

# **Surgery-Based Salvage for Locoregional Recurrent Salivary Gland Carcinoma: Comparative Survival Evidence from a Systematic Review and Meta-analysis**

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## ABSTRACT

**Objectives:** To compare survival outcomes between surgery-based salvage and non-surgical management in patients with locoregional recurrent salivary gland carcinoma (RSGC), and to explore whether surgery-based salvage is associated with more favorable outcomes in appropriately selected patients.

**Methods:** A search was performed in MEDLINE (Ovid), EMBASE, and the Cochrane Library. Observational studies were included that reported comparative outcomes for surgery-based salvage (resection  $\pm$  adjuvant therapy) versus non-surgical management (re-irradiation, brachytherapy, systemic therapy, or palliative treatment) in locoregional recurrent disease. Patients with distant metastasis at recurrence were excluded from the pooled analysis. Primary outcomes were overall survival (OS) and disease-free survival (DFS). Hazard ratios (HRs) were calculated as non-surgical management versus surgery-based salvage and pooled using a random-effects model. Risk of bias was assessed using RoBANS 2.0.

**Results:** Five retrospective comparative studies ( $N = 163$ ) met the inclusion criteria. Four studies contributed to a meta-analysis for OS ( $N = 153$ ) and DFS ( $N = 145$ ). In pooled observational analyses, non-surgical management showed higher hazard estimates for OS (pooled HR = 3.40; 95% confidence interval [CI], 1.17–9.84;  $p = 0.024$ ) and DFS (pooled HR = 3.09; 95% CI, 1.21–7.91;  $p = 0.019$ ) than surgery-based salvage. Heterogeneity was considerable for OS ( $I^2 = 80.1\%$ ) and moderate for DFS ( $I^2 = 56.4\%$ ). Most studies had moderate-to-high risk of bias, particularly for participant comparability and residual confounding.

**Conclusion:** Available comparative observational evidence suggests that surgery-based salvage may be associated with more favorable survival outcomes in appropriately selected patients with locoregional RSGC. However, the evidence base is small, retrospective, and clinically heterogeneous; therefore, these findings should be interpreted as exploratory rather than confirmatory, and treatment decisions should be individualized within a multidisciplinary approach.

**Keywords:** Locoregional recurrence, Meta-analysis, Salivary gland carcinoma, Salvage surgery, Systematic review

## HIGHLIGHTS

1. Comparative outcomes for salvage strategies in locoregional recurrent salivary gland carcinoma were synthesized in a meta-analysis of observational studies.
2. Pooled hazard ratios (non-surgical vs. surgery-based salvage) suggested approximately three-fold higher estimated hazards of death and recurrence with non-surgical management, with substantial heterogeneity.
3. Treatment effects were directionally consistent across studies; however, clinical heterogeneity was considerable, and risk of bias was moderate-to-high, particularly for comparability and residual confounding.
4. These exploratory findings suggest that surgery-based salvage is an important curative-intent option for appropriately selected patients with resectable recurrence, supporting individualized multidisciplinary decision-making.

## INTRODUCTION

Primary salivary gland carcinomas are rare and histologically heterogeneous, accounting for <5% of all head and neck cancers [1-3]. Due to the low incidence, the availability of high-level evidence to guide management is limited. Despite advances in multimodal treatment, locoregional recurrent salivary gland carcinoma (RSGC) remains a challenging problem, and recurrent disease is associated with poorer survival outcomes [4]. Patients with locoregional recurrence, with or without distant metastasis, face a challenging clinical scenario in which the potential for disease control remains, yet the optimal salvage strategy has not been clearly defined, and the prognosis of repeated treatment is often poor [5,6].

For patients with RSGC, various salvage approaches may be considered, including radical resection, with or without adjuvant radiotherapy, and/or systemic therapy, re-irradiation techniques, and palliative management [7-9]. A recent systematic review suggested that salvage surgery can achieve a five-year overall survival (OS) rate in the 60–70% range, and it may provide superior long-term disease control to non-surgical strategies in selected patients; however, these observations are accompanied by treatment-related morbidity and substantial selection bias inherent to non-randomized comparisons [5,8]. For patients with unresectable disease, re-irradiation and systemic therapy remain important options; however, reported outcomes generally show modest gains in survival, with high rates of progression, and direct comparative evidence across modalities is limited [10,11]. Consequently, the management of locoregional RSGC varies widely across institutions, and treatment decisions are typically individualized through multidisciplinary discussion in the absence of a clearly defined optimal strategy.

Given this clinical context, the evidence for managing locoregional RSGC is not well established. Although previous reports have suggested that surgery-based salvage may offer better long-term survival and disease control than non-surgical management in selected patients, these findings have not been quantified in a comparative meta-analysis, and the overall certainty of the evidence has not been evaluated in a structured manner [12,13]. Therefore, a systematic review and meta-analysis of observational studies was conducted that compared OS and disease-free survival (DFS) between surgery-based salvage (surgical resection, with or without adjuvant therapy) and non-surgical management in patients with locoregional RSGC. The aims were to synthesize the available comparative evidence to explore whether surgery-based salvage is associated with more favorable survival outcomes in selected patients, and to support multidisciplinary treatment decision-making for patients with locoregional RSGC.

## **MATERIALS AND METHODS**

### *Reporting Guidelines and Study Design*

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The study protocol and methodological framework were also guided by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations, where applicable [15].

### *Patient, Intervention, Comparator, Outcome (PICO) Framework*

The research questions were structured using the PICO framework. The patients were those who had locoregional RSGC. The intervention was surgery-based salvage, defined as salvage resection with or without adjuvant local or systemic therapy. The comparator was heterogeneous

non-surgical management, including study-specific non-operative modalities such as radiation, brachytherapy, systemic therapy, or palliative treatment. The primary outcomes were OS and DFS. Original clinical studies that reported comparative data were included.

### *Literature Search Strategy*

A systematic literature search was performed on May 22, 2025, in MEDLINE (Ovid), EMBASE, and the Cochrane Library to identify studies on locoregional RSGC, with no restrictions on publication year. Search terms included “local recurrence”, “salvage therapy”, “surgery”, and “salivary gland cancer”, combined with Boolean operators (AND/OR) in various configurations. The full electronic search strategies for all databases are provided in Supplementary Table S1.

### *Study Selection*

Studies were deemed eligible if they reported survival or clinical outcomes, such as OS, DFS, or locoregional control, in patients with RSGC. Studies were only included if the outcomes for the surgical treatment and non-surgical management groups could be clearly extracted, and were reported separately for patients with recurrent disease. Studies were excluded if they were non-English publications, case reports, small case series, review articles, letters, editorials, expert opinions, conference abstracts without full text, or unpublished. Patients with distant metastases at recurrence were also excluded from the pooled analysis.

