

# Management of the N0 neck in recurrent laryngeal squamous cell carcinoma

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**Abstract.** The most effective therapeutic approach for the node-negative (N0) neck in patients with recurrent laryngeal squamous cell carcinoma (SCC) remains a subject of dispute. In the present study, the records of 163 patients with recurrent laryngeal SCC were retrospectively reviewed. All patients had a N0 neck at recurrence. At the time of recurrence, the N0 neck was managed using a wait-and-see strategy (observation group) or treatment (treatment group). A total of 125 (76.7%) patients accepted the wait-and-see strategy and 38 (23.3%) patients underwent treatments, including surgery, radiotherapy and/or chemotherapy. The Kaplan-Meier method with the computation of log-rank was used for analysis of survival. The t-test,  $\chi^2$  test or Fisher's exact test was used for comparisons of non-survival data in the groups.  $P < 0.05$  was considered to indicate a statistically significant difference in the two-sided tests. The 3- and 5-year overall survival rates after recurrence were 64.5 and 54.6% for the observation group, and 49.9 and 42.5% for the treatment group, respectively ( $P = 0.011$ ). The present study suggests that a wait-and-see policy is a satisfactory management option for the N0 neck in recurrent laryngeal SCC.

## Introduction

Head and neck cancer is a broad term that encompasses epithelial malignancies arising in the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx (1). Approximately 59,300 new cases and 12,300 fatalities due to head and neck cancer were expected to occur in the United States in 2015 (2). Laryngeal

squamous cell carcinoma (SCC) accounts for 22.9% of all cases of head and neck cancer (2). Treatment failure is common in laryngeal SCC, and the probability of recurrence increases with T stage from 11 to 27% in early-stage disease (T1-T2), to 31-40% in advanced stage disease (T3 and T4) (3-6). Based on the primary tumor location, laryngeal SCC can be classified as supraglottic, glottic or subglottic. The incidence of subglottic carcinoma is relatively rare, accounting for 1-8% of all cases of laryngeal SCC (7). The majority of subglottic carcinomas are often diagnosed at a late stage of the disease, at which point surgery is difficult; furthermore, the neck may be directly involved without evidence of cartilage invasion, and the insidious neck involvement contributes to a poorer prognosis and a higher postoperative recurrence rate (8).

The larynx and the surrounding area are the most frequent sites of recurrence in laryngeal cancer, followed by the regional lymph nodes and distant sites, with recurrence at a combination of these sites being less frequent (3,9). The optional management strategies for the primary tumor in recurrent laryngeal SCC are salvage surgery, including salvage total laryngectomy (STL), salvage partial laryngectomy (SPL) or endoscopic resection with a CO<sub>2</sub> laser (ERL), followed by re-irradiation with or without chemotherapy; supportive treatment and palliative chemotherapy are less effective options. Surgery is predominantly used for salvage in patients with recurrent laryngeal cancer following the failure of non-surgical treatments (radiation or chemoradiation) (10-12). ERL is only suitable for a small group of patients with early-stage disease. As it has equivalent outcomes and lower rates of treatment-associated morbidity, ERL is currently used more frequently than open SPL for the treatment of recurrent early-stage disease (10). As conservative surgical techniques, SPL and ERL should only be considered for selected groups of patients without advanced loco-regional disease (10,11). For patients who have previously undergone surgery, a second or third surgery is usually the first choice for radical treatment over radiotherapy and chemotherapy (13,14). Patients with recurrent advanced-stage disease and those with subglottic extension should generally be treated using STL. The use of adjuvant therapy depends on a number of risk factors. Re-irradiation with or without chemotherapy is commonly reserved for inoperable recurrent locally advanced disease; as an adjunct or palliative treatment, this strategy is the only technique that may achieve long-term loco-regional

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control and possibly prolong survival (15). Although a relatively high incidence of treatment-related complications has been reported, re-irradiation should be considered for patients in whom salvage surgery is not feasible (15). Therefore, re-irradiation with concurrent systemic therapy is recommended when: i) The sites of recurrence are not resectable; ii) the surgical margins are positive in the primary surgery; and iii) the patient has not previously undergone radiotherapy and their general condition is suitable for radiotherapy. Similar to metastatic disease, palliative systemic chemotherapy is the preferred treatment approach for patients with recurrence who are not eligible for either surgery or radiotherapy. The 5-year overall survival rate for patients with local recurrence varies greatly, from 18 to 65%, although certain studies have reported the 5-year overall survival rate for patients with nodal or systemic recurrence to be as low as 2% (5,16-19).

