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Local recurrence and survival after treatment of oral squamous cell carcinoma of the maxilla: a systematic review and meta-analysis

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Abstract

Objectives: Oral squamous cell carcinoma involving the maxilla (MSCC) is a rare malignancy. The aim was to perform a systematic review and meta-analysis of available literature on local recurrence (LR), overall survival (OS) and associated risk factors of MSCC.

Study Design: The Cochrane, PubMed and EMBASE databases were searched with related keywords and synonyms. The pooled proportions of both LR and OS were subsequently calculated with 95% confidence intervals.

Results: 2638 articles were screened on title and abstract, 131 articles were screened full-text, and 20 were included. The pooled 5-year LR rate was 19.3%, and the 5-year OS rate was 53.7%. The subgroup analysis between surgery only and surgery with (neo)adjuvant treatment resulted in: OR .76 (95% CI .41 – 1.40).

Conclusions: Postoperative (chemo)radiotherapy or preoperative intra-arterial chemoradiotherapy improves survival when adverse tumour characteristics are present. Posterior tumour extension into the soft palate, pterygoid muscle, pterygoid process and infratemporal fossa was significantly associated with decreased OS in multiple studies. More research into the risk-reduction of local recurrence is warranted.

Clinical relevance

This review provides an overview of available literature on oral squamous cell carcinoma of the maxilla concerning local recurrence, survival and related risk factors. A subgroup analysis concluded that different (neo)adjuvant treatments improve survival when adverse tumour characteristics are present.

Introduction

Squamous cell carcinoma involving the maxilla (MSCC) is a rare subtype of oral cancer. It originates from epithelial cells lining the oral cavity, starting at the maxillary alveolus or hard palate. MSCC usually causes symptoms like tumorous lesions, non-healing wounds and ill-fitting dentures in the early stage.

Surgical treatment is the gold standard for oral MSCC and is accompanied by (neo-)adjuvant treatment on indication, depending on tumour stage and cervical lymph node involvement. Complete resection of the maxillary tumour is the primary goal but can be challenging due to the complex anatomy, poor visibility and poor access. Incomplete resection of large tumours and subsequent local recurrence account for a large proportion of patient mortality in MSCC. Moreover, various survival-related risk factors have been identified for MSCC [1, 2]. Unfortunately, research on this rare subsite of oral cancer is still scarce.

This study aimed to perform a systematic review and meta-analysis of available data on surgical treatment outcomes (i.e., local recurrence (LR), overall survival (OS) for patients with MSCC. The second objective was to identify factors associated with LR and OS.

Materials and Methods

This study was conducted using a systematic review protocol (PRISMA) [3].

A systematic search was performed using the Cochrane, PubMed and EMBASE databases for original relevant articles, published until the 4th of June 2021. A combination of keywords, MeSH terms and Emtree terms were used to search for titles and abstracts in the databases. The keywords “squamous cell carcinoma of the maxilla”, “surgical treatment”, “local recurrence”, “overall survival”, “risk factors”, and their synonyms were used. Human studies with available full-text articles were potentially eligible if they reported on the surgical treatment for MSCC and reported on the primary outcomes of LR and OS and associated risk factors after a 5-year follow up. Study designs like other systematic reviews or case reports were excluded. Studies with wrong domains (e.g., mandibular tumours), or wrong

determinants (e.g., mandibulectomy) or wrong outcomes (e.g., quality of life) were also excluded. After removing duplicates, two authors (FJBS & DAAR) independently screened all titles and abstracts according to the predefined inclusion and exclusion criteria. If there was disagreement, then consensus was reached by discussion. The resulting full-text articles were then screened in detail for final selection. Snowballing was performed by checking all citations and references in the full-text articles for missed studies in the systematic search. The two authors independently extracted data from the included studies using standardised data extraction forms. In case of disagreement, a consensus was reached by discussion. The following data variables were extracted if present: first author, publication year, study type, inclusion period, sample size, primary tumour location, tumour stage, histology, treatment modalities, follow-up length, primary outcome variables (LR rate, OS rate), secondary outcome variables, associated risk factors, statistical methods, the total number of patients with LR and finally the total number of surviving patients. In the case of missing outcome variables, data were synthesised from raw data when sufficiently available. In case outcome data could not be synthesised from raw data, then the particular study would not be included in that specific analysis. The quality assessment of the individual studies was done by the two authors independently, using the Newcastle-Ottawa scale for non-randomised studies [4]. A quality score was calculated as the sum of all the scores in the assessment (max. 9). Higher scores indicate higher quality and lower risk of bias. Studies with scores <7 were considered of low quality. Low-quality studies were not included in the meta-analysis. Two outcomes were of interest in the meta-analysis: the 5-year LR rate and the 5-year OS rate. The 5-year LR rate was defined as the percentage of patients who developed tumour recurrence at the primary tumour site within 5 years of surgical treatment, and the percentage of patients who survived 5 years after surgical treatment was defined as the 5-year OS rate.