### *Data Collection*

Data were extracted regarding the study design and follow-up, patient demographics, histopathological subtype, recurrence pattern, prior treatment, details of treatment (composition of intervention and comparator arm), distant-metastasis exclusions, and outcomes of interest, including OS, DFS, locoregional control, and treatment-related complications/toxicities. Data were extracted independently by two reviewers, and discrepancies were resolved by consensus.

### *Quality Assessment*

Risk of bias in the included non-randomized studies was independently assessed by two reviewers using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) version 2.0 across its pre-specified domains [16]. Each domain was categorized as low, unclear, or high risk of bias and was assessed using RevMan 5.4. Discrepancies were resolved by consensus. Publication bias was evaluated by visual inspection of funnel plots and by formal tests for funnel plot asymmetry, implemented in R (R Foundation for Statistical Computing, Vienna, Austria). Since only a small number of studies were available, formal tests for funnel-plot asymmetry were considered exploratory and interpreted cautiously.

### *Statistical Analysis*

Statistical analyses were performed in R using the meta package (version 8.0-1). For OS and DFS, hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted directly when clearly reported. For studies without reported HRs, effect estimates were reconstructed from published survival data using the method described by Tierney et al [17]. All estimates were pooled using an inverse-variance weighted random-effects model with restricted maximum likelihood (REML) estimation of between-study variance. Between-study heterogeneity was

assessed using Cochran's Q and the I<sup>2</sup> statistic. Forest plots were constructed to visualize individual and pooled effect sizes. Exploratory meta-regression and small-study/publication-bias assessments were performed; however, given the small number of included studies, these analyses were considered underpowered and interpreted cautiously [18,19]. Statistical significance was set at  $p < 0.05$ .

To explore potential heterogeneity, meta-regression analyses were conducted using study-level covariates (mean age and proportion of female patients) for which data were available. Regression coefficients ( $\beta$ ), R<sup>2</sup> values, and corresponding P values were reported.

## RESULTS

### *Study Selection*

The initial literature search identified 5,298 records. After removing duplicates and performing automated exclusions, 2,235 records underwent title and abstract screening. In total, 141 full-text reports were retrieved and assessed for eligibility. Most exclusions were due to non-recurrent or mixed cohorts, lack of a comparative non-surgical group, ineligible interventions, or insufficient reporting of outcomes. Overall, five studies met all inclusion criteria and were included in the final analysis [20-24]. The study selection process is presented in a PRISMA flow diagram (Figure 1). The included studies compared the survival outcomes between salvage surgery with or without adjuvant therapy, and non-surgical management, in patients with locoregional RSGC.

### *Study Characteristics*

Five retrospective observational studies comprising 163 patients were included, with individual sample sizes ranging from 10 to 64 patients. For this review, local recurrence was defined as

recurrence within the primary salivary gland or operative bed, regional recurrence as cervical nodal recurrence, and locoregional recurrence as local and/or regional recurrence in the absence of distant metastasis at the time of recurrence. The included studies differed in recurrence pattern: Zhang et al. enrolled patients with local recurrence only, whereas Nisa et al. and Kobayashi et al. included cohorts with both locoregional recurrence and distant metastasis. Studies with mixed recurrence patterns were retained only when the locoregional subgroup could be clearly separated, and patients with distant metastasis at recurrence were excluded from the pooled analysis in two studies [20,21]. The included studies were histopathologically heterogeneous and included mucoepidermoid carcinoma, acinic cell carcinoma, adenocarcinoma, squamous cell carcinoma, and other salivary gland malignancies. Treatment strategies varied across studies, but they generally compared surgery-based salvage with or without adjuvant therapy, with non-surgical management, including re-irradiation, brachytherapy, and palliative treatment. Notably, the clinical circumstances driving treatment selection, as well as the composition of the intervention and comparator arms, varied considerably across cohorts. Zhang et al. compared resection followed by brachytherapy with brachytherapy alone in local recurrent disease. Kobayashi et al. compared definitive surgery in operable recurrent cases with a non-surgical inoperable subgroup, where 12 patients underwent definitive surgery, while 3 were deemed unsuitable due to carotid artery invasion, or extensive skull base invasion. In Nisa et al., salvage surgery was pursued in patients with isolated local or regional recurrence, while the non-surgical group largely reflected palliative management for unresectable disease. Kagan et al. reported surgery, radiotherapy, and combination treatment at the recurrence level. Karam et al. reported a previously irradiated recurrent cohort treated with stereotactic body radiotherapy, with surgery performed in a subset of patients. Clinical and treatment characteristics are summarized

in Table 1. OS was reported in all studies, whereas DFS, progression-free survival, or locoregional control were reported in selected cohorts.

The source of the comparative effect estimates also differed across studies. Karam et al. reported direct comparative HRs for surgery using Cox regression [23]. Kobayashi et al. and Zhang et al. reported Kaplan–Meier survival outcomes with log-rank comparisons but did not provide direct HRs [20,24]. Nisa et al. reported median OS and progression-free survival values with Kaplan–Meier/log-rank analysis, without reporting a comparative HR [21]. Kagan et al. reported group-level survival summaries and recurrence-level treatment data, but not a patient-level time-to-event HR [22]. Accordingly, the pooled analyses incorporated both directly reported and estimated comparative survival effects.

### *Risk of Bias*

The risk of bias was assessed using RoBANS 2.0. Most studies had a moderate-to-high risk of bias, particularly in domains related to participant comparability and control of confounding variables. In contrast, exposure measurement and outcome assessment were rated as low risk. There was variability in the blinding of outcome assessment and selective outcome reporting. Overall, the methodological quality of the included studies was limited, reflecting the inherent constraints of a retrospective observational design (Figure 2).

### *Overall Survival*

Four studies with 153 patients were included in the pooled analysis of OS [20,22-24]. Among these, Karam et al. provided a direct comparative HR for surgery versus non-surgical management, whereas the comparative effects for Kobayashi et al., Kagan et al., and Zhang et al.

were estimated from published survival information. Using an inverse-variance random-effects model, the pooled comparative estimate favored surgery-based salvage (pooled HR = 3.40; 95% CI, 1.17–9.84;  $p = 0.024$ ), where the effect was expressed as non-surgical management vs surgery-based salvage (Figure 3A). There was considerable between-study heterogeneity, indicating variability in the magnitude of the effect across cohorts ( $I^2 = 80.1\%$ ). Study-specific estimates ranged from an HR of 1.40 to 12.26, and two studies showed statistically significant estimates favoring surgery-based salvage (Kagan et al., 1976; Kobayashi et al., 2009) [20,22], whereas the remaining studies had point estimates favoring surgery but with wider confidence intervals crossing unity (Karam et al., 2012; Zhang et al., 2015) [23,24]. Despite the between-study heterogeneity, all study-specific point estimates favored surgery-based salvage, although the magnitude and precision of the effect varied across cohorts.

