

Title:

Impact of cervical lymph node metastasis on transoral surgery for hypopharyngeal squamous cell carcinoma: A retrospective multicenter study.

Running title: Impact of cervical lymph node metastasis on transoral surgery for hypopharyngeal cancer.

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Abstract

Background: Hypopharyngeal carcinoma is likely to spread to the lymph nodes, but there is no established strategy for management in transoral surgery.

Methods: We compared oncologic and functional outcomes in a retrospective multicenter study of patients who underwent transoral surgery for hypopharyngeal carcinoma between 2015 and 2021.

Results: Two hundred and thirty-two patients were included. Comparing patients with and without adjuvant radiotherapy, 3-year regional recurrence-free survival (RRFS) was not significantly different in pN2b and pN2c, but was significantly worse in pN3b without adjuvant radiotherapy. In patients without neck dissection, the 3-year RRFS was 85.6%, 76.8%, and 70.0% for T1, T2, and T3 primary lesions, respectively, and was significantly worse for T2 or higher ($p = 0.035$).

Conclusions: In the absence of extracapsular invasion, regional control did not deteriorate without adjuvant therapy. If prophylactic neck dissection is not performed, careful follow-up is necessary if the primary lesion is T2 or greater.

Introduction

Hypopharyngeal carcinoma accounts for 3~7% of all head and neck cancers and is a relatively rare disease¹⁾²⁾. Radiotherapy combined with chemotherapy (CRT) has been developed in the past 20 years, and such non-surgical treatment to preserve the larynx has been widely used with improved clinical outcomes such as survival rate³⁾. However, it has been noted out that these intensified treatments cause a significant increase in treatment-related adverse events such as mucositis, xerostomia, and long-term dysphagia⁴⁾. To prevent such adverse events, trans-cervical larynx-preserving partial pharyngectomy has been used as an alternative to CRT⁵⁾, and in recent years, transoral surgery has been performed as a less invasive surgery mainly for early stage HPC. Transoral surgery includes transoral laser microsurgery (TLM)⁶⁾, endoscopic laryngopharyngeal surgery (ELPS)⁷⁾ and transoral videolaryngoscopic surgery (TOVS)⁸⁾, which have been developed and widely used in Japan, and transoral robotic surgery (TORS)⁹⁾, a technique that has spread worldwide and has recently been used for hypopharyngeal carcinoma¹⁰⁾¹¹⁾, and good outcomes in terms of local control and survival have been reported for each technique. However, because hypopharyngeal carcinoma often presents with lymph node metastasis even when the primary lesion is relatively small¹⁾, not only minimally invasive surgery of the primary tumor but also treatment strategies for the cervical lymph nodes are important, but there have been no reports on these strategies to date. Therefore, we conducted a multicenter retrospective study of the characteristics of cervical lymph node metastasis in patients with hypopharyngeal carcinoma who underwent transoral non-robotic surgery, which has been mainly performed in Japan up to date.

Materials and Methods

The study was conducted by the Kyoto University Hospital and Affiliated Facilities Head and Neck Clinical Oncology Group (Kyoto-HNOG), includes a total of 13 tertiary care hospitals belong, and Fujita Health University Hospital. A retrospective chart review was performed of patients who underwent transoral non-robotic surgery for hypopharyngeal carcinoma with curative intent between 2015 and 2021. Eligibility criteria were patients who had undergone transoral surgery with curative intent for histopathologically confirmed squamous cell carcinoma of the hypopharynx and who also underwent neck dissection for lymph node metastasis, if clinically evident. Although there was no standardised protocol for the preoperative assessment of lymph node metastasis across all institutions, all institutions used multiple investigations, including computed tomography, magnetic resonance imaging, ^{18}F -fluorodeoxyglucose-positron emission tomography and ultrasound. Both primary and recurrent cases were included. Patients were excluded if the primary lesion was diagnosed as T4 in the 8th edition of the AJCC/UICC TNM staging system, if they had received preoperative treatment, if they had previously undergone open surgery for head and neck malignancy, or if transoral surgery was for diagnostic purposes or for debulking with gross residual tumor.