Funnel plots were computed to assess the presence of reporting biases. Tests of heterogeneity were performed with the inconsistency index (I^2). The I^2 cut-off values of

<30%, 30-59%, 60-75% and >75% were used to indicate low, moderate, substantial and considerable heterogeneity respectively [5, 6]. If the heterogeneity was significant ($p < .05$), the random-effects model was emphasised in the meta-analysis to account for the random variation within studies and the variation between different studies [7]. The pooled proportions of both LR and OS were subsequently calculated with 95% confidence intervals [6, 8], and forest plots were computed with the results of all studies in chronological order. The data that support the findings of this study are available from the corresponding author upon reasonable request. Statistical analyses were performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

Results

The flowchart of the search is presented in Figure 1. The combined search in Cochrane, PubMed and EMBASE yielded 2947 articles. After removing 309 duplicates, 2638 titles and abstracts were screened, and 2557 articles were excluded. After that, 131 studies were eligible for full-text screening. Subsequently, 111 articles were excluded after the full-text screening, mainly because the study designs and the domains were incompatible. In total, 20 articles were included after the completion of the literary search.

Study Characteristics

An overview of all the included studies and their characteristics is presented in Table 1 [2, 9-27]. All 20 included studies were observational. The results of the quality assessment are presented in Table 2. All articles were of good quality. The publication years of the included articles ranged from 2008 to 2020, with reported inclusion periods ranging from 1975 to 2018. Sample sizes varied between 20 – 199 patients. The sum of all included MSCC patients is 1531 (the samples of Slieker et al. [2] and Slieker et al. [27] are the same and therefore counted once). All studies had solely included patients with squamous cell carcinoma.

Most studies presented their data on tumour staging, except for one study [25]. The

proportion of patients with advanced tumour stages (T3-4) was 731/1447 (51%), and early tumour stages (T1-2) was 716/1447 (49%).

Treatment modalities of 1185/1531 (77%) patients were specified and 346/1531 (23%) were not [12, 16, 21, 24]. Nine different treatment modalities were reported: 748/1185 (63%) patients had surgery only, 277/1185 (23%) had surgery with postoperative radiotherapy, 51/1185 (4%) had surgery with postoperative (chemo)radiotherapy, 40/1185 (3%) had preoperative intra-arterial chemotherapy with radiotherapy and surgery, 10/1185 (0.8%) had preoperative intravenous chemotherapy with radiotherapy and surgery, 3/1185 (0.3%) had preoperative radiotherapy with surgery, 27/1185 (2%) had no surgery and chemoradiotherapy, 19/1185 (2%) had no surgery and radiotherapy only, and 10/1185 (0.8%) patients had palliative treatment.

Primary radiotherapy or chemoradiotherapy was performed with curative intent in 28/46 (61%) patients [9, 10, 20], with palliative intent in 3/46 (7%) patients [9], while 3/46 (7%) patients refused surgery [20] and in 12/46 (26%) patients the reason was unspecified [9, 25, 26]. In any event, patients who had primary radiotherapy or chemoradiotherapy had significantly lower survival rates compared to patients with primary surgical treatment [9, 10, 20].

The following indications for postoperative radiotherapy in 155/277 (56%) patients were listed:

Advanced tumour stage [11, 13, 14, 19, 20, 22-24], close/positive surgical margins (after reresection) [11, 13-15, 19, 22-24], cervical lymph node involvement [13-15, 19], extracapsular spread [13-15, 20], bone/vascular/perineural invasion and non-cohesive growth [19, 20, 22]. The indication for postoperative radiotherapy was not specified for 104/259 (40%) patients [9, 10, 17, 18, 25].

The reported indications for surgery with postoperative chemoradiotherapy were similar to the indications for postoperative radiotherapy [19, 20, 23, 27]. One study specified that chemotherapy was contraindicated if the patient was >70 years or had any other

contraindications for chemotherapy [27].

One study administered preoperative intravenous chemoradiotherapy followed by surgery in 10 patients because of the advanced tumour stage and found a significant correlation between LR and preoperative chemoradiotherapy [23]. However, exact treatment regimens were not reported.

Another study used preoperative intra-arterial chemotherapy followed by surgery to treat 40 patients with T2-4 stage tumours and tumour involvement of the soft palate, pterygoid muscle, and pterygoid process [26].

Preoperative intra-arterial chemoradiotherapy was conducted with fluorouracil 100 – 300 mg daily for 21 days via cannulation of the superficial femoral artery. Furthermore, 42 patients with T1-2 tumours located anteriorly were treated with surgery only [26].

Meta-analysis: LR rates

The results of the meta-analyses are presented in Table 3, column A. The forest plot is presented in Figure 2A. The primary outcome, '5-year LR rate', was extracted or synthesised from 14/20 studies. In total, 5-year LR was reported in 230/1168 patients. The reported 5-year LR rates varied between 9.0% - 46.8%. The pooled random-effects 5-year LR rate was 19.3% (range 15.1% - 23.9%). The LR rates have been stable throughout the years, except for one outlier [10].

Meta-analysis: OS rates

The results of the meta-analyses are presented in Table 3, column B. The forest plot is shown in Figure 2B. The outcome '5-year OS rate' was extracted or synthesised from 19/20 studies.

