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# EVALUATE THE OVERALL SURVIVAL RATE OF SALVAGE SURGERY IN RECURRENT HEAD AND NECK SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

**Ata Garajei[1], Mehran Daneshmand[2*], Ali Aghaei Meybodi[3], Hamed Mahmoudi[4]**

[1]Associate Professor, Department of Oral and Maxillofacial Surgery, School of Dentistry, and Department of Head and Neck Surgical Oncology and Reconstructive Surgery, The Cancer Institute, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

[2]DMD, OMFS, Fellow in oral/Head and Neck Oncology Fellowship Program, Department of Oral and Maxillofacial Surgery, School of Dentistry, and Department of Head and Neck Surgical Oncology and Reconstructive Surgery, The Cancer Institute, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

[3]DMD, OMFS Fellow in oral/Head and Neck Oncology Fellowship Program, Department of Oral and Maxillofacial Surgery, School of Dentistry, and Department of Head and Neck Surgical Oncology and Reconstructive Surgery, The Cancer Institute, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

[4]Resident of Oral and Maxillofacial Surgery, School of Dentistry, Tehran University of Medical Science, Tehran, Iran

***Corresponding Author**: Mehran Daneshmand, **Email:** Mehrandaneshmand66@gmail.com

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**Abstract**

**Background and aim:** The purpose of this study was evaluate the overall survival rate of salvage surgery in recurrent head and neck squamous cell carcinoma.

**Method:** Databases of PubMed, Scopus, Web of Science, EBSCO, ISI Web of knowledge and Embase were searched for systematic literature until March 2023. Data analysis was performed using STATA/MP V17 software. 95% confidence interval for effect size with fixed effect model and Inverse-variance method were calculated.

**Result:** In the initial review, duplicate studies were eliminated and abstracts of 1340 studies were reviewed, the full text of 103 studies was reviewed by two authors, finally, six studies were selected. Hazard ratio was 0.23 (HR, 0.23 95% CI 0.06, 0.41; $p<0.05$). Overall survival after five years was 0.40 (OS, 0.40 95% CI 0.18, 0.63; $p<0.05$).

**Conclusion:** Based on the current meta-analysis, the survival benefits for patients with HNSCC who underwent salvage surgery were more than patients receiving other treatment methods such as radiation therapy and chemotherapy.

**Key words:** salvage surgery, chemotherapy, head and neck squamous cell carcinoma, head and neck carcinoma, Overall survival

## Introduction

Reports indicate that about three percent of all cancers in the world are head and neck cancer; The death rate is 330 thousand deaths per year and the rate of infection is 650 thousand people annually(1). Head and neck squamous cell carcinoma (HNSCC) accounts for more than 90% of head and neck cancers(2). HNSCC is mostly observed in the oropharynx, oral cavity and larynx. After definitive treatment of HNSCC, evidence shows that recurrence occurs in 30% of cases and depends on several clinical and pathological factors, including surgical margin and nodal status, perineurial invasion, lymphovascular invasion, and disease stage(3). Recurrence is the main cause of death in patients with HNSCC, and these patients have a lower chance of recovery(4). Generally, the treatment includes surgery with adjuvant treatment or chemotherapy(5). In metastatic patients, palliative treatment is used, which includes chemotherapy and immunotherapy alone or in combination(6). Studies have shown that in patients for whom salvage surgery is used, the survival rate is 5 years; Of course, it depends on the location and stage of HNSCC(7). A study has shown that salvage therapy for recurrent oropharyngeal cancer significantly improved survival outcomes over a surgical approach; The 5-year survival rate in this study was reported to be 26% for surgery and 16% for radiation therapy(7). Considering the above, it is not clear whether surgery is a better treatment option for HNSCC or using non-surgical options. In previous studies, the results of salvage surgery have been investigated in different groups of patients(6, 7). The present study was conducted with the aim of evaluating the overall survival rate of salvage surgery in recurrent HNSCC.

## Method

### *Search strategy*

In the current study, all international databases, PubMed, Scopus, Science Direct, ISI and Embase were examined, searching until March 2023 based on keywords related to the objectives of the study. The current study was conducted based on the PRISMA 2020 checklist(8).