This study includes different methods of transoral non-robotic surgery. The surgical field of view was secured by FK-WO retractor (Olympus Medical Systems, Tokyo, Japan), curved rigid laryngoscope (Nagashima Medical Instrument Company, Ltd., Tokyo, Japan), or straight rigid laryngoscopes including the Weerda-type distending laryngoscope (Karl Storz, Tuttlingen, Germany). The surgical field was visualized using a flexible gastrointestinal endoscope, a conventional rigid endoscope, a flexible endoscope that can be angled in four directions such as Endoeye flex (Olympus Medical Systems), or a

microscope. When neck dissection was indicated, it was performed as a concurrent or staged procedure, depending on the philosophy and surgical practice of the institution. In addition, adjuvant therapy was not standardized and was administered according to the recommendations of the local institutional multidisciplinary tumor board. Patients with adverse pathologic features after surgery received adjuvant therapy with radiation alone (RT) or CRT. Adverse pathologic features included positive or close margins, lymphovascular invasion, perineural invasion, or advanced T classification. Radiotherapy and chemotherapy protocols varied between institutions.

Data collection included preoperative patient characteristics, history of head and neck cancer treatment, primary subsite, TNM staging, method of transoral surgery, presence of tracheostomy, postoperative adjuvant therapy, and oncologic and functional outcomes. Oncologic outcomes were evaluated based on disease-specific survival (DSS; event: death from hypopharyngeal carcinoma) and regional recurrence-free survival (RRFS; event: cervical lymph node recurrence). The functional outcome was dysphagia at 1 month and 1 year after transoral surgery, defined as the inability to take an adequate amount of food orally, requiring oral or tube feedings to supplement nutrition. Institutional review board approval was obtained for a waiver of consent for this retrospective review at each institution. Each record was de-identified and then collected from each institution using a standardized data collection form. Individual institutions collected data sets, and the analysis was pooled across institutions.

Statistical analysis was performed using R software, version 4.2.2 (The R foundation for Statistical Computing, Vienna, Austria). We described the patient and lesion characteristics using median and interquartile range (IQR) for continuous variables and number and percentage (%) for categorical variables. Kaplan-Meier methods were used

for oncologic outcomes, with the log-rank test used to compare between groups, and 95% confidence interval (CI) were calculated. Categorical variables were compared between groups for functional outcomes using Fisher's exact test. All p-values <0.05 were considered to be statistically significant.

Results

Patient and lesion characteristics

Two hundred and thirty-two patients met the criteria for analysis in the study, with a median follow-up of 33 months (IQR: 18-55). Patient and lesion characteristics are shown in Table 1, divided into two groups: one with neck dissection (the ND group) and the other without neck dissection (the non-ND group). A total of 179 patients in both groups had a preoperative diagnosis of cN0, but only 7 of them (3.9%) underwent prophylactic neck dissection. Few of the patients in the ND group had prior transoral surgery or (C)RT, but in the non-ND group, 16 (9.3%) had prior transoral surgery and 14 (8.1%) had prior (C)RT. There were 103 (59.9%) T1 cases in the ND group and 19 (31.7%) in the non-ND group, a significant difference in pT classification. The pN classification of the ND group was pN0 in 10 cases (16.7%), pN1 in 9 cases (15.0%), pN2a in 2 cases (3.3%), pN2b in 18 cases (30.0%), pN2c in 2 cases (3.3%), and N3b in 19 cases (31.7%). In adjuvant therapy, CRT was performed in 4 patients (2.3%) and RT in 4 patients (2.3%) in the non-ND group, while CRT was performed in 18 patients (30.0%) and RT in 10 patients (16.7%) in the ND group, a significant difference.

Oncologic outcome

Survival analysis of patients with and without lymph node metastasis showed that 3-year DSS were significantly lower in the group with lymph node metastasis than in the

group without lymph node metastasis (88.8% vs. 98.5%, $p = 0.0014$), but RRFS was similar in both groups at approximately 83% (Figure 1). Next, we performed a survival analysis of patients with lymph node metastases differentiated by adjuvant therapy (Figure 2). The 3-year DSS was 90.0%, 87.5%, and 88.1% in the no adjuvant therapy, adjuvant RT, and adjuvant CRT groups, with no significant difference, and the 3-year RRFS was 78.3%, 72.9%, and 94.1%, respectively, slightly better in the adjuvant CRT group but not significantly. Further analysis of pN classification showed no difference in 3-year DSS between patients with and without adjuvant (C)RT for pN2b and pN2c, and no improvement in 3-year RRFS with adjuvant (C)RT, whereas 3-year DSS was worse without adjuvant (C)RT for pN3b, although not significantly, and 3-year RRFS was significantly worse (Figure 3). Two of the 11 patients with pN1 or pN2a had received adjuvant RT, but there were no regional recurrences with or without adjuvant RT.

