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The Prevalence of Hearing Loss Following Parotid Cancer Radiotherapy and Its Associated Factors: A Meta-Analysis Study

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ABSTRACT

Treatment of parotid cancer with radiotherapy can lead to hearing loss. The purpose of this systematic review is to evaluate the hearing loss caused by parotid cancer radiotherapy. In this article, a systematic search of Web of Science, PubMed, Google Scholar, Elsevier, Scopus, Embase and ProQues to June 2019 including patients with parotid cancer treated with radiotherapy was performed. In total, six studies were included in the meta-analysis. All these articles were follow-up studies and reported the percentage of hearing loss. The percent of hearing loss was 0.25 (95% CI: 0.07, 0.42, I2=91.6%, 6 studies). The publication bias was evaluated using Begg's and Egger's tests. P-values of Begg's and Egger's tests were 0.497 and 0.262 respectively.
Parotid cancer radiotherapy patients may experience hearing loss. Hence it is recommended in treatment planning, that the hearing structure is drawn as an organ at risk in parotid cancer radiotherapy.

Keywords: *Hearing Loss, Parotid Cancer, Radiotherapy*

Introduction

More than 50% of salivary gland neoplasms are benign. About 70-80% of salivary gland neoplasms are created in the parotid gland (Thielker *et al*., 2018). The parotid gland is the biggest salivary gland and is composed of serous acini. This gland is located under the external ear canal and around the mandibular ramus (Sood *et al*., 2016).

The probability of parotid gland malignant tumor is rare. The salivary malignant neoplasm is about 0.5% of all malignancies including approximately 3-5% of all neck and head cancers. In most patients, the salivary gland malignant neoplasm starts in decades 6 and 7 of life (DeVita *et al*., 2011).

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Radiotherapy is one of the methods for salivary gland cancer treatment after a surgical operation to remove the remaining cells. Also, radiotherapy is used alone or with chemotherapy in cases where surgery is not possible. Radiotherapy helps to reduce signs such as pain, bleeding, and trouble swallowing in patients with advanced cancer of the salivary gland (Mc Loughlin *et al*., 2019).

Parotid radiotherapy has some side effects such as harm to the cochlea and auditory nerve. These harms can lead to hearing loss (Stramandinoli-Zanicotti *et al*., 2013). Although these complications are reduced in newer techniques such as Intensity-Modulated Radiation Therapy (IMRT), still hearing loss is one of the problems of patients undergoing radiotherapy (Theunissen *et al*., 2014).

There were many studies about the effect of parotid radiotherapy on hearing loss. Some of them have investigated the effect of parotid radiotherapy on hearing loss. Evans *et al*. concluded that the onetime radiation of 60 cGy causes hearing loss, but the fractional radiation as 200-220 cGy in each session has no effect on hearing (Evans *et al*., 1988). However, in some studies, the fractional radiation in the long-term following had an effect on hearing loss (van der Putten *et al*., 2006). There is no consensus regarding about the effect of parotid radiotherapy on hearing in studies. According to disagreement about the effect of parotid radiotherapy on hearing loss in some studies, the present meta-analysis was conducted to address this gap.

Materials and Methods

Eligibility Criteria

The outcome of this study was hearing loss which is any problem in the outer or middle ear that prevents correct sound guidance. The hearing loss is 25-65 dB and with mild or middle level (Bance, 2007). The exposure in this study was parotid radiotherapy. The radiotherapy dose was related to the number of radiotherapy sessions. Some studies that have investigated the effect of parotid radiotherapy on hearing loss were included irrespective of gender, race, age, date of publication, and language (Bhandare *et al*., 2010a). The studies that have evaluated the effect of radiotherapies of other parts on hearing loss were excluded.

Search Strategies

All major electronic databases (PubMed, Web of Knowledge, Scopus, and Embase) were searched till June 2019. Also, the references list of included studies was assessed. Moreover, we contacted the authors to find

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additional studies. The following keywords were used for the search (Hearing loss OR Reduced hearing OR Hearing impairment) AND (Parotid radiotherapy OR Radiotherapy OR Parotid).

