Predicting Factors for Oncological and Functional Outcome in Hypopharyngeal Cancer

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Abstract

Objectives: Hypopharyngeal squamous cell carcinoma (SCC) is a rare but aggressive malignancy, with low survival rates and high incidence of tumor and treatment-related morbidity. This study aims to analyze the long-term oncologic and functional outcomes of a large cohort of patients and to determine prognostic factors.

Methods: The records of all patients diagnosed with hypopharyngeal SCC and treated with curative intent at our tertiary referral center were reviewed. Patient and initial disease characteristics, features and complications of primary treatment, recurrence patterns and corresponding treatments and the oncologic and functional long-term outcome were determined.

Results: For a total of 179 patients primary radiotherapy (RT) was the predominant treatment modality (78%), whereas 22% underwent primary surgery. The median, 2-year and 5-year overall survival (OS) for the study cohort was 47 months, 64% and 43%. The median survival after first and second relapse was seven and six months, respectively. The 2 and 5-year relapse-free survival (RFS) was 52% and 36%. The median RFS after first relapse and salvage treatment was nine months. A nodal status of ≥cN2 (HR=1.89, CI:1.21-3.05, $p<0.005$) and any other primary tumor localization than pyriform sinus (HR=1.60, CI: 1.04-2.42, $p<0.05$) were identified as independent risk factors for shorter OS and RFS. Regarding functional outcome, the 2- and 5-year laryngectomy-free-survival was 55% and 37%, respectively.

Conclusion: In this large cohort with long-term follow-up any other primary tumor localization than pyriform sinus and a nodal status of ≥cN2 were identified as risk factors for reduced OS and RFS.

Key words: hypopharyngeal cancer, oncologic outcome, functional outcome, relapse, quality of life, tracheostomy, feeding tube

Level of evidence: 4

Introduction

Hypopharyngeal squamous cell carcinoma (SCC) is a rare malignancy accounting for approximately 3% to 5% of all head and neck cancers, with poor survival rates.[1] This may be explained by late appearance of symptoms, aggressive local growth, extensive submucosal spread, anatomical proximity to the larynx, high rates of lymph node involvement and a high incidence of distant metastasis (up to 60%) at initial presentation or during follow-up.[2-4] Moreover, almost 50% of the patients are affected by recurrences, mostly occurring within 12 months after completion of treatment.[5] Predisposition to develop secondary malignancies due to smoking, associated significant comorbid illnesses, common association with major alcohol abuse and frequent nutritional depletion are known factors worsening the prognosis of hypopharyngeal SCC.[1]

Treatment strategies have changed significantly over the past few decades. The traditional treatment approach for locally advanced hypopharyngeal SCC has been pharyngo-laryngectomy (PL), with or without adjuvant radiotherapy +/- chemotherapy.[1] However, radical surgery and subsequent reconstructive procedures may result in deterioration or loss of speech and swallowing functions, and accordingly in poor quality of life.[2] The necessity for improving survival along with functional improvements with larynx preservation to maintain the functions of speech and respiration, led to organ preservation approaches such as induction chemotherapy followed by radiotherapy in good responders or definitive concurrent chemoradiotherapy.[6,7] These strategies have become common with comparable outcomes (equivalent survival rates and locoregional control (LRC)) to surgical approaches.[8] However, toxicity is high after chemoradiotherapy and is associated with considerable side effects such as xerostomia, mucositis and later fibrosis contributing to decreased oral intake.[2]

Dysphagia can ultimately lead to malnutrition, severe weight loss, permanent tracheostomy, gastrostomy tube dependence, pharyngo-esophageal stenosis requiring dilatation and aspiration pneumonia which may lead to death.[9,10]

Until today, the ideal treatment strategy for advanced hypopharyngeal SCC is a matter of discussion.[1,11] There is also a lack of understanding of the course of disease of this tumor due to the low incidence, the poor prognosis and the outcomes biased by the patient treatment selection of case series and observational studies.[11] This single-institution retrospective study of an academic tertiary referral center aims to analyze the prognostic factors and report on survival, relapse patterns and long-term functional outcome of patients diagnosed with and curatively treated for hypopharyngeal SCC.

