherapy had certain therapeutic benefits in terms of 5-year OR, RR, and distant MR.

There are two types of radiotherapy for ACC of lacrimal gland: IR or EBRT. IR includes ^{125}I implantation, neutron and proton implantation; ERBT includes local gamma knife radiotherapy, 3D gamma knife therapy, and 2D gamma knife therapy. Our study showed that both IR and ERBT had good

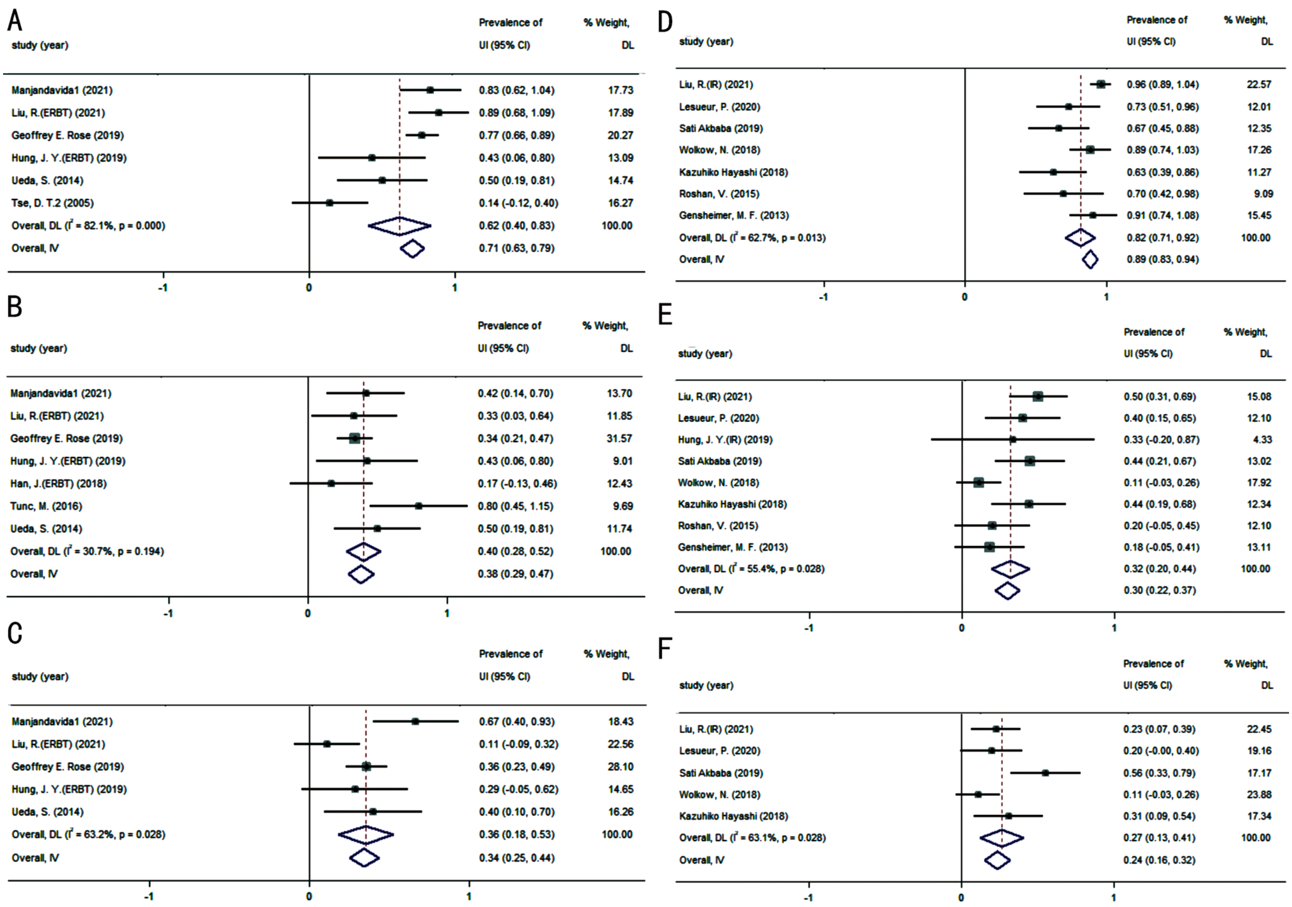

Figure 5 Pooled estimates of external beam radiotherapy (ERBT) and implantation radiotherapy (IR) A: Pooled 5-year OR of EBRT; B: Pooled 5-year RR of EBRT; C: Pooled 5-year MR of EBRT; D: Pooled 5-year overall survival rate of IR; E: Pooled 5-year recurrence rate of IR; F: Pooled 5-year metastasis rate of IR.