Then, analysis of regional recurrence in patients who underwent only transoral surgery and no neck dissection for cN0 showed 1-year and 3-year RRFS of 95.0% (95% CI: 90.7 – 99.4) and 85.6% (95% CI: 77.7 – 94.2) for pT1, 81.9% (95% CI: 72.3 – 92.8) and 76.8% (95% CI: 65.9 – 89.5) for pT2, and 70.7% (95% CI: 47.6 – 100) and 70.0% (95% CI: 46.7 – 100) for pT3, respectively (Figure 4), with pT1 having significantly fewer regional recurrences ($p = 0.035$). Salvage treatment for regional recurrence by pT classification in patients without prophylactic neck dissection is shown in Table 2. All patients with regional recurrence were salvaged for curative intent, and most of them underwent surgery. Survival analysis of patients who underwent only transoral surgery without neck dissection with or without regional recurrence showed no difference in 3-year DSS, which was good in all cases (Figure 5).

Functional outcome

Table 3 shows the frequency of dysphagia in the groups that underwent transoral surgery alone and those that underwent transoral surgery with neck dissection. In the group that underwent transoral surgery alone, there were 7 cases (4.1%) of dysphagia at 1 month and 4 cases (2.4%) at 1 year postoperatively, while in the group that underwent transoral surgery with neck dissection, there were 5 cases (8.3%) and 4 cases (7.3%), respectively, with no statistically significant difference. Table 4 shows the frequency of each dysphagia due to adjuvant therapy in the patients who underwent transoral surgery and neck dissection. There were 4 cases (12.5%) of dysphagia at 1 month and 3 cases (11.1%) at 1 year postoperatively in the group with no adjuvant therapy, 1 case (5.6%) and 1 case (5.6%), respectively, in the group with adjuvant CRT, and no cases of dysphagia in the group with adjuvant RT.

Discussion

Hypopharyngeal carcinoma has a poor prognosis among head and neck cancers, and no consensus has been reached on treatment choices and appropriate combinations of surgery and RT or CRT. CRT has been the mainstay of treatment for hypopharyngeal cancer with the goal of organ preservation. However, it has become clear that organ preservation by nonsurgical treatment does not necessarily lead to functional preservation, and early and late toxicity is also evident. Therefore, transoral surgery has been developed as a refined function-preserving procedure. Initially, TORS was mainly indicated for tumors in the oropharynx, but the indication has gradually expanded to include the supraglottic larynx and hypopharynx. Especially in Japan, transoral non-robotic surgery using various instruments, such as ELPS and TOVS, has been performed for laryngo-pharyngeal cancer. Although there are various reports on the indications and local control results of such

transoral surgery for hypopharyngeal carcinoma, there are no studies on the appropriate treatment in combination with transoral surgery for lymph node metastases, which are relatively common in hypopharyngeal carcinoma. Therefore, we performed this retrospective multicenter study of cervical lymph node metastasis in patients with transoral nonrobotic surgery for hypopharyngeal carcinoma.

In our study, survival was significantly worse in patients with lymph node metastases than in those without lymph node metastases, but regional control was comparable. And in patients with lymph node metastasis, adjuvant CRT improved regional control but not survival. In addition, when comparing by extent of lymph node metastasis, regional control was also improved only in patients with pN3b. The difference in survival between patients with and without cervical lymph node metastases, even though there is no difference in the frequency of regional recurrence, may be partly due to the difficulty of salvage treatment for regional recurrence after neck dissection. Tsou et al. performed a retrospective study showing that disease-specific survival with surgery alone was superior in stage I-II hypopharyngeal carcinoma, but significantly worse than surgery plus adjuvant CRT in stage III and stage IV¹²⁾. There have been several reports of transoral surgery for hypopharyngeal carcinoma, and adjuvant (C)RT has often been performed. In a report on TLM, Martin et al. reported that adjuvant RT was performed in 52% of all patients, and the 5-year DSS was 96% for stage I-II, 86% for stage III, and 57% for stage IV¹³⁾. Weiss et al. reported that 48% of all patients underwent adjuvant CRT, and 5-year OS was 68.2% for stage I-II, 65.9% for stage III, and 44.5% for stage IV¹⁴⁾. In a report on TORS, Mazerolle et al. reported 57 cases, 98% of which were T1-2, and more than 50% of all patients received adjuvant therapy, with a 4-year OS of 66%¹¹⁾. In a report on TOVS, adjuvant RT was performed in 25% of all cases, which was similar to our study,

but neoadjuvant chemotherapy was performed in 28%, mainly in those with advanced primary lesions, with 5-year DSS in 94.3% and 5-year DFS in 73.0% of cases¹⁵). Although it is difficult to make a simple comparison because these reports used the 7th edition of the AJCC/UICC TNM staging system, and did not examine the effect of extracapsular invasion of lymph node metastases, our study showed no improvement in survival with postoperative RT or CRT in the absence of extracapsular invasion of lymph node metastases, suggesting that adjuvant therapy is not necessary for all cases of hypopharyngeal carcinoma with cervical lymph node metastases treated with transoral surgery and neck dissection. In our opinion, it may be reasonable to determine the indication for adjuvant therapy of cervical lymph node metastasis based on the adverse features such as extracapsular invasion.