Studies Selection

Results of search from various databases were merged by EndNote software and duplicate studies were removed. Then, two authors (FS and AA) reviewed the titles and abstracts of studies independently to remove irrelevant studies. The disagreement between the two authors was solved by discussion. Then, we examined the full text of relevant articles. The Kappa coefficient was 81.5% between authors.

Data Extraction

Two authors (FS and AA) independently extracted data from the articles and entered them into an electronic data collection form. The disagreement was solved by discussion. The authors were contacted to request additional information. The electronic data collection form included the following data: author's name, year of study, country of study, age mean, dose of radiotherapy, follow-up time, sample size, frequency of radiotherapy, and percent of hearing loss with 95% Confidence Intervals (CI).

Quality Assessment

The quality of entered articles to our studies was evaluated using the Newcastle Ottawa Statement (NOS) (Wells *et al*., 2009). The NOS is a checklist of items for assessing the risk of bias in included studies. This checklist allocates a maximum of nine stars by the following items: selection, outcome, exposure, and comparability. The articles with seven or more stars were considered high-quality studies in this meta-analysis.

Bias and Heterogeneity

The Q-test was used for heterogeneity assessment (Higgins and Green, 2008). Also, the I2 test was used for the quantity of heterogeneity (Higgins *et al*., 2003). The Begg and Egger tests were used to assess the possibility of publication bias (Begg and Mazumdar, 1994, Egger *et al*., 1997).

Summary Measures

The percent of hearing loss was used in this study. The data were analyzed and the results were reported using random-effect model. All statistical analyses were conducted at significant level of 0.05 and by Stata software version 11.

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Subgroup Analysis

In this study the subgroup analysis was conducted by following items: a) follow-up time (lower than 8 years and upper than 8 years) and b) quality of studies (high quality and low quality).

Results

We reviewed a total of 1863 references including 1785 references by search in electronic databases and 78 references by references list of articles until June 2019. We excluded 912 duplicate references and 811 irrelevant references by reading the title and abstract. Full-text of 62 articles were retrieved for more assessment. Fifty-six articles do not have inclusion criteria and were excluded in this section. Six articles had inclusion criteria for the final analysis (Fig. 1).

