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Impact of postoperative neck radiotherapy on regional control in pathologically node-negative head and neck cancer: A meta-analysis

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► ***Review article***

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ABSTRACT

***Background**:* The appropriate extent of the radiation field (primary site ± neck) in pathologically node-negative (pN0) head and neck cancer (HNC) with adverse features at the primary site remains controversial. We investigated the effect of adjuvant neck radiotherapy (RT) on regional control and survival in patients with pN0 HNC. ***Materials and Methods**:* A systematic search of databases (MEDLINE, EMBASE, and Cochrane library) was performed for literature published until January 2021. Studies of HNC patients with pN0 neck that reported on the regional recurrence (RR) rate and regional recurrence-free survival (RRFS) with respect to adjuvant neck RT were included. ***Results**:* Five studies comprising 553 patients, with a median follow-up of 50 months, were included. The overall RR rates were 2.0% (3/153) for patients treated with adjuvant neck RT and 6.5% (26/400) for patients treated with neck dissection (ND) only. Patients who received adjuvant neck RT had a 0.37-fold (95% confidence interval [CI]=0.13–1.04, P=0.06, I^2=0%) lower risk of RR than did patients with ND only. The addition of adjuvant neck RT did not significantly improve RRFS (hazard ratio=0.58, 95% CI=0.16–2.08, P=0.41, I^2=0%). ***Conclusions**:* Given the RR rate of 6.5% in the RT-negative group, ND alone appears to be sufficient for treating neck disease in pN0 HNC. However, the neck RT group had a lower RR rate than that of the non-RT group, suggesting that pN0 HNC patients with a high risk of recurrence may benefit from elective neck RT.

INTRODUCTION

Regional lymph node (LN) metastasis is one of the important prognostic factor in head and neck cancer (HNC), and proper management of neck is crucial for the better oncologic outcomes. Treatment modalities for the neck include neck dissection (ND) and/or radiation therapy (RT). Elective ND is associated with better regional control and survival compared to that with observation in clinically uninvolved neck (cN0) HNC [1, 2].

After resection of the primary tumor and ipsilateral ND at risk of occult neck metastases for cN0 HNC, adjuvant RT is indicated according to unfavorable pathological findings such as T3-4 stage, high grade, perineural invasion, lymphovascular invasion, and close resection margin [3]. However, the appropriate extent of the RT field (primary site only or primary site and the neck) in pathologically node-negative (pN0) HNC with adverse features at the primary site remains controversial [4-7]. This may be an important clinical issue as this scenario is not uncommon in our clinical experience.

The reason for limiting the RT field to the primary site is the concern for late treatment-related toxicities, such as soft tissue fibrosis, nerve injury, carotid artery stenosis, lymphedema, and swallowing difficulties, associated with a larger treatment volume. Prior studies have demonstrated that limiting the treatment volume improves degree of treatment-related toxicities and quality of life (QoL) [8, 9]. However, irradiating pN0 nodal stations is required because residual lymphatic's or vessels could harbor tumor cells that, unless treated, would be at increased risk for regional recurrence [7]. Ultimately, balancing the risks of radiation toxicity and neck recurrence is essential when considering additional postoperative RT to a pN0 neck.

The aim of this meta-analysis was to determine whether postoperative neck RT confers any benefit on regional control and regional recurrence-free survival (RRFS) rates in patients with pN0 HNC after ND.

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MATERIALS AND METHODS

Data search

Our study had followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A systematic search of the MEDLINE, EMBASE, and the Cochrane library databases for English-language publications was conducted in January 2021. We searched these databases using the following keywords: ("head and neck" OR "oral" OR "oropharynx" OR "hypopharynx" OR "larynx") AND ("postoperative" OR "postop" OR "postoperation" OR "dissection") AND ("radiation" OR "radiotherapy") AND ("regional" OR "LN" OR "lymph") AND ("pN0" OR "negative" OR "pathologic" OR "pathologically"). The reference lists of the search results were also examined to identify additional studies. Periodic restriction was not performed.