Material and Methods

Our institutional and regional review board (Inselspital, Bern University Hospital, Bern, Switzerland, KEK Nr. 117/14) granted approval to perform the present study.

The paper and electronic records of all patients diagnosed with hypopharyngeal SCC between 2003 and 2015 at our tertiary referral center were reviewed (n=270). A total of 91 patients were excluded due to: a) non-curatively intended treatment (palliative situations) (n=39), b) presence of any synchronous (n=26) or c) previously diagnosed (n=26) malignant tumor. Finally, 179 patients with accomplished curatively intended treatment were enrolled in the present study.

Patient's and initial disease characteristics were assessed and staged with the Union for International Cancer Control (UICC) 7th edition. Features and complications of primary treatment, recurrence patterns and corresponding treatments and the oncologic and functional long-term outcome at last follow-up were documented.

The time-to-event outcomes were calculated based on the date of diagnosis, and evaluated by Kaplan-Meier curves and log-rank test. In order to isolate the adverse

factors influencing the outcome parameters, multivariate Cox proportional hazard and nominal logistic models with variables yielding p values <0.1 via univariate analyses were built, and backwards elimination was performed. Statistical analysis was done with JMP software (version 14.0 SAS Institute, Cary, NC, USA). Statistical significance was set to a two-tailed alpha of <0.05. The actuarial rates and risk estimations were calculated with 95% confidence intervals (CI).

Results

Initial patient's and disease characteristics (n=179) are summarized in **Table 1**. Median follow-up of surviving patients was 51.5 months. Primary radiotherapy was the predominant treatment modality (78%), whereas 22% underwent primary surgery. Induction chemotherapy with was given to 19 patients (10.6%) followed by primary radiotherapy (n=18) or surgery (n=1). Forty-six patients underwent up-front neck dissection (ND) prior to primary radiotherapy and 122 patients received primary radiotherapy with concomitant chemotherapy (three-weekly cisplatin n=75, carboplatin and 5-fluoruracil n=11, weekly cetuximab n=29, missing information n=7).

For 100 patients, primary radiotherapy was delivered by intensity modulated techniques (static field n=46 and volumetric modulated arc n=54 with sequential boost technique: 54/72 Gy), The remaining 39 received the primary radiotherapy with 3-dimensional conformal technique. The standard total dose was 72 Gy in 2 Gy daily fractions (prescribed at median, D95% of PTV ≥ 95%). However, the treatment was interrupted between 66 and 70 Gy in 13 patients due to toxicity or patients' decision, and boosted up to 78 Gy in 3 patients in order to compensate for treatment breaks.

The 40 primary surgically treated patients underwent either transoral resection (23 patients), partial open laryngectomy (3 patients) or PL (14 patients). The surgical defect was reconstructed by pectoralis major myocutaneous flap in 4 patients, by radialis free

flap in one patient and by gastric pull-up in one patient, whereas primary closure of the defect was possible in the remaining patients. Twenty-nine patients underwent ND with primary tumor surgery. Thirty-two of the 40 surgically treated patients (80%) received adjuvant radiotherapy (intensity modulated n=18) with the standard prescribed dose of 66 Gy in 2 Gy daily fractions. However, one patient received 64 Gy, and ten patients received higher doses between 68 and 72 Gy due to various reasons (e.g. compensation for treatment breaks, R2 resection, suspicious post-operative lymph nodes). ~~and 18 of them~~ Eighteen patients received concomitant chemotherapy (three-weekly cisplatin n=14, carboplatin and 5-fluoruracil n=4).