In total, 864/1499 patients survived after 5 years. The reported 5-year OS rates varied between 25% - 82.2%. The pooled random-effects 5-year OS rate was 53.7% (range 46.3% - 61.1%). The forest plot demonstrates that the 5-year OS rate was lower in 5 studies [9-11, 15, 20].

Subgroup analysis: surgery only vs surgery with (neo)adjuvant treatment

Four studies from which the 5-year OS rate per treatment group could be extracted or synthesised [13, 17, 26, 2/27]. However, one study did not specify their treatment protocol in any way and was consequently removed from the subgroup analysis [17].

In the remaining three studies [13, 26, 2/27], all patients were primarily treated with surgery only or surgery with (neo)adjuvant treatment.

In case of advanced disease, close/positive surgical margins (after reresection), cervical lymph node involvement, extracapsular spread, unfavourable histopathological features [13, 26, 2/27] and involvement of soft palate/pterygoid process/pterygoid muscles [26], either postoperative radiotherapy [13], postoperative (chemo)radiotherapy [2/27] or preoperative intra-arterial chemoradiotherapy [26] was reported.

The results of the subgroup analysis are listed in Table 3, column C. The forest plot is displayed in Figure 2C. The pooled random-effects odds ratio (OR) on the 5-year OS rate between the two treatment groups was not statistically significant: OR .76 (95% CI .41 – 1.40).

Funnel plots and heterogeneity tests

Funnel plots of the studies are presented in Figure 3. The funnel plot of the LR meta-analysis is symmetric, with one outlier [10]. Heterogeneity was substantial (I^2-index of 71.97%, $p \leq .0001$), but if the outlier [10] was removed from the analysis, heterogeneity was not significant (p=.20).

The funnel plot of the OS meta-analysis is asymmetrical. Heterogeneity was considerable (resp. I^2-indexes of 88.2%, $p \leq .0001$).

The funnel plot of the subgroup analysis of patients treated with surgery (with or without (neo)adjuvant treatment) was symmetrical. Heterogeneity was not significant (p=.29).

Risk factors - LR

LR was significantly correlated with four risk factors (Table 4).

Positive surgical margins were significantly associated with LR in one study [12]. Patients with positive surgical margins were treated with adjuvant radiotherapy in this specific study [12]. However, two other studies had different treatment protocols. They found no statistical correlation with positive surgical margins [19, 27]: either the patients with positive surgical margins were treated with reresection if possible, and adjuvant (chemo)radiotherapy [27], or the patients were treated with adjuvant (chemo)radiotherapy [19].

Similarly, perineural invasion was significantly associated with LR in one study (p=.0423) [19], but this was not corroborated in another study (p=.599) [27]. The same was found for vascular invasion [19, 27]. Again, both studies had different treatment protocols. One applied adjuvant (chemo)radiotherapy [19, 27], but the other study also performed reresection in case both adverse tumour characteristics and positive surgical margins were present [27].

In addition, tumour location was correlated with LR in one study [21] but not in another study [23]. Both studies defined tumour location differently, either hard palate/maxillary alveolus [21] or molar and retromolar area [23].

Risk factors – OS

Various factors were correlated with OS (Table 4). Age [2, 20], advanced tumour stage (T3-4) [10, 17, 22, 24, 25] and positive surgical margins [2, 11-13, 17, 20, 25] were all correlated with decreased OS rates in multiple studies.

In addition, three histopathological tumour characteristics were correlated with decreased OS rates: large tumour volume [23], ulcerative tumour [23] and non-cohesive tumour growth [2]. However, these histopathological risk factors have not been verified in other studies.

Furthermore, posterior tumour location, defined as tumour involvement of the soft palate, infratemporal fossa, pterygoid muscles and pterygoid process, was correlated with decreased OS rates in multiple studies [10, 13, 26]. Moreover, tumour involvement of the nasal fossa, maxillary sinus and orbital floor was also correlated with decreased OS rates [20]. One study demonstrated that significant postoperative midfacial defects are also associated with reduced OS rates [24].

Five studies reported that cervical lymph node involvement was correlated with decreased OS rates [2, 17, 20-22]. On the other hand, three studies found no significant correlation between cervical lymph node involvement and survival [13, 25, 26]:

In the first study, there were 46/78 (59%) patients with T1-2 tumours, and additionally, all patients with T3-4 tumours were deemed at high risk for regional failure and were therefore treated with neck dissections [13].

In the second study, 71/77 patients had a primary surgical resection, and a large proportion (59/71) of these patients had neck dissections, of which 22/59 were elective (12 T1, 10 T2) [25].

The third study used a standardised treatment protocol for late-stage T2 and T3-4 tumours, consisting of maxillary resection with neck dissection, neo-adjuvant intra-arterial chemotherapy, and cervical lymph node involvement adjuvant radiotherapy of the neck. Although in the univariate analysis, cervical lymph node involvement was significantly correlated with decreased OS rates (p=.015), cervical lymph node involvement was not significant in multivariate analysis (p=.076) [26].

