



The Correlation between Tumor Expansion, Neck Nodules, and Free Margin with the Stomal Recurrence Incidence after a Total Laryngectomy

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Abstract: Background: Stomal recurrence means a recurrence experienced by patients with laryngeal carcinoma after total laryngectomy with a high mortality rate. It is essential to identify the risk factors to predict stomal recurrence. However, factors contributing to stomal recurrence indicate controversial results. Tumor expansion, thyroid nodules, and free margins become the risk factors that are easily identified.

The objective: This study aims to describe the correlation between tumor expansion, thyroid nodules, and free margins with stomal recurrence after total laryngectomy.

Methods: This study applied an analytical observational study with retrospective cohort studies by employing secondary data. The samples included patients who had experienced a total laryngectomy from January 1, 2015, to December 31, 2019, and those who met the study criteria. The samples were divided into groups of T3 and T4 tumor expansion, groups of N1 and N2+ thyroid nodules, as well as groups of positive and negative free margins. These samples were associated with the stomal recurrence and categorized into yes and no accordingly. The Chi-Square Test was employed for correlation analysis and followed by multiple logistic regression. The results were considered correlated if the P-value was less than 0.05.

Results: This study obtained 92 patients with 87 males and 5 females. The analysis of the correlation between tumor expansion and stomal recurrence suggested a P-value of 0.770, which was greater than 0.05. Meanwhile, the correlation between thyroid nodules and free margins with stomal recurrence indicated a P-value of 0.068 and 0.147, greater than 0.05.

Conclusion: There was no significant correlation between tumor expansion, thyroid nodules, and free margins with stomal recurrence after a total laryngectomy.

Keywords: total laryngectomy, tumor expansion, thyroid nodules, free margin, stomal recurrence.

I. INTRODUCTION

Stomal recurrence refers to infiltrating diffuse tumors of the junction of the trachea and skin after a total laryngectomy, with an incidence rate of 1.7% to 25%. It is primarily diagnosed in the first year after a total laryngectomy. Stomal recurrence signifies a recurrence after a total laryngectomy with a high mortality rate. The management of stomal recurrence is considered complicated and is associated with low life expectancy [1]. Aggressive surgical therapy and radiotherapy cannot cure stomal recurrence. In consequence, the patient may die from airway obstruction or massive bleeding [2]. It is important to recognize the risk factors for stomal recurrence to reduce the incidence of stomal recurrence since it potentially causes death, worsens life expectancy, and increases the time and cost of hospitalization [3].

Research that has been conducted on the factors that contribute to the incidence of stomal recurrence denoted controversial results. The incidence of stomal recurrence is influenced by age, tumor location, stage, and treatment modalities [4]. Other factors influencing the incidence of stomal recurrence include tumor invasion into the thyroid and cricoid cartilages, extracapsular, perineural, lymphatic, tumor expansion (T), and thyroid nodules (N) [5].

Larger tumor size relates to a greater number of carcinoma cells, a greater degree of radioresistance, increased tumor hypoxia, and a higher tendency to metastasize [6]. Early-stage laryngeal carcinoma has good local control, which enables good treatment results, while advanced-stage laryngeal carcinoma is often reported to undergo stomal recurrence [4]. T4 lesion becomes a significant risk factor for stomal recurrence, and the risk in T4 patients is higher than in T3 patients [3].

Laryngeal carcinoma with cervical lymphatic metastases has a higher risk than those without the same metastases. Pretracheal and paratracheal lymph nodes are the adverse factors in the incidence of stomal recurrence in postlaryngectomy patients. It is associated with incomplete paratracheal dissection during laryngectomy [3].

Complete excision of the tumor at the primary location is essential to ensure the local control that is histologically confirmed as a free margin. The presence of a tumor at the surgical margin is referred to as a positive tumor margin [7]. The presence of a tumor at the surgical margin becomes a factor in the incidence of stomal recurrence. Several studies have reported the use of radiotherapy to prevent this incidence. Multivariate analysis proved that the primary tumor location, tumor stage, and positive surgical margins were significant independent risk factors [8].

