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Review

Elective versus therapeutic neck dissection in node-negative oral cancer: Evidence from five randomized controlled trials

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SUMMARY

The aim of this study was to compare the outcomes of elective neck dissection (END) with that of a more conservative approach comprising of observation plus therapeutic neck dissection for nodal relapse (OBS), by conducting a meta-analysis of randomized controlled trials (RCTs) that compare these two surgical approaches in patients. RCTs conducted prior to May 2015 were identified from electronic databases such as MEDLINE EMBASE and Cochrane Library. Reference lists within the retrieved articles were used as secondary reference sources. Disease-free survival (DFS) and overall survival (OS) were the primary outcome measures. Five RCTs with a combined subject population of 779 patients were included. Meta-analysis of these 5 RCTs showed that DFS in END group was higher than that in the OBS group with a significant inter-group difference (Risk Ratio [RR]:1.33; 95% Confidence Interval [CI] 1.06, 1.66); $P = 0.01$; five trials, 779 participants]. However, there was a significant statistical heterogeneity among the studies (I-squared = 56%, $P = 0.06$). Four studies had reported on OS. Meta-analysis of these 4 RCTs revealed a higher OS in the END group as compared to that that in the OBS group with a significant inter-group difference (RR: 1.18; 95% CI 1.07, 1.29); $P = 0.0009$; four trials, 708 participants]. The statistical heterogeneity of these 4 studies is small (I-squared = 14%, $P = 0.32$). The results of this meta-analysis suggest that END at the time of resection of the primary tumor confers a DFS and OS benefit in patients with clinically node-negative oral cancer.

Introduction

Oral cancer is the sixth most common cancer in the world and accounts for nearly 3% of all cancer cases [1]. The most common tumor in the oral cavity is oral squamous cell carcinoma (OSCC), an aggressive cancer frequently associated with poor prognosis. Surgery is still the preferred treatment [2–4]. Neck dissection plays an important role in the treatment of OSCC and is an indispensable part of many OSCC treatments [4]. However, iatrogenic injury to the anatomically contiguous vital structures in the neck, either during surgery or that resulting from postoperative complications, is a risk. Although OSCC is a locally aggressive disease with a strong tendency for loco-regional metastasis, some patients with clinically node-negative (cN0) OSCC do not actually have cancer cells in the cervical lymphatic tissue. In such cases, elective neck dissection could potentially result in avoidable morbidity and its associated costs such as prolonged hospital stay. Conversely, cN0 patients with actual micro metastases, but, in whom, neck dissection is not included in the management plan, may experience increased mortality [5]. In other words, there is no greater controversy related to the management of oral cancers than that surrounding the choice of treatment strategy for OSCC, especially in cN0 patients [6–10].

Treatment of early stage cN0 OSCC has been a contentious issue since the past 50 years. Surgery is still the preferred treatment in these cN0 OSCC patients. The two main surgical strategies for addressing the neck involvement include: (1) a conservative approach consisting of observation with therapeutic neck dissection only in the event of nodal relapse; (2) Elective neck dissection at the time of the excision of the primary tumor. Proponents of elective neck dissection cite decreased relapse rates and better disease-free survival (DFS) as well as overall survival (OS) [10–15]. However, some studies found no statistically significant

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difference with respect to DFS or OS between the two strategies [6,7,16]. Results from a few randomized controlled trials (RCTs) and retrospective studies have largely been inconclusive. Although the elective neck dissection approach may improve DFS and/or OS, the observation approach has the potential advantage of avoiding an additional surgical procedure in more than 70% of patients. Furthermore, neck dissection could increase treatment costs including that of treatment and complications. These considerations have resulted in variability in global practices.

The purpose of this research is to compare the outcomes of elective neck dissection (END) with those of a conservative surgical strategy comprising of observation followed by therapeutic neck dissection in the event of nodal relapse (OBS), in cN0 OSCC, by conducting a meta-analysis of the RCTs that have compared these two approaches.

Materials and methods

Inclusion criteria

Studies were included if they met all the following inclusion criteria: (a) patients diagnosed with cN0 OSCC without any treatment before surgery; (b) patients treated with oral surgical excision of the primary tumor with or without neck dissection; (c) reported clinical outcomes of END and OBS; (d) reported outcome measures included OS or DFS; (e) randomized controlled trials without limitations on publication status; (f) something about summary data being available for the outcomes of interest.