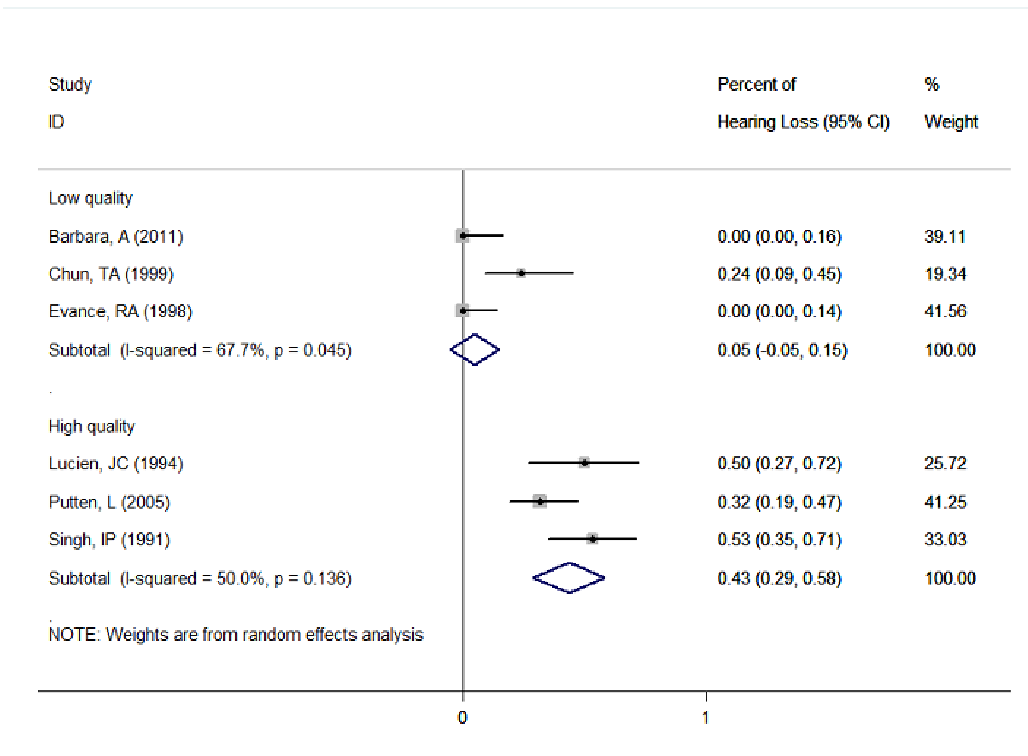

Figure 1: Flow of information through the different phases of the systematic review.

All these articles were follow-up studies and reported the percentage of hearing loss. The quality of included studies was evaluated using NOS which three studies (Anteunis *et al*., 1994, Singh and Slevin, 1991, van der Putten *et al*., 2006b) were high quality and three studies were (Evans *et al*., 1988, Chen *et al*., 1999) of low quality. The results of this study review are summarized in Table 1.

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Table 1: Summary of studies results.

1St author, year	Country	Age mean	Study	Sex	Effect size	Sample Size	NOS quality
Evance, RA 1998	Scotland	65	Follow-up	Both	Percent	20	****
Singh, IP 1991	Italy	59	Follow-up	Both	Percent	28	*******
Lucien, JC 1994	Netherland	50	Follow-up	Both	Percent	18	*******
Chun, TA 1999	Taiwan	49	Follow-up	Both	Percent	21	*****
Putten, L 2005	Netherland	56	Follow-up	Both	Percent	52	*******
Barbara, A 2011	Italy	56	Follow-up	Both	Percent	17	******

Percent of hearing loss caused by parotid radiotherapy is shown in Fig. 2. According to this forest plot, the percent of hearing loss was 0.25 (95% CI: 0.07, 0.42, I2=91.6%, 6 studies). The publication bias was evaluated using Begg's and Egger's tests. P-values of Begg's and Egger's tests were 0.497 and 0.262 respectively. These results show that there was no evidence of publication bias among studies addressing the percent of hearing loss caused by parotid radiotherapy.