In most reports of transoral surgery for hypopharyngeal carcinoma, neck dissection was performed in a high percentage of cases, including prophylactic cases. In the TLM reports, neck dissection was performed in 88% to 93% of cases¹³⁾¹⁴), in the TORS reports in 72% to 100% of cases¹⁰⁾¹¹⁾¹⁶), and in the TOVS report from Japan, neck dissection was performed only when lymph node metastasis was suspected preoperatively¹⁵). In the present study, when transoral surgery alone was performed for patients with hypopharyngeal carcinoma without preoperative suspicion of lymph node metastasis, regional recurrence was observed in about 20% of patients with T2 primary lesions and in about 30% of patients with T3 primary lesions, and most of these cases occurred within one year. However, even when regional recurrence occurred in patients who did not undergo neck dissection, survival did not worsen in any of the T classifications and salvage treatment, mainly surgery, was effective. However, it is necessary to follow patients carefully for one year after surgery and to establish a system for prompt salvage

treatment if recurrence is suspected. These results suggest that prophylactic neck dissection may not always be necessary in transoral surgery for hypopharyngeal cancer, but this should be investigated in future randomised controlled trials.

Regarding postoperative functional outcomes in the present study, there was no significant difference in the incidence of dysphagia requiring nutritional support due to inadequate food intake with or without neck dissection or adjuvant (C)RT. Tomifuji et al. also found no association between dysphagia after TOVS and neck dissection or adjuvant (C)RT¹⁵⁾, suggesting that neck dissection and adjuvant (C)RT are not risk factors for severe dysphagia. However, although the study was of oropharyngeal carcinoma, the phase II clinical trial ORATOR¹⁷⁾ of TORS + neck dissection versus definitive (C)RT reported better swallowing-related quality of life outcomes in the definitive (C)RT arm at 1 year, possibly in part because 71% of the TORS + neck dissection group also received adjuvant (C)RT, suggesting that the combination of transoral surgery with neck dissection and adjuvant (C)RT may increase the risk of dysphagia, including mild dysphagia. We believe that skipping neck dissection or adjuvant therapy should be considered as an option if it does not compromise the oncologic outcome.

Although the role of transoral surgery in the treatment of hypopharyngeal carcinoma has not yet been established, transoral surgery, like open surgery, has the main advantage over definitive CRT in that important pathological data can be obtained from the specimen and the indication for postoperative treatment can be determined based on adverse pathological features, and it also has better functional outcomes than external incision surgery¹⁸⁾. To date, there have been only a few multicenter studies of transoral surgery for hypopharyngeal carcinoma, and the present study included a larger number of patients. We believe that the present study demonstrates that adjuvant (C)RT and prophylactic neck

dissection can also be limited to selected cases based on pathologic features in hypopharyngeal carcinoma where the primary lesion is considered an indication for transoral surgery.

On the other hand, this observational study has several limitations. First, it is a retrospective study and thus has several biases. The heterogeneity in the determination of indications for surgery and adjuvant treatment between centers, as well as the variability and missing data in the reported pathological data, limit a definitive comparative analysis. Prospective studies with standardized endpoints and protocols are needed to overcome this problem. In addition, the mean follow-up time is approximately 33 months, which may limit definitive conclusions regarding oncologic outcomes. Nevertheless, this study may still be useful in achieving good oncologic outcomes with a less invasive combination of transoral surgery and other treatments for hypopharyngeal carcinoma.

Conclusion

A multicenter retrospective study of transoral non-robotic surgery for patients with hypopharyngeal carcinoma was conducted to compare treatment and outcomes for cervical lymph node metastases. There was no improvement in survival with adjuvant (C)RT in patients with cervical lymph node metastases treated with transoral surgery and neck dissection in the absence of extracapsular invasion. When transoral surgery alone was performed in patients without cervical lymph node metastasis, more than 20% of patients with primary lesions of T2 or greater developed regional recurrence within 1 year, so careful follow-up is necessary.

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Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Figure legends

Table 1: Patient and lesion characteristics

Abbreviations: ND, neck dissection. TOS, transoral surgery. RT, radiotherapy. CRT, chemoradiotherapy.