As described above, the optimal treatments for the primary tumor in recurrent laryngeal SCC are well established. However, there is no generally accepted treatment approach for the N0 neck in recurrent laryngeal SCC. The reported disease-specific 5-year survival rate after salvage laryngectomy ranges from 25-88.6% (12,19-21).

The reported rates of pathologically-confirmed positive lymph node involvement in patients with a clinically-diagnosed N0 neck receiving salvage laryngeal surgery following recurrence range from 3-20% (22-28). The main therapeutic choices for the N0 neck in recurrent laryngeal SCC are intervention or a wait-and-see policy. Intervention policies include neck dissection, irradiation or comprehensive therapy based on a combination of surgery, radiotherapy and chemotherapy. Whether these treatments can provide additional protection from local, regional or distant recurrence remains to be elucidated. However, certain studies have reported that interventions, particularly neck dissection, are associated with higher rates of complications, such as salivary fistula or leakage, wound infection and wound dehiscence (28). At the same time, such interventions may lead to unnecessary pain and suffering, prolong the overall treatment time and increase the economic burden to patients. For these reasons, a wait-and-see policy has been proposed as an alternative management for the N0 neck in recurrent laryngeal SCC.

In the present retrospective study of medical records from two institutions, a series of 163 consecutive patients with recurrent laryngeal SCC who had a N0 neck at recurrence were reviewed. The N0 neck was managed using intervention treatments or a wait-and-see policy. The aim of the study was to assess the outcomes of these management strategies in terms of overall survival, and provide knowledge that may help to tailor the most appropriate treatment for the N0 neck in patients with recurrent laryngeal SCC.

## Materials and methods

**Characteristics of the patients and enrollment criteria.** A total of 2,091 patients with laryngeal SCC were retrospectively analyzed [1,621 patients treated between 1996 and 2009 at Sun Yat-sen University Cancer Center (Guangzhou, China) and 470 patients treated between 2006 and 2013 at Zhejiang Cancer Hospital (Zhejiang, China)]. Of these 2,091 patients, 309 (14.8%) were diagnosed with recurrent laryngeal SCC. Of

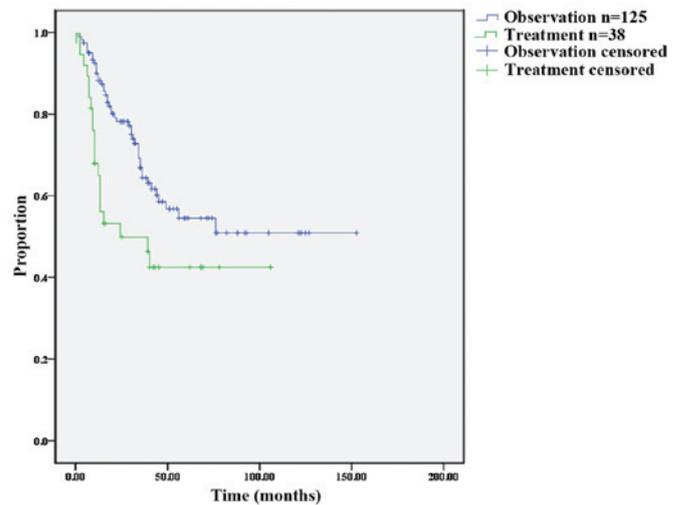


Figure 1. Comparison of survival following recurrence between patients in the observation and treatment groups. Significance in survival was noted in the observation group. P-value is 0.011.

these, 163 patients had a node-negative (N0) neck at recurrence. Only patients in whom the initial cancer was completely cured with radiation therapy, surgery and/or in combination with chemotherapy were included in this study. Patients with any clinical evidence of lymph node metastases or distant metastases at the time of recurrence were excluded from the analysis.