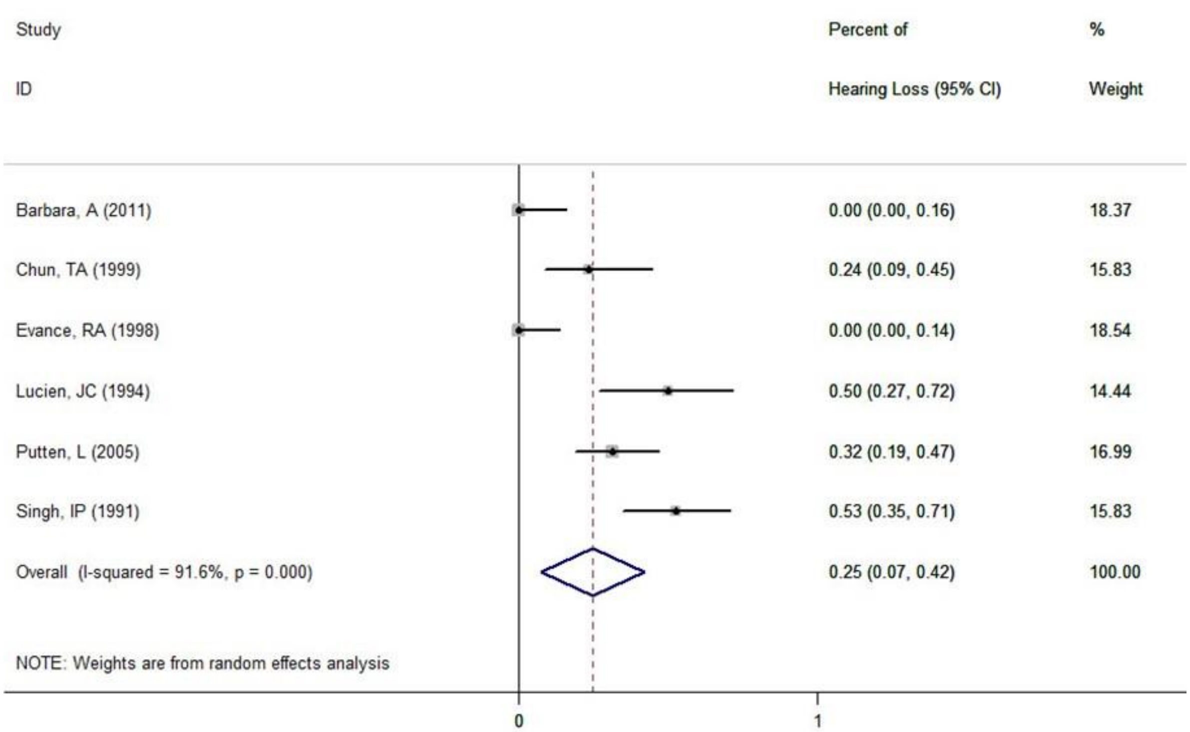

Figure 2: Forest plot of the percent of hearing loss caused by parotid radiotherapy.

The percent of hearing loss caused by parotid radiotherapy was investigated by dose of radiotherapy and shown in Fig. 3. According to this figure, the percentage of hearing loss in more than 8 years following studies was 0.38 (95% CI: 0.10, 0.67, I2=80.2%, 2 studies) and this percentage was higher for follow-up studies less than 8 years.

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Also, the percentage of hearing loss caused by parotid radiotherapy according to the quality of studies is shown in Fig. 4. The percent of hearing was 0.05 (95% CI: -0.05, 0.15, I2=67.7%, 3 studies) based on low-quality studies and was not significant. According to high-quality studies, the percent of hearing loss was 0.43 (95% CI: 0.29, 0.58, I2=50.0%, 3 studies) and was stronger than low-quality studies.