#### *Disease-Free Survival*

Four retrospective studies with 145 patients were included in the pooled analysis of DFS [20–22,24]. None of these studies reported a direct comparative HR for DFS. Therefore, all comparative effect estimates in this synthesis were estimated from published survival information, including Kaplan–Meier outcomes, or survival data. Using a random-effects model, the pooled comparative estimate favored surgery-based salvage (pooled HR = 3.09; 95% CI, 1.21–7.91;  $p = 0.019$ ), where the effect was expressed as non-surgical management vs surgery-based salvage (Figure 3B). There was moderate between-study heterogeneity ( $I^2 = 56.4\%$ ), indicating variability across studies, but less than that observed for OS. Across individual studies, the direction of the effect consistently favored surgery-based salvage; however, precision was limited in smaller cohorts, as reflected by wider confidence intervals. Similarly, study-specific

estimates for DFS favored surgery-based salvage across the included cohorts, although several estimates were imprecise based on the small sample sizes.

### *Meta-Regression Analysis*

Exploratory meta-regression analyses were performed to investigate whether between-study heterogeneity in the treatment effect could be explained by pre-specified covariates. The proportion of female patients showed inverse trend in the effect estimates for OS ( $\beta = -1.729$ ,  $p = 0.244$ ,  $R^2 = 65\%$ ) and DFS ( $\beta = -2.314$ ,  $p = 0.159$ ,  $R^2 = 100\%$ ), but the associations were not statistically significant (Supplementary Figure S1A and S1B). In addition, mean age was not significantly associated with OS ( $\beta = 0.023$ ,  $p = 0.620$ ,  $R^2 = 0\%$ ) (Supplementary Figure S1C). However, these analyses were underpowered and should not be overinterpreted, since only a small number of studies were available.

### *Publication Bias*

Potential publication bias was explored using funnel plots of OS and DFS (Figure 4). Visual inspection suggested mild asymmetry; however, a formal assessment was limited by the small number of studies. Overall, the funnel plots did not have a definitive pattern that was consistent with small-study effects, although publication bias cannot be excluded.

## **DISCUSSION**

In this systematic review and exploratory meta-analysis of locoregional RSGC, surgery-based salvage with or without adjuvant therapy was associated with more favorable OS and DFS than heterogeneous non-surgical management in the included retrospective cohorts. When effect

estimates were expressed as non-surgical management versus surgery-based salvage, non-surgical management was associated with approximately three-fold higher risk of death or disease progression (OS: HR 3.40, 95% CI 1.17–9.84; DFS: HR 3.09, 95% CI 1.21–7.91). Given the small evidence base, substantial heterogeneity, and the potential for selection bias, these results should be interpreted cautiously as exploratory rather than confirmatory, and may support surgery-based salvage in appropriately selected patients.

The overall direction of the effect in the pooled analysis is consistent with that in the included studies. Kobayashi et al. reported significantly higher long-term survival for patients who underwent salvage surgery than for those treated non-surgically, and Zhang et al. reported superior outcomes for resection plus brachytherapy compared to brachytherapy alone [20,24]. However, the results were inconsistent across studies. Nisa et al. did not report a significant difference in OS between salvage surgery and palliative management, whereas Kagan et al. and Karam et al. reported poor survival after recurrence despite aggressive local treatment [21-23]. Although the magnitude of the observed association appeared to differ across cohorts, the included studies generally reported more favorable outcomes with surgery-based salvage treatment.

In this review, the comparison across studies was not simply between surgery and non-surgery. The surgical arm often underwent multimodal treatment rather than surgery alone. For example, as most studies combined surgical resection with adjuvant local therapy, the between-group difference may reflect the contribution of adjuvant treatment in addition to resection. The composition of the non-surgical arm significantly varied across studies. In Zhang et al., the comparator consisted of brachytherapy alone, which may have reduced the difference between groups as an active salvage treatment. In contrast, Nisa et al. and Kobayashi et al. provided

palliative or non-surgical treatment in patients with unresectable disease, which may have enlarged the advantage of surgery-based salvage. In Karam et al., the comparison was within a previously irradiated cohort, which further complicates interpretation. Therefore, the pooled comparison should be interpreted as a comparison between surgery-based salvage strategies and heterogeneous non-surgical management across different clinical settings, rather than as an independent effect of surgery.

In clinical practice, salvage resection is generally considered an important treatment option for patients with resectable locoregional recurrence, as reflected in current guidelines. The National Comprehensive Cancer Network Head and Neck Cancer Guidelines identify resectability as a key determinant when considering salvage surgery for RSGC [25]. Similarly, the American Society of Clinical Oncology guidelines recommend revision resection for patients with resectable locoregional recurrence, with reconstruction and rehabilitation as indicated [26]. However, evidence supporting these recommendations is limited, relying largely on expert consensus and retrospective observational studies, as comparative data on RSGC are scarce.

Despite these limitations, the available studies have generally demonstrated favorable outcomes with surgery-based salvage treatment. Iseli et al. reported that patients with locally-recurrent adenoid cystic carcinoma who underwent salvage surgery had significantly longer survival than those managed without salvage surgery [27]. A systematic review by Mannelli et al. pooled 365 patients who underwent salvage surgery for RSGC and reported an OS of 70% and a DFS of 42% in this cohort [5]. Another systematic review by Wang et al. reported that surgical treatment was associated with improved OS in patients with RSGC [28]. Taken together, these findings are consistent with our results, supporting surgery-based salvage as an important treatment option

for resectable locoregional recurrence, where achieving complete macroscopic resection may provide durable local control.

In our analysis, there was considerable between-study heterogeneity, particularly for OS ( $I^2 = 80.1\%$ ). This is likely to be due to differences in patient characteristics and treatment approaches across cohorts. The included studies enrolled heterogeneous cohorts with a broad range of histopathological variants, including adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, adenocarcinoma, and squamous cell carcinoma. They also differed in recurrence patterns (local versus locoregional), prior treatment exposure, and salvage treatment modalities. In addition, the non-surgical management comparator group was inconsistent across studies, ranging from re-irradiation modalities, including brachytherapy and SBRT, to palliative strategies, each representing a different therapeutic intent. This variability likely influenced the pooled estimates in opposing directions. Studies in which the surgery arm included multimodal curative-intent treatment may have overstated the benefit of surgery-based salvage, while those with active non-surgical comparators such as brachytherapy or SBRT may have understated it. Conversely, studies in which the comparator reflected palliative or non-operative management may have further widened the apparent between-group difference.

