

# Postoperative Radiotherapy Improved Survival in pT1-2N1 Oral and Oropharyngeal Cancer Without Adequate Neck Dissection

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## Research

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## Abstract

**Background:** To assess the benefit of postoperative radiotherapy in patients with pT1-2N1M0 oral and oropharyngeal cancer by the quality of neck dissection.

**Methods:** In the Surveillance, Epidemiology, and End Results database, pT1-2N1M0 oral and oropharyngeal cancer patients treated by primary tumor resection and neck dissection with or without radiotherapy were enrolled between 2004 and 2015. Univariate and multivariate analysis were used to explore the effect of adjuvant radiotherapy on 5-year overall survival (OS) and disease-specific survival (DSS).

**Results:** Of the 1,765 patients identified, 1,108 (62.8%) had oral cancer, 1,141 (64.6%) were men, and 1,067 (60.5%) underwent adjuvant radiotherapy. After adjusting for confounding factors, postoperative radiotherapy reduced the adjusted hazard ratio (aHR) of 5-year OS to 0.64 (95% confidence interval [CI], 0.49-0.84) in those with <18 lymph nodes removed, but not in those with 19-24 lymph nodes removed (aHR, 0.78; 95% CI, 0.73-1.13), and in those with  $\geq 25$  lymph nodes removed (aHR, 0.96; 95% CI, 0.75-1.24). For 5-year DSS, similar effect was observed. The adjusted hazard ratio was 0.66 (95% confidence interval, 0.45-0.97) in those with <18 lymph nodes. The protective effect was not seen in those with 18-24 lymph nodes (aHR, 1.07; 95% CI 0.59-1.96), and in those with  $\geq 25$  lymph nodes (aHR, 1.12; 95% CI, 0.81-1.56). Sensitivity testing also showed a robust protective effect of postoperative radiotherapy in patients with <18 lymph nodes removed.

**Conclusion:** Radiotherapy significantly improved survival in patients with pT1-2N1M0 oral and oropharyngeal cancer without adequate neck dissection.

## Background

Oral and oropharyngeal cancer remain among the most common malignancies in the world. Approximately 50% of these patients present with early stage (stage I-II) disease and primary surgery alone is the standard treatment, following National Comprehensive Cancer Network (NCCN) guidelines. Although most early stage oral and oropharyngeal patients have a favorable prognostic outcome, previous literatures have reported locoregional recurrence in 30–35% of patients, and around 20% will eventually die of the disease.<sup>1,2</sup> The use of postoperative radiotherapy could improve tumor control and survival in those with advanced local disease (T3-4), close or positive margins, perineural or vascular invasion, multiple positive lymph nodes (LNs) (N2-3), and extracapsular extension.<sup>3</sup> However, the routine use of postoperative radiotherapy for T1-2 stage disease limited to a single, ipsilateral positive LN not larger than 3 cm (i.e., N1) without adverse features remains controversial.<sup>4</sup>

Cervical positive LNs, those most commonly related to recurrence, are recognized as among the most important prognostic factors in head and neck cancer.<sup>5</sup> Recent studies have confirmed that the number of evaluated LNs correlates with outcomes.<sup>6,7</sup> Ebrahimi et al. reported that an LN yield < 18 was associated with worse 5-year overall (hazard ratio [HR], 2.0; 95% confidence interval [CI], 1.1–3.6), disease-specific (HR, 2.2; 95% CI, 1.1–4.5), and disease-free survival (HR, 1.7; 95% CI, 1.1–2.8). Thus, LN yield  $\geq 18$  has been proposed as a cut-off point for good-quality neck dissection. Inadequate LN harvests may lead to stage migration and subsequent underestimation of disease severity.<sup>8,9</sup> Although postoperative radiotherapy was considered in those with pN1 disease, scant studies investigated the survival benefit of postoperative radiotherapy for those without adequate LN dissection.

Thus, in this study, we used data from the Surveillance, Epidemiology, and End Results (SEER) database to assess the relationship between postoperative radiotherapy and outcomes by quality of neck dissection in oral and oropharyngeal cancer patients with pT1-2N1 disease.