therapeutic effects, which is consistent with the conclusions of other studies. Li *et al*[45] found that there was no significant difference in local control, control of metastasis to regional lymph nodes, or control of distant metastasis between the IR and ERBT groups. In the retrospective comparison case series, the clinical records of 27 patients with primary LGACC and 8 patients with recurrent LGACC were compared, and no statistically significant difference was found in the efficacies of IR and ERBT in terms of distant metastasis rates[16]. Previous studies have reported distant metastasis rates of 11%–56% and external radiation rates of 11%–67% for IR[7,17]. In our study, the 5-year OR, 5-year RR, and 5-year MR with IR were better compared to EBRT. This is possibly because carbon ion irradiation and proton radiotherapy have the same physical dose distribution, which can have a stronger killing effect with lower adverse reactions. Neutron radiotherapy is an effective treatment that can prolong the survival of patients and control the local recurrence rate. In addition, in our included studies, ERBT treatment included studies of low dose radiation, but IR only included studies of high dose radiation, which may also explain why the treatment effect of IR is slightly better than ERBT. So, higher quality and larger prospective studies are needed to compare internal and external radiotherapy. In the treatment of a variety of lip cancer, ERBT and internal beam radiotherapy are usually used in combination, which has a good therapeutic effect[46]. Up to now, there is no study on the combination of the two in the treatment of LGACC.

Chemotherapy alone is not ideal for the treatment of metastatic adenoid cystic carcinoma, as platinum and anthracycline compounds have relatively good anti-tumor effects but highly toxic side effects[47-48]. In our study, compared with surgery combined with adjuvant radiotherapy or surgery combined with adjuvant chemoradiotherapy, the 5-year OR of patients treated with intra-arterial chemotherapy and chemoradiotherapy is higher, and the RR and MR are similar. Studies using intra-arterial chemotherapy and chemoradiotherapy have reported 5-year OR between 60% and 85%[11,17,38], which is consistent with our results. Although we included all available articles on intra-arterial chemotherapy, fewer patients were treated with intra-arterial chemotherapy than with other approaches, and we are cautious in concluding that this approach is more effective. In addition, attention must be paid to potential side effects, some of which can be toxic. In this paper, there were 5 cases of febrile neutropenia caused by arterial intubation and 1 case of blindness and eyelid necrosis caused by ocular arterial embolism. Cisplatin toxicity, particularly ototoxicity, and adriamycin toxicity, particularly cardiotoxicity, should be considered when using this treatment regimen. At present, the articles reporting (IACC) are all from the United States, and IACC still needs to be promoted and used in more countries to test its therapeutic effect.

Compared with non-high-grade transformation primary LGACC high-grade transformation cells, LGACC-high-grade transformation primary cells have faster proliferation, stronger migration ability, and poorer sensitivity to chemotherapy drugs[49]. Age, histopathological type, bone invasion and tumor extent are factors affecting the prognosis of ACC[50]. If there are enough patients described in the future, a subgroup analysis should be conducted to compare the therapeutic effects of different treatments.

There are several limitations in our review. First, despite the best efforts we made, the number and type of studies included were limited. Due to the rarity of the disease, no RCTs were found to meet the inclusion criteria, and only relative poor-quality evidence was available. But a very rare disease can be well identified by this study design, which is valuable for its purposes. The number of studies included in the pooled retention of surgical treatment was only four, and the heterogeneity of them was considerably high. To minimize the heterogeneity, a random effect model was applied. The number of treatment side effects described in the included articles was too small to analyze treatment side effects.

In conclusion, the treatment effect of LGACC patients with comprehensive treatment measures such as surgery combined with postoperative radiotherapy or chemotherapy is better than that of surgery alone. Patients treated with surgical intraarterial chemotherapy and adjuvant chemoradiotherapy had better outcomes, but they had fewer patients. For LGACC patients, comprehensive treatment should be adopted in order to improve the survival rate and prevent recurrence and metastasis.

ACKNOWLEDGEMENTS

Authors' contributions: Yan HH analyzed and wrote the manuscript; Wang N select the study; Guo QH, Xu LY and Li J extract the data and assess the quality of study; Ma JM read and criticized the manuscript.