Exploratory meta-regression using mean age and proportion of female patients did not identify statistically significant associations with the pooled effect estimates. However, as only a small number of studies were available, these analyses were underpowered and should not be interpreted as evidence that age or sex did not contribute to the observed heterogeneity [29]. Age and sex were examined as they are well-acknowledged prognostic factors in head and neck cancer and in the salvage setting [30-32], nonetheless, the present dataset was too limited to determine whether between-study differences in these variables influenced the comparative

outcomes. A formal subgroup analysis by treatment type was not feasible, as each subtype was represented by only one study, or by very few patients, which would have produced potentially misleading estimates. In addition, several clinically important factors that may influence outcomes, such as margin status, perineural invasion, nodal involvement, time to recurrence, constraints from prior radiotherapy, and detailed histopathology, have not been consistently reported across studies [33,34]. As a result, the impact of these factors could not be evaluated in the subgroup analyses or meta-regression. Considering that these variables may directly affect resectability, treatment decisions, and underlying risks, differences in their distribution across cohorts may have contributed to the heterogeneity in the pooled estimates.

Risk of bias is an important consideration when interpreting the findings. All included studies were retrospective, non-randomized comparisons; therefore, they were prone to selection bias and residual confounding due to non-random treatment allocation [35]. In clinical practice, the decision to perform salvage surgery is based on factors such as extent of disease, resectability, prior treatment exposure, comorbidities, and functional status [36,37]. As a result, patients who undergo surgery may represent a more favorable risk group, whereas non-surgical cohorts may include a higher percentage of patients with unresectable, multifocal, or aggressive disease progression. This imbalance can overstate the benefits of surgery, particularly when confounding factors are not adequately adjusted. These concerns are consistent with the RoBANS 2.0 assessment, which identified limitations in domains related to comparability of participants, participant selection, and control of confounding. Publication bias also cannot be ruled out, as funnel plots for both OS and DFS showed mild visual asymmetry, and formal tests for small-study effects were underpowered given the limited number of available studies [38].

Accordingly, overall confidence in the estimates was limited, particularly for DFS, due to risk of bias and heterogeneity.

Beyond survival outcomes, inconsistently reported adverse events, functional outcomes, and quality of life represent a notable limitation of this study. There was insufficient detail to permit a pooled analysis, despite the fact that both salvage treatment strategies may be associated with significant morbidity. Surgery-based salvage often requires extended resection, facial nerve sacrifice, and complex reconstruction, which may result in functional deficits and cosmetic changes. In Nisa et al., salvage procedures often required extended revision parotidectomy, and facial nerve management was a recurring concern in the Kobayashi and Zhang cohorts as well [20,21,24]. By contrast, re-irradiation carries risks of acute and late radiation toxicity, and further treatment options may be limited after high cumulative doses [39-41]. Zhang et al. reported severe skin ulceration, and Karam et al. described soft tissue necrosis in patients receiving higher cumulative radiation doses [23,24]. Taken together, any potential survival benefit should be weighed against the consequences of treatment, and management decisions should carefully balance oncologic outcomes with toxicity, functional preservation, and quality of life.

Overall, the present synthesis suggests that surgery-based salvage may be associated with more favorable survival outcomes in appropriately selected patients with resectable locoregional recurrence who are eligible for surgery. Nevertheless, given the limitations of the evidence, these results should not be interpreted as establishing the superiority of surgery over non-surgical management for patients with RSGC, but rather as exploratory and hypothesis-generating observations that may help inform multidisciplinary decision-making in selected patients. In clinical practice, the best candidates for surgery-based salvage are those in whom complete (R0) resection is achievable with acceptable functional morbidity, and who have adequate

performance status to tolerate surgery. In contrast, patients with unresectable tumors, multifocal recurrence, or systemic progression are more likely to be managed with non-surgical modalities, such as re-irradiation, systemic therapy, or palliative care [42,43]. Therefore, treatment decisions should be individualized, considering histopathology, resectability, prior treatment exposure, comorbidities, and importantly, patient goals and preferences.

This review has several strengths. It was conducted under a protocol consistent with the PRISMA/MOOSE guidance, focused on locoregional recurrence without distant metastases, and included comparative cohorts evaluating surgery-based salvage versus non-surgical management. To our knowledge, this is the first meta-analysis to quantitatively synthesize survival outcomes by comparing surgery-based salvage with non-surgical management for patients with RSGC, providing pooled estimates from limited evidence.

The limitations of this review are inherent to the clinical context. RSGC is rare and heterogeneous, and salvage decisions are determined by resectability and patient condition. As a result, randomized comparative trials are not feasible, and the available evidence largely consists of small, retrospective, non-randomized comparative studies. Perhaps the most consequential limitation is selection bias and confounding by indication. Surgery-based salvage was generally offered to patients with technically resectable locoregional disease, whereas non-surgical management was more often selected for those with unresectable recurrence, gross residual disease, prior irradiation, or palliative-intent. This imbalance in patient selection increases the risk of residual confounding, limits the precision of the pooled estimates, and the observed survival differences cannot be interpreted as evidence of treatment superiority or causal benefit. The pooled comparative estimates should therefore be understood as associations drawn from clinically heterogeneous retrospective cohorts. Despite these constraints, this review provides a

synthesis of available comparative evidence, offering clinically relevant information to support treatment decision-making for patients with RSGC.

Future studies should therefore generate high quality evidence, such as multi-institutional cohorts with standardized data on recurrence, histopathology, outcomes, and treatment variables, including prior radiotherapy dose/fields and systemic regimens. Moreover, standardized reporting of surgical morbidity, late toxicity after re-irradiation, and patient-reported outcomes is necessary to clarify the benefit–risk profiles of salvage treatment strategies.

## CONCLUSION

Available comparative observational evidence suggests that surgery-based salvage may be associated with more favorable OS and DFS in appropriately selected patients with locoregional RSGC without distant metastases who are eligible for surgery. However, the current evidence base is very limited and consists of small, retrospective, and clinically heterogeneous studies that are vulnerable to selection bias, confounding by indication, and imprecise pooled estimates. These findings should therefore be interpreted as exploratory or hypothesis-generating rather than confirmatory, and should not be taken as evidence that surgery-based salvage is superior for all patients with recurrent disease. Treatment decisions should be individualized within a multidisciplinary setting, considering the histopathology, resectability, prior treatment exposure, performance status, potential morbidity, and patient preferences.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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## FIGURE LEGENDS

**Figure 1.** PRISMA flow diagram of study selection.

**Figure 2.** Risk of bias assessment of the included studies. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

**Figure 3.** Forest plots of hazard ratios for non-surgical management versus surgery-based salvage. (A) Overall survival. (B) Disease-free survival.