Two studies specifically investigated elective neck dissection as a potential prognostic factor [16, 18]:

One study reported that elective neck dissection had significant survival benefits for patients with T2-T4 tumours (p=.048) [16]. The other study said that elective neck dissection was significantly correlated with lower regional recurrence rates (p=.031) and improved overall survival rates (p=.043).

Furthermore, one study noted that tumour recurrence was significantly correlated with lower rates of OS (p<.0005), although no significant difference between local or regional recurrence could be calculated (p=.778) [12].

The significant correlation between tumour recurrence and OS rate was corroborated in another study. However, this study analysed either LR (p<.01) separately or LR grouped with regional recurrence (p=.001) [17]. Moreover, two additional studies reported that local

recurrence not surgically salvageable or requiring extensive salvage surgery was significantly correlated with decreased rates of OS [10, 27].

Lastly, patients with distant metastasis had significantly decreased OS rates (p=.04) [25].

Discussion

The first objective of this study was to analyse the 5-year LR and OS rates of MSCC. The pooled 5-year LR rate was 19.3%. None of the reported 5-year LR rates was significantly different, except for one study [10]. The high LR rate in this study [10] might be partially explained by the large proportion of patients (30%) who had primary treatment with concurrent chemoradiotherapy. Also, a large proportion of their patients had positive/close margins (36%), which were subsequently treated with postoperative radiotherapy [10], which in turn is correlated with a higher risk of LR [12]. Treatment of positive/close margins by reresection and postoperative (chemo)radiotherapy might decrease the risk of LR because no statistical correlation with LR was found for these treatment protocols [19, 27].

The pooled 5-year OS rate was 53.7%. In most studies, the 5-year OS rates varied between 44% - 92%, except for 5 studies whose 5-year OS rates varied between 25% - 34.2% [9, 10, 11, 15, 20]. Two factors might explain the lower OS rates in these studies: a substantial proportion of cases with (chemo)radiotherapy as primary treatment [9, 10, 20] and a large proportion of cases with advanced tumour stages [10, 11, 15, 20].

Furthermore, elective neck dissection was also associated with improved 5-year OS rates [16, 18]. A recently published meta-analysis corroborates the beneficial effect of elective neck dissection on survival in MSCC patients [28].

What is more, the subgroup analysis of surgery vs surgery with (neo)adjuvant (chemo)radiotherapy resulted in non-significant OR .76 (.41 – 1.40) for patients in the (neo)adjuvant treatment group. These results mean that current (neo)adjuvant treatment protocols for adverse tumour characteristics successfully improve OS rates for MSCC patients. Curiously, the (neo)adjuvant treatment regimens were slightly different in all three

studies of the subgroup analysis, but none were significantly better or worse [13, 26, 2/27]. Therefore, more research is warranted to ascertain which (neo)adjuvant treatment protocol is optimal for MSCC.

The second objective was to identify risk factors associated with LR and OS of MSCC. There were only 5 studies that conducted risk factor analyses with regards to LR. The results were contradictory for all identified risk factors [12, 19, 21, 27]. Therefore, more research into risk factors for LR of MSCC is necessary to aid the physician in clinical decision-making. After all, local recurrence not surgically salvageable or requiring extensive salvage surgery was associated with decreased OS rates [2, 10].

Various OS-related risk factors identified for MSCC are similar to those previously identified for oral cancer in general (e.g., age, advanced tumour stage, surgical margins, cervical lymph node involvement, distant metastasis) [29].

One risk factor specific to MSCC was associated with lower rates of OS in multiple studies: posterior tumour extension defined as an extension into the soft palate, infratemporal fossa, pterygoid muscles and/or pterygoid process [10, 13, 26]. Additionally, tumour involvement of the nasal fossa, maxillary sinus and orbit was also associated with decreased OS rate in one study [20]. Interestingly, tumour locations defined as dorsal to the premolar [17], dorsal to the first molar [20] and the (retro)molar area [23] were not significantly correlated with OS. Although not oral cancer, similar correlations between tumour extension and overall survival were reported for sinonasal squamous cell carcinoma [30-32].

Although the quality assessment score of most studies was good, all studies were at risk of information bias because of their observational nature. The risk of information bias is most likely the result of the low incidence of MSCC. Most single-centre studies had small sample sizes, which they accumulated over many years. Just one of the included single-centre studies had a sample size larger than 150 cases [18]. This study had an inclusion period of 26 years, which means that patient volumes in hospitals are meagre. High patient volumes in specialised cancer centres are associated with better survival outcomes [33-35]. And so, for

MSCC patients, higher patient volumes might benefit treatment outcomes and allow for higher-level research [36, 37].

One way to increase patient volumes might be to designate specific head and neck cancer centres as dedicated maxillary cancer centres with a dedicated maxillary cancer team.

Conclusion

Local recurrence rates were comparable across studies. More research into the risk-reduction of local recurrence is warranted. Surgical resection of the primary tumour with elective neck dissection improves survival. Postoperative radiotherapy, postoperative chemoradiotherapy and preoperative intra-arterial chemoradiotherapy all improve survival when adverse tumour characteristics are present. Finally, tumour extension into the soft palate, infratemporal fossa, pterygoid muscles and the pterygoid process is associated with lower survival in MSCC.