Oncologic Outcomes

Figure 1 illustrates overall and relapse-free survival (RFS) curves. The median, 2- and 5-year overall survival (OS) for the study cohort was 47 months, 64% and 43%, respectively. The median, 2- and 5-year RFS for the study cohort was 25 months, 52% and 36%, respectively. The 2- and 5-year LRC was 65% and 58%, respectively. The median survival after first relapse was 7 months (21 months with and 6 months without salvage therapy) and the median survival after second relapse was 6 months. The median RFS after first relapse and salvage treatment was 9 months.

Tumor recurrence was observed in 88 patients (49%), a second relapse in 16 patients (9%). Fifty-five patients (30.7%) were alive and without evidence of disease at last follow-up, whilst 17 patients (9.5%) were alive with persistent or recurrent disease. Thirty-seven patients (20.7%) died free of disease, whilst 70 patients (39.1%) died with disease.

The multivariate analysis revealed as independent risk factors for shorter OS and RFS any primary tumor localization other than pyriform sinus and the presence of a nodal status of cN2 and higher. In contrast, other factors assessed in the multivariate analysis

as gender, age and tumor (T-stage) were not significantly associated with a shorter OS and RFS. The results of the multivariate analysis are summarized in **Table 2a**.

Risk of Tracheotomy/Pharyngo-laryngectomy and Feeding Tube

The incidence of undergoing a PL and/or tracheotomy at any time point was 47%, (PL: 13%, n=24). The risk of requiring a feeding tube (FT) at any time point was 71.5%. Similarly, 73 patients (41%) had a tracheotomy and/or PL at last follow-up, and 78 patients (43.6%) had a FT at last follow-up. Advanced tumor size (cT≥3), higher nodal status (cN≥2) and any primary tumor localization other than pyriform sinus remained as adverse factors for LFS after backwards elimination. The results of the multivariate analysis are summarized in **Table 2b**. Further information on tracheostomy and feeding tube categorized by primary therapy are summarized in **Table 3**.

The 2- and 5-year laryngectomy-free-survival (LFS) for the study cohort was 55% and 37%, respectively (**Figure 2A**). **Figure 2B** depicts the LFS distributed for initial tumor size and extent, grouped as early (T1-T2) and locally-advanced (T3-T4).

Early and Late Complications

Four patients (2.9%) died within 30 days after primary radiotherapy. Three of them died from tumor hemorrhage and one from multiorgan dysfunction. Furthermore, the following complications were clinically observed: hypopharyngeal stenosis (66%), laryngeal stenosis (35%), soft tissue necrosis/flap failure/fistula (8%) and chondroradionecrosis (4%). Further information on complications categorized by primary therapy are summarized in **Table 3**.

Outcome after Salvage Treatment

Tumor recurrence was observed in 88 patients (49%); of those 16 (18%) were treated with surgical salvage, 3 (3.5%) with salvage radiotherapy, and 9 (10%) with both combined. Sixty patients (68.5%) required or requested palliative treatment or best supportive care. **Table 4** provides additional information on the patterns and treatment of first relapse.

Four patients died during or within 30 days after the salvage treatment (tumor hemorrhage: 1 patient, pulmonary embolism: 1 patient, multiorgan dysfunction: 1 patient, postoperative cardiac arrhythmia: 1 patient). Following additional rates of complications were observed: FT requirement/hypopharyngeal stenosis (63.6%), laryngeal stenosis (30.7%), soft tissue necrosis/flap failure/fistula (12.5%), aspiration pneumonia (4.5%) and chondroradionecrosis (1%).

A second relapse occurred in 16 patients (9%). The mean time interval between first and second recurrence was 10.6 months (range: 0-127). Eleven patients required or requested palliative treatment, 6 of them received chemotherapy, 3 received radiotherapy. Only five patients were treated with curative intent by salvage surgery (n=3) or salvage radiotherapy (n=2).