A total of 163 patients (160 males, 98.2%; 3 females, 1.8%) were retrospectively analyzed (123 patients treated at Sun Yat-sen University Cancer Center and 40 patients treated at Zhejiang Cancer Hospital), with a median age of 59 years (range, 41-83 years) and male:female ratio of 160:3. The basal demographic and clinical characteristics of each patient at initial diagnosis were recorded, including gender, age, blood type, smoking index, alcohol consumption, initial cancer stage and histological grade, as well as the initial treatments and salvage treatments. All the patients were restaged according to the International Union Against Cancer 2002 cancer staging system (<http://www.uicc.org/tnm-classification-malignant-tumours-6th-edition>).

The complete demographic and clinicopathological features of the 163 patients are shown in Table I. At initial diagnosis, 105 (64.4%) of the 163 patients exhibited glottic carcinoma, 52 (31.9%) exhibited supraglottic carcinoma and 6 (3.7%) exhibited subglottic carcinoma. A total of 78 patients (47.9%) exhibited well-differentiated tumors, 66 (40.5%) exhibited moderately differentiated tumors and 19 (11.7%) exhibited poorly differentiated tumors. Overall, 70 (42.9%) patients exhibited T1 tumors, 58 (35.6%) exhibited T2, 20 (12.3%) exhibited T3 and 15 (9.2%) exhibited T4. The majority of them (140, 85.9%) were N0 in the neck, 6 (3.7%) were N1, 16 (9.8%) were N2 and 1 (0.1%) was N3. The initial tumor and neck stages of the patients are summarized in Table II.

Tables III and IV summarize the initial and salvage treatments for the 163 patients. At the two hospitals in this study, the management strategy for the N0 neck in recurrent laryngeal SCC varied depending on the primary physician and the choice of the patient. The N0 neck was managed using a wait-and-see policy following salvage treatment for the

Table I. Clinicopathological features of the 163 patients with recurrent laryngeal squamous cell carcinoma.

Clinicopathological features	Observation group (n=125)	Treatment group (n=38)	P-value
Age, years			
Median (range)	59 (41-79)	58 (42-83)	0.978 <sup>a</sup>
Total length of follow-up, months			
Median (range)	50 (8-176)	41 (7-123)	0.043 <sup>a</sup>
Post-salvage follow-up, months			
Median (range)	32 (1-153)	14 (0-106)	0.079 <sup>a</sup>
Smoker, n (%)			
Yes	109 (87.2)	29 (76.3)	0.124 <sup>b</sup>
No	16 (12.8)	9 (23.7)	
Alcohol consumer, n (%)			
Yes	52 (41.6)	14 (36.8)	0.707 <sup>b</sup>
No	73 (58.4)	24 (63.2)	
Gender, n (%)			
Male	123 (98.4)	37 (97.4)	0.552 <sup>b</sup>
Female	2 (1.6)	1 (2.6)	
Blood type, n (%)			
A	32 (25.6)	12 (31.6)	0.597 <sup>b</sup>
B	34 (27.2)	12 (31.6)	
AB	11 (8.8)	4 (10.5)	
O	48 (38.4)	10 (26.3)	
Differentiation, n (%)			
Good	59 (47.2)	19 (50.0)	0.868 <sup>b</sup>
Moderate	52 (41.6)	14 (36.8)	
Poor	14 (11.2)	5 (13.2)	
Tumor location, n (%)			
Glottic	79 (63.2)	26 (68.4)	0.839 <sup>b</sup>
Supaglottic	41 (32.8)	11 (28.9)	
Subglottic	5 (4.0)	1 (2.6)	

<sup>a</sup>T-test; <sup>b</sup> $\chi^2$  test.

primary tumor in 125/163 (76.7%) patients (observation group) and 38/163 (23.3%) patients received comprehensive treatment for the N0 neck either simultaneously or following salvage treatment for the primary tumor (treatment group). Unilateral and bilateral neck dissection were analyzed together as neck dissection.