According to the explanation above, the researchers attempt to conduct a study to prove the correlation between tumor expansion, thyroid nodules, and free margins with the incidence of stomal recurrence after total laryngectomy.

II. Research Method

Population and Sample

The patients studied met the inclusion criteria (patients with complete medical record data, including age, gender, histopathological results after total laryngectomy, CT scan results before surgery from Dr. Soetomo Public Hospital Surabaya, histopathological results of stomal recurrence, and had received adjuvant therapy) and exclusion criteria (patients with laryngeal cancer who had received radiation therapy or chemotherapy before total laryngectomy).

Data and Sources of Data

This study was a retrospective study conducted in Dr. Soetomo Public Hospital Surabaya, Indonesia. This study employed data from January 1, 2015, to December 31, 2019, collected through consecutive sampling. Researchers conducted an ethical test before conducting this study (Ethics No. 0087/KEPK/X/2020). The procedure of this study included the collection of medical record data consisting of patient characteristics, tumor expansion, thyroid nodules, free margins, and the incidence of stomal recurrence.

Theoretical framework

Tumor expansion in this study was the expansion of the primary tumor from the results of preoperative CT scan readings from Dr. Soetomo Public Hospital Surabaya according to AJCC 8 criteria read by a radiologist and performed a maximum of three months before total laryngectomy. Tumor extensions were grouped into T3 and T4 by not differentiating tumor location.

The thyroid nodules were cervical lymph node metastases identified by preoperative CT scan readings at Dr. Soetomo Public Hospital Surabaya following the AJCC 8 criteria read by a radiologist and performed a

maximum of three months before total laryngectomy. Thyroid nodules were grouped into N1 and N2+ (consisting of N2 or N3).

The free margin, in this case, was a tumor-free surgical margin based on histopathological results after total laryngectomy read by an Anatomical Pathologist at Dr. Soetomo Public Hospital Surabaya. The margin was positive if the distance between the surgical edge and the tumor was <1 millimeter, the margin was negative if it was 1 millimeter.

Stomal recurrence was found around the permanent stoma occurring at least three months after total laryngectomy. It was evidenced by the biopsy results and read by an Anatomical Pathologist at Dr. Soetomo Public Hospital Surabaya, which indicated positive squamous cell carcinoma metastases. All data collected in the data collection sheet were arranged in tabular form and processed statistically. Statistical analysis employed a chi-square test, while multivariable analysis employed multiple logistic regression. The results of this study were determined by a significance level (α) of 0.05. Statistical test used GNU PSPP version 1.2.0.

III. RESULTS AND DISCUSSION

3.1 Result in this study

The number of patients in the study was 92. The youngest patient was 22 years old, and the oldest was 77 years old, with a mean of 56.14 and a standard deviation (SD) of 11.31. In this study, the diagnosed patients were primarily discovered in the age group of 51-60 years old with 31 patients or 33.70% and followed by the age group of 61-70 years old with 25 patients or 27.20%. Based on gender, the proportion of 17.4:1 was obtained with 87 male patients or 94.60% and 5 female patients or 5.40%. The majority of these patients were indicated to be from the T4 tumor expansion group, with 60 patients or 65.20%. There were 55 patients, or 59.80%, who were diagnosed with N2+ thyroid nodules. Meanwhile, the patients diagnosed with positive margins amounted to 51 patients or 55.40%. The stomal recurrence after total laryngectomy did not occur in 65 patients or 70.70% (Table 1).