**Figure 4.** Funnel plots for assessing publication bias. (A) Overall survival. (B) Disease-free survival.

Table

**Table 1.** Characteristics and outcomes of included studies

|  | Total<br>N | Pooled<br>N | DM<br>exclusion | Histopathological<br>type                                                                                                        | Recurrence<br>pattern                                                                | Intervention                                                                             | Comparator                                    | Prior treatment                                                                               | Outcome<br>measure |
|--|------------|-------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------|
|  | 20         | 10          | 10              | SDC (6), MEC (4), AC (3), SCC (2), AdCC (2), EMC (1), large cell ca (1), CEPA (1)                                                | Local/regional (10)<br>Locoregional+DM (8)<br>DM-only (2)                            | Surgery-based salvage (n=8):<br>surgery alone (4)<br>surgery+RT (2)<br>surgery+re-RT (2) | Palliative/non-surgical (n=2)                 | Initial surgery in all; postoperative RT ± CTx in all                                         | OS, DFS, PFS       |
|  | 56         | 56*         | Not applicable  | SCC (26); AC (30)                                                                                                                | Predominantly locoregional (56)<br>DM not presented                                  | Surgery+irradiation (n=45)                                                               | RT alone (n=11)                               | Initial surgery in all; adjuvant RT/CTx not specified                                         | OS, DFS            |
|  | 64         | 64          | Not applicable  | AdCC (18), MEC (17), MMT (7), ACC (6), MyoEC (6), AC (4), BCA (1), sebaceous ca (1), LEC (1), PCC (1), OA (1), sialoblastoma (1) | Local recurrence only (64)                                                           | Surgery+brachytherapy (n=40)                                                             | Brachytherapy alone (n=24)                    | Primary parotidectomy (50)<br>Parotidectomy+RT (14)                                           | OS, LC             |
|  | 20         | 15          | 5               | AdCC (5), MEC (3), ACC (3), SDC (3), CEPA (2), AC (2), EMC (1), malignant oncocytoma (1)                                         | Mixed locoregional (15)<br>DM (5)                                                    | Surgery alone (n=12)                                                                     | Non-surgical (n=3)<br>treatment not specified | Initial surgery in all; postoperative RT (5)                                                  | OS, DFS            |
|  | 18         | 18          | Not applicable  | SCC (7), AdCC (2), AC (2), ACC (2), MEC (1), not specified (4)                                                                   | Recurrent previously irradiated salivary gland malignancy; locoregional setting (18) | Surgery+adjuvant SBRT (n=8)                                                              | SBRT alone (n=10)                             | Previously irradiated cohort; concurrent CTx (7); prior SBRT as part of primary treatment (2) | OS, PFS, LRC       |

Total N indicates the cohort size reported in the source study. Pooled N indicates the locoregional subset for pooled analysis after excluding distant metastasis (DM) at recurrence.

**Abbreviations.** AC, adenocarcinoma; ACC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; BCA, basal cell adenocarcinoma; CEPA, carcinoma ex pleomorphic adenoma; CTx, chemotherapy; DFS, disease-free survival; DM, distant metastasis; EMC, epithelial-myoepithelial carcinoma; LC, local control rate; LEC, lymphoepithelial carcinoma; LRC, locoregional control rate; MEC, mucoepidermoid carcinoma; MMT, malignant mixed tumour; MyoEC, myoepithelial carcinoma; ND, neck dissection; OA, oncocytic adenoma; OS, overall survival; PCC, papillary cystadenocarcinoma; PFS, progression-free survival; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SCC, squamous cell carcinoma; SDC, salivary duct carcinoma.

Figure 1.