**Follow-up.** Outpatient check-ups were the main means of follow-up. No patient was lost to follow-up subsequent to diagnosis of recurrence. Clinical examinations, magnetic resonance imaging (MRI), computed tomography (CT), abdominal sonography or fiberoptic endoscopy were performed every 2-3 months for the first 2 years after treatment and subsequently every 6 months thereafter until fatality or the date of last follow-up. Positron emission tomography (PET)-CT was performed if recurrent disease could not be identified or was suspected on routine CT. Bone scans were performed when bone metastasis was suspected. Other tests were carried out at the discretion of the treating physician. Median length of follow-up was determined from the date of initial visit to the

hospital and from the date of recurrence to the last date of recorded follow-up, and the median follow-up time was determined using the reverse Kaplan-Meier method. The median total length of follow-up was 50 months (range, 7-176 months). The median length of postsalvage follow-up was 31 months (range, 0-153 months).

**Statistical analyses.** The primary endpoint was overall survival (OS) following recurrence, which was calculated from the date of recurrence to the date of fatality or the last date the patient was known to be alive. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Comparisons of non-survival data were analyzed using the t-test,  $\chi^2$  test or Fisher's exact test in groups.  $P < 0.05$  was considered to indicate a statistically significant difference in the two-sided tests.

**Ethics statement.** The present study was approved by the Research Ethics Committee of Sun Yat-sen University Cancer Center and Zhejiang Cancer Hospital.

Table II. Initial staging of the 163 patients with laryngeal squamous cell carcinoma with a N0 neck at recurrence.

Stage	Observation group, (n=125) no. (%)	Treatment group, (n=38) no. (%)	P-value
T			
T1	51 (40.8)	19 (50.0)	0.725 <sup>a</sup>
T2	47 (37.6)	11 (28.9)	
T3	15 (12.0)	5 (13.2)	
T4	12 (9.6)	3 (7.9)	
N			
N0	108 (86.4)	32 (84.2)	0.763 <sup>b</sup>
N1	5 (4.0)	1 (2.6)	
N2	11 (8.8)	5 (13.2)	
N3	1 (0.8)	0 (0.0)	

<sup>a</sup> $\chi^2$  test; <sup>b</sup>Fisher's exact test.

## Results

**Patient variables.** The present study involved a total of 163 patients with biopsy-proven recurrent laryngeal SCC who had an N0 neck at recurrence. The N0 neck was managed using a wait-and-see policy in 125/163 (76.7%) patients (observation group) and 38/163 (23.3%) patients received comprehensive treatment for the N0 neck (treatment group). The median total

length of follow-up was 50 months (range, 7-176 months) in the observation group and 40.5 months (range, 7-123 months) in the treatment group. The median length of post-salvage follow-up was 31 months (range, 0-153 months) in the observation group and 14 months (range, 0-106 months) in the treatment group. At the time of enrollment, 109 (87.2%) patients in the observation group were smokers and 52 (41.6%) consumed alcohol, compared to 29 (76.3%) and 14 (36.8%) in the treatment group. The basal demographic and clinicopathological features of the observation and treatment groups were not significantly different, except for the total length of follow-up and primary salvage treatment. The majority of patients in the observation group underwent SPL (77/125; 61.6%) compared to only 2/38 (5.3%) in the treatment group; 39/125 (31.2%) patients in the observation group received STL compared to 10/38 (26.3%) in the treatment group. The initial treatments for the remaining patients were surgery with radiation and/or chemotherapy, concurrent chemoradiation, or radiation with chemotherapy.

**Treatments.** The initial treatment decisions for the neck were based on N stage. With regards to salvage management for the neck following recurrence, the patients in the observation group did not receive any treatment. The patients in the treatment group received salvage neck treatment including neck dissection, radiation and/or chemotherapy. The decision to undergo salvage neck treatment was determined by the expertise of the primary physician and the personal views of the patient. In this cohort, 38/163 (23.3%) patients were involved in the decision-making process (based on the risk of

Table III. Initial treatments for the 163 patients with recurrent laryngeal SCC.