Table2: Adjuvant therapy and salvage treatment for regional recurrence by pT classification in patients without prophylactic neck dissection.

Abbreviations: TOS, transoral surgery. (C)RT, (chemo)radiotherapy.

* $p < 0.05$.

Table3: Postoperative dysphagia with and without neck dissection.

Abbreviations: TOS, transoral surgery. ND, neck dissection.

Table 4: Postoperative dysphagia by adjuvant therapy after transoral surgery and neck dissection.

Abbreviations: TOS, transoral surgery. ND, neck dissection. CRT, chemoradiotherapy. RT, radiotherapy.

Figure 1: Disease-specific survival (DSS) and regional recurrence-free survival (RRFS) by lymph node metastasis.

A: DSS by lymph node metastasis

B: RRFS by lymph node metastasis

Figure 2: Disease-specific survival (DSS) and regional recurrence-free survival (RRFS) by adjuvant therapy.

A: DSS by adjuvant therapy

B: RRFS by adjuvant therapy

Figure 3: Disease-specific survival (DSS) and regional recurrence-free survival (RRFS) by adjuvant therapy for pN2b and pN2c, and pN3b.

A: DSS by adjuvant therapy for pN2b and pN2c

B: RRFS by adjuvant therapy for pN2b and pN2c

C: DSS by adjuvant therapy for pN3b

D: RRFS by adjuvant therapy for pN3b

Figure 4: Regional recurrence-free survival (RRFS) by pT classification in patients without prophylactic neck dissection.

Figure 5: Disease-specific survival (DSS) of patients without prophylactic neck dissection by regional recurrence.

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Table 1: Patient and lesion characteristics

Characteristic	Non-ND group N = 172 ¹	ND group N = 60 ¹	p-value ²
Age (yrs)	70.0 (63.0, 74.0)	67.0 (61.0, 73.0)	0.236
Sex			0.927
male	157 (91.3%)	55 (91.7%)	
female	15 (8.7%)	5 (8.3%)	
Prior TOS	16 (9.3%)	1 (1.7%)	0.080
Prior (C)RT	14 (8.1%)	0 (0.0%)	0.024
Subsite			0.002
Posterior wall	47 (27.3%)	7 (11.7%)	
Posterioroid	21 (12.2%)	2 (3.3%)	
Pyiform sinus	104 (60.5%)	51 (85.0%)	
Concurrent ND	0 (0.0%)	52 (86.7%)	<0.001
pT classification			<0.001
T1	103 (59.9%)	19 (31.7%)	
T2	58 (33.7%)	31 (51.7%)	
T3	11 (6.4%)	10 (16.7%)	
cN classification			<0.001
cN0	172 (100.0%)	7 (11.7%)	
cN+	0 (0.0%)	53 (88.3%)	
pN classification			<0.001
pN0		10 (16.7%)	

Characteristic	Non-ND group N = 172 ¹	ND group N = 60 ¹	p-value²
pN1		9 (15.0%)	
pN2a		2 (3.3%)	
pN2b		18 (30.0%)	
pN2c		2 (3.3%)	
pN3b		19 (31.7%)	
Adjuvant CRT	4 (2.3%)	18 (30.0%)	<0.001
Adjuvant RT	4 (2.3%)	10 (16.7%)	
To local	7 (4.1%)	18 (30.0%)	<0.001
To neck	7 (4.1%)	26 (43.3%)	<0.001

¹Median (IQR); n (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2: Adjuvant therapy and salvage treatment for regional recurrence by pT classification in patients without prophylactic neck dissection.

Characteristic	T1N0, N = 103 ¹	T2N0, N = 58 ¹	T3N0, N = 11 ¹	p-value ²
Prior TOS	11 (10.7%)	4 (6.9%)	1 (9.1%)	0.761
Prior (C)RT	7 (6.8%)	7 (12.1%)	0 (0.0%)	0.411
Adjuvant (C)RT to neck	1 (1.0%)	4 (6.9%)	2 (18.2%)	0.010*
Regional recurrence	11 (10.7%)	12 (20.7%)	4 (36.4%)	0.032*
Salvage treatment				0.196
Surgery	7 (63.6%)	11 (91.7%)	4 (100.0%)	
(C)RT	4 (36.4%)	1 (8.3%)	0 (0.0%)	

¹Median (IQR); n (%)

²Kruskal-Wallis rank sum test; Fisher's exact test

Table 3: Postoperative dysphagia with and without neck dissection.

