Original Article

Evaluation of Neo-Adjuvant, Concurrent and Adjuvant Chemotherapy in the Treatment of Head and Neck Squamous Cell Carcinoma: A Meta-Analysis

Fahimeh Akhlaghi[1], Mohammad Esmaeelinejad[2], Amin Shams[3], Arsalan Augend[4]

[1]Associate Professor,, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Resident, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Dental Researcher, Dental Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[4]Private Practice, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Shahid Beheshti University of Medica Sciences, Tehran, Iran

Abstract

Objective: Squamous cell carcinoma (SCC) is the most common malignancy of the oral cavity. This study aims to evaluate different treatment procedures including neo-adjuvant, concurrent and adjuvant therapy in treating squamous cell carcinoma of the head and neck by a meta-analysis.

Materials and Methods: The authors searched all electronic databases (Medline, Embase and Cochrane) for all the articles published from 1970 to January 2011. Data of the evaluated treatment procedures (chemotherapy or radiotherapy), number of patients, publishing date and the authors' names have all been extracted from the articles and have been categorized in a table.

Results: Forty-six researches are included in this study. All three ways show that using chemotherapy after or with radiotherapy improves the vitality rate significantly (p-value< 0.01).

Conclusion: It is concluded that after deciding not to perform a surgery for treating SCC, the recommended treatment plan is chemotherapy and radiotherapy simultaneously.

Key Words: Chemotherapy; Meta-Analysis; Radiotherapy; Carcinoma; Squamous Cell

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Corresponding author:
M. Esmaeelinejad, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

esmaeelnejad@gmail.com

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INTRODUCTION

Nowadays, malignancies are being treated by a team including surgeons, oncologists, radiologists, physiotherapists, dentists and several other groups [1]. Routine treatment plans for these lesions are surgery, radiotherapy, chemotherapy and combination treatments [2-4]. In combined treatments, chemotherapy may be before (neo-adjuvant therapy), concurrent or after (adjuvant therapy) local surgical treatments [5-7]. Squamous cell carcinoma (SCC) is one of these malignancies. SCC is the most

common malignancy of the oral cavity. Approximately, 94% of all oral malignancies are squamous cell carcinoma. Within the adult population of the United States, oral carcinoma has been reported as one of the 25 most common oral mucosal lesions, and approximately 22,000 new cases are diagnosed annually. Approximately 5300 Americans die of this disease each year [8, 9]. This shows the importance of detecting an appropriate treatment plan for these malignancies. Several systematical reviews and meta-analyses have evaluated different treatment plans for squamous cell carcinoma [8-10], but there is some bias in these review articles. In almost all of them, several biases such as publication bias [11-14] and heterogeneity [15-17] are found. Publication bias is one of the limitations of meta-analysis. This means that the authors are more leaned to select articles with significant results. It is difficult to avoid heterogeneity in a meta-analysis because of dissimilarity of different studies. In order to avoid these errors, publication bias has been estimated by the method of the Rosenthal's file drawer. There has been heterogeneity in some meta-analysis articles, so we used both fixed and random effects to avoid this problem in this study. This study aims to evaluate the effects of different treatment procedures including neo-adjuvant, concurrent and adjuvant therapy on treating squamous cell carcinoma of the head and neck by a meta-analysis.

MATERIALS AND METHODS

Data sources and search strategy

According article abstracts published from 1970 to June 2009, a search with these keywords was done:

a- "head and neck squamous cell carcinoma" (medical subject heading, or MeSH)

b- "oral" (MeSH), "survival" (MeSH)

c- "treatment" (MeSH), "chemotherapy" (MeSH), "radiotherapy" (MeSH), "radiation" (MeSH) or "chemoradiation" (MeSH)

The EMBASE and Cochrane databases were searched using (a) "head and neck", (b) "neoplasm", (c) "squamous cell carcinoma" as text words.

Among them articles within the below inclusion criteria were selected:

1- Randomized clinical trial studies

2- Histologic findings were the major diagnostic factor

3- Tumor origin was in the head and neck area

4- The results could be reported as log hazard ratio

5- No far metastases were seen

Study selection

All titles and abstracts retrieved by this search were assessed to find out whether they were related to the subject or not. All papers assessed in this analysis were clinical investigations that had evaluated this tumor. In all the investigations, this tumor was located in the head or neck without any distant metastasis and the diagnosis was proved by a histopathologiy report. All vitro studies, article reviews, case-reports and letters were omitted. Investigations that evaluated the effects of methotrexate or bleomycin were also excluded, because it has been proved that these medications cause severe mucosal reactions that increase during radiotherapy [18, 19].