Discussion

In this study, we report long-term oncologic and functional outcome after curatively intended hypopharyngeal SCC treatment of all non-distant metastatic tumor stages. The 5-year OS and RFS was 43% vs. 36%, respectively. Fifty-five (30.7%) out of 179 patients were alive and without evidence of disease at last follow-up. The multivariate model identified any primary tumor localization other than pyriform sinus and a nodal status of cN≥2 as risk factors for reduced OS and RFS. The 5-year LFS was 37%. Overall, any tracheostomy and/or PL and FT were observed in 46.9% and 71.5% of

the whole cohort within all stages, respectively. Of those, 40.8% had a tracheostomy and/or PL at last follow-up and 43.6% remained dependent on FT.

Hypopharyngeal SCC is a rare but aggressive malignancy with low survival rates confirmed by our results. Similarly, a study by Joo et al. (2011) identified advanced stage neck disease (pN≥2) and posterior pharyngeal wall subsite as risk factors for disease-specific survival (DSS) in hypopharyngeal SCC patients with larynx-preserving partial hypopharyngectomy with or without postoperative radiotherapy.[8] Taguchi et al. (2013) also showed that N stage (cN≥2c) is a significant prognostic factor of DSS for patients with advanced SCC of the hypopharynx undergoing chemoradiotherapy. Even with the high-dose regimen, patients with advanced nodal disease, especially cN≥2c, had low DSS rates.[12]

Since the negative influence of a higher nodal burden has been emphasized several times, it can be assumed that such patients would probably benefit from a planned ND. Thariat et al. (2010) investigated the need for planned ND after (chemo)radiotherapy for node positive patients with carcinomas of the pharynx and larynx. They found little justification for systematic ND after (chemo)radiotherapy. The majority of patients with complete response to (chemo)radiotherapy did not undergo ND and had a 5-year neck control rate of 92%. After partial response, the addition of a ND resulted in higher neck control. In conclusion, patients with complete response could be observed, patients with partial response benefit from a ND to prevent regional relapse according to this study.[13]

Our study suggests not only a high nodal status (cN≥2), but also any primary subsite other than pyriform sinus as independent risk factor for OS and RFS in hypopharyngeal SCC patients. However, we have to consider whether tumors of the pyriform sinus can be detected and treated earlier and easier, for example by endoscopy. Furthermore, larger tumors in our study were categorized as "multiple localizations". This rather

imprecise term certainly includes some locally advanced tumors including the pyriform sinus, where the primary site was indeterminable.

In this investigation, tumor recurrence was observed in 88 patients (49%) after primary treatment, of those 57.5% and 46.8% in the primary surgery and primary radiotherapy subgroups, respectively. Since salvage therapy involves a high morbidity rate in a patient collective with poor life expectancy, we have to raise the question whether the resulting benefit for the patient justifies the effort and the associated morbidity. In our cohort, 16 patients (57% of the 28 patients with curatively intended treatment for first relapse) ended up with a second relapse. Only five of them could be treated with curative intent. The median survival after first relapse was 7 months (21 with salvage therapy, 6 without) and the median survival after second relapse was 6 months. The median RFS after first relapse and salvage treatment was 9 months. It is the duty of the treating multidisciplinary team to evaluate survival and functional results and their impact on patient's quality of life to adequately counsel the patients. Finally, the patient should be able to make an informed decision and have the possibility to trade off chance of survival against treatment related morbidity.[14,15]

Due to the relative lack of symptoms for early-stage of disease, the majority of patients with hypopharyngeal SCC present with locoregionally advanced disease at the time of their diagnosis with a substantial risk of subclinically present distant metastatic spread.[16] Approximately 60-80% of the patients with newly diagnosed hypopharyngeal SCC already have clinically apparent ipsilateral and up to 40% have contralateral neck lymph node involvement. Hypopharyngeal tumors generally affect the lymph nodes more often than laryngeal tumors and if they are involved, this is more likely to lead to death than laryngeal tumors with affected lymph nodes.[5]