Initial treatments	Observation group (n=125), no. (%)	Treatment group (n=38), no. (%)	P-value
Initial primary treatment			
Surgery	62 (49.6)	16 (42.1)	0.405 <sup>a</sup>
RT	22 (17.6)	5 (13.2)	
Chemoradiation	1 (0.8)	0 (0.0)	
Surgery+RT	30 (24.0)	13 (34.2)	
Surgery+chemotherapy	3 (2.4)	0 (0.0)	
Surgery+chemoradiation	3 (2.4)	0 (0.0)	
RT+chemotherapy	3 (2.4)	3 (7.9)	
Surgery+chemotherapy+RT	1 (0.8)	1 (2.6)	
Initial neck treatment			
No treatment	71 (56.8)	15 (39.5)	0.242 <sup>a</sup>
Neck dissection	31 (24.8)	11 (29.0)	
Lymph node puncture	2 (1.6)	1 (2.6)	
Chemoradiation	1 (0.8)	0 (0.0)	
Surgery+RT	8 (6.4)	6 (15.8)	
Surgery+chemotherapy	1 (0.8)	0 (0.0)	
Surgery+chemoradiation	2 (1.6)	0 (0.0)	
RT	5 (4.0)	1 (2.6)	
RT+chemotherapy	3 (2.4)	3 (7.9)	
Surgery+chemotherapy+RT	1 (0.8)	1 (2.6)	

<sup>a</sup>Fisher's exact test. SPL, salvage partial laryngectomy; STL, salvage total laryngectomy; RT, radiation.

Table IV. Salvage treatments for the 163 patients with recurrent laryngeal SCC.

Salvage treatments	Observation group (n=125), no. (%)	Treatment group (n=38), no. (%)	P-value
<b>Salvage primary treatment</b>			
SPL	77 (61.6)	2 (5.3)	<0.001 <sup>a</sup>
STL	39 (31.2)	10 (26.3)	
Chemo-radiation	0 (0.0)	10 (26.3)	
Surgery+RT	3 (2.4)	7 (18.4)	
Surgery+chemotherapy	2 (1.6)	4 (10.5)	
Surgery+chemoradiation	4 (3.2)	4 (10.5)	
RT+chemotherapy	0 (0.0)	1 (2.6)	
<b>Salvage neck treatment</b>			
Neck dissection	0 (0.0)	4 (10.5)	
RT	0 (0.0)	8 (21.1)	
Chemo-radiation	0 (0.0)	13 (34.2)	
Surgery+RT	0 (0.0)	7 (18.4)	
Surgery+Chemotherapy	0 (0.0)	4 (10.5)	
Surgery+Chemo-radiation	0 (0.0)	1 (2.6)	
RT+Chemotherapy	0 (0.0)	1 (2.6)	

<sup>a</sup>Fisher's exact test. SPL, salvage partial laryngectomy; STL, salvage total laryngectomy; RT, radiation.

occult disease and lack of further treatment options following salvage surgery). In total, 16/38 (42%) patients underwent neck dissection-based treatment (current chemoradiation in 1 patient, simultaneous chemotherapy in 4, radiotherapy in 7 and neck dissection alone in 4 patients); 8/38 (21%) patients had radiotherapy alone; 13/38 (34%) patients had concurrent chemoradiation and 1/38 (3%) patient underwent radiation and adjuvant chemotherapy.

**Survival rates.** The 3- and 5-year overall survival rates after recurrence were 64.5 and 54.6% for the observation group versus 49.9 and 42.5% for the treatment group; the observation group had a significant long-term survival advantage compared to the treatment group (P=0.011). These results suggest that interventions for the N0 neck in recurrent laryngeal SCC are associated with poorer survival following recurrence compared to a wait-and-see policy.

**Discussion**

There are no established standards for management of the N0 neck following recurrence in laryngeal SCC; the options include observation, or radiotherapy, surgery and/or chemotherapy; however, the survival rates for these techniques remain to be elucidated.