Foundations: Supported by Natural Science Foundation of Beijing (No.7222025); Beijing Hospitals Authority' Ascent Plan (No.DFL20190201); Beijing Science and Technology Rising Star Program.

Conflicts of Interest: Yan HH, None; **Liu R,** None; **Wang N,** None; **Xu LY,** None; **Guo QH,** None; **Li J,** None; **Ma JM,** None.

REFERENCES

1 Ahmad SM, Esmaeli B, Williams M, Nguyen J, Fay A, Woog J, Selvadurai D, Rootman J, Weis E, Selva D, McNab A, DeAngelis D, Calle A, Lopez A. American joint committee on cancer classification predicts outcome of patients with lacrimal gland adenoid cystic carcinoma. *Ophthalmology* 2009;116(6):1210-1215.

2 Moeyersoms AHM, Gallo RA, Zhang MG, Stathias V, Maeng MM, Owens D, Abou Khzam R, Sayegh Y, Maza C, Dubovy SR, Tse DT, Pelaez D. Spatial transcriptomics identifies expression signatures specific to lacrimal gland adenoid cystic carcinoma cells. *Cancers* 2023;15(12):3211.

3 da Silva FJ, Carvalho de Azevedo J Jr, Ralph ACL, de Jesus Viana Pinheiro J, Freitas VM, Calcagno DQ. Salivary glands adenoid cystic carcinoma: a molecular profile update and potential implications. *Front Oncol* 2023;13:1191218.

4 Persson M, Andersson MK, Sahlin PE, Mitani Y, Brandwein-Weber MS, Frierson HF Jr, Moskaluk C, Fonseca I, Ferrarotto R, Boecker W, Loening T, El-Naggar AK, Stenman G. Comprehensive molecular characterization of adenoid cystic carcinoma reveals tumor suppressors as novel drivers and prognostic biomarkers. *J Pathol* 2023;261(3):256-268.

5 Parlak S, Bulut EG. Adenoid cystic carcinoma of lacrimal gland with bone remodeling. *J Craniofacial Surg* 2020;31(7):e693-e694.

6 Emerick C, Mariano FV, Vargas PA, Nör JE, Squarize CH, Castilho RM. Adenoid cystic carcinoma from the salivary and lacrimal glands and the breast: different clinical outcomes to the same tumor. *Crit Rev Oncol Hematol* 2022;179:103792.

7 Akbaba S, Lang K, Held T, Herfarth K, Rieber J, Plinkert P, Auffarth GU, Rieken S, Debus J, Adeberg S. Carbon-ion radiotherapy in accelerated hypofractionated active raster-scanning technique for malignant lacrimal gland tumors: feasibility and safety. *Cancer Manag Res* 2019;11:1155-1166.

8 Esmaeli B, Yin VT, Hanna EY, Kies MS, William WN Jr, Bell D, Frank SJ. Eye-sparing multidisciplinary approach for the management of lacrimal gland carcinoma. *Head Neck* 2016;38(8):1258-1262.

9 Karp JM, Gordon AJ, Hu K, Belinsky I, Jacobson A, Li ZJ, Persky M, Persky M, Givi B, Tam MM. Pathologic features, treatment, and clinical outcomes of lacrimal gland cancer. *Cureus* 2023:15(8): e44466.

10 Zhang SY, Wu QJ, Liu D, Yu HJ, Zhong YH, Zhou YF. Successful management of adenoid cystic carcinoma of the lacrimal sac with apatinib combined with concurrent chemoradiotherapy: a case report. *Ann Palliat Med* 2021;10(7):8334-8339.

11 Tse DT, Benedetto PW, Tse BC, Feuer WJ. Neoadjuvant intra-arterial cytoreductive chemotherapy for lacrimal gland adenoid cystic carcinoma: a long-term follow-up study of a trimodal strategy. *Am J Ophthalmol* 2022;240:239-251.

12 Bowen RC, Ko HC, Avey GD, Hartig GK, Hu R, Harari PM, Lucarelli MJ. Personalized treatment for lacrimal sac adenoid cystic carcinoma: case report and literature review. *Pract Radiat Oncol* 2019;9(3):136-141.

13 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group PP. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4(1):1-9.

14 Liu R, Li J, Zhang X, Ge X, Ma JM. Differences in clinical features and prognosis between orbit adenoid cystic carcinoma and adenocarcinoma: a study from the SEER 18 database. *Tumori J* 2022;109:61-70.