Data extraction

Identification information such as journal information, publishing date and authors' names have been blocked out during the assessment to prevent possible reviewer bias. Data of evaluated treatment procedures (chemotherapy or radiotherapy), number of patients, publishing date and authors' names have been extracted from the articles and have been categorized in a table.

Statistical methods

First, hazard ratio has been calculated for all the papers.

Table 1. The List and Definition of the Variables Used in Data Analysis

Variable	Type	Role	Description	Scale/Unit
Log Hazard Ratio	Quantitative - Continuous	Dependent	Logarithm Of Hazard ratio	-
Duration After Randomization	Quantitative - Continuous	Independent	According Months	Month
Chemotherapy Method	Qualitative- Nominal	Ground Variable	1- Cisplatin 2- Carboplatin 3- Mitomycin 4- Fluorouracil	-
Radiotherapy Method	Qualitative- Nominal	Ground Variable	1- Conventional Fractionation 2- Hyper Fractionation	-
Studied Article	Qualitative- Nominal	Ground Variable- (Meta- Covariate)	Article Title	-
Total Heterogeneity Squares	Quantitative - Continuous	Independent	The sum of the difference between results and real values	-
Rosenthal File Drawer	Quantitative - Continuous	Independent	Number of unpublished articles with opposite conclusions that will not reject our results	-
Minimum Follow-Up Duration	Quantitative - Continuous	Independent	Minimum time after randomization until a case was excluded	Month
Maximum Follow-Up Duration	Quantitative - Continuous	Independent	Maximum time until no case will be available anymore	Month