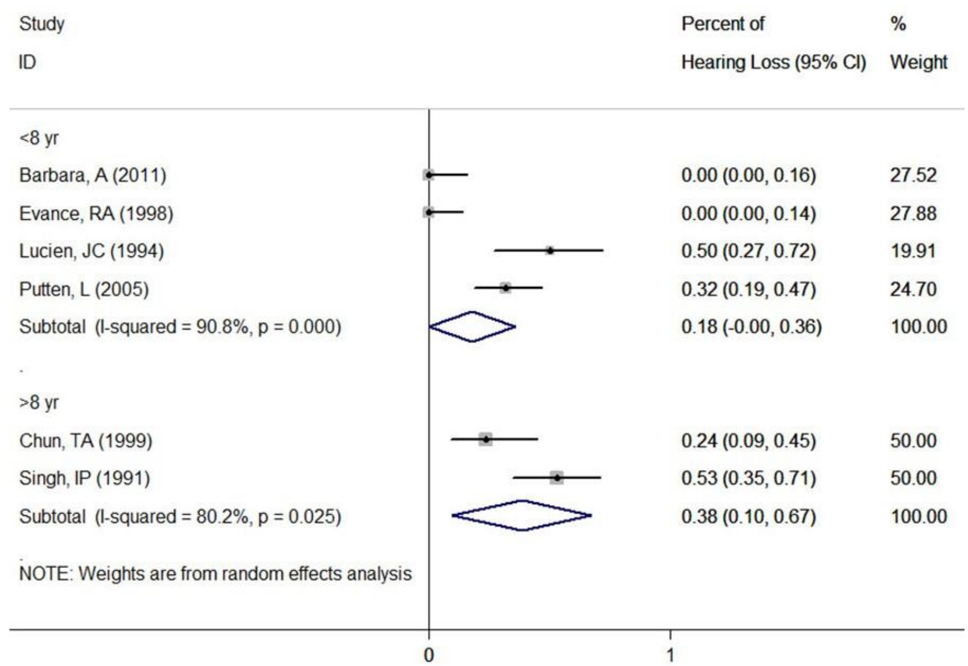

Figure 3: Forest plot of the risk of hearing loss caused by parotid radiotherapy by follow-up times.

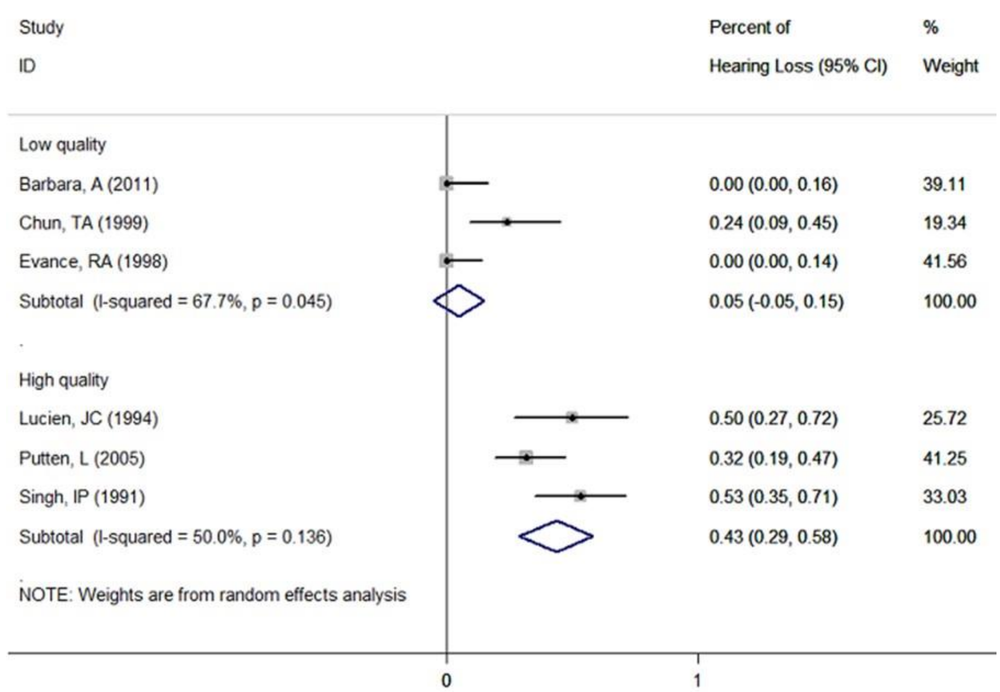

Figure 4: Forest plot of the risk of hearing loss caused by parotid radiotherapy by quality of studies.

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Discussion

We updated our search from September 1, 2018, to June 2019 using search terms in all major electronic databases (PubMed, Web of Knowledge, Scopus, and Embase). In this research, six articles on hearing loss caused by parotid radiotherapy were fully reviewed. The findings of these studies were consistent with our meta-analysis results. It showed the relationship between hearing loss and parotid irradiation. The percent of hearing loss caused by parotid radiotherapy was investigated by the dose of radiotherapy as shown in Fig. 3.

Patients with parotid tumors malignancies are currently treated by surgical resection, chemotherapy, and/or radiation therapy (RT) (Bass *et al*., 2016, Halperin *et al*., 2013). RT is a common management of parotid. The selection of treatment depends on the size and location of the tumor, the stage of the disease, the patient's performance and overall goal of treatment (curative or palliative) (Halperin *et al*., 2013).