Study selection

Studies were eligible for this meta-analysis if they met all of the following inclusion criteria: (1) clinical trial, prospective or retrospective study; (2) inclusion of ≥20 pN0 patients with HNC treated with ND; and (3) provided data on regional recurrence and RRFS in relation to postoperative neck RT status. Duplicate studies, reviews, conference abstracts, and editorials were initially filtered by an author of this study. If there were multiple studies from a single center, we selected only one study using the following criteria, prioritized in numerical order: (1) the study with the largest number of patients and (2) the most recently published study. Subsequently, abstracts of the remaining studies were reviewed to filter studies that were irrelevant to the subject of this study or did not meet the inclusion criteria. Finally, a full-text review was conducted for the remaining studies to determine whether they fully met the inclusion criteria. Two authors independently examined the articles identified in the search as potentially relevant trials, and discrepancies were resolved by consensus.

Data extraction

The following data were recorded by two independent reviewers using a standardized form: (1) general information of the study including country, institution, first author, design of study, data-accrual period, and year of publication; (2) patient characteristics, including the number of patients, pathologic N stage, and postoperative RT field; and (3) treatment results including length of follow-up, regional recurrence, and RRFS.

Quality assessment

Given that most included studies were non-randomized and observational, the quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) score [10]. A score of 7–9 and 4–6 on the NOS indicated high-quality and medium-quality studies, respectively.

Statistical analysis

Regional recurrence was defined as any recurrence in the draining neck LN. The effects of adjuvant neck RT on regional control were assessed using risk ratios (RRs) with 95% confidence intervals (CIs). Forest plots were generated to display the results of each analysis, and statistical significance was set at $P<0.05$. A random-effects model was used if the data were significantly heterogeneous ($I^2>50\%$) [11]. Otherwise, a fixed-effects model was used for the calculation. Funnel plots were used to assess publication bias [12]. RRFS data were extracted using the methodology described by Parmar *et al.* [13].We derived a univariate hazard ratio (HR) and 95% CI directly from each study if provided by the authors. Otherwise, number of events, and number at risk, *P*-values of a log-rank test, and 95% CI were extracted to estimate the HR indirectly using Review Manager software (version 5.3, USA). The effect of adjuvant neck RT after ND on RRFS was measured using the effect size of HR with 95% CI.

RESULTS

In the initial literature search, 875 studies were identified. In the first screening, conference abstracts (289), reviews (63), duplicated studies (4), and short survey (1) were excluded. Titles and abstracts of the remaining 518 studies were carefully reviewed, and 504 studies were excluded due to irrelevancy to the subject of this study. The full text of the remaining 14 articles was reviewed to evaluate whether they fulfilled all the inclusion criteria. Finally, five studies [6, 14-17] comprising 553 patients were included in the present meta-analysis. The details of the inclusion process are described in figure 1.

Four of the five studies were retrospectively designed. Two studies were from the United States and one each was from the Republic of Korea, Germany, and India. The median follow-up time ranged from 41 to 68 months. According to the NOS scale, four studies were high-quality and one was medium-quality. Two studies [6, 17] reported RRFS related to postoperative neck RT. The characteristics of the included studies are summarized in table 1. After visual assessment of the funnel plot we suggested that publication bias was not presented (figure 2).

There were three cases of regional recurrence in the ND followed by adjuvant RT group (3/153; 2.0%) and 26 in the ND alone group (26/400; 6.5%); this difference was marginally statistically significant (RR=0.37, 95% CI=0.13–1.04, $P=0.06$). A fixed-effects model was used to analyze RR due to the low heterogeneity ($I^2=0\%$). A forest plot of the RR is shown in figure 3. The addition of adjuvant neck RT

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was not associated with an improvement in RRFS (HR=0.58, 95% CI=0.16–2.08, *P*=0.41, I^2=0%) (figure 4). The prescribed RT dose to pN0 nodal stations ranged from 60 to 66 Gy with conventional fractionation.