Credit author statement

F.J.B. Slieker: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing ς original draft, project administration

D.A.A. Rombout: conceptualization, methodology, investigation, writing ς review & editing

R. de Bree: conceptualization, resources, writing - review & editing, supervision

E.M. Van Cann: conceptualization, validation, resources, writing ς review & editing, supervision

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Figure 1: flowchart of the literary search

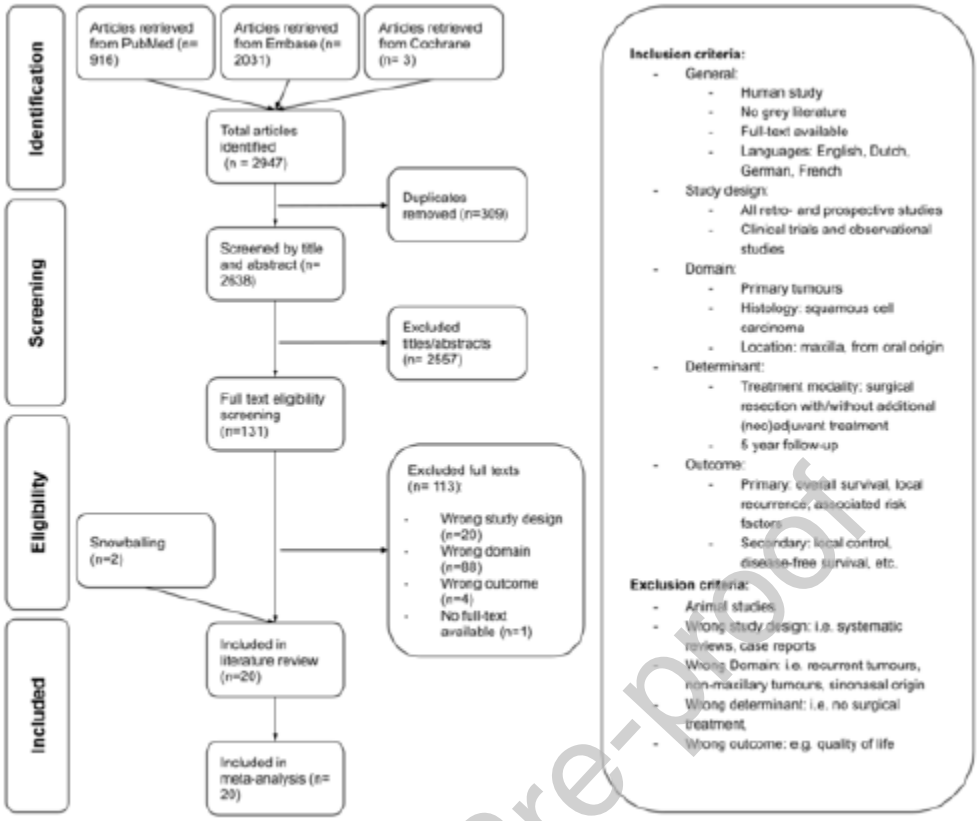
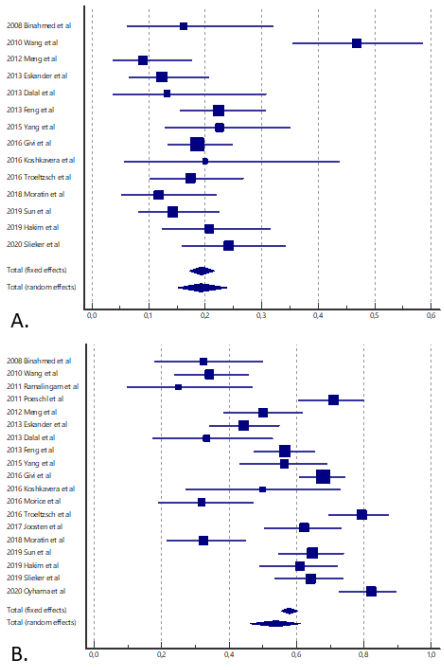


Figure 2: forest plots of the meta-analyses:
A. Forest plot of 5-year LR rates: studies are listed on the y-axis. The x-axis is the LR rate (x100%).
B. Forest plot of the 5-year OS rates: studies are listed on the y-axis. The x-axis is the OS rate (x100%).
C. {dzōƎ№2dzLJ l·yl·fèǎlǎ 2Ŧ ǘ№Ŝl·ǘYŜyǘ Ǝ№2dzLJǎ ΨǎdzN№ƎŜ№è 2yfèΩ Øǎ ΨǎdzN№ƎŜ№è Ь óyŜ2úl·Řƨdzǿl·yǘ ǘ№Ŝl·ǘYŜyǘY
studies are listed on the y-axis.
On the x-axis are the odds ratios (<1 favours the surgery group, >1 favours the (neo)adjuvant group)