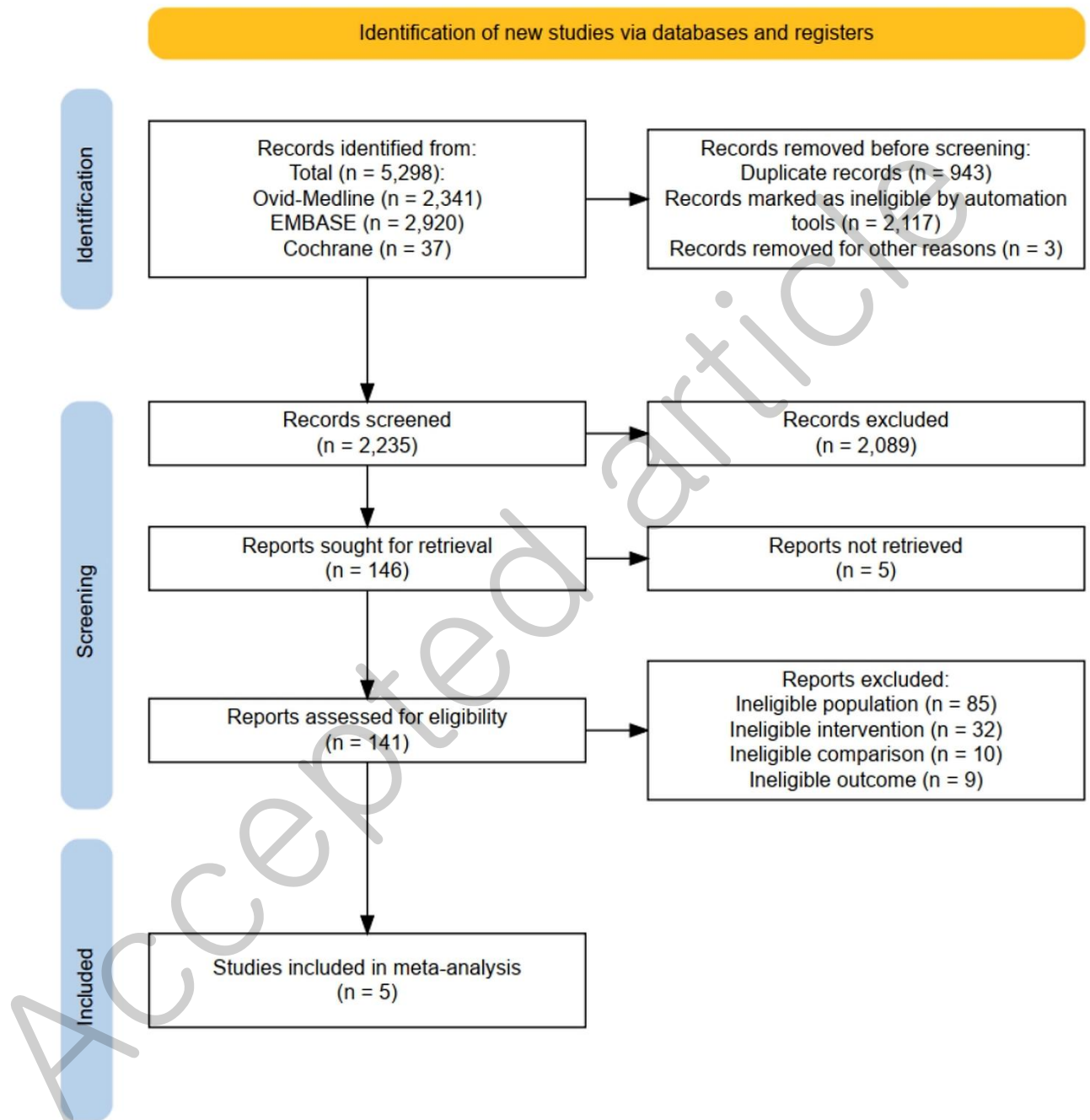


Figure 2.

A

|                    | Comparability of participants | Selection of participants | Confounding variables | Exposure measurement | Blinding of outcome assessment | Outcome assessment | Incomplete outcome data | Selective outcome reporting |
|--------------------|-------------------------------|---------------------------|-----------------------|----------------------|--------------------------------|--------------------|-------------------------|-----------------------------|
| Kagan A (1976)     | ⊖                             | ⊕                         | ⊖                     | ⊕                    | ?                              | ⊕                  | ⊕                       | ?                           |
| Karam SD (2012)    | ⊖                             | ⊖                         | ⊕                     | ⊕                    | ?                              | ⊕                  | ⊖                       | ?                           |
| Kobayashi K (2009) | ?                             | ?                         | ?                     | ⊕                    | ?                              | ⊕                  | ?                       | ?                           |
| Nisa L (2018)      | ⊖                             | ⊖                         | ⊖                     | ⊕                    | ⊖                              | ⊕                  | ?                       | ?                           |
| Zhang J (2015)     | ⊖                             | ⊖                         | ⊖                     | ⊕                    | ⊖                              | ⊕                  | ?                       | ⊖                           |

B

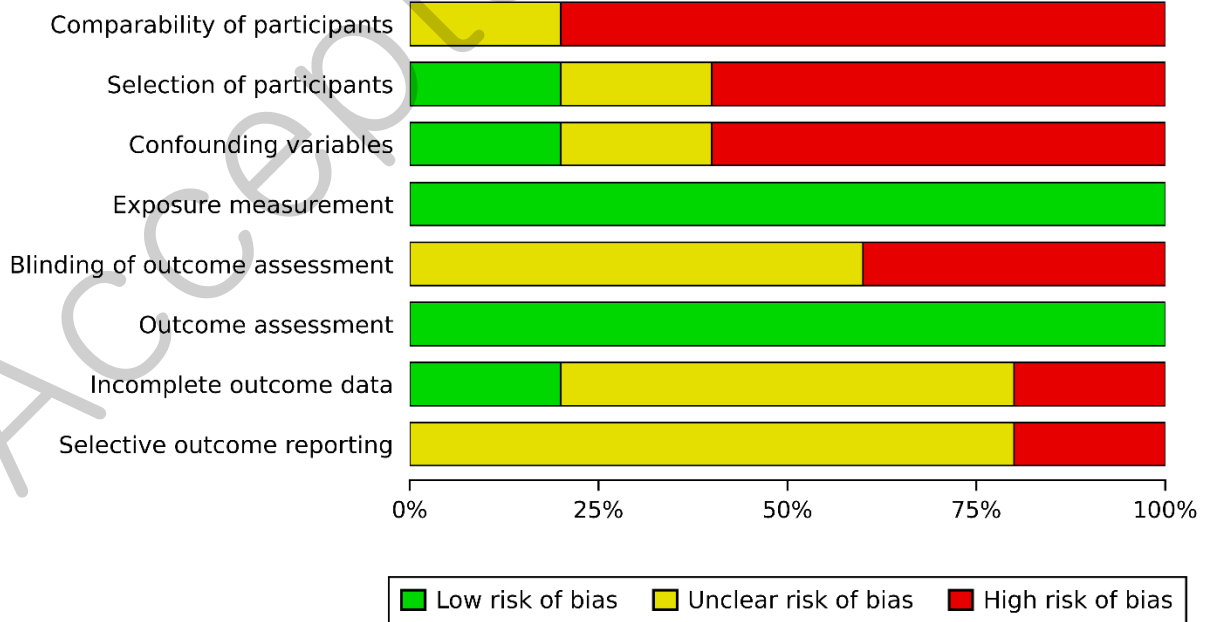


Figure 3.

