Risk Analysis for Tracheostomy Dependency in Curatively Treated Laryngeal Cancer with Organ Preservation

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Short running title

Tracheostomy in Laryngeal Cancer

Conflict of Interest

The authors declare no conflict of interest.

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Key words: laryngeal cancer, tracheostomy, organ preservation, radiotherapy, permanent dependency

Abstract

Background: A tracheostomy has an enormous negative impact on the patient's quality of life. The aim of this study is to describe risk factors for permanent tracheostomies in patients undergoing curative organ-preserving treatment of laryngeal cancer.

Methods: The charts of all patients with laryngeal cancer diagnosed at our tertiary referral center were reviewed. Cases receiving a tracheostomy before, during or after primary organ-preserving treatment were eligible.

Results*:* A total of 87 tracheotomized patients were enrolled in the present study. During follow-up 48 patients (55%) required a permanent tracheostomy, whilst 39 patients (45%) were decannulated. Multivariate analysis revealed primary radiotherapy (OR=12.857, p<0.001) and recurrence (OR=25.84, p<0.001). as independent factors of permanent tracheostomy.

Conclusion*:* This study identifies primary curative RT and tumor relapse as independent risk factors of permanent tracheostomy dependency in laryngeal cancer patients undergoing a tracheostomy during or after primary curative organ-preserving treatment.

Introduction

Tracheostomy is widely recognized as one of the surgical procedures most feared by patients suffering from laryngeal cancer. If necessary, it represents a cumbersome consequence of an obstructive laryngeal tumor and/or its treatment. In this context, the cause of airway obstruction is usually a bulky tumor, fixed vocal cords or sequelae of laryngeal cancer treatment. Although inevitable in acute airway compromise, we have to keep in mind that a tracheostomy has an enormous negative impact on patients' quality of life, especially regarding speech and swallowing.[1]

A recent analysis revealed an overall incidence of tracheostomies in advanced laryngeal and hypopharyngeal cancer undergoing chemoradiation (CRT) of 34%.[2] CRT protocols for laryngeal cancer allow the preservation of the organ with good locoregional disease control.[3,4] Despite this organ preservation strategy, a high number of head and neck cancer patients remain dependent on feeding tube and tracheostomy.[5] Radiotherapy (RT) causes fibrosis and edema, which may lead to an impaired laryngeal mobility and airway obstruction, requiring a life-saving tracheostomy.

Risk factors for long-term tracheostomy dependency include a pretreatment tracheostomy, subglottic extension of the tumor and salvage neck dissection[6]. Moreover, patients requiring a tracheostomy prior to CRT are subject to a higher short-term mortality compared to those without tracheostomy.[2]

Regarding the extensive morbidity of chronic tracheostomy as well as its financial burden, the knowledge on the long-term evolution of these patients is important, especially since alternative protocols for the airway management have been proposed.[7]

The aim of this study is to describe the evolution of tracheostomy dependency in patients with curatively intended treatment for laryngeal cancer with organ preservation. Furthermore, we describe possible risk factors for permanent tracheostomy dependency among already tracheostomized patients during primary treatment.

Patients and Methods

Ethical considerations

Our institutional and regional review board (Inselspital, University Hospital Bern, Bern, Switzerland, KEK-Nr. 117/14) granted approval to perform the present study. Formal written informed consent was not required for this type of study.

Retrospective cohort study

The paper and electronic records of all patients diagnosed and with accomplished curatively intended treatment for laryngeal squamous cell carcinoma between 2003 and 2014 at our tertiary referral center were reviewed. Of those, cases undergoing an organ-preserving treatment necessitating a tracheostomy before, during or after primary treatment were included. Patients requiring first tracheostomy after recurrence and those treated with primary total laryngectomy (TLE) were excluded from the present study. Further exclusion criteria were: presence of a concomitant malignant tumor, interrupted primary treatment and non-curative situations. A follow-up of at least 2 years was required.

Patients' characteristics, initial tumor classification and localization, features of primary treatment, type and time of recurrence and its treatment were assessed. Regarding the tracheostomy, the time of initial tracheostomy was divided in three groups: acute (pre- and peri-treatment), early (>3 months/≤2 years after treatment)

and late (>2 years after treatment). Furthermore, the occurrence of emergency situations leading to an urgent tracheostomy, versus planned or perioperative tracheotomies were differentiated. The situation regarding tracheostomy dependency at last follow-up was documented for each patient.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7, statistical significance was set for a two-tailed alpha to 0.05. According to the final outcome regarding the tracheostomy (permanent or transient), groups were compared by Fisher's exact test for nominal parameters. A multivariate nominal logistic regression analysis was performed to assess the impact of different risk factors on tracheotomies to remain permanent, including variables with $p<0.1$ but keeping only variables with $p<0.05$ for the final calculation using backwards elimination.