## Methods

### Data source and study population

SEER is an open access resource of data on patients from the United States for cancer-based epidemiology analyses. Data identification and extraction is done using the Surveillance Research Program, National Cancer Institute SEER\*Stat software ([seer.cancer.gov/SEER\\*stat](http://seer.cancer.gov/SEER*stat)) Version 8.3.2. Patients with newly-diagnosed oral and oropharyngeal cancer post primary tumor resection and neck dissection with pathological pT1-2N1M0 without extranodal extension were identified from 2004 to 2015. Patients were identified using the International Classification of Disease for Oncology, third edition (ICD-O-3) codes for oral cavity (C01-C06; C14) and oropharynx (C09-C10). These patients were staged according to the 6th edition American Joint Committee on Cancer (AJCC) classification system.<sup>10</sup> Patients with missing data such as age, gender, radiotherapy, clear AJCC TNM stage, and follow-up data were excluded. Finally, a total of 1,765 patients were recruited into this analysis (Fig. 1). Patients were divided into those who received radiotherapy within six months of surgery (the postoperative radiotherapy group) and those who did not (the observation group). The end points were the 5-year overall survival (OS) and disease-specific survival (DSS) rates. Deaths due to cancer were recorded as events and deaths secondary to other causes, at 5 years following diagnosis or the last follow up date, were recorded as censored.

### Statistical analysis

All statistical operations were performed using SPSS (version 15, SPSS Inc., Chicago, IL, USA). Categorical variables were compared with Pearson's chi-square test or Fisher's exact test. Differences in continuous variables were analyzed with one-way ANOVA. The Kaplan-Meier method was used to estimate the 5-year OS and DSS rates for the postoperative radiotherapy and the observation group. In multivariate Cox regression analyses, the therapeutic effect of postoperative radiotherapy was analyzed after adjusting for age, gender, pathological T classification, level of differentiation, year of diagnosis, and marital status. A sensitivity test were also used to evaluate the association between postoperative radiotherapy and survival outcomes.<sup>11</sup> A two-sided p-value ( $P < 0.05$ ) was considered significant.<sup>12</sup>

## Results

As shown in Table 1, a total of 1,765 newly-diagnosed oral and oropharyngeal cancer patients treated with primary tumor resection and neck dissection were enrolled, 1,108 (62.8%) diagnosed with oral cancer and 657 (37.2%) diagnosed with oropharyngeal cancer. Of these, 1,141 (64.6%) were men, the mean (standard deviation) age was 60.9 (12.4) years, and 1,067 (60.5%) underwent adjuvant radiotherapy. Patients with < 18 LNs retrieved were more likely to be older and have pT1 disease.

Table 1  
Demographic and clinical characteristics of the oral and oropharyngeal cancer patients, n = 1,765.

	Total	18 < LNs	18 ≤ LNs < 25	25 ≤ LNs	P value
Variable	n = 1,765	n = 598	n = 289	n = 878	
RT	1,067 (60.5)	354 (59.2)	184 (63.7)	529 (60.3)	0.436
Gender					
Female	624 (35.4)	230 (38.5)	100 (34.6)	294 (33.5)	0.139
Male	1,141 (64.6)	368 (61.5)	189 (65.4)	584 (66.5)	
Age, years ( Mean ± SD)	60.9 ± 12.4	62.8 ± 12.6	60.7 ± 11.9	59.7 ± 12.2	< 0.001
Pathological T classification					
T1	883 (50.0)	332 (55.5)	138 (47.8)	413 (47)	0.004
T2	882 (50.0)	266 (44.5)	151 (52.2)	465 (53)	
Differentiation					
Well	166 (9.4)	65 (10.9)	21 (7.3)	80 (9.1)	0.095
Moderately	1,021 (57.8)	329 (55)	186 (64.4)	506 (57.6)	
Poorly	578 (32.7)	204 (34.1)	82 (28.4)	292 (33.3)	
Site					
Oral cavity	1,108 (62.8)	360 (60.2)	185 (64)	563 (64.1)	0.277
Oropharynx	657 (37.2)	238 (39.8)	104 (36)	315 (35.9)	
Abbreviation: LNs, lymph nodes; RT, radiotherapy.					