Furthermore, patients with hypopharyngeal SCC generally have a poor functional outcome. In our cohort any kind of tracheostomy (including PL) was observed in 46.9%

of patients, of which 40.8% were permanent tracheostomies (50% surgical and 38.1% RT group). Regarding permanent FT dependency similar numbers were observed with 43.6% permanent FT placement (32.5% surgical and 46.8% RT group). These numbers indicate a high morbidity of hypopharyngeal SCC treatment. Petersen et al. (2019) assessed in a recent study the functional outcomes of hypopharyngeal SCC patients treated with radiotherapy or chemoradiotherapy. Functional outcome was measured using laryngo-oesophageal dysfunction-free survival rate (LDFS). The 2-year and 5-year LDFS following chemoradiotherapy was higher than the corresponding rate following radiotherapy. In summary, functional outcomes following chemoradiotherapy or radiotherapy appear to be disappointing and demand improved treatment strategies.[17]

New therapeutic approaches are constantly being developed and investigated in order to improve the functional outcome of these patients with the aim of achieving similar survival rates. A positive influence of induction chemotherapy on the long-term functional outcome of hypopharyngeal SCC patients subsequently treated with (chemo)radiotherapy could be shown. Vourexakis et al. (2014) evaluated the following functions: oral communication, airway patency and oral feeding. The subjects were good responders to induction chemotherapy for pyriform sinus SCC (n=28), subsequently treated with adjuvant radiotherapy, with (n=13) or without (n=15) concomitant chemotherapy. Only 7% of patients in their study needed a tracheostomy during or after treatment and only 7% had PL for a late local relapse. At least 3 years after the end of therapy, all patients were exclusively fed by mouth and the majority of them didn't need to modify their eating habits. All patients judged their voice performance as adequate for everyday oral communication. Therefore, patients with hypopharyngeal SCC who respond favorably to induction chemotherapy present a

good functional outcome when treated with (chemo)radiotherapy. Nevertheless, it is important to note that these data do not provide a high level of evidence.[18]

Chen et al. (2017) studied the effect of daily fraction size on laryngoesophageal dysfunction among patients treated by chemoradiotherapy for locally advanced SCC of the larynx and hypopharynx. When comparing 2 versus > 2 Gy daily fractionation, there was no difference in 2-year OS, LFS and LRC. But they were able to show a difference in LDFS. Use of 2 Gy versus > 2 Gy fractionation improved LDFS (2-year LDFS 49% vs. 27%, respectively), as well as patient-reported swallowing function and voice.[10]

In the last few years, the quest for surgical treatment options offering conserved laryngeal function led to the development and validation of partial transoral and open surgeries. Hung et al. (2017) demonstrated transoral laser microsurgery (TLM) achieving good oncologic results and satisfactory speech and swallowing function, in patients with early and selective moderately advanced hypopharyngeal SCC. The 5-year OS and DSS rates were 59% and 77%, respectively. The 5-year laryngeal-preservation rate was 89%. They explained their results by the reduced need for radiotherapy in primary surgical treatment and by reduced radiotherapy dose in postoperative radiotherapy compared to primary radiotherapy.[2]

We acknowledge the limitations of the present study mainly due to its retrospective nature and its inherent challenges, for example, the possible presence of confounding variables, the vulnerability to the development of a selection bias and the fact that we cannot determine causation, only association. Besides, our study has an asymmetry in terms of group size in terms of primary treatment modality (radiotherapy vs. surgery).

Conclusion

In this study, we report long-term oncologic and functional outcome after curatively intended hypopharyngeal SCC treatment of all loco-regionally confined tumor stages. Any primary tumor localization other than pyriform sinus and nodal status cN≥2 are related to a poorer OS and RFS. Advanced tumor size (cT≥3), any primary tumor localization other than pyriform sinus and nodal status cN≥2 seem to be adverse factors impairing LFS. In this cohort permanent tracheostomy placement was observed in 40.8% and permanent FT dependency in 43.6% of patients. Appropriate patient selection may be the key to improve oncologic and functional outcomes and should be discussed by multidisciplinary teams.