### *Keywords and the MeSH terms:*

(((((("Head and Neck Neoplasms"[Mesh]) AND ( "Head and Neck Neoplasms/mortality"[Mesh] OR "Head and Neck Neoplasms/prevention and control"[Mesh] OR "Head and Neck Neoplasms/radiotherapy"[Mesh] OR "Head and Neck Neoplasms/surgery"[Mesh] OR "Head and Neck Neoplasms/therapy"[Mesh] )) OR "Squamous Cell Carcinoma of Head and Neck"[Mesh]) OR ( "Squamous Cell Carcinoma of Head and Neck/diet therapy"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/drug therapy"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/mortality"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/prevention and control"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/radiotherapy"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/surgery"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/therapy"[Mesh] )) AND "Bloodless Medical and Surgical Procedures"[Mesh]) AND "Survival Rate"[Mesh].

### *Eligibility criteria*

**Inclusion criteria:** Only articles published in English, , prospective and retrospective studies and randomized clinical trials, no limit on sample size, and complete data.

**Exclusion criteria:** studies without control group, case-control studies, cross-sectional studies, case series, case reports, in-vitro and reviews papers; animal studies and studies without full text access.

the Google Scholar search engine was used to search for articles and the PICO strategy to answer the research questions (Table 1).

**Table1. PICO strategy.**

| PECO strategy | Description |
|---|---|
| **P** | Population: Head and neck squamous cell carcinoma |
| **I** | Intervention: salvage surgery |
| **C** | Comparison: nonsurgical management |
| **O** | Outcome: survival rate |

***Data collection***

Two reviewers independently screened each record and each report was retrieved. All studies were selected based on inclusion and exclusion criteria. The specifications of samples of the selected studies were extracted based on a checklist that included 9 items, the items were: author's name, publication year, study design, sample size, mean of age, Follow-up, groups.

***Risk assessment***

Newcastle-Ottawa Scale (NOS) (9) used to assessed quality of the cohort and cross-sectional studies, case-control and case series studies, This scale measures three dimensions (selection, comparability of cohorts and outcome) with a total of 9 items. In the analysis, any studies with NOS scores of 1-3, 4-6 and 7-9 were defined as low, medium and high quality, respectively.

the quality of randomized control clinical trial studies was evaluated using the Cochrane Collaboration's tool(10). The scores of this tool are between 0 and 6, and higher score showed higher quality of study; the scoring of each item is 1 for low risk and 0 for high and unclear risk.

***Data analysis***

Meta-analysis was performed using STATA/MP. V17 software. Mantel-Haenszel methods are fixed-effect meta-analysis methods using a different weighting scheme that depends on which effect measure. 95% confidence interval for hazard ratio with fixed effect model and Mantel-Haenszel method were calculated. Potential heterogeneity between studies was reported with the $I^2$ coefficient (low:50%<; moderate: 50%-75%; high:>50%).

## Result

***Study selection***

In the initial search using keywords, 428 articles were found, and all references were entered into EndNote X8 software. Among these articles, 10 articles were duplicated, 8 articles were due to Records marked as ineligible by automation tools, and 7 articles were due to other reasons were removed and finally the abstracts of 403 articles were reviewed and 249 articles that did not meet the inclusion criteria were removed at this stage. The full text of 154 articles

was fully reviewed by two blinded observers. Incomplete articles, without data, inconsistency with the objectives of the study were excluded 141 articles) and finally therteen articles were selected (Figure 1).

***Study characteristics***

six studies were selected and included in the study. A total of 3343 patients between the ages of 55 years and 62.2 years were examined. Table 2 shows a summary of Data extracted.

***Risk assessment***

According NOS tool, four studies had a total score of 6/9 (moderate quality), one study had a total score of 7/9 (high quality) (Tabel 3). According Cochrane Collaboration's tool, one RCT study had low risk of bias (Table 4).

***Meta analysis***

Hazard ratio was 0.23 (HR, 0.23 95% CI 0.06, 0.41; $p<0.05$) with low heterogeneity ($I^2=0\%$; P =0.91) (Fig.2). there was significant difference between salvage surgery and control group (p=0.01).