Characteristic	TOS only N = 172 ¹	TOS + ND N = 60 ¹	p-value ²
Dysphagia at 1 month	7 (4.1%)	5 (8.3%)	0.307
Dysphagia at 1 year	4 (2.4%)	4 (7.3%)	0.108

¹n (%)

²Fisher's exact test

Table 4: Postoperative dysphagia by adjuvant therapy after transoral surgery and neck dissection.

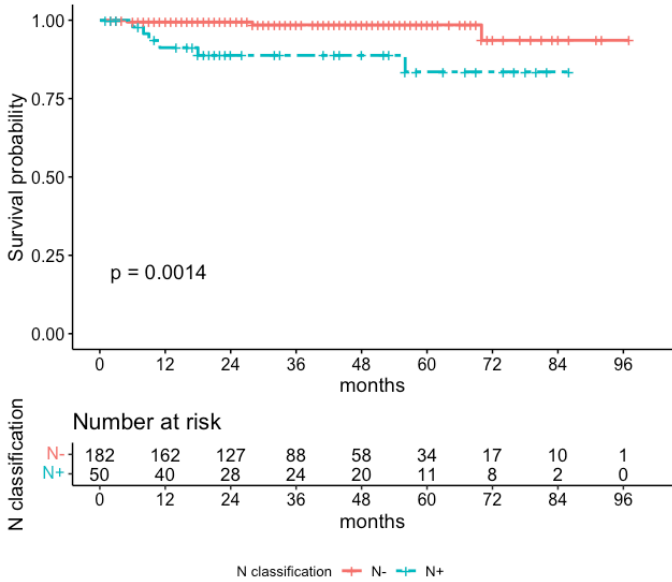
Characteristic	TOS + ND only N = 32¹	TOS + ND + adjuvant CRT N = 18¹	TOS + ND + adjuvant RT N = 10¹	p-value²
Dysphagia at 1 month	4 (12.5%)	1 (5.6%)	0 (0.0%)	0.559
Dysphagia at 1 year	3 (11.1%)	1 (5.6%)	0 (0.0%)	0.657

¹n (%)

²Fisher's exact test

Figure 1: Disease-specific survival (DSS) and regional recurrence-free survival (RRFS) by lymph node metastasis.

A



B

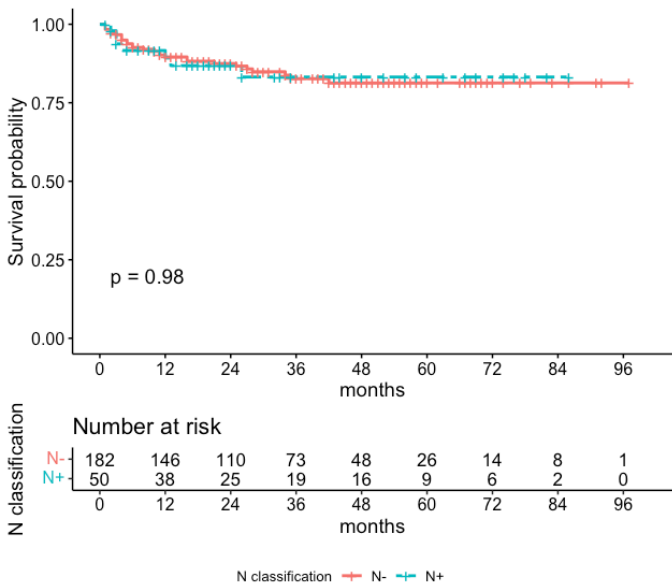
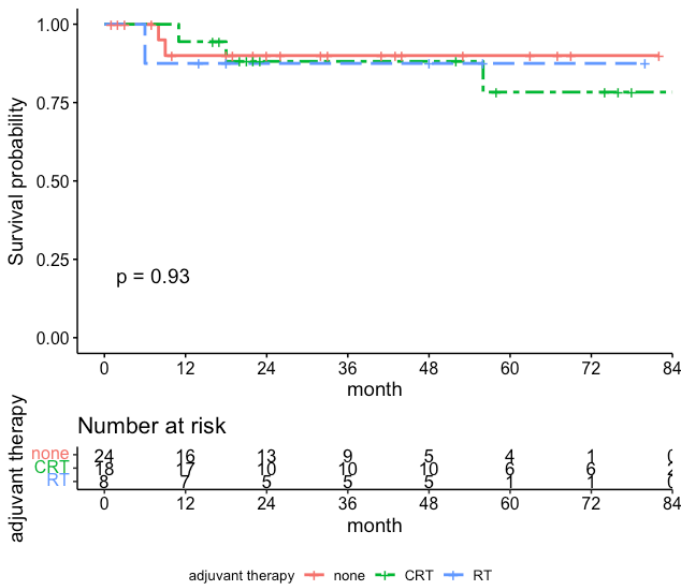


Figure 2: Disease-specific survival (DSS) and regional recurrence-free survival (RRFS) by adjuvant therapy.