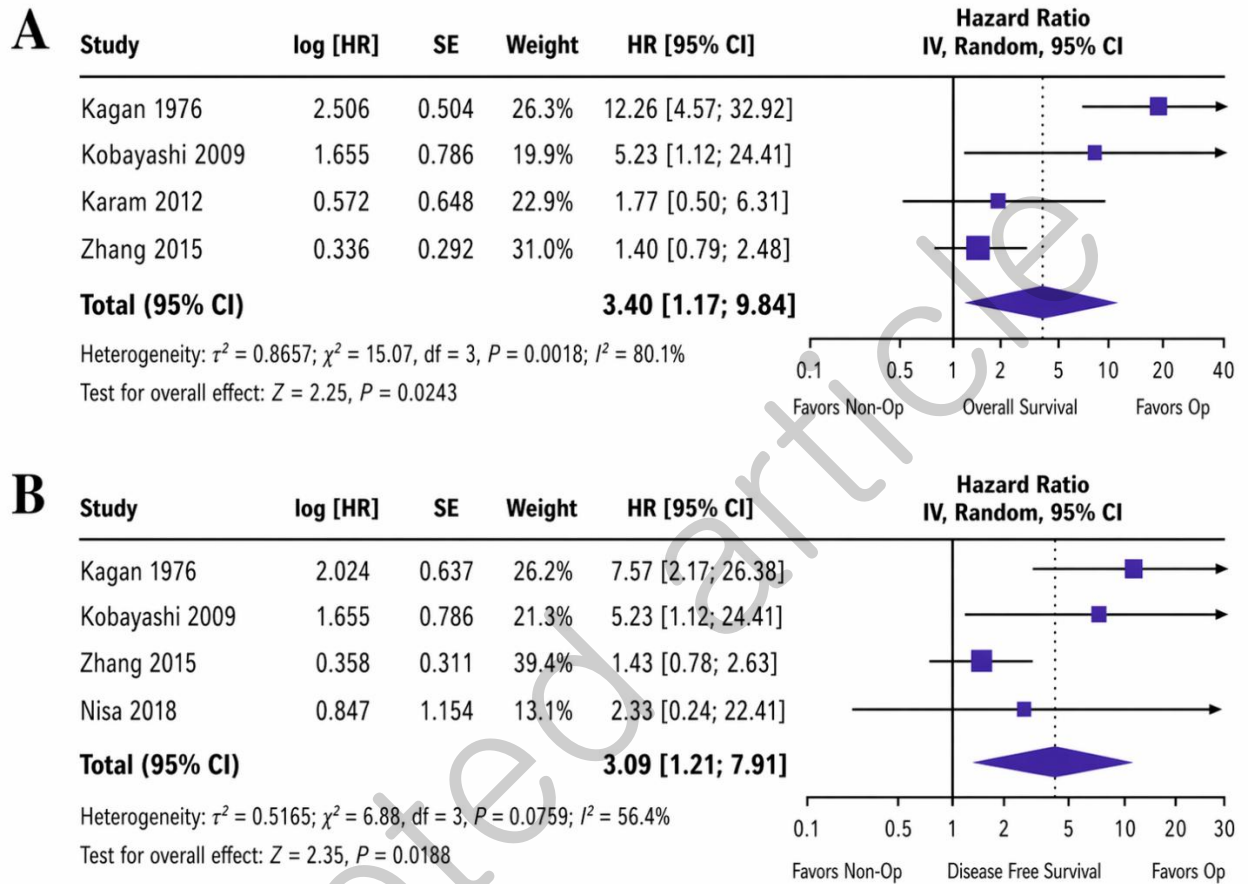
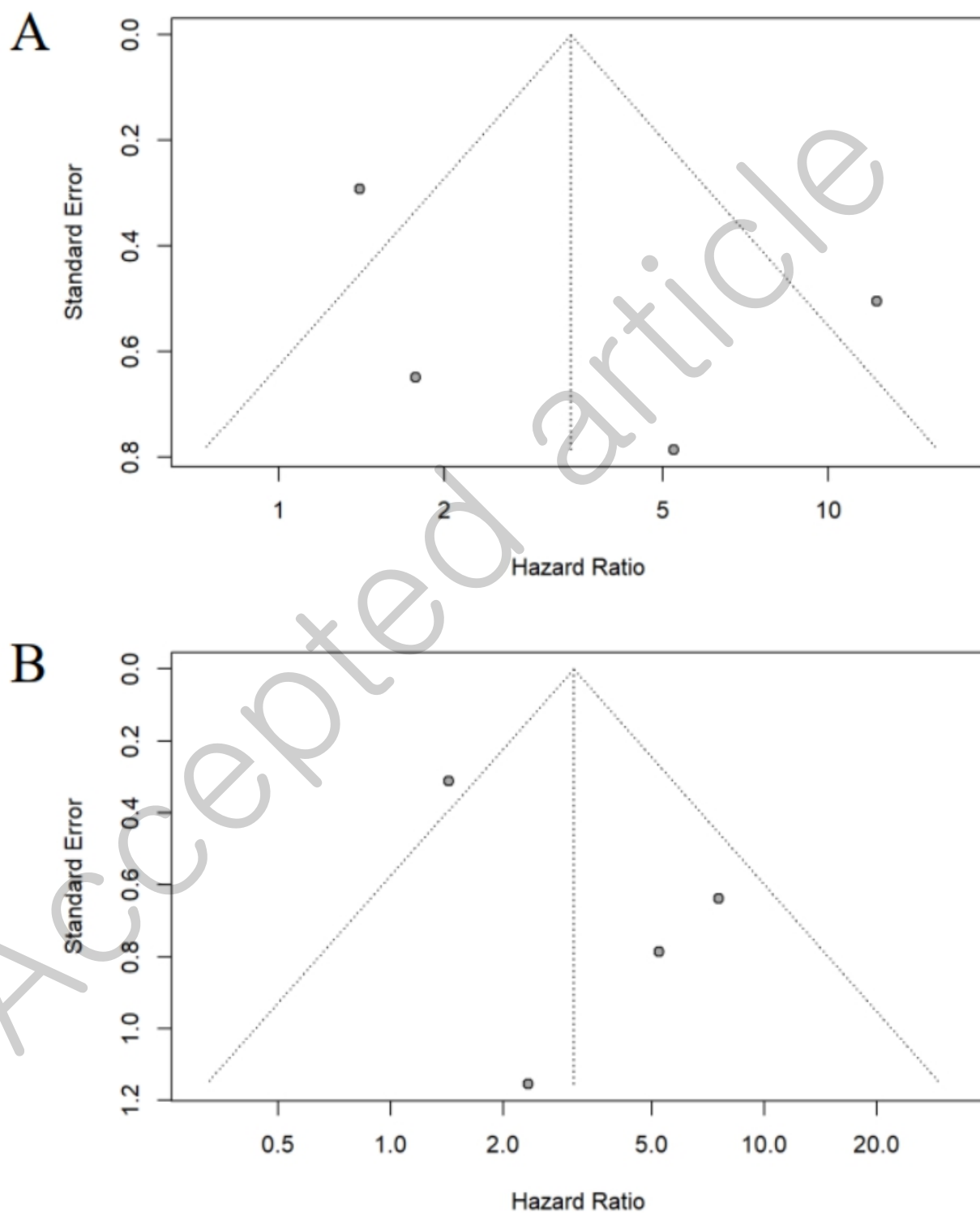


Figure 4.