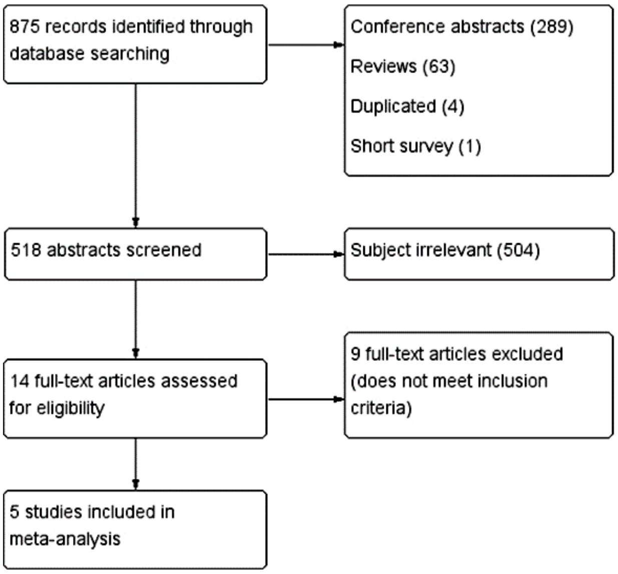

Figure 1. Flow diagram of the study selection process.

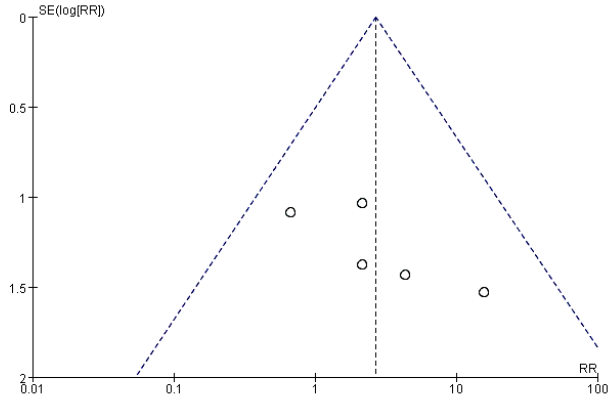

Figure 2. Funnel plot generated from five studies.

Table 1. Characteristics of included studies.

First author	Study design	Collection of patient data	Country	Primary sites	No. of patients	Follow-up (median, months)	RT dose (median, Gy)	NOS score
Ambrosch [12]	R	1986-1997	DE	OC, OPx, Lx, HPx	249	41	NR	7
Schiff [13]	R	1980-1995	US	OC	119	68	NR	7
So [14]	R	1995-2016	KR	OC	41	47	60	7
Contreras [15]	P	2007-2013	US	OC, OPx, Lx, HPx, UP	72	53	66	9
Subramaniam [16]	R	NR	IN	OC	72	NR	60	6

NOS=Newcastle-Ottawa Scale, P=prospective, R=retrospective, NR=Not reported, DE=Germany, US=United States, KR=Republic of Korea, IN=India, OC=Oral cavity, OPx=Oropharynx, Lx=Larynx, HPx=Hypopharynx, UP=Unknown primary.

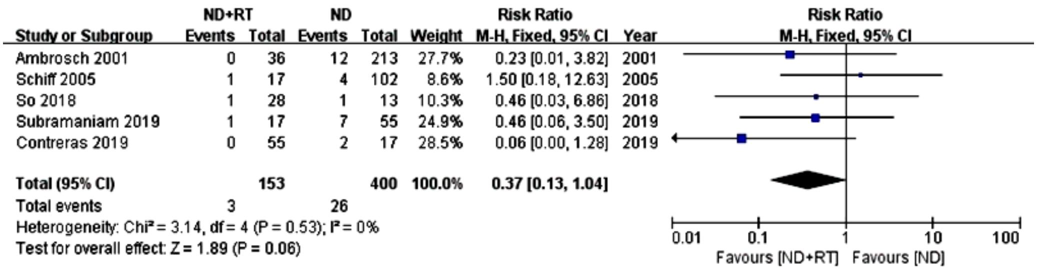

Figure 3. Forest plot of the risk ratio for regional recurrence comparison: neck dissection followed by neck radiotherapy vs. neck dissection alone.