Literature search

A systematic literature search was performed using MEDLINE, EMBASE, and the Cochrane Library databases for studies conducted prior to May 2015. The MEDLINE database was searched for the following keywords: (a) "randomized controlled trial" and (b) "oral cancer" and (c) "neck dissection" and (d) "N0 neck" (or MeSH). The EMBASE and Cochrane databases were searched for (a) "randomized controlled trial" and (b) "oral cancer" and (c) "neck dissection" and (d) "N0 neck" as text words. Reference lists within the retrieved articles were used as secondary reference sources. All retrieved papers were screened to identify potentially eligible researches. Only RCTs which compared END with OBS in patients with OSCC, which had no clinical or radiological evidence of neck node metastasis, were eligible for inclusion in the meta-analysis.

Exclusion criteria

Studies published in languages other than English were excluded, as were the studies that did not provide sufficient information on prognosis.

Quality assessment and data analysis

The quality and risk of bias in all the included trials were independently assessed by Zhen-Hu Ren and Jian-Lin Xu, based on the recommendations from the Cochrane Handbook of Systematic Review of Interventions (www.cochrane-handbook.org). The criteria included allocation concealment, random sequence generation, blinding for participants and personnel, selective outcome reporting, blinding of outcome assessments, incomplete outcome data, and other biases. The risk of bias was categorized as 'high risk of bias', 'low risk of bias' or 'unclear risk of bias' in each domain, with notes justifying the risk categorization (Cochrane Handbook for Systematic Reviews of Interventions). Any disagreements were resolved by discussion.

Data on trial characteristics, including trial site, year, trial methods, participants, interventions, outcomes (DFS, OS, etc.) were extracted and entered in the Review Manager 5.3. The number of participants randomized and the number analyzed in the experimental and control arms were extracted from each group for each outcome. An attempt was made to contact the study authors for any relevant missing or unclear data. Authors were also asked to confirm whether the study was duplicated, and whether there was any doubt if the studies shared the same patients. Zhen-Hu Ren extracted the data, which was checked by Chen-Ping Zhang. In case of multiple publications from a particular research group reporting data from overlapping samples, the study that reported the largest or latest dataset was included. Differences in opinion were resolved by consensus.

Statistical analysis

All individual outcomes were pooled using RevMan 5.3 (Cochrane Collaborative, Oxford, England). Risk ratio (RR) was used to compare dichotomous outcomes. All measures of effect are presented with respective 95% confidence intervals (CI). The outcomes were aggregated and analyzed using a random-effect model in case of significant heterogeneity and fixed-effect model in the absence of significant heterogeneity. Statistical heterogeneity was assessed by Chi-squared distributed Q statistic and I-squared. Subgroup analyses were conducted in case of significant statistical heterogeneity (I-squared $\geqslant 50\%$). Sensitivity analyses and subgroup analyses were performed to assess inter-group differences with respect to primary outcomes.

Publication bias

The possibility of publication bias was assessed by quantitatively performing Begg's test and Egger's test (STATA 12.0) for any asymmetry with a 5% significance level.

Trial sequential analysis (TSA)

According to Cochrane Handbook for systematic reviews of interventions, if all eligible trials are included, the systematic reviews or meta-analyses are considered to be the best available evidence. However, 'the best available evidence' might not be equal to 'sufficient evidence' or 'strong evidence'. To resolve this question, we applied the TSA to estimate the robustness of conclusions. We calculated the required power to collect adequate information and evaluate how many subjects would be necessary to make these robust conclusions. The required power was based on the assumption of a plausible relative risk of 10% with low risk bias, and we adopted the risks for a type I error (a) of 5%, a type II error (b) of 20% [17,18]. Based on the required power and risk for type I and type II errors, TSA monitoring boundaries were built. TSA monitoring boundary crossing the Z-curve before the required power is reached, is indicative of a robust verdict with further research being unnecessary. In other cases, it is necessary to continue performing more research.

Results

Search findings

A total of 827 records were retrieved on database search and 12 additional records were identified after reviewing the reference lists of retrieved articles. After deleting the duplications, 814 papers were left. 792 papers were excluded as being irrelevant to OSCC or survival, or due to the lack of prognostic data.