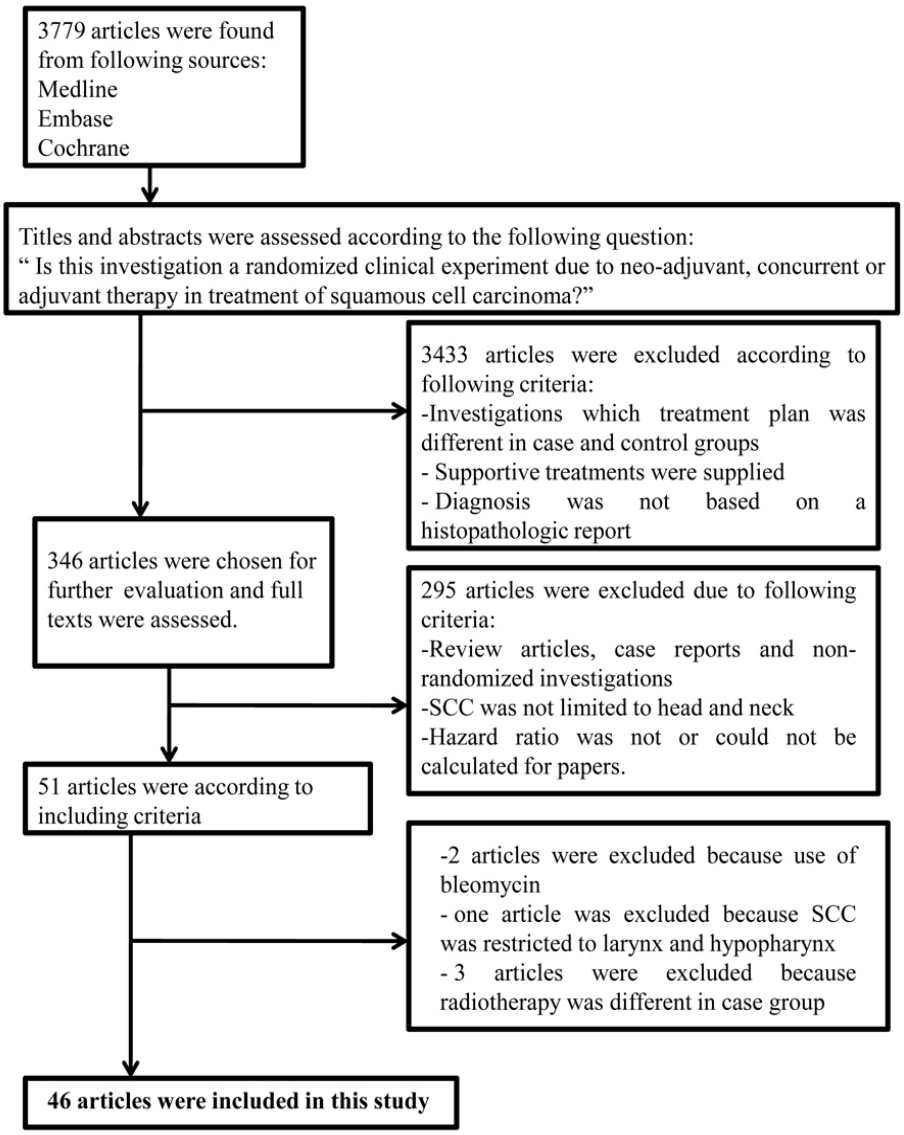

Fig 1. Information Flow Diagram

Then, all the data have been analyzed as fixed, random effect, size, measurement as well as the general linear model (Table 1). All insufficient data have been evaluated by palmar method. After that, the heterogeneity test has been performed and publication bias has been estimated by the method of the Rosenthal's file drawer. All the analyses have been processed by MATLAB R2007b (version 7.5.0.342) and Statistical Package for Social Science statistical software (version 16; SPSS Inc. Chicago, Illinois).

RESULTS

There have been 346 articles identified from the initial search criteria (Fig 1). After reading and evaluating the abstracts, unrelated articles to inclusion criteria have been ignored.

At last, 46 researches have been included in this study.

Seventeen papers of all investigations have been related to concurrent therapy (first group), 14 have been about neo-adjuvant therapy (second group) and 15 have been related to adjuvant therapy (third group).