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Tables

Table I: Patient's and initial disease characteristics

	Whole Cohort	Primary Surgery with or without adjuvant treatment	Primary Radiotherapy with or without systemic treatment
Parameter	**n**	**n**	**n**
Total	179	40	139
Male sex	155 (87%)	35 (87.5%)	120 (86.3%)
Median age, years (range)	59 (35-87)	57.5 (44-81)	59 (35-87)
Tumor subsite			
Sinus pyriformis	134 (75%)	29 (72.5%)	105 (75.5%)
Posterior pharyngeal wall	17 (9%)	2 (5%)	15 (10.8%)
Post-cricoid region	2 (1%)	1 (2.5%)	1 (0.7%)
Multiple subsites involved	26 (15%)	8 (20%)	18 (13%)
cT stage			
1	17 (9%)	9 (22.5%)	8 (5.8%)
2	50 (28%)	7 (17.5%)	43 (30.9%)
3	48 (27%)	7 (17.5%)	41 (29.5%)
4a	59 (33%)	17 (42.5%)	42 (30.2%)
4b	5 (3%)	0 (0%)	5 (3.6%)
cN stage			
0	45 (25%)	15 (37.5%)	30 (21.6%)
1	17 (10%)	3 (7.5%)	14 (10%)
2	113 (63%)	21 (52.5%)	92 (66.2%)
3	4 (2%)	1 (2.5%)	3 (2.2%)
Clinical UICC$^{7th\ ed.}$ Stage			
I	9 (5%)	7 (17.5%)	2 (1.4%)
II	17 (9.5%)	2 (5%)	15 (10.8%)
III	22 (12.3%)	4 (10%)	18 (13%)
IVA	124 (69.3%)	26 (65%)	98 (70.5%)
IVB	7 (3.9%)	1 (2.5%)	6 (4.3%)

Table II: Multivariate model after backwards elimination for overall survival, relapse-free survival and locoregional relapse

Variable	HR for overall survival (95% CI)	p value	HR for relapse-free survival (95% CI)	p value	HR for loco-regional relapse (95% CI)	p value
cN≥2	1.89 (1.21-3.05)	**<0.005**	1.56 (1.05-2.36)	**<0.05**	1.44 (0.87-2.47)	0.161
Subsite other than pyriform sinus	1.60 (1.04-2.42)	**<0.05**	1.74 (1.16-2.55)	**<0.05**	1.50 (0.40-1.16)	0.149
Age>59	1.35 (0.92-1.98)	0.126	1.23 (0.87-1.75)	0.2456	1.03 (0.65-1.65)	0.881
Male sex	1.47 (0.81-2.95)	0.217	1.47 (0.37-1.17)	0.169	1.49 (0.29-1.35)	0.278
cT≥3	1.18 (0.76-1.86)	0.464	0.90 (0.61-1.34)	0.5976	0.82 (0.50-1.38)	0.447

HR: hazard ratio; CI: confidence interval

Table III: Multivariate Cox proportional hazards model for laryngectomy-free survival

Variable	Multivariate model		After backwards elimination	
	HR (95% CI)	p value	HR (95% CI)	p value
cN≥2	1.65 (1.07-2.61)	**<0.05**	1.66 (1.08-2.63)	**<0.05**
Subsite other than pyriform sinus	1.83 (1.21-2.71)	**<0.005**	1.80 (1.19-2.66)	**<0.05**
cT≥3	1.49 (0.98-2.33)	0.0621	1.54 (1.01-2.39)	**<0.05**
Age>59	0.94 (0.65-1.36)	0.7512		
Male sex	1.35 (0.76-2.60)	0.318		