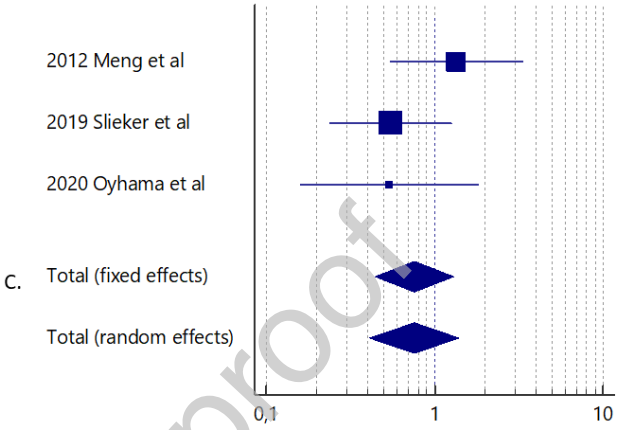
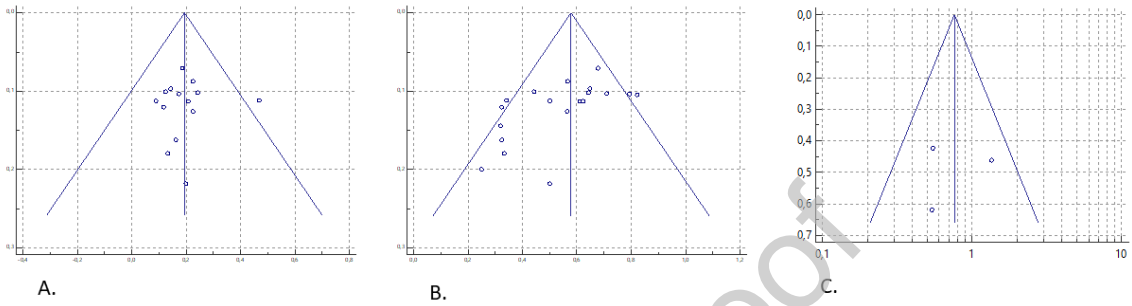


Figure 3: funnel plots:
A. Funnel plot of the meta-analysis on the 5-year LR rate
B. Funnel plot of the meta-analysis on the 5-year OS rate
C. Funnel plot of the subgroup analysis of treatment groups



A. B. C.

Table 1: overview of included studies.

Legend: RT = radiotherapy, Ch = chemotherapy, ChRT = chemoradiotherapy, (Ch)RT = chemotherapy and/or radiotherapy, intra-art. = intra-arterial

First author	Publication year	Inclusion period	Sample size (n=)	Histological tumour type	T-stage of SCC-tumours	Treatment modalities of SCC tumours	5yr local recurrence rates	5yr overall survival outcomes
Binahmed et al [9]	2008	1975 - 2004	37	Only SCC	T1 = 6 T2 = 9 T3 = 4 T4 = 15 Lost = 3	Surgery only = 14 Surgery with postop. RT = 9 RT only = 5 ChRT = 1 Palliative treatment = 8	6/37 (16%)	12/37 (33%)
Wang et al [10]	2010	1997 - 2007	79	Only SCC	T1 = 4 T2 = 28 T3 = 24 T4 = 23	Surgery only = 37 Surgery with postop. RT = 18 (Ch)RT = 24	37/79 (47%)	27/79 (34%)
Ramalingam et al [11]	2011	1999 - 2009	24	Only SCC	T1 = 3 T3 = 9 T4 = 12	Surgery only = 9 Surgery with postop. RT = 15	N/A	6/24 (25%)
Poeschl et al [12]	2011	1992 - 2007	93	Only SCC	T1 = 9 T2 = 14 T3 = 9 T4 = 61	86 Patients had surgery and some had postop. RT, but it is not specified exactly how many had postop. RT. (Ch)RT = 7	N/A	66/93 (71%)
Meng et al [13]	2012	2003 - 2009	78	Only SCC	T1 = 21 T2 = 25 T3 = 3 T4 = 29	Surgery only = 46 Surgery with postop. RT = 32	7/78 (9%)	39/78 (50%)
Eskander et al [14]	2013	1994 - 2008	97	Only SCC	T1 = 15 T2 = 28 T3 = 5 T4 = 49	Surgery only = 67 Surgery with postop. RT = 30	12/97 (12%)	43/97 (44%)
Dalal et al [15]	2013	2000 - 2010	30	Only SCC	T1 = 1 T2 = 2 T3 = 2 T4 = 25	Surgery only = 15 Surgery with postop. RT = 15	4/30 (13%)	10/30 (66.7%)
Feng et al [16]	2013	1998 - 2011	129	Only SCC	T1 = 27 T2 = 39 T3 = 21 T4 = 42	All patients had surgery, some had postop. RT, but not specified exactly.	29/129 (22%)	73/129 (56.5%)
Yang et al [17]	2015	2003 - 2012	62	Only SCC	T1 = 8 T2 = 20 T3 = 19 T4 = 15	Surgery only = 49 Surgery with postop. RT= 13	14/62 (23%)	35/62 (57%)
Givi et al [18]	2016	1985 - 2011	199	Only SCC	T1 = 76 T2 = 53 T3 = 6 T4 = 64	Surgery only = 155 Surgery with postop. RT = 44	37/199 (19%)	135/199 (68%)
Koshkavera et al [19]	2016	Not specified	20	Only SCC	T1 = 3 T2 = 9 T3 = 6 T4 = 2	Surgery only = 8 Surgery with postop. RT = 7 Surgery with postop. ChRT = 5	4/20 (20%)	10/20 (50%)
Morice et al [20]	2016	2006 - 2013	47	Only SCC	T1 = 6 T2 = 5 T3 = 1 T4 = 35	Surgery only = 19 Surgery with postop. RT = 13 Surgery with postop. (Ch)RT = 8 RT only = 3 ChRT only = 2 Palliative treatment = 2	N/A	15/47 (32%)