Table 1: Patient Characteristics

Variabel		n (%)
Patients' age	21-30	2 (2.20)
	31-40	6 (6.50)
	41-50	18 (19.60)
	51-60	31 (33.70)
	61-70	25 (27.20)
	71-80	10 (10.90)
Gender	Male	87 (94.60)
	Female	5 (5.40)
Tumor Expansion	T3	32 (34.80)
	T4	60 (65.20)
Neck Nodules	N1	37 (40.20)
	N2+	55 (59.80)
Free Margins	Positive	51 (55.40)
	Negative	41 (44.60)
Stomal Recurrence	Yes	27 (29.30)
	No	65 (70.70)

Table 2. The correlation between tumor expansion and stomal recurrence

T	Stomal Recurrence		Total	P
	Yes	No		
	n (%)	n (%)	n	
T4	17 (28.30)	43 (71.70)	60	0.770
T3	10 (31.30)	22 (68.80)	32	
Chi-Square Test				

There were 17 patients or 28.30% in the T4 group and 10 patients or 31.30% in the T3 group who experienced stomal recurrence. Patients who did not experience recurrent stoma in the T4 group reached 43 people or 71.70%, and in the T3 group reached 22 people or 68.80%. The Chi-Square Test results obtained a P-value of 0.770, indicating a non-significant correlation between tumor expansion and stomal recurrence after total laryngectomy, greater than 0.05 (Table 2).

Table 3. Correlation between thyroid nodules and stomal recurrence

N	Stomal Recurrence		Total	P
	Yes	No		
	n (%)	n (%)	n	
N2+	20 (36.40)	35 (63.60)	55	0.772
N1	7 (18.90)	30 (81.10)	37	

Chi-Square Test

Stomal recurrence was experienced by 20 patients or 36.40% in the N2+ group and 7 patients or 18.90% in the N1 group. Meanwhile, patients who did not experience a stomal recurrence in the N2+ group reached 35 people or 63.60%, and the N1 group amounted to 30 people or 81.10%. The Chi-Square Test results obtained a P-value of 0.072, which was less than 0.25, indicating that thyroid nodules were included as candidates in the multiple logistic regression analysis (Table 3).

Table 4. Correlation between free margins and stomal recurrence

Margin	Stomal Recurrence		Total	P
	Yes	No		
	n (%)	n (%)	n	
Positive	18 (35.30)	33 (64.70)	51	0.162
Negative	9 (22.00)	32 (78.00)	41	

Chi-Square Test

Stomal recurrence was experienced by 18 patients or 35.30% in the positive margins group and 9 patients or 22.00% in the negative margin group. Meanwhile, as many as 33 patients or 64.70% in the positive margin group and 32 patients or 78.00% in the negative margin group did not experience stomal recurrence. The Chi-Square Test results obtained a P-value of 0.162, which was less than 0.25, indicating that free margins were included as candidates in the multiple logistic regression analysis (Table 4).

Table 5. Correlation between thyroid nodules and free margins with stomal recurrence

	β regression coefficient	P
Nodules		0.068
Nodules (N2+)	-0.93	0.068
Tumor margins		0.147
Tumor margins (positive)	-0.71	0.147
Constant	1.89	0.000

Multiple logistic regression test

The multiple logistic regression analysis results indicated a significant correlation between thyroid nodules and free margins with stomal recurrence, where the P-value was greater than 0.05 (Table 5).

3.2 Discussion

The laryngeal carcinoma was primarily detected in people between 51-60 years old. The incidence of laryngeal carcinoma increased in parallel with age, peaking in the eighth decade. Three-quarters of the diagnoses were identified in people aged over 60 years old [9]. The number of male patients in this study was found to be dominant with a ratio of 17.4:1. The incidence of laryngeal carcinoma generally relates to tobacco and alcohol consumption habits, and only a few women have these habits. Tobacco was reported to cause the risk of developing laryngeal carcinoma by 78%, drinking alcohol by 34%, and the combination of the two increased the risk to 82% [10].