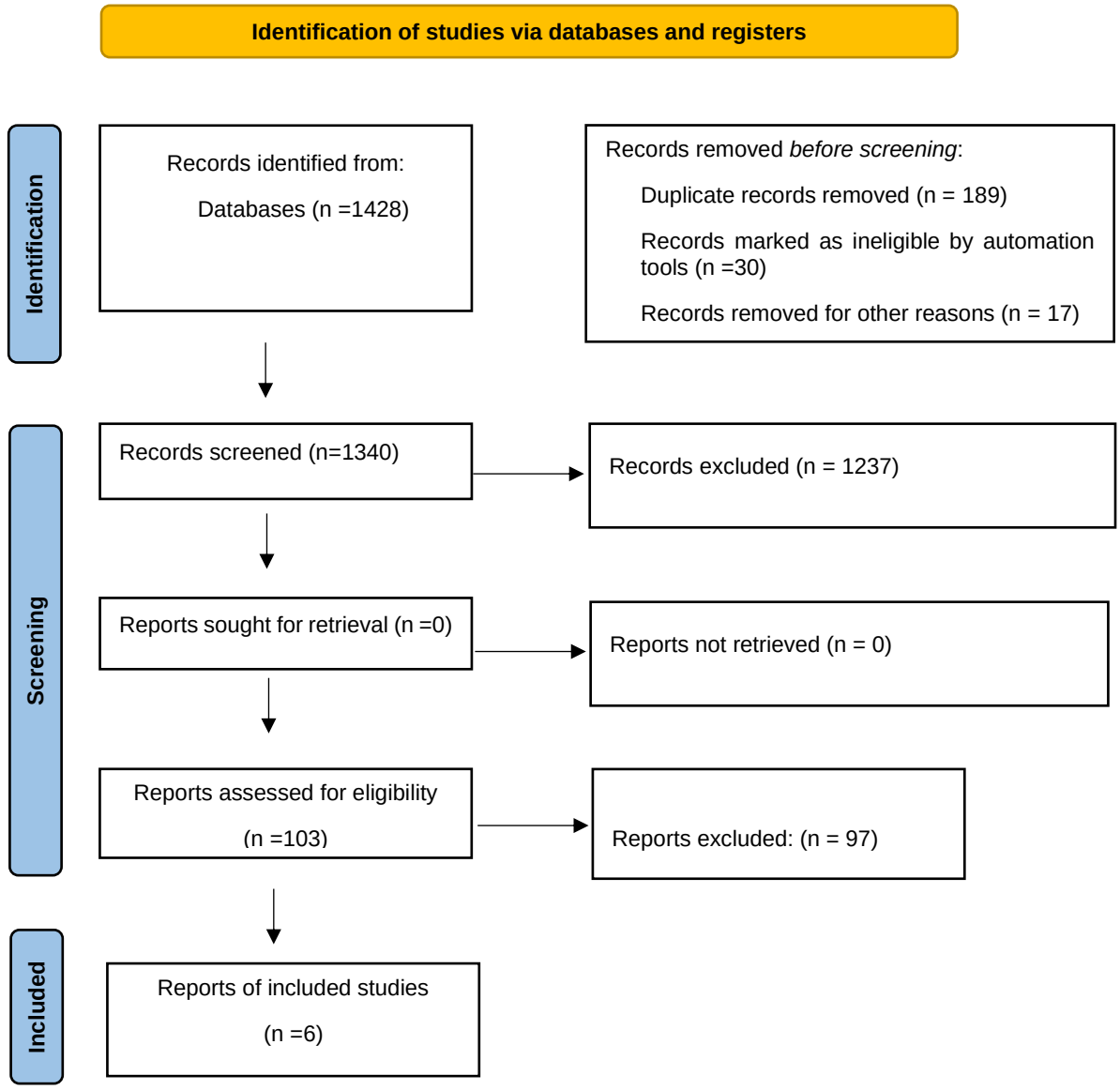


**Figure 1. PRISMA 2020 Checklist**

**Table 2. Data extracted from studies selected for systematic review and meta-analysis.**

| Study. Years | Study design | Number of patients | groups | | Mean of age | Type of control treatment | Follow-up (months) |
|---|---|---|---|---|---|---|---|
| | | | salvage surgery | control | | | |
| Patil et al., 2020 (11) | RCT | 113 | 91 | 22 | 55 | chemotherapy, supportive care; | 28 |
| de Ridder et al., 2020 (12) | retrospective cohort | 198 | 104 | 94 | NR | radiotherapy, Chemoradiotherapy, supportive care; | 10 |
| Chu et al., 2018 (13) | retrospective cohort | 46 | 35 | 11 | 50.43 | chemotherapy | 50 |
| Chang et al., 2017 (13) | retrospective cohort | 2927 | 2247 | 680 | NR | chemotherapy | 39 |
| Tam et al., 2017 (14) | retrospective cohort | 59 | 39 | 20 | 62.2 | radiotherapy, chemotherapy, Chemoradiotherapy, supportive care; | 99 |
| Guo et al., 2015 (15) | retrospective cohort | 94 | 61 | 33 | 48.1 | chemotherapy, RT, Chemoradiotherapy | 15 |