Results

A total of 477 patients underwent curatively intended treatment for laryngeal cancer at our tertiary reference cancer center from 2001 until 2014. Between diagnosis and last follow-up, the incidence of tracheostomy in the CRT group (n=359) was 18.4% and 4.2% of tracheostomies remained permanent. In patients treated with partial laryngectomy (n=17) or transoral surgery (n=62), the incidence of tracheostomy was 26.6% (0% permanent). Thirty-nine patients were treated with primary total laryngectomy, resulting in permanent tracheostomy. Of the whole cohort (n=477), 87 patients requiring a tracheostomy before, during or after primary treatment with organ preservation were enrolled in the present study. Patients underwent either primary RT (n=55, 63.2%), or surgery (n=32, 36.8%) followed in n=22 cases by adjuvant RT. Totally 26 patients (29.9%) underwent neck dissection and 37 patients (42.5%)

received concomitant chemotherapy to RT (CRT). Initial patient's characteristics are summarized in Table 1. Median follow-up of the 87 tracheostomized patients was 48 months. 5-years recurrence-free survival, local and loco-regional control rates were 49%, 58% and 57%, respectively.

The overall decannulation-rate was 45% (n=39), whilst in 48 patients (55%) the tracheostomy remained permanent until last follow-up. A total of 59 (67.8%) patients underwent an emergency tracheotomy, while 28 (32.2%) received a planned tracheotomy. Forty-four patients (50.6%) needed a tracheostomy before or during treatment, whereas 43 patients (49.4%) required tracheostomy more than 3 months after the end of the therapy.

In 15 patients, the tracheostomy remained permanent from primary treatment until the end of follow-up. However, nearly all patients without relapse had their tracheostomy removed (88%). In contrast, all 43 patients with recurrence ended up with a permanent tracheostomy. The longitudinal evolution of these patients is summarized in Figure 1.

Primary definitive RT was applied in 75.8% of the patients, additionally 16 of 21 (76.2%) operated patients underwent adjuvant RT. Irradiation techniques were: 3.8% 2D conventional RT, 48.1% 3D conformal and 48.1% IMRT/VMAT, without statistically significant effect on the outcome regarding permanent tracheostomy. Median total dose was 72 Gy (range: 60-76), applied with 2 Gy per fraction. Regarding concomitant systemic treatment, we observed 4.6% of induction/neoadjuvant chemotherapy in the whole cohort. Of those treated with RT, concomitant systemic treatment was applied in 56.1%. No statistically significant association regarding the risk of tracheostomies to remain permanent was observed.

Univariate outcome analysis

The results of the univariate analysis regarding the evolution of tracheostomies are summarized in Table 2. The most important risk factors for permanent tracheostomy were primary RT (OR=12.857, 95% CI: 3.41 - 48.49, p<0.001), recurrence (OR=25.84, 95% CI: 7.938 - 73.87, p<0.001) and emergency tracheostomy due to respiratory distress (OR=5.46, 95% CI: 2.17-13.74, p<0.001).

Moreover, we performed a comparison between the surgical and the RT subgroup in our cohort. We observed no significant difference regarding demographic distribution, tumor classification or tumor relapse.

Multivariate analysis

Variables remaining statistically significant as independent predictors of a permanent tracheostomy in the multivariate analysis were primary RT (OR=57.04, 95%CI: 5.36-607.49, p=0.008) and relapse (OR=81.22, 95% CI: 9.95-663.20, p<0.0001). The results of the multivariate analysis are summarized in Table 3.

Discussion

This study identifies possible risk factors for tracheostomies to remain permanent in patients with primary curative, organ-preserving treatment for laryngeal carcinoma. A tracheostomy represents a brutal stigmatization as well as a severe cut into a patient's quality of life.[1] Therefore, the prognosis regarding a potential decannulation in the future is crucial to patient's counseling and may even have an impact on further therapeutic decisions. Our study reports a long-term decannulation rate of only 45% emphasizing the importance of the questions raised.

Unexpectedly, the initial tumor and nodal classifications had no impact on the long-term and durable dependency on a tracheostomy in our cohort. The only surrogate

factor regarding the primary tumor characteristics was a higher decannulation rate for supraglottic tumors. Similarly, a recent study by Jefferson et al. (2015) identified subglottic extension as risk factor for chronic tracheostomy dependency.[6] However, they analyzed laryngeal and hypopharyngeal tumors together in a cohort of exclusively CRT treated patients. In fact, the high decannulation rates for supraglottic tumors in our cohort may be explained by the surgically treated patients. In this context we have to emphasize, that the distribution of T classifications was not different between the surgically treated and the irradiated patients in the present study. Of course, T classification and tumor localization are important main factors regarding indication for primary tracheostomy, especially in a setting with acute respiratory distress. According to our results, these considerations appear to be different regarding the long-term evolution of the tracheostomy according.