The incidence of stomal recurrence reached 29.30%. This number is greater than the previous studies, which ranged from 5-25% [3]. The time interval for stomal recurrence started from 3 to 17 months after total laryngectomy with a mean of 8.85 months. T4 lesion appears as one of the significant risk factors of stomal recurrence. A meta-analysis of risk factors for stomal recurrence after total laryngectomy reported that the risk of stomal recurrence was higher in T3 and T4 than in T1 and T2, and the risk of stomal recurrence was higher in patients with T4 than the ones with T3 [3]. It is due to the advanced tumor stage caused more extensive carcinoma lesions, resulting in hypolaryngeal and tracheal invasions and making it difficult to completely resect the tumor and cause recurrence of carcinoma [8].

In this study, tumor expansion did not affect the incidence of stomal recurrence. The advanced T stage was associated with resection margins during surgery. An increased incidence of positive resection margins was anticipated when dissecting locally advanced carcinomas. Revision surgery indicated good results in this case, and postoperative radiotherapy provided a protective benefit against local recurrence even though the surgical margins were positive and additional surgery was not required [7].

Another similar study conducted in Serbia revealed that stomal recurrence occurred in 8.12% of T3 patients and 10.24% of T4 patients, meaning no significant difference between the T3 and T4 groups [2]. Thyroid nodules metastases in patients with head-neck squamous cell carcinoma were a poor prognostic factor, leading to a high risk of recurrence and reducing survival rates to above 50%. Functional neck dissection was performed by removing the entire lymph node group while preserving the neck structure to reduce morbidity during and after surgery. Selective neck dissection at a specific level according to the tumor location was the gold standard for surgery [11]. Statistically, the lymphatic invasion was significant in the recurrent group compared to the non-recurrent group [5].

In this study, thyroid nodules had no effect on the incidence of stomal recurrence because, according to lymph node metastasis theory, it was related to the location of the primary tumor. It was evidenced by the abundance of lymphatic drainage in the supraglottis, which generally causes metastatic nodules [12]. However, primary tumors in the glottis and subglottis had significantly higher recurrence rates than supraglottic tumors [2]. The incidence of regional lymph node metastasis had been reported to reach 44% in supraglottic carcinoma, 20% in subglottic carcinoma, and 5% in glottic carcinoma [13]. The results of this study corresponded to that

of a meta-analysis stating that pretracheal and paratracheal lymph node metastasis were primarily associated with additional prognostic factors for stomal recurrence in patients with laryngeal carcinoma who underwent laryngectomy [3]. There was no difference in the incidence of recurrent stoma in patients with and without lymph node metastasis. Another reason for the low incidence of postoperative metastasis resulted from postoperative radiotherapy [13].

The purposes of total laryngectomy were to remove all malignant tissue and obtain a negative margin. A positive final margin was a strong predictive factor associated with poor survival in patients with total laryngectomy. A positive margin reflected spread through lymphovascular pathways or more extensive mucosal disorders or areas affected by the carcinoma. A positive initial margin was associated with local treatment failures but did not increase remote treatment failures. These findings supported the hypothesis of locally aggressive tumor biology without an increased likelihood of distant metastases after resection [14].

Local recurrence was strongly associated with positive margins in the initial frozen section analysis. However, revisions had been made so that reaching negative margins would still display a higher recurrence rate than negative initial margins. The <5 millimeter margin was associated with aggressive tumor characteristics. The positive margin served as a parameter with a significant effect on local recurrence and accordingly becoming a high predictor of local recurrence [15].

In this study, the free margin did not affect the incidence of stomal recurrence. No recurrence occurred during the follow-up period in the positive margin group due to the benefits of postoperative radiotherapy and chemotherapy. Microscopic tumor residues were managed to be treated effectively with radiation therapy. Local control could be achieved by radiation therapy alone or combined with chemotherapy as postoperative adjuvant therapy [5]. Having similar results, a study in Turkey demonstrated no significant difference in the closest margin distance between the recurrent (3.6 mm) and non-recurrent (4.3 mm) groups. Also, it denoted no significant difference between the groups with positive and negative margins in causing recurrence [5]. There was a non-significant correlation between tumor expansion, thyroid nodules, and free margins with the incidence of stomal recurrence in patients with laryngeal carcinoma after total laryngectomy.

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