**Table3. Risk of bias assessment (NOS tool)**

| Study. Years | **Selection (5 score)** | | | | **Comparability (2 score)** | **Outcome (2 score)** | | Total score |
|---|---|---|---|---|---|---|---|---|
| | representative sample | Sample size | Non respondents | Ascertainment of the exposure | Based on design and analysis | Assessment of outcome | Statistical test | |
| de Ridder et al., 2020 (12) | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 7 |
| Chu et al., 2018 (13) | 1 | 1 | 1 | 0 | 2 | 0 | 1 | 6 |
| Chang et al., 2017 (13) | 1 | 1 | 1 | 0 | 2 | 0 | 1 | 6 |
| Tam et al., 2017 (14) | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Guo et al., 2015 (15) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |

**Table 4. Risk of bias assessment (Cochrane Collaboration's tool)**

| study | Random sequence generation | allocation concealment | blinding of participants and personnel | blinding of outcome assessment | incomplete outcome data | selective reporting | Total score |
|---|---|---|---|---|---|---|---|
| Patil et al., 2020 (11) | + | + | ? | + | + | + | 5 |

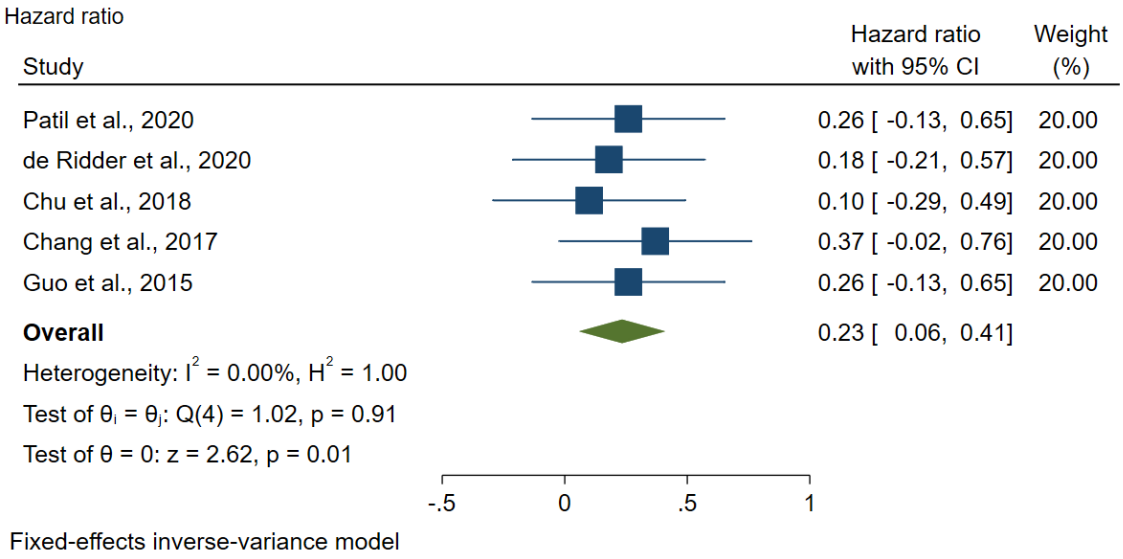


**Figure 2. forest plot showed hazard ratios**

Overall survival after two years was 0.59 (OS, 0.59 95% CI 0.36, 0.81; p<0.05) with low heterogeneity ($I^2$=0%; P =0.64) (Fig.3).