The most important risk factor for long-term tracheostomy dependency in our cohort was primary RT. Irradiation related tissue toxicity leads to an inflammatory reaction of the larynx and surrounding tissues. The abundant fibrous scarring of the larynx impedes with its mobility and the concomitant mucosal edema leads to further airway obstruction. Finally, chondronecrosis may additionally exacerbate the post-therapeutic laryngopharyngeal dysfunction.

Moreover, it has been proposed, that tracheostomy is an adverse prognostic factor for the oncological outcome of patients suffering from laryngeal cancer.[2,8] However, this observation was not confirmed in cases of locoregionally advanced laryngeal cancers.[6] Our study identifies locoregional relapse as an adverse factor for chronic tracheostomy dependency in patients undergoing tracheostomy for the initial treatment. This observation is most probably related to the additional required treatment in case of tumor persistence or relapse.

Considering most probably reduced rates of loco-regional control offered by CRT in tracheotomized patients[2,8] and the higher risk for permanent tracheostomies associated with RT according to our results, the question about the best management of these patients is raised. The quest for surgical options while preserving the laryngeal function led to the development and validation of partial transoral and open surgeries. Langerman et al. (2012) demonstrated, that debulking is a safe and effective method in patients with tumor-related airway obstruction.[7] No patient treated by debulking required long-term tracheostomy and all completed the following CRT without need for tracheostomy. Eighty-two percent of the patients were able to completely avoid tracheostomy during and after treatment, whilst only two patients had late tracheostomy within the first year of completing CRT.[7] Similarly, Du et al. (2016) presented their experience with tumor debulking as a potential alternative to tracheostomy in the management of laryngeal cancer airway obstruction.[9] As long as intubation (e.g. fiber optic naso-tracheal intubation) is achievable, a debulking of the tumor may be reasonable in order to prevent tracheostomy. However, we have to take into account that this kind of surgery may not be always available in emergency situations.

With the refinement of the surgical techniques, the functional outcomes of surgery may be further improved. Baron and Remacle (2008) showed the advantages of transoral endoscopic laser microsurgery (TLM), including less need for tracheostomy and nasogastric feeding.[10] The work of Silver et al. (2009) established that the results of TLM are equivalent to those obtained by conventional conservation surgery, with better postoperative function, less morbidity and usually without the need for tracheostomy.[11] They also pointed out, that with the development of laser surgery, the use of emergency tracheostomy became less necessary.[11] As our results

indicate, patients undergoing emergency tracheostomy have a 5.5-fold (95% CI: 2.17-13.74) increased risk of remaining tracheostomy-dependent.

Thomas et al. (2012) performed a systematic review about open conservation partial laryngectomy, with statistical pooling of outcomes.[12] Although the functional outcomes were not reported in a standardized fashion in most studies, the high overall tracheostomy decannulation rate of 96.3% - with only two studies reporting a decannulation rate <90% - reflects a good functional preservation. The average larynx preservation rate came to 90.9%.[12] In the same way, Paleri et al. (2011) published a systematic review and meta-analysis about the oncologic outcomes of open conservation laryngectomy for recurrent laryngeal carcinoma after radiotherapy failure.[13] The pooled mean decannulation rate in their article was 95.1%.[13] Similarly, in a study on the advantages of open partial laryngectomy for salvage treatment after CRT, the tracheostomy tube was definitively removed in 90% of patients.[14] Another study reported the use of supracricoid laryngectomy in selected patients. In this case series 23 out of 24 patients (95%) were decannulated within a median time of 37 days.[15]

From an oncologic, functional and socio-economic point of view, patients requiring tracheostomy during primary curative treatment for laryngeal cancer represent a challenging subgroup. As mentioned above, the main result of our study identifies RT and tumor relapse as risk factors for tracheostomies to remain permanent. According to the literature, alternative options to tracheostomy for airway management are available and its feasibility and efficacy are described.[7-15] Finally, TLE would remain an option for salvage treatment.[16]