## Supplementary Materials

**Supplementary Table S1.** Full electronic search strategy

| Database<br>s   | Search strategy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Ovid<br>MEDLINE | <p>((("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] OR "Salvage Therapy"[Mesh] OR "recurren*"[tw] OR "salvage"[tw]) AND ((("Salivary Gland Neoplasms"[Mesh] OR "salivary gland neoplasm*"[tw] OR "cancer of salivary gland*"[tw] OR "salivary gland cancer*"[tw] OR "SGC"[tw] OR "SGCs"[tw] OR "cancer of the salivary gland*"[tw] OR "salivary gland tumor*"[tw] OR "salivary gland tumour*"[tw] OR "salivary gland carcinoma*"[tw] OR "salivary gland malignan*"[tw] OR "salivary neoplasm*"[tw] OR "salivary cancer*"[tw] OR "salivary tumor*"[tw] OR "salivary tumour*"[tw] OR "salivary carcinoma*"[tw] OR "salivary malignan*"[tw]) OR ((("Neoplasms"[Mesh] OR "Salivary Gland Neoplasms"[Mesh] OR "cancer*"[ti] OR "neoplas*"[ti] OR "tumor*"[ti] OR "tumour*"[ti] OR "carcinoma*"[ti] OR "malignan*"[ti]) AND ("Salivary Glands"[Mesh] OR "Salivary Gland Neoplasms"[Mesh] OR "salivary gland*"[ti] OR "saliva gland*"[ti] OR "parotid"[ti] OR "parotis"[ti] OR "submandibular gland*"[ti] OR "sublingual gland*"[ti]))) AND ("surgery"[subheading] OR "remov*"[tw] OR "excisi*"[tw] OR "excise*"[tw] OR "resect*"[tw] OR "dissect*"[tw] OR "Dissection"[Mesh] OR "extirpat*"[tw] OR "Neck Dissection"[Mesh] OR "Neck Dissection/methods"[Mesh] OR "neck dissection"[tw] OR "elective neck dissection"[tw] OR ("END"[tw] AND "neck*"[tw] AND "dissect*"[tw]) OR "elective surgical"[tw] OR "elective surger*"[tw] OR "lymph node excision"[tw] OR "lymphnode excision"[tw] OR "neck radical dissection"[tw] OR "radical"[tw])) NOT ("Animals"[mesh] NOT "Humans"[mesh])) NOT (("Adolescent"[mesh] OR "Child"[mesh] OR "Infant"[mesh]) NOT "Adult"[mesh])) AND "English"[lang]</p> |

|        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| EMBASE | <p>((('recurrence'/exp OR 'local neoplasm recurrence'/exp OR 'salvage therapy'/exp OR recurren*:ti,ab OR salvage:ti,ab) AND ('salivary gland tumor'/exp OR 'salivary gland neoplasm*':ti,ab OR 'cancer of salivary gland*':ti,ab OR 'salivary gland cancer*':ti,ab OR 'SGC':ti,ab OR 'SGCs':ti,ab OR 'cancer of the salivary gland*':ti,ab OR 'salivary gland tumor*':ti,ab OR 'salivary gland tumour*':ti,ab OR 'salivary gland carcinoma*':ti,ab OR 'salivary gland malignan*':ti,ab OR 'salivary neoplasm*':ti,ab OR 'salivary cancer*':ti,ab OR 'salivary tumor*':ti,ab OR 'salivary tumour*':ti,ab OR 'salivary carcinoma*':ti,ab OR 'salivary malignan*':ti,ab OR (('neoplasm'/exp OR 'salivary gland tumor'/exp OR cancer*:ti OR neoplas*:ti OR tumor*:ti OR tumour*:ti OR carcinoma*:ti OR malignan*:ti) AND ('salivary gland'/exp OR 'salivary gland tumor'/exp OR 'salivary gland*':ti OR 'saliva gland*':ti OR parotid:ti OR parotis:ti OR 'submandibular gland*':ti OR 'sublingual gland*':ti))) AND ('surgery'/exp OR remov*:ti,ab OR excisi*:ti,ab OR excise*:ti,ab OR resect*:ti,ab OR dissect*:ti,ab OR 'dissection'/exp OR extirpat*:ti,ab OR 'neck dissection'/exp OR 'neck dissection':ti,ab OR 'elective neck dissection':ti,ab OR (END:ti,ab AND neck*:ti,ab AND dissect*:ti,ab) OR 'elective surgical':ti,ab OR 'elective surger*':ti,ab OR 'lymph node excision':ti,ab OR 'lymphnode excision':ti,ab OR 'neck radical dissection':ti,ab OR radical:ti,ab)) NOT (('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT (('child'/exp OR 'adolescent'/exp OR 'infant'/exp) NOT 'adult'/exp)) AND [english]/lim</p> |
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| <p>Cochrane<br/>Library</p> | <p>((([mh "Recurrence"] OR [mh "neoplasm recurrence, local"] OR [mh "Salvage Therapy"] OR "recurren*":ti,ab OR "salvage":ti,ab) AND ([mh "Salivary Gland Neoplasms"] OR "salivary gland neoplasm*":ti,ab OR "cancer of salivary gland*":ti,ab OR "salivary gland cancer*":ti,ab OR "SGC":ti,ab OR "SGCs":ti,ab OR "cancer of the salivary gland*":ti,ab OR "salivary gland tumor*":ti,ab OR "salivary gland tumour*":ti,ab OR "salivary gland carcinoma*":ti,ab OR "salivary gland malignan*":ti,ab OR "salivary neoplasm*":ti,ab OR "salivary cancer*":ti,ab OR "salivary tumor*":ti,ab OR "salivary tumour*":ti,ab OR "salivary carcinoma*":ti,ab OR "salivary malignan*":ti,ab OR (([mh "Neoplasms"] OR [mh "Salivary Gland Neoplasms"] OR "cancer*":ti OR "neoplas*":ti OR "tumor*":ti OR "tumour*":ti OR "carcinoma*":ti OR "malignan*":ti) AND ([mh "Salivary Glands"] OR [mh "Salivary Gland Neoplasms"] OR "salivary gland*":ti OR "saliva gland*":ti OR "parotid":ti OR "parotis":ti OR "submandibular gland*":ti OR "sublingual gland*":ti))) AND ([mh /SU] OR "remov*":ti,ab OR "excisi*":ti,ab OR "excise*":ti,ab OR "resect*":ti,ab OR "dissect*":ti,ab OR [mh "Dissection"] OR "extirpat*":ti,ab OR [mh "Neck Dissection"] OR "Neck Dissection":ti,ab OR "elective neck dissection":ti,ab OR ("END":ti,ab AND "neck*":ti,ab AND "dissect*":ti,ab) OR "elective surgical":ti,ab OR "elective surger*":ti,ab OR "lymph node excision":ti,ab OR "lymphnode excision":ti,ab OR "neck radical dissection":ti,ab OR "radical":ti,ab)) NOT ([mh "Animals"] NOT [mh "Humans"]) NOT (([mh "Adolescent"] OR [mh "Child"] OR [mh "Infant"]) NOT [mh "Adult"])) AND (english):la</p> |
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### Supplementary Figure legend

**Supplementary Figure S1.** Meta-regression bubble plots for Overall Survival (OS) and Disease-Free Survival (DFS). (A) OS vs. Proportion of female patients. (B) DFS vs. Proportion of female patients. (C) OS vs. Mean age.

Accepted article

Supplementary Figure S1.