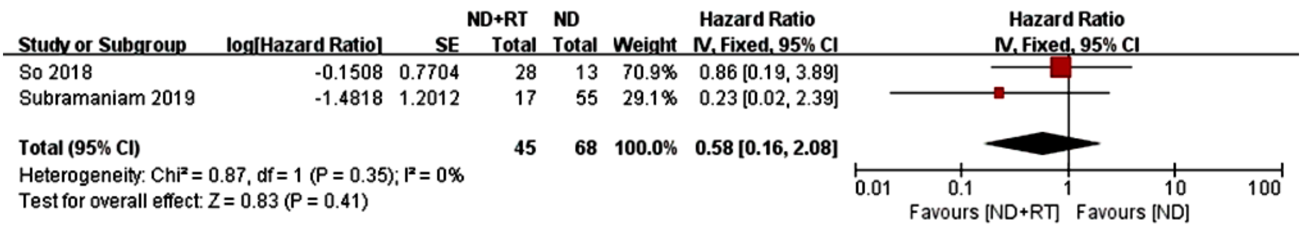

Figure 4. Forest plot of the hazard ratio for regional recurrence-free survival comparison: neck dissection followed by neck radiotherapy vs. neck dissection alone.

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DISCUSSION

The present study investigated whether the postoperative RT to a pN0 neck is beneficial for regional recurrence in patients with HNC. The outcomes of 553 cases of pN0 HNC patients confirmed that adjuvant neck RT reduced regional recurrence. However, the regional control rate was 93.5% for the unirradiated pN0 neck. Therefore, ND alone is likely sufficient to manage a pN0 neck and may improve long-term QoL outcomes by sparing the neck from irradiation. On the basis of these data, we would not recommend that routine postoperative RT include the neck in pN0 patients with adverse features at the primary site.

The reports on effect of postoperative neck RT on the risk of regional recurrence in pN0 HNC patients is inconsistent. Regional recurrence rates of 10–17% have been reported in patients with pN0 neck disease after ND alone [6, 18, 19]. However, Contreras et al. [16], from Washington University, reported no neck recurrence in 72 patients with pN0 neck regardless of adjuvant neck RT. In this meta-analysis, we could derive the regional control rate according to the RT field by combining studies to increase the number of cases for analysis.

There was a marginally significant difference in regional recurrence rates between patients treated with ND followed by neck RT and those treated with ND alone. Adjuvant RT was administered more frequently in patients with unfavorable tumor characteristics than in patients with favorable characteristics. There were more advanced primary tumors (pT3–T4 classification) in patients who received adjuvant RT (55%) than in those who received ND alone [14]. In addition, better regional control in the neck RT-positive group was reported than the neck RT-negative group (93.8% vs. 83.3%) in propensity score matching study for pN0 oral tongue cancer patients [6]. Therefore, improvement in regional control in the RT-positive group, which has more adverse prognostic factors than ND alone group, suggests a prognostic benefit of including the neck in adjuvant RT for pN0 HNC patients.

Among the indications for adjuvant RT in pN0 oral tongue cancer, which have been explored in few reports, lymphovascular invasion was associated with poor locoregional control and overall survival [3]. In another study, perineural invasion was found to be an independent predictor of nodal disease, and adjuvant RT improved locoregional control [20]. The presence of these risk factors is related to poor oncologic outcomes and warrants consideration of including the neck along with the primary site in the postoperative RT field. Although the regional recurrence rates are low, we suggest that more aggressive postoperative treatment of the neck may be needed in patients with a high risk of recurrence. These patients might benefit from adjuvant neck RT, and further research related to this will be helpful in improving their prognosis.

This meta-analysis on the efficacy of neck RT is hampered by the heterogeneity regarding patient selection, surgical extent of the primary tumor, type of ND, indications for adjuvant RT, and extent of the RT field in the included studies. Moreover, this analysis was limited by the small number of included studies and their small sample size. Meta-analyses of observational studies are controversial because the heterogeneity of designs and populations between studies might affect pooled estimates [21].

Despite these limitations, combining studies increases the number of cases for analysis and may assist clinicians in estimating the effect of postoperative neck RT on pN0 HNC. There are few retrospective analyses and one prospective study examining these effects [6, 14-17]; thus, a meta-analysis might be an appropriate research approach.

In conclusion, we reported a low rate of regional recurrence regardless of performing postoperative neck RT in patients with pN0 HNC, and elective ND alone was sufficient to control neck disease. However, the neck RT group had a significantly lower regional recurrence rate than that of the no neck RT group, suggesting that patients with a high risk of recurrence may benefit from elective neck RT. Further studies are needed to identify patients at high risk of regional recurrence.

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