We also have to consider the results of non-surgical options as reported by the Department of Veterans Affairs Laryngeal Cancer Study Group.[17] In this trial a new role for chemotherapy in patients with advanced laryngeal cancer was hypothesized and the results showed a high

rate of laryngeal preservation in patients treated by induction chemotherapy followed by definitive RT with similar rates of overall survival as compared to surgery followed by RT.[17] Forastiere et al. (2013) reported after an observation time of 10 years, that the patients group treated by RT alone had the worst laryngectomy free survival (17.2%) as compared to the CRT (23.5%) and induction chemotherapy followed by CRT (28.9%) arms. Interestingly, improved locoregional control and larynx preservation rates for concomitant CRT as compared to induction chemotherapy followed by CRT or RT alone were observed.[18] However, induction/neoadjuvant chemotherapy may serve as an in vivo strategy to select patients suitable for CRT or TLE in advanced laryngeal cancer.[19] The authors report promising functional and oncological outcomes in patients selected for CRT after a single cycle of induction chemotherapy. This concept allows to identify non-responders to CRT and avoids a full course of CRT before surgical salvage. Moreover, no permanent tracheostomies were observed in this cohort of patients, when not requiring TLE. [20]

Depending on functional resources for reeducation and comorbidities of every patient in question, the decision about the optimal therapy should be taken in an interdisciplinary team and in accordance with the patient. In the context of the presented literature and according to our results, we may consider offering affected patients a more tailored approach. However, this would first need to be prospectively validated.

We acknowledge the limitations of the present study mainly due to its retrospective nature and its inherent challenges, for example the vulnerability to the development of a selection bias, the possible presence of confounding variables and the fact that we can’t determine causation, only association. Besides, our study has an asymmetry in terms of group size (surgery vs. RT). On the other hand, the long-term follow-up (median: 48.1 months) allows a full longitudinal observation of the cohort.

Conclusion

This study suggests primary curative RT and tumor relapse as independent adverse factors of permanent tracheostomy dependency in laryngeal cancer patients undergoing a tracheostomy during or after primary curative organ-preserving treatment. Other possible risk factors for permanent tracheostomy are: male gender, supraglottic localization and tracheostomy performed for acute respiratory distress. These results may play an important role in the development of nomograms for tailored treatment strategies for patients at risk to undergo tracheostomy before, during or after larynx cancer therapy.

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Tables

	Whole cohort (n=87)		*Temporary tracheostomy (n=39)*		*Permanent tracheostomy (n=48)*	
Male gender	80	91.9%	33	84.6%	47	97.9%
Age (years, range)	59.8	41-80	58.3	41-73	60.9	42-80
Initial tumor and treatment characteristics (No. of patients, %)						
Supraglottic	44	50.6%	25	64.1%	19	39.6%
Glottic	30	34.5%	10	25.6%	20	41.7%
Subglottic	2	2.3%	1	2.6%	1	2.1%
Transglottic	11	12.6%	3	7.7%	8	16.6%
T1	18	20.7%	7	17.9%	11	23.1%
T2	30	34.5%	15	38.5%	15	31.3%
T3	27	31.0%	12	30.8%	15	31.3%
T4	12	13.8%	5	12.8%	7	14.6%
N0	55	63.2%	22	56.4%	33	68.8%
N+	32	36.8%	17	43.6%	15	31.2%
TNM Stage I/II	41	47.1%	16	41.0%	25	52.1%
TNM Stage III/IV	46	52.9%	23	59.0%	23	47.9%
Surgery	10	11.5%	7	18.0%	3	6.2%
Radiotherapy	55	63.2%	16	41.0%	39	81.3%
Multimodal	22	25.4%	16	41.0%	6	12.5%
ND	26	29.9%	20	51.3%	6	12.5%
Concomitant CX	37	42.5%	16	41.0%	21	43.8%
Relapse and relapse treatment characteristics (No. of patients, %)						
Relapse	43	49.4%	5	12.8%	38	79.2%
Local	29	67.4%	2	40.0%	27	71.1%
Regional	3	7.0%	2	40.0%	1	2.6%
Loco-regional	9	20.9%	0	0%	9	23.7%
Metastatic only	2	4.7%	1	20.0%	1	2.6%
Salvage surgery	24	55.8%	0	0%	24	63.2%
Salvage Radiotherapy	3	7.0%	2	40.0%	1	2.6%
Palliation	16	37.2%	3	60.0%	13	34.2%
Tracheostomy characteristics (No. of patients, %)						
Peri-treatment	44	50.6%	24	61.5%	20	41.7%
Early post-treatment (>3 months, ≤2 years)	32	36.8%	10	25.6%	22	45.8%
Late post-treatment (>2 years)	11	12.6%	5	12.9%	6	12.5%
Urgent (respiratory distress)	59	67.8%	15	38.5%	38	79.2%
Planned TST	28	32.2%	24	61.5%	10	20.8%
Permanent TST after primary treatment	15	17.2%	0	0%	15	31.2%
Salvage TLE	23	26.4%	0	0%	23	47.9%
Permanent TST at last follow up	48	55.2%	0	0%	48	100%
Follow-up (months, median)	48.1		52.3		43.4	

Abbreviations: CX: chemotherapy, ND: neck dissection, SD: standard deviation, TLE: total laryngectomy, TST: tracheostomy

Table 1: Patient's, treatment and tracheostomy characteristics. Data is shown for the whole cohort and grouped according to tracheostomy removal during follow up.