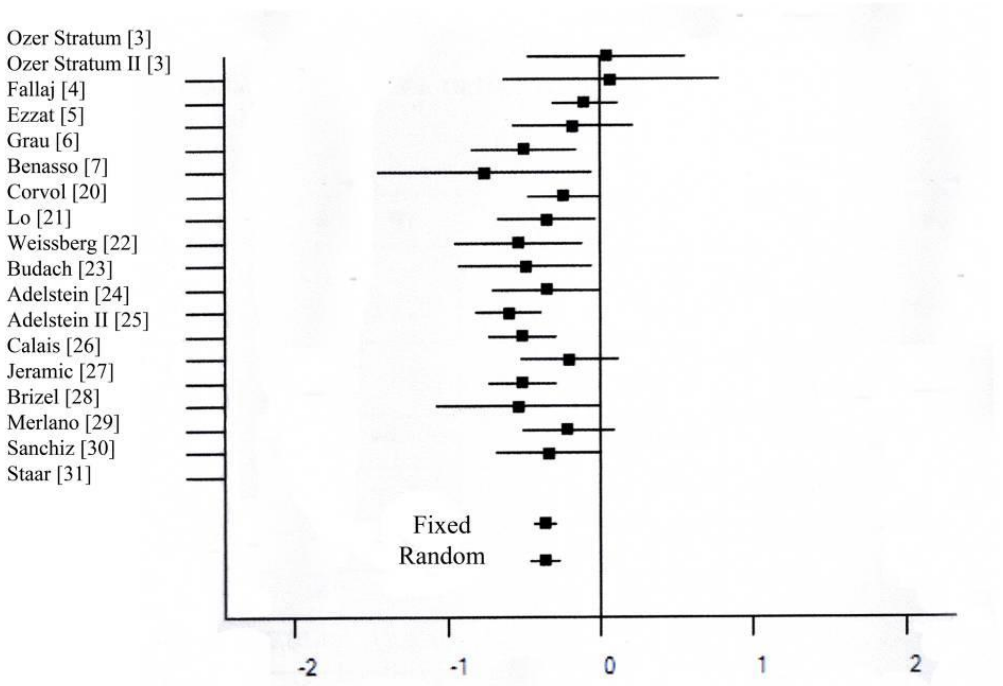

Fig 2. Concurrent chemo-radiation versus radiation alone

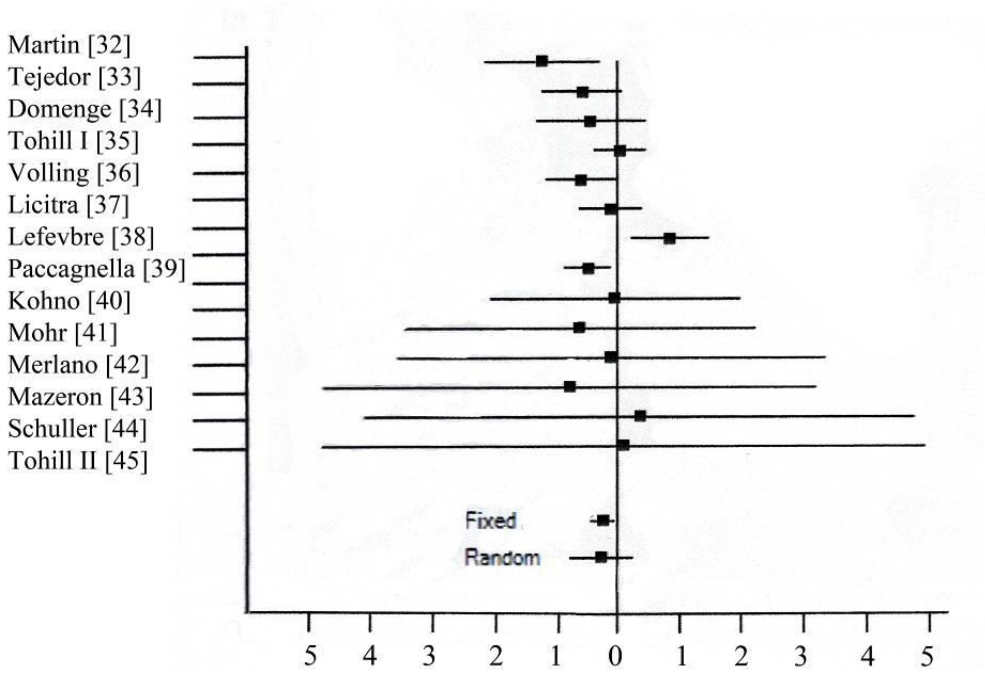

Fig 3. Evaluation of investigations about neo-adjuvant chemotherapy

Statistical analysis of the first group has been carried out by fixed, random effect, size, measurement as well as the general linear model.

All three ways show that using chemotherapy and radiotherapy together and simultaneously improves the vitality rate significantly (p-

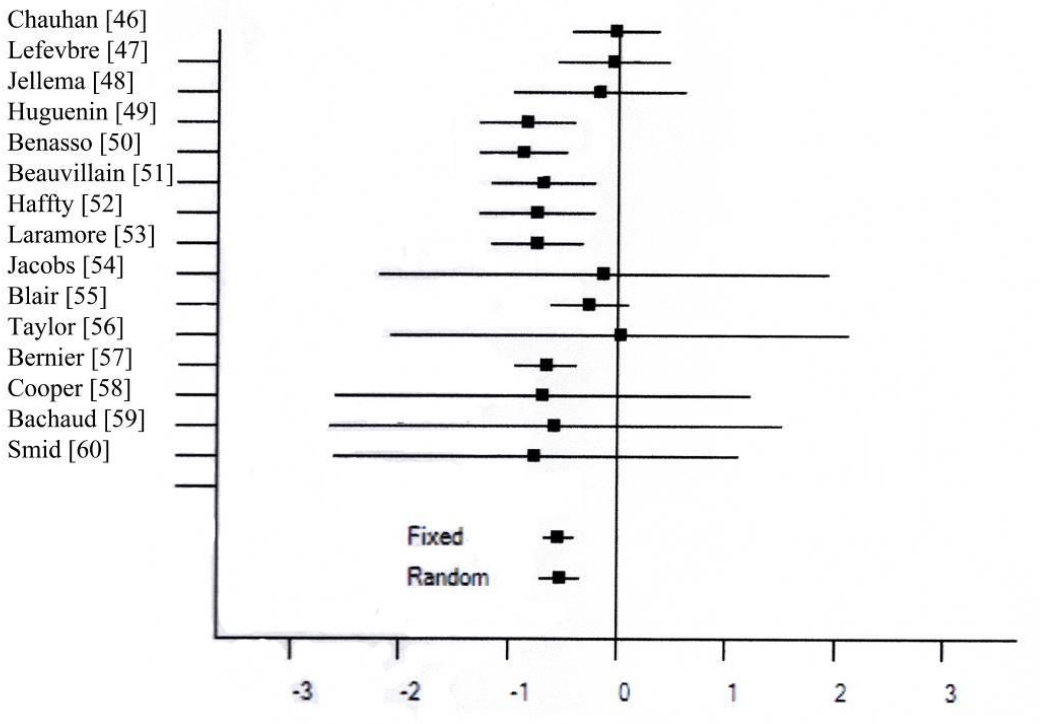

Fig 4. Evaluation of investigations about adjuvant chemotherapy

value< 0.01) (Fig 2).

Heterogeneity test for these articles is not significant (p-value> 0.05). Estimated Rosenthal's number for evaluating publication bias is 258.6 articles.