A



B

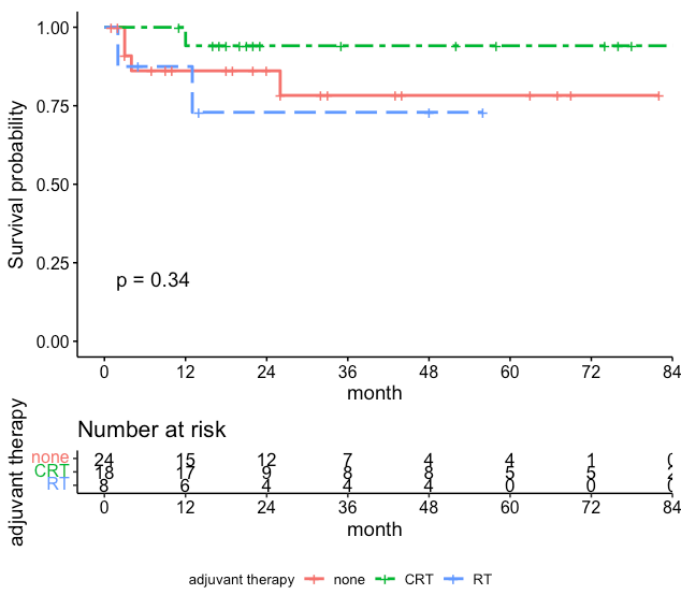
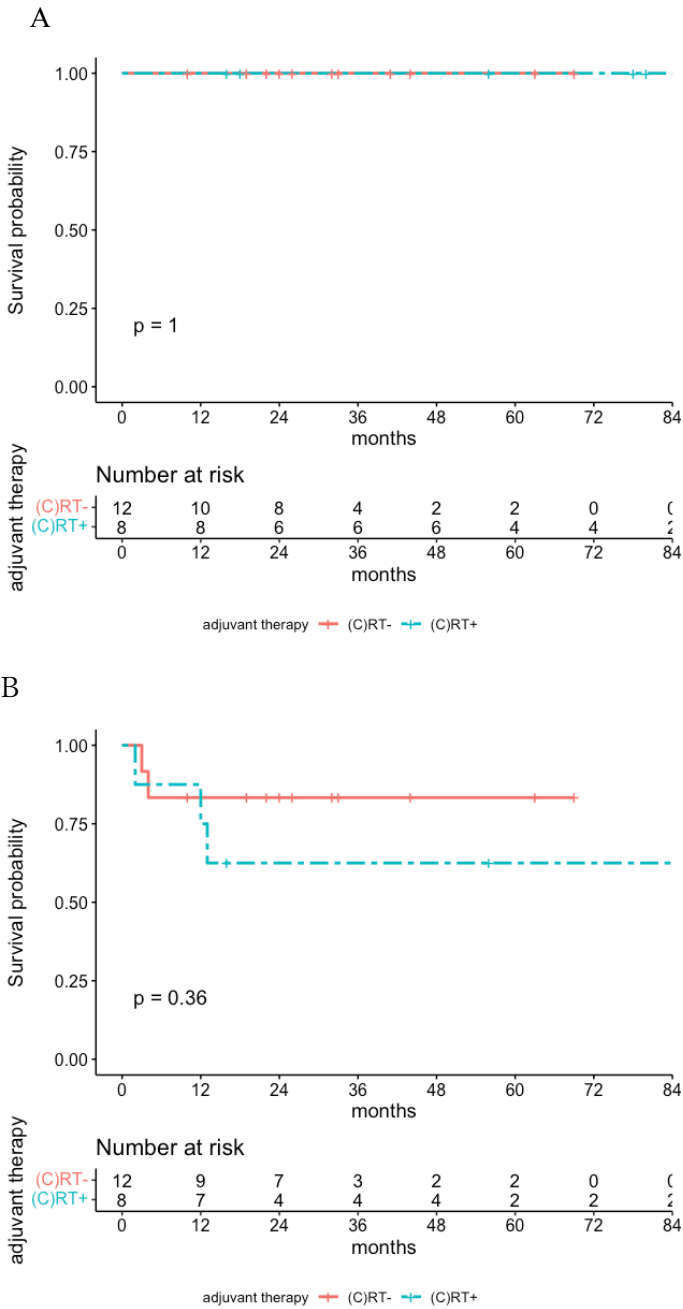
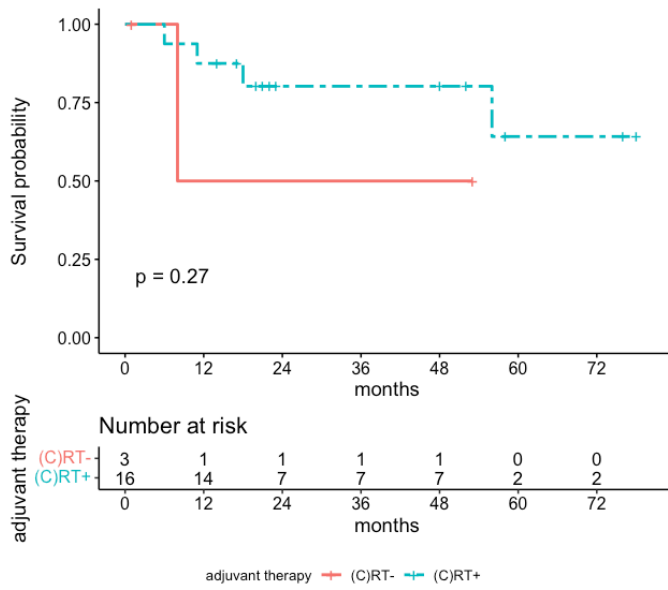