Variable		*No. of transient tracheostomies*	*No of permanent tracheostomies*	*p-value*
Gender	Male	33	47	**0.042**
	Female	6	1	
Tumor localization	Supraglottic	25	19	**0.024**
	Glottic	10	20	0.173
	Subglottic	1	1	>0.999
	Transglottic	3	8	0.332
Tumor classification	T1	7	11	0.606
	T2	15	15	0.505
	T3	12	15	>0.999
	T4	5	7	>0.999
Nodal classification	N0	22	33	0.269
	N+	17	15	
TNM stage	Stage I/II	16	25	0.305
	Stage III/IV	23	23	
Therapy	Surgery only	7	3	0.059
	Radiotherapy	16	39	**<0.001**
	Multimodal	16	6	**0.003**
	Neck dissection	20	6	**<0.001**
	No neck dissection	19	42	
	Chemotherapy	16	21	0.830
	No Chemotherapy	23	27	
Relapse	Relapse	5	38	**<0.001**
	No relapse	34	10	
Tracheostomy	Peri-treatment	24	20	0.085
	Post-treatment	15	28	
	Emergency	15	38	**<0.001**
	Planned	24	10	

Table 2: Univariate statistical analysis. Comparisons between groups were performed using two-sided Fisher's exact test.

Variable	*Univariate*			*Multivariate model*			*Backwards elimination*		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Gender M/F	0.117	0.01-0.79	0.042						
Stage ≥III	0.64	0.27-1.50	0.305						
Supraglottic	0.367	0.16-0.87	**0.024**	1.45	0.32–6.66	0.633			
Definitive RT	12.857	3.41-48.49	**<0.001**	30.55	2.43–384.9	**0.008**	57.04	5.36 – 607.5	**<0.001**
Any RT in treatment	3.281	0.79-13.66	0.103						
Surgery only	0.258	0.06-1.05	0.059						
ND	0.136	0.05-0.38	**<0.001**	0.19	0.03–1.46	0.112			
Relapse	25.84	7.94-73.87	**<0.001**	94.21	10.1–876.2	**<0.0001**	81.22	9.95 – 663.2	**<0.001**
Acute vs. planned TST	5.46	2.17-13.74	**<0.001**	2.37	0.52–10.7				

Abbreviations: ND: neck dissection, RT: radiotherapy, TST: tracheostomy

Table 3: Odds-ratios (OR) for permanent tracheostomy and multivariate linear regression analysis using backwards elimination of identified risk factors.

Figure Legend

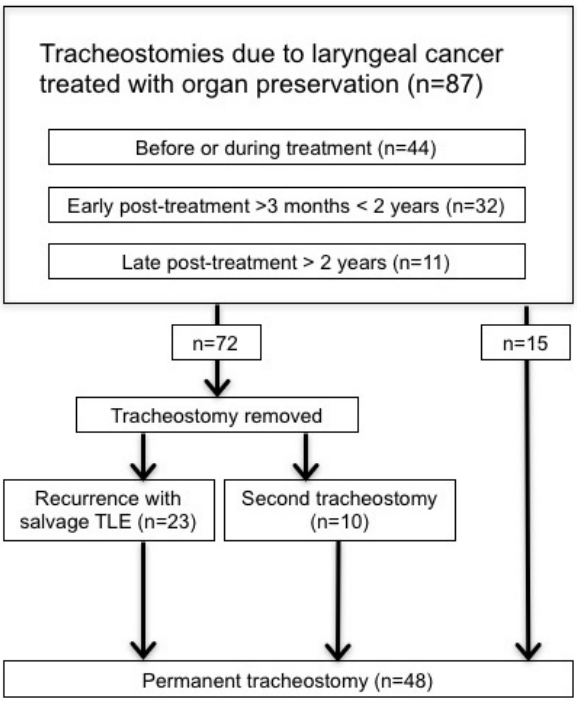

Figure 1
Long-term evolution of tracheostomies due to laryngeal cancer treated with organ preservation. The median follow-up was 48 months.