15 Manjandavida FP, Honavar SG, Murthy R, Das S, Vemuganti GK, Mulay K, Reddy VAP. Does multimodal treatment improve eye and life salvage in adenoid cystic carcinoma of the lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2021;8(4):348-354.

16 Liu R, Ge X, Yang BT, Zhang H, Zhang JX, Ma JM. Similar therapeutic effects of 125I seed radiotherapy and γ-ray radiotherapy on lacrimal gland adenoid cystic carcinoma. *Int J Ophthalmol* 2021;14(4):547-553.

17 Lesueur P, Rapeaud E, De Marzi L, Goudjil F, Levy C, Galatoire O, Jacomet PV, Dendale R, Calugaru V. Adenoid cystic carcinoma of the lacrimal gland: high dose adjuvant proton therapy to improve patients outcomes. *Front Oncol* 2020;10:135.

18 Yang J, Zhou C, Wang Y, Fan X, Jia R. Multimodal therapy in the management of lacrimal gland adenoid cystic carcinoma. *BMC Ophthalmol* 2019;19(1):125.

19 Rose GE, Gore SK, Plowman NP. Cranio-orbital resection does not appear to improve survival of patients with lacrimal gland carcinoma. *Ophthalmic Plast Reconstr Surg* 2019;35(1):77-84.

20 Hung JY, Wei YH, Huang CH, Chen LW, Fuh CS, Liao SL. Survival outcomes of eye-sparing surgery for adenoid cystic carcinoma of lacrimal gland. *Jpn J Ophthalmol* 2019;63(4):344-351.

21 Akbaba S, Lang K, Held T, *et al*. Carbon-ion radiotherapy in accelerated hypofractionated active raster-scanning technique for malignant lacrimal gland tumors: feasibility and safety. *Cancer Manag Res* 2019;11:1155-1166.

22 Wolkow N, Jakobiec FA, Lee H, Sutula FC. Long-term outcomes of globe-preserving surgery with proton beam radiation for adenoid cystic carcinoma of the lacrimal gland. *Am J Ophthalmol* 2018;195:43-62.

23 Hayashi K, Koto M, Ikawa H, Ogawa K, Kamada T. Efficacy and safety of carbon-ion radiotherapy for lacrimal gland carcinomas with extraorbital extension: a retrospective cohort study. *Oncotarget* 2018;9(16):12932-12940.

24 Han JS, Kim YD, Woo KI, Sobti D. Long-term outcomes of eye-sparing surgery for adenoid cystic carcinoma of lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2018;34(1):74-78.

25 Tunc M, Guney Y. Cyberknife treatment in adenoid cystic carcinoma of the lacrimal gland. *Acta Ophthalmol* 2016;94.

26 Sanders JC, Mendenhall WM, Werning JW. Adenoid cystic carcinoma of the lacrimal gland. *Am J Otolaryngol* 2016;37(2):144-147.

27 Noh JM, Lee E, Ahn YC, Oh D, Kim YD, Woo KI, Ko YH, Kim S. Clinical significance of post-surgical residual tumor burden and radiation therapy in treating patients with lacrimal adenoid cystic carcinoma. *Oncotarget* 2016;7(37):60639-60646.

28 Esmaeli B, Yin VT, Hanna EY, *et al*. Eye-sparing multidisciplinary approach for the management of lacrimal gland carcinoma. *Head Neck* 2016; 38(8):1258-1262.

29 Roshan V, Pathy S, Mallick S, Chander S, Sen S, Chawla B. Adjuvant radiotherapy with three-dimensional conformal radiotherapy of lacrimal gland adenoid cystic carcinoma. *J Clin Diagn Res* 2015;9(10):XC05-XC07.

30 Ueda S, Goto H, Matsubayashi J, Nagao T. Adenoid cystic carcinoma of the lacrimal gland: clinicopathological study. *Nippon Ganka Gakkai Zasshi* 2014;118(11):963-967.

31 Ghonsikar V, Pushker N, Bajaj M, Chawla B, Kashyap S, Bakhshi S, Sen S. Is exenteration must in each case of adenoid cystic carcinoma of lacrimal gland. *Invest Ophthalmol Vis Sci* 2014;55(13):2780.

32 Fellman M, Carter K, Call CB, Esmaeli B. Disease recurrence after intraarterial chemotherapy in 2 patients with adenoid cystic carcinoma of lacrimal gland. *Can J Ophthalmol* 2013;48(2):e17-e18.