Troeltzsch et al [21]	2016	2006 - 2013	92	Only SCC	Tis = 1 T1 = 26 T2 = 25 T3 = 7 T4 = 33	All patients had surgery, some had postop. RT, but not specified exactly.	16/92 (17%)	73/92 (79%)
Joosten et al [22]	2017	1990 - 2014	77	Only SCC	T1 = 21 T2 = 26 T3 =1 T4 = 29	Surgery only = 63 Surgery with postop. RT = 14	N/A	48/77 (62%)
Moratin et al [23]	2018	1999 - 2016	68	Only SCC	T1 = 24 T2 = 18 T3 = 5 T4 = 18 Lost* = 3	Surgery only = 23 Surgery with postop. RT = 35 Preop. (Ch)RT with Surgery = 10	8/68 (12%)	43/68 (63%)
Sun et al [24]	2019	2000 - 2012	137 (105*)	Only SCC	T1 = 20 T2 = 54 T3 = 23 T4 = 40	Surgery only = 93 Surgery with postop. RT = 12 *Excluded from further analysis = 32	15/105 (14%)	68/105 (65%)
Hakim et al [25]	2019	1991 - 2018	77	Only SCC	Not specified	Surgery only = 51 Surgery with postop. RT = 20 RT only = 6	16/77 (21%)	47/77 (61%)
Slieker et al [2]	2019	2000 - 2015	95	Only SCC	T1-2 = 44 T3-4 = 51	Surgery only = 57 Surgery with postop. (Ch)RT = 38	N/A	61/95 (64%)
Oyhama et al [26]	2020	1999 - 2014	90	Only SCC	T1 = 15 T2 = 32 T3 = 13 T4 = 30	Surgery only = 42 Preop. RT with surgery = 3 Preop. intra-art (Ch)RT with surgery = 40 RT only = 5	N/A	74/90 (82%)
Slieker et al [27]	2020	2000 - 2015	95	Only SCC	T1-2 = 44 T3-4 = 51	Surgery only = 57 Surgery with postop. (Ch)RT = 38	23/95 (24%)	N/A

Table 2: Newcastle-Ottawa quality assessment results.
In every category, each study could score either no points (/), or one point (*) and in some cases two points (**). The letters between parentheses correspond with the specific answers in the Newcastle-Ottawa Quality Assessment scale. For instance, in the column Selection - ascertainment of exposure, the (a) corresponds with 'secure record (e.g. surgical records)'. See Newcastle-Ottawa Quality Assessment Scale for more details.

Study (first author)	Selection - representativeness of the cases	Selection - selection of the non-exposed cohort	Selection - ascertainment of exposure	Selection - outcome not present at start study	Comparability of cases and controls based on design or analysis	Outcome - Assessment of outcome	Outcome - follow-up long enough for outcome?	Outcome - Adequacy of follow-up of cohorts	Total score (max. 9)
Binahmed	* (a)	* (a)	* (a)	*	*	* (b)	*	/ (d)	7
Dalal	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Eskander	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Feng	* (a)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Givi	* (a)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Hakim	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Joosten	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Koshkaver a	* (a)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Meng	* (b)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Moratin	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Morice	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Oyhama	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Poeschl	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Ramalinga m	* (b)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Slieker	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Slieker	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Sun	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Troeltzsch	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Wang	* (b)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Yang	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8

Table 3: pooled results of the meta-analyses on LR (column A), OS (column B) and the subgroup analysis (column C)