Table 2 and Fig. 2 illustrate the impact of postoperative radiotherapy on 5-year OS and DSS according to the quality of the retrieved LNs (poor-quality: <18 LNs retrieved; good-quality: 18–24 LNs retrieved; high-quality: ≥ 25 LNs retrieved). Compared to the observation group, the postoperative radiotherapy group had better 5-year OS rates and DSS rates (all,  $P < 0.05$ ) in those with poor-quality neck dissection (< 18 LNs retrieved). This phenomenon was not observed in those with good-quality and high-quality neck dissection. After adjusting for other factors, the impact of postoperative radiotherapy was as follows: for those with < 18 LNs retrieved, the 5-year OS adjusted hazard ratio (aHR) was 0.64 (95% confidence interval [CI], 0.49–0.84); for those with 18–24 LNs retrieved, the aHR was 0.78 (95% CI, 0.73–1.13); for those with ≥ 25 LNs retrieved, the aHR was 0.96 (95% CI, 0.75–1.24). For 5-year DSS, in those with < 18 LNs retrieved, the aHR was 0.66 (95% CI, 0.45–0.97); for those with 18–24 LNs retrieved, the aHR was 1.07 (95%, 0.59–1.96); for those with > 25 LNs retrieved, the aHR was 1.12 (95% CI, 0.81–1.56) (Table 3). Postoperative radiotherapy had a protective effect on survival in patients with poor-quality neck dissection (< 18 LNs retrieved) alone. We also performed a sensitivity test. We assumed that some oral and oropharyngeal cancer patients might receive postoperative radiotherapy due to pathological risk features of the primary tumor, instead of nodal disease. The risk of lymphovascular, perineural invasion, or positive margin in pT1-2 disease was about 15%.<sup>13</sup> Sensitivity test showed that the protective effect of postoperative adjuvant radiotherapy remained robust in those with poor-quality neck dissection (< 18 LNs retrieved) alone (aHR, 0.61; 95% CI, 0.45–0.81)(Table 4).

Table 2

The relationship between postoperative radiotherapy and observation groups in 5-year overall and disease-free survivals among different quality of neck dissection, n = 1,765.

	LN<18				18 ≤ LN<25				25 ≤ LN			
	Total	Event (%)	Survival rate (%)	P value	Total	Event (%)	Survival rate (%)	P value	Total	Event (%)	Survival rate (%)	P value
<b>Overall Survival</b>	598	215(36.0)	60.7	< 0.001	289	88(30.5)	65.1	0.025	878	263(30.0)	64.1	0.848
Without RT	244	111(45.5)	50.4		105	40(38.1)	56.4		349	103(29.5)	65.1	
With RT	354	104(29.4)	67.8		184	48(26.1)	70.0		529	160(30.3)	63.4	
<b>Disease-Specific Survival</b>	598	109(18.2)	78.0	0.003	289	47(16.3)	80.6	0.559	878	164(16.7)	76.7	0.199
Without RT	244	56(23.0)	71.7		105	18(17.1)	78.5		349	57(16.3)	79.5	
With RT	354	53(15.0)	82.1		184	29(15.8)	81.8		529	107(20.2)	74.8	

Abbreviation: LN, lymph nodes; RT, radiotherapy.

Table 3

Multivariate analyses of risk factors regarding 5-year overall and disease-free survivals using Cox regression model among different quality of neck dissection, n = 1,765.

	LN<18		18 ≤ LN<25		25 ≤ LN	
	HR (95% C.I)	P value	HR (95% C.I)	P value	HR (95% C.I)	P value
<b>Overall Survival</b>						
With RT	0.64 (0.49–0.84)	0.001	0.73 (0.48–1.13)	0.158	0.96 (0.75–1.24)	0.769
Male	0.86 (0.66–1.13)	0.279	1.01 (0.64–1.60)	0.961	1.08 (0.83–1.40)	0.557
Age	1.03 (1.02–1.05)	< 0.001	1.04 (1.02–1.06)	< 0.001	1.01 (1.002–1.02)	0.022
Pathological T classification: T2	1.62 (1.23–2.12)	0.001	1.89 (1.21–2.96)	0.005	1.72 (1.34–2.22)	< 0.001
Differentiation: Poorly	1.11 (0.81–1.52)	0.515	1.29 (0.80–2.10)	0.301	1.18 (0.89–1.55)	0.246
Site: Oropharynx	0.43 (0.30–0.62)	< 0.001	0.46 (0.26–0.82)	0.008	0.34 (0.24–0.47)	< 0.001
<b>Disease-Specific Survival</b>						
With RT	0.66 (0.45–0.97)	0.033	1.07 (0.59–1.96)	0.822	1.12 (0.81–1.56)	0.491
Male	0.74 (0.51–1.08)	0.122	1.08 (0.58–2.01)	0.820	1.01 (0.73–1.40)	0.957
Age	1.02 (1.001–1.03)	0.043	1.03 (1.004–1.06)	0.023	1.00 (0.99–1.01)	0.715
Pathological T classification: T2	1.54 (1.06–2.25)	0.025	2.27 (1.21–4.26)	0.011	1.54 (1.12–2.12)	0.008
Differentiation: Poorly	1.26 (0.82–1.93)	0.297	1.68 (0.88–3.22)	0.117	1.34 (0.95–1.89)	0.098
Site: Oropharynx	0.33 (0.19–0.55)	< 0.001	0.19 (0.07–0.50)	0.001	0.28 (0.18–0.44)	< 0.001