Statistical analysis of the second group by fixed effect showed that chemotherapy before local surgical treatment improved the vitality rate significantly (p-value> 0.01), although statistical analysis by random effect and linear model was not significant (p-value> 0.05) (Fig 3). The heterogeneity test for these articles was significant (p-value< 0.05). Estimated Rosenthal's number for evaluating publication bias was 2.646 articles.

Statistical analysis of the third group was performed by fixed, random effect size measurement as well as the general linear model.

All three ways show that using chemotherapy after radiotherapy improves the vitality rate significantly (p-value< 0.01) (Fig 4).

The heterogeneity test for these articles was not significant (p-value>0.05). Estimated Rosenthal's number for evaluating publication bias was 162.44 articles.

DISCUSSION

In this study, in order to evaluate different treatment procedures, data were analyzed as fixed, random effect size measurement as well as the general linear model.

Random effect size measurement is based on covariance. It is a more trustful analysis than the two other models because of its large certainty.

If random effect model shows the efficacy of a treatment procedure, we can be almost sure that it will also be significant using the fixed effect or the linear model, but it is not correct in the other ways. It means that we get a pessimistic view about the effects of treatments by using the random effect model.

Statistical analysis by fixed effect model is less confident, so we cannot decide according to its results. Linear model is a moderate way and it is almost between the two other ways. Rosenthal's file drawer was used to estimate the publication bias. Rosenthal's number indicates the number of not published papers with findings against the results of the meta-analysis in order to invalidate the results of that review. All three statistical procedures show that using chemotherapy simultaneously or after surgery is significantly effective. This finding shows that null hypothesis is ignored, and we can be confident about the results. This finding is correct for each subcategory of concurrent chemotherapy. Actually, chemotherapy and radiotherapy simultaneously with some drugs such as carboplatin, mitomycin and fluorouracil can be effective. The estimated Rosenthal's number for the concurrent group is 258.6 meaning that there must be at least 258 articles with opposite results in order to ignore the efficacy of chemotherapy and radiotherapy simultaneously. Great Rosenthal's number with nonexisted heterogeneity proves the efficacy of this treatment procedure with great confidence. This finding cannot be changed in the future unless at least 258 articles prove the opposite result. So we can reasonably be sure that concurrent chemotherapy with carboplatin, mitomycin and fluorouracil is an effective treatment procedure to suppress SCC in the head and neck regions and there is no need to perform researches about the efficacy of this treatment plan unless to find and examine new drugs. Treatment procedures in the adjuvant group were similar and routine, and almost all the investigations were based on cisplatin. So sufficient investigations for other treatment procedures were not available. The same results were found for the adjuvant group. The significance of all three statistical analyses with great Rosenthal's number (K> 162.44) and nonexisted heterogeneity prove the high confidence of the efficacy of this treatment plan. Therefore, there was enough medical evidence for the efficacy of adjuvant therapy with cisplatin, but sufficient findings for the other procedures were not found. So it is suggested to plan new researches using new drugs. In neo-adjuvant group, only statistical analysis by fixed effect model showed the efficacy of this treatment, but the other two statistical procedures were not significant. On the other hand, Rosenthal's number for this group was very low (K= 2.656).

It means that only three researches with contradictory results were sufficient to ignore this finding, which was not unachievable. Existence of heterogeneity in this group does not lead to a confident decision. So, sufficient medical evidence was not present and more investigations need to be carried out in the future on this treatment plan. According to the findings of the present analysis it is possible to achieve a standard treatment protocol based on the available evidence. After clinical examinations and diagnosis, a clinician should judge between performing a surgical treatment and considering another treatment plan. So any clinician should first answer these questions:

a-Is it possible to remove the whole part of the tumor or surgical performance is being used to reduce the bulk of the tumor?

b-Is surgical treatment indicated for the patient according to his/her medical history?

c-What is the influence of surgical treatment on the patient's quality of life?

d-Does the patient agree with this treatment?

e-Is the clinician capable of performing this surgery?

If the clinician decided not to perform a surgical procedure, the appropriate treatment plan according to this study would be concurrent chemotherapy. If surgical procedure were the choice treatment, it would better be followed by simultaneous radiotherapy and chemotherapy.

CONCLUSION

We may conclude from this study that after deciding not to perform surgery for treating

SCC, the recommended treatment plan is chemotherapy and radiotherapy simultaneously. Although there is enough evidence for adjuvant therapy, this treatment plan is based on all local treatments, not only radiotherapy.
After deciding to perform surgery, the recommended treatment plan after surgery is chemotherapy and radiotherapy (adjuvant therapy).

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