The present study confirms that a wait-and-see policy is most suitable for the N0 neck in patients with recurrent laryngeal SCC who have been assessed via a comprehensive series of physical and imaging examinations. This finding is supported by a number of previous studies. Farrag *et al* (27) suggested the negative predictive value (NPV) of CT prior to salvage treatment was 97%. Yao *et al* (29) reported that PET scans were a useful tool when selecting patients for neck dissection due to a high sensitivity and NPV. With the continuous development

of diagnostic techniques, the detection rate of neck disease is increasing, occasionally the neck dissection can be withheld in a subset of patients with recurrent laryngeal SCC. Bohannon *et al* (28) reported that dissection of the N0 neck provided no survival advantage compared to observation, as patients who underwent neck dissection suffered significantly higher rates of complications. Van der Putten *et al* (12) also reported higher rates of complications following bilateral neck dissection in patients with neck dissection. In the study by Li *et al* (11), of the 72 early-stage patients, 15 (21%) patients without neck dissection had an improved survival compared to the 57 (79%) patients with neck dissection (P=0.042). By contrast, Wax and Touma (25) and Yao *et al* (26) recommended neck dissection in recurrent supraglottic carcinoma and advanced (rT3-T4) disease. Koss *et al* (30) suggested that STL with neck dissection improved survival compared to STL alone in recurrent laryngeal SCC.

The present study indicates that a wait-and-see policy is a reasonable strategy for management of the N0 neck in recurrent laryngeal SCC. Previous studies assessed populations of patients with recurrent disease following radiotherapy alone or chemoradiation; neck dissection was the only treatment for the N0 neck in recurrent disease and a wait-and-see policy was not adopted in these studies. In the current study, the entire cohort received comprehensive therapy, including surgery, radiation and chemotherapy for the primary tumor, as well as salvage treatment of the neck during initial treatment. Following recurrence, 125 patients accepted a wait-and-see policy for the N0 neck and 38 underwent comprehensive treatment for the N0 neck. The 3- and 5-year overall survival rates after salvage treatment for the primary tumor were 64.5 and 54.6% for the observation group and 49.9 and 42.5% for the treatment group, respectively; the wait-and-see policy provided a significant survival advantage (P=0.011). In the treatment group,

16 (42%) patients underwent neck dissection-based treatments (accompanied by concurrent chemoradiation in 1 patient, by simultaneous chemotherapy in 4, by radiotherapy in 7, and neck dissection alone in 4), 8 (21%) patients underwent radiotherapy alone, 13 (34%) received concurrent chemoradiation, and 1 (3%) underwent radiation and adjuvant chemotherapy. In conclusion, the wait-and-see policy is more optimal compared to any treatment for the N0 neck in recurrent laryngeal SCC, and this approach not only shortens the treatment time but also reduces complications and suffering for the patient. In addition, it can also avoid unnecessary economic burden and medical costs.

The present study demonstrates that it is important to identify the subsets of patients undergoing salvage treatment for recurrent laryngeal cancer that do not require treatment for the N0 neck. However, it should be realized that this study must be interpreted cautiously, as a number of factors may potentially affect the results. The advances in diagnosis and radiotherapy enable precise outlining of the target volumes and organs at risk, which may result in improved outcomes regarding local tumor control and reduction in side effects (31). Secondly, with the lymph nodes as the immune organs, radiotherapy and neck dissection will injure it. Suppressed immunity and complications may contribute to increase the rate of fatality. Therefore, the beneficial effect of intervention policy could easily be overshadowed by the fact that the treatment group have suppressed immunity and a higher rates of complications, which may mistakenly be thought as a reason for the difference in outcome. Finally, there were significantly more patients with early stage (T1-2: 128 patients) compared to advanced stage (T3-4: 35 patients) disease in this cohort, the lower rate of lymph node metastasis in the observation group may have also contributed to the higher OS rates for the wait-and-see policy.

In a retrospective study of this nature in which the cohort spans the course of more than a decade, it was extremely difficult to identify whether there were cases of secondary relapse and it was not easy to record complications and functional outcomes. Additionally, the present study was limited by a lack of tumor staging data for the patients at the time of recurrence. Further prospective studies should be designed to assess the incidence of complications, functional outcomes and probabilities of relapse and metastasis to answer such a complex issue in more detail.

In conclusion, a wait-and-see policy is a good option for the N0 neck in recurrent laryngeal SCC. Extensive imaging examinations, such as CT, MRI and PET-CT, should be employed to develop appropriate treatment plans. More studies are required to fully understand the role of a watch-and-wait policy in management of the N0 neck in recurrent laryngeal SCC.

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