HR: hazard ratio; CI: confidence interval

Table IV: Complications and functional outcome after first treatment

Parameter	Whole Cohort n	Primary Surgery with or without adjuvant treatment n	Primary Radiotherapy with or without systemic treatment n
Total	179	40	139
Hypopharyngeal stenosis	118 (66%)	18 (45%)	100 (72%)
Operative dilatation	11 (6%)	2 (5%)	9 (6.5%)
Laryngeal stenosis	63 (35%)	21 (52.5%)	56 (40.3%)
Asymptomatic (observation)	1 (0.5%)	0 (0%)	1 (0.7%)
Symptomatic without respiratory distress	4 (2%)	1 (2.5%)	3 (2.2%)
Limiting self-care	1 (0.5%)	1 (2.5%)	3 (2.2%)
Life-threatening	57 (32%)	5 (12.5%)	52 (37.4%)
Chondroradionecrosis	7 (4%)	2 (5%)	5 (3.6%)
Soft tissue necrosis, flap failure, fistula	14 (8%)	4 (10%)	10 (7.2%)
Any tracheostomy*	84 (46.9%)	21 (52.5%)	63 (45.3%)
Permanent tracheostomy*	73 (40.8%)	20 (50%)	53 (38.1%)
Any feeding tube	128 (71.5%)	22 (55%)	106 (76.3%)
Permanent feeding tube	78 (43.6%)	13 (32.5%)	65 (46.8%)
Death due to treatment (during 30 days post-treatment)	4 (2.2%)	0 (0%)	4 (2.9%)

* Including total pharyngolaryngectomies in the surgical group

Table V: First relapse and its treatment

	Whole Cohort	Primary Surgery with or without adjuvant treatment	Primary Radiotherapy with or without systemic treatment
Parameter	**n**	**n**	**n**
Total	88 (49% of 179)	23 (57.5% of 40)	65 (46.8% of 139)
Localization of first relapse			
Local	32 (36%)	8 (34.8%)	24 (36.9%)
Isolated regional	12 (14%)	7 (30.4%)	5 (7.7%)
Locoregional	9 (10%)	3 (13%)	6 (9.2%)
Locoregional and distant	21 (24%)	2 (8.7%)	19 (29.2%)
Distant only	14 (16%)	3 (13%)	11 (16.9%)
Localization of distant metastases	35 (40% of 88)		
Pulmonary	14 (40%)	2 (40%)	12 (40%)
Bone	5 (14.3%)	2 (40%)	3 (10%)
Liver	1 (2.9%)	0 (0%)	1 (3.3%)
Other	4 (11.4%)	0 (0%)	4 (13.3%)
Multiple sites	11 (31.4%)	1 (20%)	10 (33.3%)
Treatment			
Salvage surgery	16 (18%)	6 (26.1%)	10 (15.2%)
Salvage RT	3 (3.4%)	2 (8.7%)	1 (1.5%)
Salvage surgery + RT	9 (10.1%)	4 (17.4%)	5 (7.6%)
Palliative chemotherapy	30 (33.7%)	4 (17.4%)	26 (39.4%)
Palliative RT	6 (6.7%)	1 (4.3%)	5 (7.6%)
Palliative RT + chemotherapy	1 (1.1%)	0 (0%)	1 (1.5%)
Best supportive care	24 (27%)	6 (26.1%)	18 (27.3%)
Type of salvage surgery	25 (28.4% of 88)	10	15
ND only	9 (36%)	6 (60%)	3 (20%)
Open partial pharyngolaryngectomy	4 (16%)	2 (20%)	2 (13.3%)
Open total pharyngolaryngectomy	10 (40%)	1 (10%)	9 (60%)
Transoral partial pharyngolaryngectomy	1 (4%)	1 (10%)	0 (0%)
Lung wedge resection	1 (4%)	0 (0%)	1 (6.7%)
Flap for salvage	9 (36%)	2 (20%)	7 (50%)