\*Adjusted for age, gender, pathological T classification, differentiation, site, race, marital and insurance.  
\*\*Abbreviation: LN, lymph nodes; RT, radiotherapy.

Table 4

Multivariate analyses of risk factors regarding 5-year overall and disease-free survivals using Cox regression model among different quality of neck dissection, a sensitivity test (85%), n = 1,605.

	LN<18		18 ≤ LN<25		25 ≤ LN	
	HR (95% C.I.)	P value	HR (95% C.I.)	P value	HR (95% C.I.)	P value
<b>Overall Survival</b>						
With RT	0.61 (0.45–0.81)	0.001	0.70 (0.45–1.11)	0.128	0.99 (0.76–1.28)	0.931
Male	0.88 (0.66–1.18)	0.397	1.14 (0.69–1.87)	0.606	1.06 (0.81–1.39)	0.672
Age	1.04 (1.03–1.05)	< 0.001	1.04 (1.02–1.06)	0.001	1.01 (1.001–1.02)	0.038
Pathological T classification: T2	1.70 (1.28–2.25)	< 0.001	1.88 (1.17–3.03)	0.009	1.69 (1.30–2.20)	< 0.001
Differentiation: Poorly	1.10 (0.79–1.54)	0.562	1.27 (0.77–2.10)	0.357	1.20 (0.90–1.61)	0.209
Site: Oropharynx	0.48 (0.33–0.69)	< 0.001	0.52 (0.29–0.93)	0.028	0.33 (0.23–0.47)	< 0.001
<b>Disease-Specific Survival</b>						
With RT	0.62 (0.41–0.93)	0.020	1.06 (0.57–1.99)	0.848	1.20 (0.86–1.67)	0.297
Male	0.76 (0.51–1.13)	0.169	1.12 (0.58–2.19)	0.732	0.97 (0.70–1.36)	0.868
Age	1.02 (1.01–1.04)	0.011	1.03 (0.99–1.06)	0.054	1.00 (0.98–1.01)	0.696
Pathological T classification: T2	1.65 (1.11–2.46)	0.013	2.01 (1.04–3.91)	0.039	1.49 (1.07–2.08)	0.017
Differentiation: Poorly	1.24 (0.79–1.96)	0.353	1.71 (0.87–3.35)	0.119	1.38 (0.97–1.98)	0.077
Site: Oropharynx	0.37 (0.21–0.63)	< 0.001	0.17 (0.06–0.48)	0.001	0.29 (0.19–0.46)	< 0.001
*Adjusted for age, gender, pathological T classification, differentiation, site, race, marital and insurance.						
**Abbreviation: LNs, lymph nodes; RT, radiotherapy.						

## Discussion

In contrast to the latest NCCN guidelines which suggest adjuvant radiotherapy for patients with pN1 disease, our results demonstrated that postoperative radiotherapy was effective only in those without good-quality neck dissection (LN yield < 18).<sup>14,15</sup> The protective effect of adjuvant radiotherapy failed to reach statistical significance for those with LN yield > 18. Because of the protective role of postoperative radiotherapy in oral and oropharyngeal cancer patients with pT1-2N1M0 disease without good-quality neck dissection, the NCCN guidelines for adjuvant radiotherapy in pN1 disease without adverse features may need to be modified according to the quality of retrieved LNs.