Hearing loss is one of the most common normal-tissue complications of EBRT in the head and neck region (Nader and Gidley, 2019, Schultz *et al*., 2010). Damage to any part of the auditory system may cause hearing loss. This type of toxicity has been categorized into conductive hearing loss (CHL), sensorineural hearing loss (SNHL), or a combination of these two types. The total dose of EBRT and the location of the tumor are the most important factors in the incidence of hearing impairment. Therefore, the dose received by the auditory system should be reduced as much as possible. Depending on the size and location of the tumor, parts or all of the structures in the auditory system may be affected, leading to CHL, SNHL or both. In EBRT to parotid cancer, usually, the inner, middle and external ear sections all receive significant doses (Jereczek-Fossa *et al*., 2003). Parotid tumors are suitable for hearing loss studies because the tumor itself does not cause hearing loss (Evans *et al*., 1988).

Our review shows that radiation sequela is often more severe at higher frequencies. Basal cells of the cochlea, which are responsible for the higher frequency than light snail Ross cells, are more sensitive, and this could be the answer to the question of why neural hearing loss occurs at higher frequencies (Hua *et al*., 2008).

Due to the small size and low relative importance, dose gradient in-ear structures, in terms of volume dosing studies in organ performance, is proposed that the ear is a parallel structure (De Marzi *et al*., 2015). Our review was conducted on this basis. Therefore, among the dosimetric parameters (average dose, maximum dose and minimum dose, etc.), the mean dose of each structure as the most suitable statistical quantity that was used to determine the prevalence and degree of hearing loss. The percent of

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hearing loss caused by parotid radiotherapy was examined by a mean dose of radiotherapy and shows in Figure 3. According to this figure, the percentage of hearing loss in more than 8 years following studies was 0.38 (95% CI: 0.10, 0.67, I2=80.2%, 2 studies) and this percentage was higher for follow-up studies less than 8 years.

CHL is the early effect and this is reversible but SNHL is a late effect (Jereczek-Fossa *et al*., 2003) and it may appear years after radiation therapy. It is reasonable that as a follow-up is longer, the effect of hearing loss is greater. Our meta-analysis results showed this.

Overall, six studies have reported permanent hearing impairment due to megavoltage radiotherapy in fractions of 1.8 to 2 Gy with a total dose of 55-60 Gy in the cochlea (Anteunis *et al*., 1994, Chen *et al*., 1999). In the QUANTEC study, Bhandare, *et al*. (2010) concluded that in conventional radiation, the mean cochlear dose should be limited to <45 Gy.

Also, the percentage of hearing according to the quality of studies is shown in Figure 4. The percent of the hearing was not significant (Anteunis *et al*., 1994, van der Putten *et al*., 2006b). According to high-quality studies the percent of hearing loss was 0.43 (95% CI: 0.29, 0.58, I2=50.0%, 3 studies) and was stronger than low-quality studies (Evans *et al*., 1988, Chen *et al*., 1999). That is because some studies were old, but overall our meta-analysis results revealed a correlation between hearing loss and parotid radiation.

Due to the limited number of articles, more studies are needed to achieve greater certainty. Because of this limitation, the incidence of hearing loss in patients with parotid cancer is not known and often ignored. Hence it is recommended in treatment planning, that the hearing structure is drawn as an organ at risk.

Conclusion

According to recent studies, hearing loss occurs with parotid radiation. As hearing is an important sense through which people interact with others and their environment, any impediment reducing the sound transmission to convey messages may lead to emotional and social consequences for patients. A meta-analysis of the auditory system as an organ at risk in parotid cancer radiotherapy provides useful information for oncologists and physicists to consider auditory system as an organ at risk in parotid cancer radiotherapy.

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Statement of Ethics: This study protocol was reviewed and approved by the Arak University of Medical Sciences Ethics Committee. The approval number was "IR.ARAKMU.REC.1395.185". Informed consent was not required for this study.

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

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