33 Gensheimer MF, Rainey D, Douglas JG, Liao JJ, Laramore GE, Jian-Amadi A, Chow LQM, Koh WJ, Parvathaneni U. Neutron radiotherapy for adenoid cystic carcinoma of the lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2013;29(4):256-260.

34 Wang XN, Qian J, Yuan YF, Zhang R, Zhang YQ. Space-occupying lesions of the lacrimal gland at one tertiary eye center in China: a retrospective clinical study of 95 patients. *Int J Ophthalmol* 2012;5(2):208-211.

35 Wilson KF, Ward PD, Spector ME, Marentette LJ. Orbitocranial approach for treatment of adenoid cystic carcinoma of the lacrimal gland. *Ann Otol Rhinol Laryngol* 2011;120(6):397-400.

36 Meel R, Pushker N, Bakhshi S. Adjuvant chemotherapy in lacrimal gland adenoid cystic carcinoma. *Pediatr Blood Cancer* 2009;53(6):1163-1164.

37 Esmaeli B, Golio D, Kies M, DeMonte F. Surgicla management of locally advanced adenoid cystic carcinoma of the lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2006;22(5):366-370.

38 Tse DT. Clinical and microdissection genotyping analyses of the effect of intra-arterial cytoreductive chemotherapy in the treatment of lacrimal gland adenoid cystic carcinoma. *Trans Am Ophthalmol Soc* 2005;103:337-367.

39 Esmaeli B, Ahmadi MA, Youssef A, Diba R, Amato M, Myers JN, Kies M, Naggar AE. Outcomes in patients with adenoid cystic carcinoma of the lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2004;20(1):22-26.

40 Tang D, Song G, Sun F. Observation of postoperative radiation therapy on adenoid cystic carcinoma of the lacrimal gland. *Yanke Yanjiu* 2002;20(1):69-71.

41 Meldrum ML. Neoadjuvant intracarotid chemotherapy for treatment of advanced adenocystic carcinoma of the lacrimal gland. *Arch Ophthalmol* 1998;116(3):315.

42 OCEBM Levels of Evidence Working Group The Oxford Levels of Evidence 2. Oxford Centre for Evidence-BasedMedicine. 2020.

https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence

43 Choi CJ, Tran AQ, Anagnostopoulos AG, Zhou HW, Tse DT, Dubovy SR. A single-institution review of lacrimal gland biopsies between 1962 and 2017. *Orbit* 2023;42(2):148-156.

44 Onaga R, Enokida T, Ito K, Ueda Y, Okano S, Fujisawa T, Wada A, Sato M, Tanaka H, Takeshita N, Tanaka N, Hoshi Y, Tahara M. Combination chemotherapy with taxane and platinum in patients with salivary gland carcinoma: a retrospective study of docetaxel plus cisplatin and paclitaxel plus carboplatin. *Front Oncol* 2023;13:1185198.

45 Li C, Liu SM, Zheng L, Huang MW, Shi Y, Lv XM, Zhang JG, Peng X, Zhang J. Comparison of outcomes using radiotherapy or brachytherapy after resection of primary adenoid cystic carcinoma in oral and maxillofacial regions. *Brachytherapy* 2021;20(1):171-177.

46 Wang JY, Murase M, Towithelertkul C, Tani H, Sumita YI. Custom-made radiotherapy prosthesis for external and internal radiotherapy in a patient with lip cancer. *J Oral Sci* 2023;65(1):65-68.

47 Laurie SA, Ho AL, Fury MG, Sherman E, Pfister DG. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. *Lancet Oncol* 2011;12(8):815-824.

48 Qi LY, Luo Q, Zhang YY, Jia FF, Zhao Y, Wang FY. Advances in toxicological research of the anticancer drug cisplatin. *Chem Res Toxicol* 2019;32(8):1469-1486.

49 Zhang CL, Zhu LM, Liu X, Jiang MX, Lin TT, He YJ. Comparison of biological behavior of lacrimal gland adenoid cystic carcinoma with high-grade transformation cells. *Int J Ophthalmol* 2023;16(2):163-171.

50 Park J, Kim HK, Kim WS, Bae TH. Extensive and aggressive growth of adenoid cystic carcinoma in the lacrimal gland. *Arch Craniofac Surg* 2020;21(2):114-118.