Several studies have demonstrated that pN1 may itself be an indication for postoperative radiotherapy after resection of oral cavity primary tumors.<sup>4,16</sup> Chen et al. reported an association of postoperative radiotherapy with improved OS for 1,467 patients from the National Cancer Database with oral (HR, 0.76; 95% CI, 0.63–0.92) and oropharyngeal cancer (HR, 0.62; 95% CI, 0.41–0.92) with pN1 disease without adverse feature, especially in those younger than 70 years or those with pT2 disease. Shrime et al., in an analysis of 1,539 patients with T-2N1 oral cancer, found that 78.6% had postoperative radiotherapy, which was associated with better 5-year OS (54.2% vs 41.4%, P < 0.001).<sup>17</sup> However, from the same SEER database, Kao et al. found no significant difference in 5-year OS between patients with N1 oral cancer with and without postoperative radiotherapy (38.7% vs 36.0%, P = 0.23).<sup>18</sup> One explanation for these different results may be that inadequate LN harvests could lead to stage migration and subsequent underestimation of disease severity, especially in those with pN1 disease.<sup>5</sup> To our knowledge, our study is the first to evaluate the benefit of postoperative radiotherapy by quality of neck dissection in patients with pN1 involvement and no risk factors. Moreover, our large cohort (n = 1,765) indicates that the effect of operative radiotherapy on survival could assist clinicians in their therapeutic planning for these patients.

Because cervical LN metastasis significantly worsens the prognosis of patients with primary head and neck cancer by 50%, in general, the status of LN metastasis must be known for proper treatment.<sup>1</sup> Many studies have used LN count as a prognostic factor in head and neck cancer patients and also as a potential quality metric for neck dissection.<sup>6,8</sup> Divi et. al examined these associations in a large cohort from the U.S. National Cancer Database.<sup>19</sup> They found an independent and significant association between examining < 18 LNs and increased risk of death (hazard ratio [HR] 1.18; 95% CI, 1.13–1.22). When patients were stratified by clinical nodal stage, the hazard of death was increased in both node negative and node positive groups (HR, 1.24; 95% CI, 1.17–1.32; HR, 1.12; 95% CI, 1.05–1.19, respectively). The study found a significant overall survival advantage when > 18 LNs are examined after neck dissection, concluding that 18 LNs is an effective cutoff for improved survival.

Although several studies have outlined the importance of LN yield on head and neck cancer, few have discussed the association of postoperative adjuvant radiotherapy with the quality of neck dissection.<sup>20,21</sup> According to the latest NCCN guidelines, postoperative adjuvant radiotherapy may be considered in those with pN1 disease without other risk features.<sup>14</sup> Our study explored the impact of postoperative radiotherapy in patients with pT1-2N1M0 without extranodal extension stratified by the number of retrieved LNs. For patients without good-quality neck dissection (LN yield < 18), postoperative adjuvant therapy could reduce the mortality rate 40%. However, patients with good-quality neck dissection (LN yield > 18) did not have a statistically significant reduction in 5-year OS or DSS (Tables 3 and 4). To spare them the potential side effects of pain, dry mouth, swallowing dysfunction, and neck fibrosis, postoperative radiotherapy could be omitted in such patients.

At present, treatment protocols for head and neck cancer, such NCCN guidelines, incorporate the TNM stage, surgical margin, pathological adverse features, and response to chemotherapy or radiotherapy.<sup>14</sup> Margin status could be regarded as a proxy of surgery quality for primary tumor resection, although compartment surgery more than wide resection had better outcomes.<sup>22</sup> However, neck dissection quality is not included in the treatment guidelines, even though retrieving more than 10 LNs in elective neck dissection and more than 15 in radical neck dissection has been suggested in order to prevent stage migration.<sup>10</sup> For head and neck patients with pN1 disease, reports of the association between disease outcomes and adjuvant radiotherapy are conflicting.<sup>23,24</sup> The confusion may stem in part from the heterogenous pattern of pN1 disease (which ranges from microscopic disease to 3 cm LNs), the extent of extracapsular spread, the various cancer subsites, and the quality of the neck dissection. In 2019, an expert panel suggested adjuvant radiotherapy in oral cancer patients with pN1 disease without good-quality neck dissection (< 18 LNs) and recommended the conduct of further prospective clinical trials.<sup>25</sup> Our report provides evidence for the therapeutic effect of adjuvant radiotherapy for patients with pT1-2N1M0 oral cancer. Among patients without good-quality neck dissection, adjuvant radiotherapy could reduce the mortality rate up to 40% (aHR, 0.61; 95% CI, 0.48–0.78). Radiotherapy appears to offset the negative effect of poor-quality neck dissection and its therapeutic effect decreased as the number of retrieved LNs increased (Fig. 2).