Figure 3: Disease-specific survival (DSS) and regional recurrence-free survival (RRFS) by adjuvant treatment for pN2b and pN2c, and pN3b.



C



D

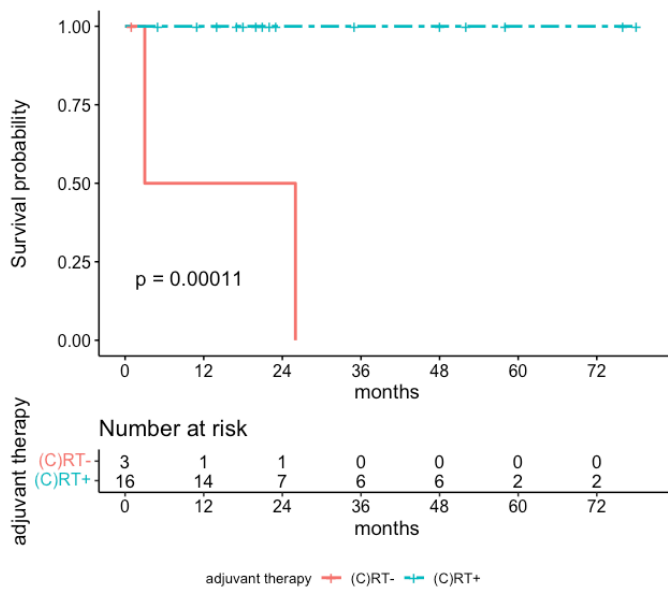


Figure 4: Regional recurrence-free survival (RRFS) by pT classification in patients without prophylactic neck dissection.

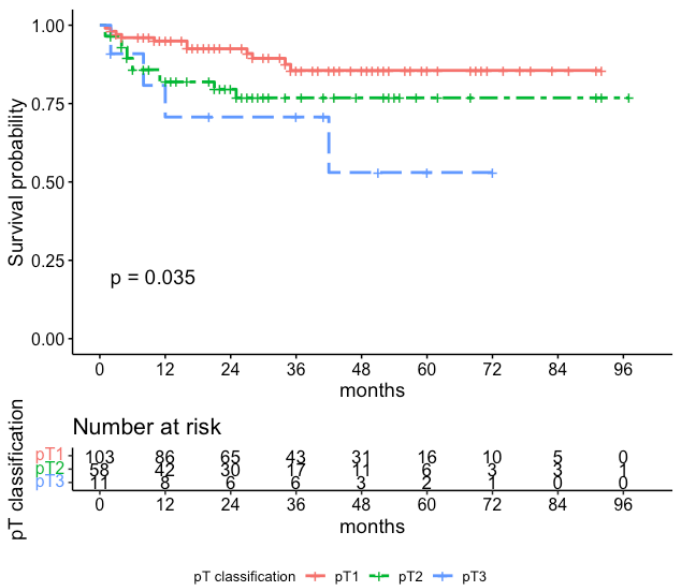


Figure 5: Disease-specific survival (DSS) of patients without prophylactic neck dissection by regional recurrence.