A. 5-year local recurrence				B. 5-year overall survival				C. Subgroup analysis: 5-year overall survival per treatment group				
Study (first author)	Total LR / SCC patients	LR rate (%)	95% CI	Study (first author)	Total alive/ SCC patients	OS rate (%)	95% CI	Study (first author)	Surgery + (neo)adjuvant treatment (total alive/total patients)	Surgery only (total alive/total patients)	Odds ratio	95% CI
Binahmed et al	8/37	16.2%	6.2% - 32.0%	Binahmed et al	12/37	32.4%	18.0% - 49.8%	Meng et al	17/32	21/46	1.35	.55 ç 3.34
Wang et al	37/79	46.8%	35.5% - 58.4%	Wang et al	27/79	34.2%	23.9% - 45.7%	Slieker et al	17/38	34/57	.55	.24 ç 1.26
Meng et al	7/78	9.0%	3.7% - 17.6%	Ramalingam et al	6/24	25.0%	9.8% - 46.7%	Oyhama et al	32/40	37/42	.54	.16 ç 1.82
Eskander et al	12/97	12.4%	6.6% - 20.6%	Poeschl et al	66/93	71.0%	60.6% - 79.9%					
Dalal et al	4/30	13.3%	3.8% - 30.7%	Meng et al	39/78	50.0%	38.5% - 61.5%					
Feng et al	29/129	22.5%	15.6% - 30.7%	Eskander et al	43/97	44.3%	34.2% - 54.8%					
Yang et al	14/62	22.6%	12.9% - 35.0%	Dalal et al	10/30	33.3%	17.3% - 52.8%					
Givi et al	37/199	18.6%	13.4% - 24.7%	Feng et al	73/129	56.6%	47.6% - 65.3%					
Koshkavera et al	4/20	20.0%	5.7% - 43.7%	Yang et al	35/62	56.5%	43.3% - 69.0%					
Troeltzsch et al	16/92	17.4%	10.3% - 26.7%	Givi et al	135/199	67.8%	60.9% - 74.3%					
Moratin et al	8/68	11.8%	5.2% - 21.9%	Koshkavera et al	10/20	50.0%	27.2% - 72.8%					
Sun et al	15/105	14.3%	8.2% - 22.5%	Morice et al	15/47	31.9%	19.1% - 47.1%					
Hakim et al	16/77	20.8%	12.4% - 31.5%	Troeltzsch et al	73/92	79.3%	69.6% - 87.1%					
Slieker et al	23/95	24.2%	16.0% - 34.1%	Joosten et al	48/77	62.3%	50.6% - 73.1%					
				Moratin et al	22/68	32.4%	21.5% - 44.8%					
				Sun et al	68/105	64.8%	54.8% - 73.8%					
				Hakim et al	47/77	61.0%	49.2% - 72.0%					
				Slieker et al	61/95	64.2%	53.7% - 73.8%					
				Oyhama et al	74/90	82.2%	72.7% - 89.5%					
Total (fixed effects)	230/1168	19.4%	17.1% - 21.7%	Total (fixed effects)	864/1499	57.8%	55.3% - 60.3%	Total (fixed effects)	66/110	92/145	.76	.44 ç 1.30
Total (random effects)		19.3%	15.1% - 23.9%	Total (random effects)		53.7%	46.3% - 61.1%	Total (random effects)			.76	.41 ç 1.40

Table 4: risk factors associated of MSCC.
Risk factors associated with either local recurrence or mortality are listed per study with the accompanying p-values. Significant p-values are bold.
Legend: N/A = not applicable.

	Binahmed	Wang	Ramalingam	Poeschl	Meng	Eskander	Dalal	Feng	Yang	Givi	Koshkavera	Morice	Troeltzsch	Joosten	Moratin	Sun	Hakim	Slieker	Oyhama	Slieker
Risk factors associated with local recurrence																				
Surgical margins	N/A	N/A	N/A	p<.0005	N/A	N/A	N/A	N/A	N/A	N/A	p=.7733	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.414
Perineural invasion	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.0423	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.599
Tumour location	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p≤.05	N/A	p>.05	N/A	N/A	N/A	N/A	N/A
Vascular invasion	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.8177	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.003
Risk factors associated with overall survival																				
Age	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p<.05	N/A	N/A	N/A	N/A	p=.20	p=.007	p=.785	N/A
Advanced T-stage (T3-4)	p=.056	p=.0001	N/A	p=.131	p=.73	N/A	N/A	N/A	p<.036	N/A	N/A	N/A	N/A	p=.007	p>.05	P<.001	p<.02	N/A	p=.607	N/A
Large tumour volume	N/A	p=.001	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ulcerative tumour	N/A	p=.0001	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Non-cohesive growth	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p<.015	N/A	N/A
Involvement of nasal fossa, maxillary sinus or orbital floor	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p<.05	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Posterior tumour location	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.841	N/A	N/A	p=.46	N/A	N/A	p>.05	N/A	N/A	N/A	p=.031	N/A
Involvement of infratemporal fossa and/or soft palate	N/A	p=.017	N/A	N/A	p=.001	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cervical lymph node involvement	N/A	N/A	N/A	N/A	p>.57	N/A	N/A	N/A	p=.018	N/A	N/A	p<.005	p<.03	p=.006	N/A	N/A	p=.39	p<.044	p=.076	N/A
Elective neck dissection	N/A	N/A	N/A	N/A	N/A	N/A	N/A	P=.048	N/A	p=.043	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Distant metastasis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.04	N/A	N/A	N/A
Surgical margins	p>.05	p=.123	p=.007	p<.0001	p=.001	N/A	N/A	N/A	p=.019	N/A	N/A	p<.05	N/A	N/A	N/A	N/A	p=.02	p<.053	N/A	N/A
Large midfacial defects (Brown class IIc/IId/III)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p<.01	N/A	N/A	N/A	N/A
Tumour recurrence (local and/or regional)	N/A	N/A	N/A	p<.0001	N/A	N/A	N/A	N/A	p=.002	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Local recurrence not surgically salvageable or requiring extensive salvage surgery	N/A	p=.001	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.009