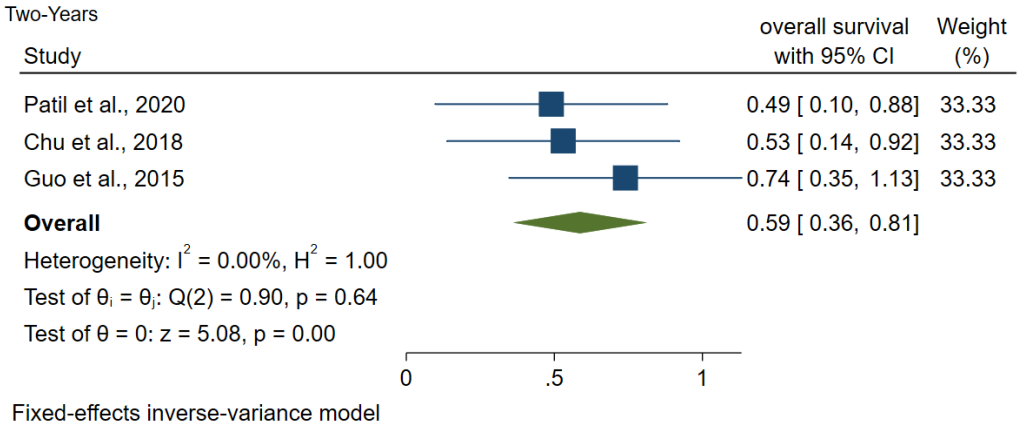


**Figure 3. forest plot showed overall survival after two years**

Overall survival after three years was 0.61 (OS, 0.61 95% CI 0.22, 1.00; p<0.05) (Fig.4).

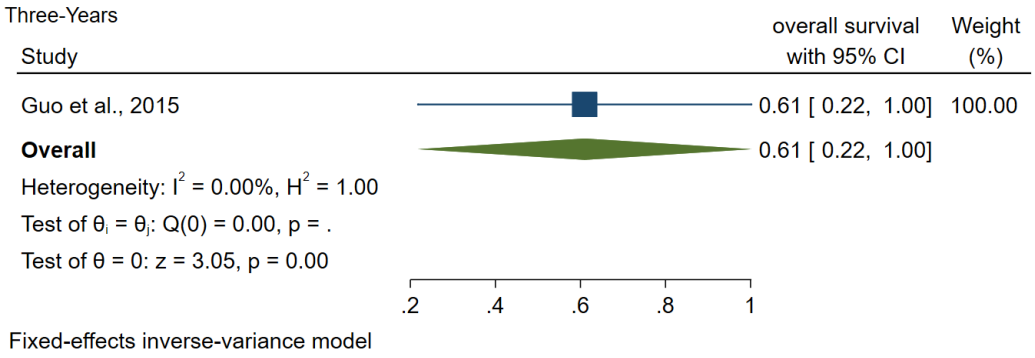


**Figure 4. forest plot showed overall survival after three years**

Overall survival after five years was 0.40 (OS, 0.40 95% CI 0.18, 0.63; p<0.05) with low heterogeneity ($I^2$=0%; P =0.87) (Fig.5).

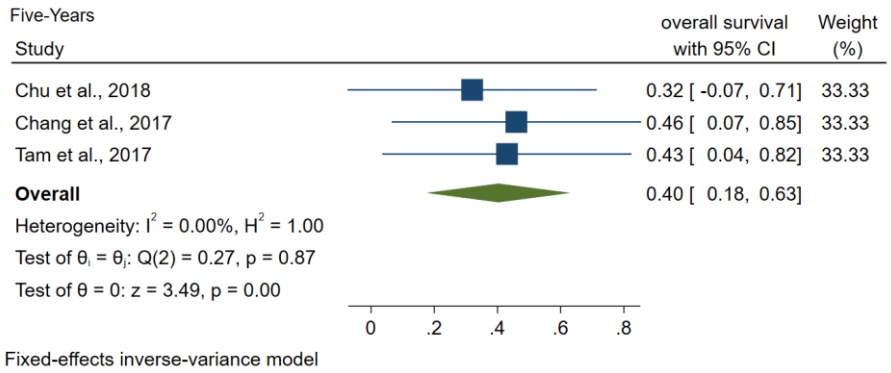


**Figure 5. forest plot showed overall survival after five years**

## Discussion

In the present study, salvage surgery was compared with other treatment methods for the treatment of HNSCC. In the selected studies, salvage surgery was performed with different combinations of chemotherapy and supportive care. According to the present meta-analysis, the risk of death in patients receiving salvage surgery was significantly lower than in the control group. Previous studies have also shown that the survival rate in patients who chose salvage surgery was higher than in patients who received other treatment methods(6, 7, 16). The heterogeneity between the studies was low. Overall survival was low in both surgery and non-surgery groups, but salvage surgery patients had a higher overall survival compared to other treatment groups across all studies at variable follow-up durations. Consistent with the results of the present study, previous meta-analyses have shown that salvage surgery is unable to determine whether salvage surgery has a survival advantage compared to non-surgical management for patients presenting with recurrence(6, 7, 17). Also, factors such as cancer location, stage, primary cancer treatment method, and patients' functional status can also cause heterogeneity between studies. Therefore, it is necessary to conduct more similar RCT studies to see more promising results and provide stronger evidence. Future studies need to investigate and compare salvage surgery and salvage re-irradiation or chemotherapy; Future studies could investigate the response rate and low side effect profile of immunotherapy; There is also a need for studies to investigate the quality of life of patients after salvage surgery.