There are several limitations in our series. First, the radiation field was not clearly described in the database. The radiation field might include the primary tumor, regional neck area, or both. These data could not be extracted from the SEER database. Second, we tried to explore the effect of postoperative radiotherapy in pT1-2N1M0 patients and assumed that the radiotherapy was probably directed to the neck region for pN1 status. However, postoperative radiotherapy could be applied to the primary site due to the pathological features of the primary tumor. The positive margin has been reported to be around 1.6% in early stage oral cancer surgery.<sup>26</sup> In T1-2 oral cancer patients, the rate of lymphovascular permeation or perineural invasion is 13.3%.<sup>26</sup> In sensitivity testing in our study, the effect of postoperative radiotherapy remained robust among patients without good-quality neck dissection, when the association of margin status, lymphovascular permeation, or perineural invasion in the primary tumor were considered. Third, the study included only pT1-2N1M0 patients. Generalization of these results to other oral cancer patients, such as those with T3-4N1M0, will require additional studies.

## Conclusions

Oral and oropharyngeal cancer patients with pT1-2N1M0 have a generally favorable prognostic outcome. However, inadequate LN harvest may lead to underestimation of disease severity. Our results suggest that postoperative radiotherapy should be considered for patients without adequate neck dissection. Modification of NCCN guidelines according to the number of retrieved LNs for postoperative radiotherapy in pN1 disease without an adverse feature may be appropriate.

## Abbreviations

NCCN, National Comprehensive Cancer Network

LNs, lymph nodes

SEER, Surveillance, Epidemiology, and End Results

ICD-O-3, International Classification of Disease for Oncology, third edition

AJCC, American Joint Committee on Cancer

TNM, tumor-node-metastasis

OS, overall survival

DSS, disease-specific survival

aHR, adjusted hazard ratio

CI, confidence interval

# Declarations

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Institutional Review Board of Chi Mei Medical Center (IRB:CMFHR10612-008).

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

**Conflicts of interest:** The authors declare that there is no conflict of interest.

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## Authors' contributions:

CCY, CHY and CCL: project conception and design, data collection, assembly, analysis and interpretation, manuscript writing. BHK, and WSL: data collection and assembly. CCY and CCL revised and approved the final manuscript. All authors read and approved the final manuscript.

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## Figures

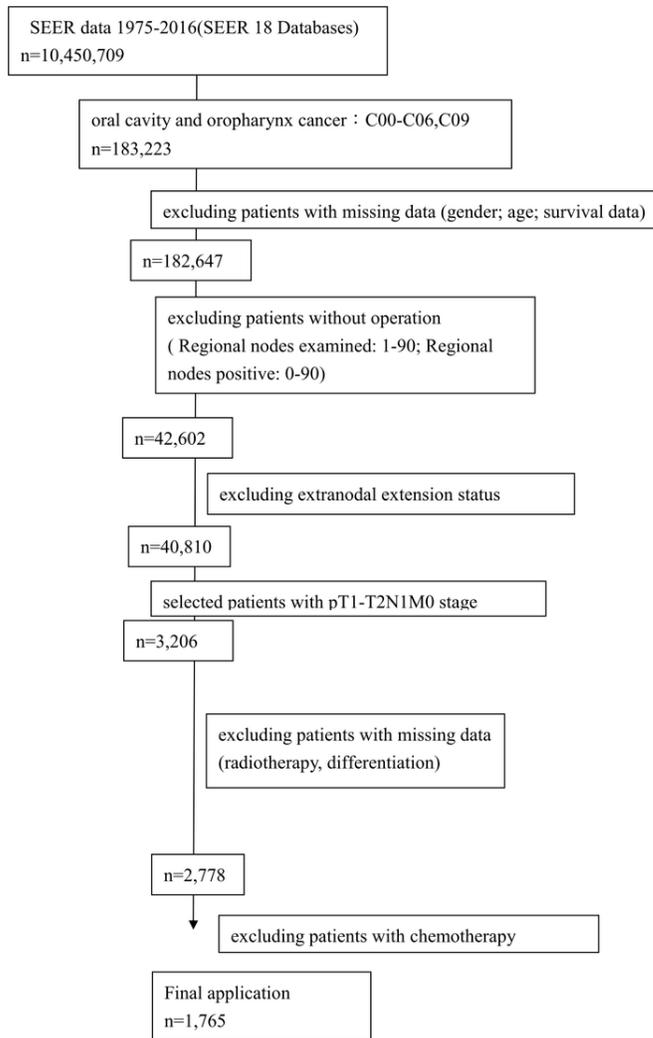


Figure 1. Patient selection flowchart.