RT: radiotherapy; ND: neck dissection

Figure Legends

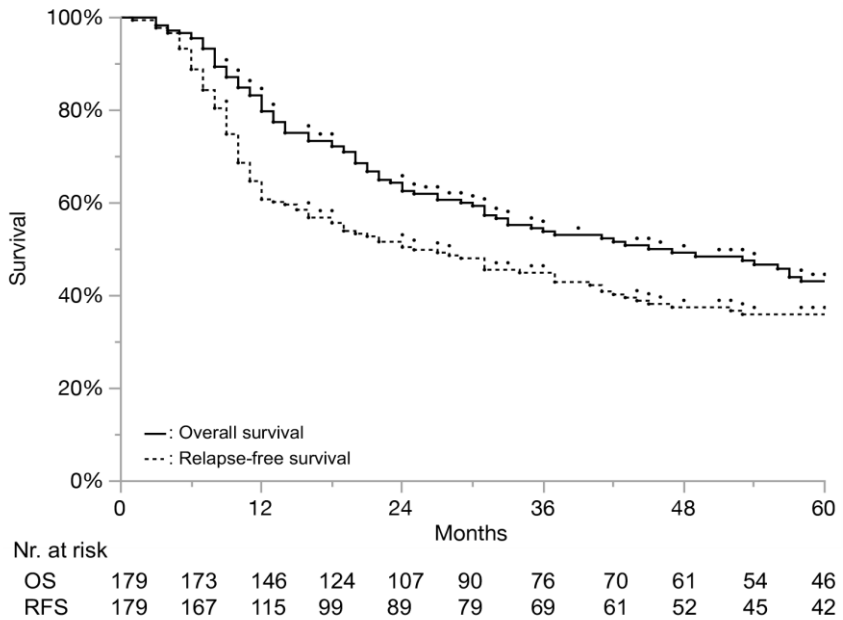

Figure 1: Overall and relapse free survival for the whole cohort

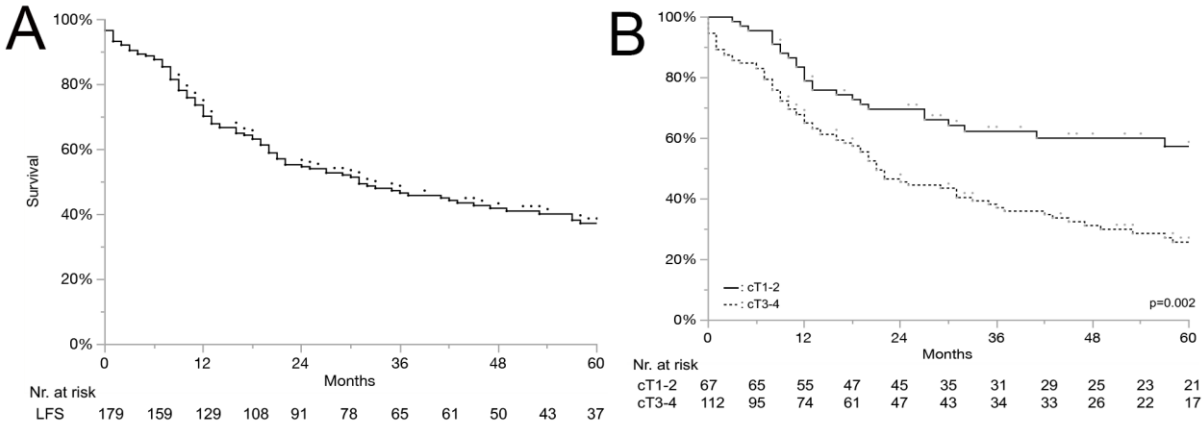

Figure 2: Panel A: Laryngectomy-free survival for the whole cohort and B: by cT stage