## Conclusion

According to the present meta-analysis, the survival benefits for patients with HNSCC who underwent salvage surgery were more than patients receiving other treatment methods such as radiation therapy and chemotherapy. Also, the mortality rate in salvage surgery group patients was lower than other treatment groups. However, the heterogeneity between subjects was high and the results of the present study should be interpreted with caution. More studies are needed to evaluate the results of survival, performance and quality of life of patients after salvage surgery. It is also suggested to compare the salvage surgery method with modern treatment methods.

## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.

2. Glode AE. Immune Checkpoint Inhibitors in Head and Neck Cancers Offer Different Treatment Approaches. Pharmacy Times Oncology Edition. 2020;2(1).
3. Tumban E. A current update on human papillomavirus-associated head and neck cancers. Viruses. 2019;11(10):922.
4. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head & neck. 2014;36(1):144-51.
5. Sticker A, Thomas S, Russell G, Waltonen J. Factors Associated with Adjuvant Treatment Delays in Patients Treated Surgically for Head and Neck Cancer. Authorea Preprints. 2022.
6. Saba NF, Mendenhall WM, Hutcheson K, Suárez C, Wolf G, Ferlito A. Salvage surgery for squamous cell carcinoma of the head and neck in the era of immunotherapy: Is it time to clarify our guidelines? Cancer. 2018;124(21):4163-4.
7. Zenga J, Gross J, Fowler S, Chen J, Vila P, Richmon JD, et al. Salvage of recurrence after surgery and adjuvant therapy: a systematic review. American Journal of Otolaryngology. 2018;39(2):223-7.
8. Tugwell P, Tovey D. PRISMA 2020. Journal of Clinical Epidemiology. 2021;134:A5-A6.
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010;25(9):603-5.
10. Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A, et al. Cochrane bias methods group; cochrane statistical methods group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ. 2011;343(7829):d5928.
11. Patil VM, Noronha V, Thiagarajan S, Joshi A, Chandrasekharan A, Talreja V, et al. Salvage surgery in head and neck cancer: Does it improve outcomes? European Journal of Surgical Oncology. 2020;46(6):1052-8.
12. de Ridder M, de Veij Mestdagh PD, Elbers JB, Navran A, Zuur CL, Smeele LE, et al. Disease course after the first recurrence of head and neck squamous cell carcinoma following (chemo) radiation. European Archives of Oto-Rhino-Laryngology. 2020;277:261-8.
13. Chang J-H, Wu C-C, Yuan KS-P, Wu AT, Wu S-Y. Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors, and treatment outcomes. Oncotarget. 2017;8(33):55600.
14. Tam S, Araslanova R, Low T-HH, Warner A, Yoo J, Fung K, et al. Estimating survival after salvage surgery for recurrent oral cavity cancer. JAMA Otolaryngology–Head & Neck Surgery. 2017;143(7):685-90.
15. Jamalpour, Z., Khodarahmi, P. A., Jamalpour, H., & Kuzhilnaya, E. (2024). Application of neuroscience and cognitive studies in psychology. *Cadernos de Educação Tecnologia e Sociedade*, *17*(1), 351-359.
16. Guo T, Qualliotine JR, Ha PK, Califano JA, Kim Y, Saunders JR, et al. Surgical salvage improves overall survival for patients with HPV-positive and HPV-negative recurrent locoregional and distant metastatic oropharyngeal cancer. Cancer. 2015;121(12):1977-84.
17. Elbers JB, Veldhuis LI, Bhairosing PA, Smeele LE, Jóźwiak K, van den Brekel MW, et al. Salvage surgery for advanced stage head and neck squamous cell carcinoma following

radiotherapy or chemoradiation. European Archives of Oto-Rhino-Laryngology. 2019;276:647-55.