## Figure 1

Patient selection flowchart.

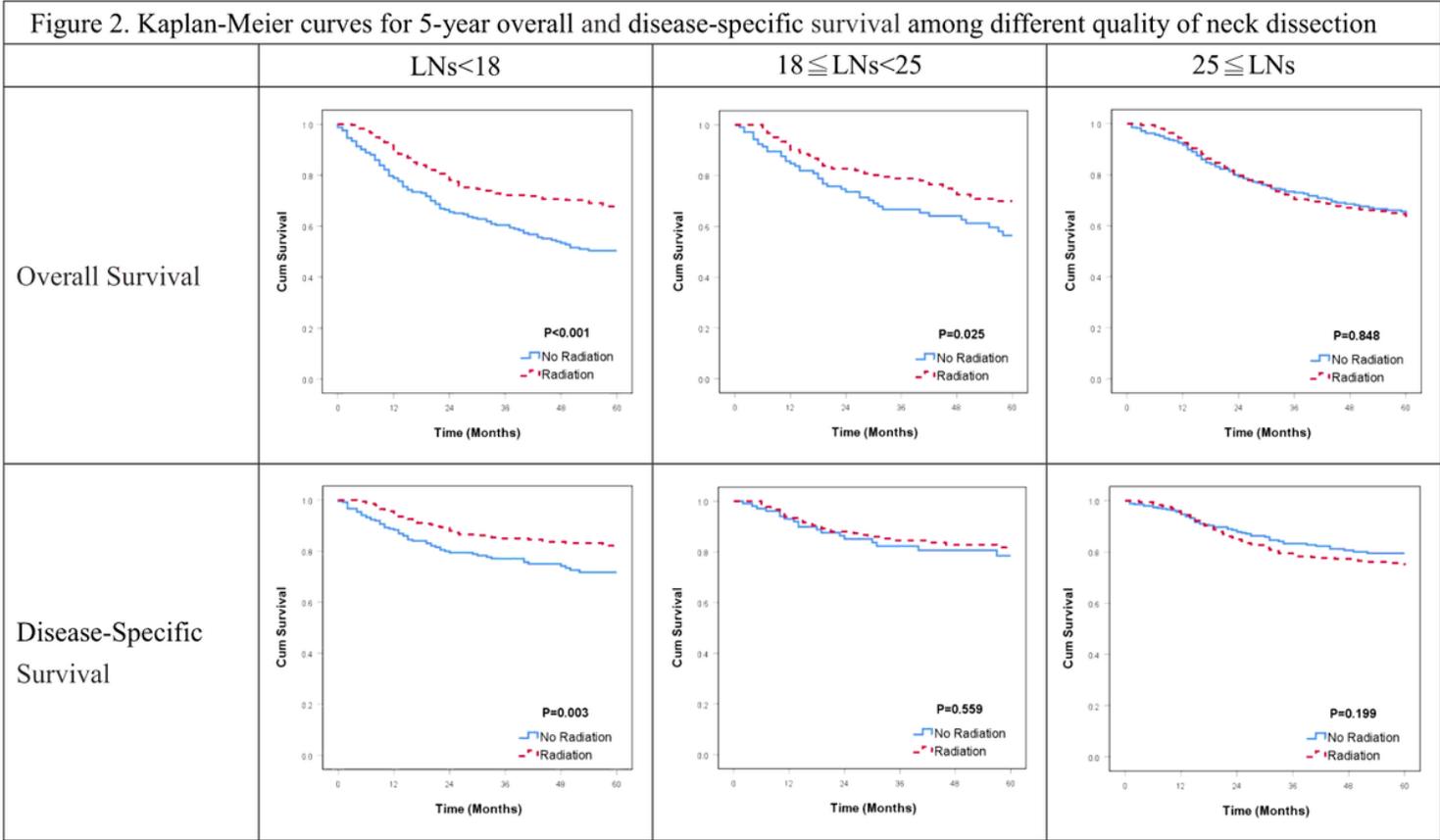


Figure 2

Kaplan-Meier curves for 5-year overall and disease-specific survival among different quality of neck dissection