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ORIGINAL ARTICLE

Primary and salvage total laryngectomy. Influential factors, complications, and survival

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Summary

Purpose: *In this retrospective study we analysed patients with advanced squamous cell carcinoma of the larynx and hypopharynx treated with primary total laryngectomy (PTL) between 1990 and 2007.*

Methods: *The patients were treated by classical PTL, radiotherapy 60-70 Gy, concomitant radio and chemotherapy (cisplatin and 5-fluorouracil) or salvage total laryngectomy (STL). They were followed up for 5 years and complications, survival, residual/recurrent disease and metastases were registered.*

Results: *STL after previous radiotherapy (STL-pRT), and after chemoradiotherapy (STL-pCTRT) caused more frequent local complications than PTL. Five-year disease-free survival (DFS) rate was significantly influenced by TNM stage and localization of the primary laryngeal tumor. For laryngeal cancer it was: 61.3% for PTL, 54.1% for STL-pCTRT, and 47.6% for STL-pRT. Incomplete responders to initial treatment had low survival rate. PTL for hypopharyngeal carcinoma and particularly salvage laryngectomy after chemoradiotherapy were associated with more frequent local complications. The 5-year DFS for hypopharyngeal cancer was lower than for laryngeal cancer.*

Conclusion: *PTL still offers the best survival rate with low complications for advanced laryngeal and hypopharyngeal squamous cell carcinoma. STL causes more frequent local complications, especially after chemoradiotherapy. Addition of chemotherapy to radiotherapy increases the survival. Five-year DFS rate depends on TNM stage and localization of the primary tumor.*

Key words: *complications, hypopharynx, larynx, total laryngectomy, survival*

Introduction

The management of malignant neoplasms of the upper aerodigestive tract remains difficult despite recent advances in surgical techniques and multidisciplinary treatment programs. High recurrence rates, low survival, and significant alterations in speech and swallowing functions are common experience for patients with malignancies in these anatomic sites. On the other hand, these patients are potentially curable and must be offered regimens that carefully consider morbidity and outcome within the context of the patient's overall medical condition [1-3].

Larynx preservation using chemoradiotherapy became increasingly popular during the latest 20 years. This concept offers potential preservation of voice and swallowing with survival similar to primary laryngectomy. Salvage laryngectomy was reserved after failure of such treatment, when persistent disease or when biopsy proved recurrent tumor is present. However, salvage surgery is accompanied with significantly larger number of complications [1,4].

Complications after total laryngectomy can be divided into local (fistula, infection, chyle leak, carotid rupture, and flap necrosis), airway and swallowing difficulties, and general (pulmonary,

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metabolic, myocardial infarction, urinary infection). Such complications significantly affect morbidity, hospitalization and costs of treatment [5-9].

Randomized comparison of primary and salvage laryngectomy groups is extremely rare. So, any study that compares survival rate and complications between these treatment modalities is important. Different surgical techniques, insufficient number of studied cases, and many variables that are implicated make drawing adequate conclusions difficult [4,10,11]. We believe that since this is a study conducted on a large number of patients at a single institution and uniform treatment protocol its value is more significant.

Herein, a retrospective analysis of patients with squamous cell carcinoma of the larynx and hypopharynx treated with primary and salvage total laryngectomy is presented, which compares the results, complications and factors related to treatment outcome.

Methods

In the period between 1990 and 2007 we performed 540 total laryngectomies for advanced squamous cell carcinoma of the larynx and hypopharynx. PRT was undertaken in 404 (75.1%) patients. For patients who refused surgery (N=132), initial radiotherapy (60-70Gy) and chemoradiotherapy (cisplatin+5-fluorouracil) were applied. These patients later received STL.

Preoperative workup included clinical ENT examination, CT of the neck, panendoscopy with biopsy, as well as blood/serum biochemistry, cardiologic and pulmonary examination. Staging was made with computed tomography (extent of disease at the primary site, lymph node status in the neck, and evaluation for metastatic disease). Age, sex, medical comorbidities, smoking and drinking habit were also registered.

All the laryngectomies were performed by four surgeons, using the same routine surgical technique. Pharynx was closed linearly or in T shape, with 000 Vicryl single stitches. Muscular reinforcement was made using the same material. Nasogastric tube was used for 7 days.

Postoperative clinical examination was performed every 3 months during 5 years. Local and general complications, survival rate, residual and recurrent disease, lymph node metastasis, and other changes were documented. Suspected residual or recurrent disease were confirmed by endoscopy and biopsy.

Statistics

Descriptive statistics (median and range) were used to describe the patient population and follow-up. Survival was calculated using the Kaplan-Meier method with log rank test. DFS was calculated from the time of treatment initiation to the time of disease progression, death or last follow-up. Chi square test was used to investigate the differences between the groups of the patients and a p value less than 0.05 denoted the presence of a statistically significant difference. All statistical analyses were performed using SPSS V.12 (SPSS Inc., Chicago, Ill).

Results

For laryngeal cancer 431 total laryngectomies were performed. There were 352 PTL, 42 STL-pRT, and 37 STL-pCTRT. For hypopharyngeal cancer 107 total laryngectomies were performed; 52 PTL, 31 STL-pRT, and 24 STL-pCTRT.

The age of the patients was under 50 years in 52.3%, while the others were older than 50 years. Males were 85.4%. Smoking was reported by 91.2%, and drinking by 88.2%. No statistically significant difference was noticed either between laryngeal and hypopharyngeal group, or between the treatment groups.

For laryngeal carcinoma the most frequent tumor site was glottic (50.5%), followed by supraglottic (32.7%), and subglottic or transglottic localization (16.7%). T3 stage (57.1%) was more frequent than T4 stage of the disease. N2 stage predominated with 43.4%, while N3 and N1 were less frequent. Only 6.7% of the patients presented without affected neck nodes. Thus, 76.6% of the patients had stage IV, and only 22.5% stage III. Statistical analysis showed no significant differences for all these parameters between PTL, STL-pCT, and STL-pCTRT groups (Table 1).

For hypopharyngeal carcinoma pyriform localization was dominant (66.4%), while other sites were less represented, especially the retrocricoid part. Concerning stage, T3 was present in 40.2% of the patients, T4 in 32.7%, while other stages were less documented. N2 and N3 were equally registered (39.2%), with other stages less present. Thus, stage IV disease was in 78.6%, and stage III in 18.7% of the patients. Statistical analysis found significant difference between the studied groups. Patients previously treated with radiotherapy and with chemoradioteharpy had more advanced disease on admission (stage IV in 67.3% of PTL, 87.1% of STL-pRT, and 91.6% STL-pCTRT) (Table 2).

Medical comorbidities were verified in 10.0% of laryngeal, and 23.4% of hypopharyngeal tumor sites. They were more frequent in the group of patients treated by primary radiotherapy ($p<0.01$ for laryngeal and $p<0.05$ for hypopharyngeal cancer).

The interval between the initial treatment and salvage laryngectomy ranged from 2 to 42

Table 1. Laryngeal carcinoma parameters: status, surgery, and complications

Parameters	*PTL*		*STL-pRT*		*STL-pCTRT*		*Total*		*p value*
	N	%	*N*	%	*N*	%	*N*	%	
Site									
Supraglottic	107	30.4	22	52.4	12	32.4	141	32.7	
Glottic	189	53.7	11	26.2	8	48.6	218	50.6	NS
Transglottic	56	15.9	9	21.4	7	19.0	72	16.7	
cT stage									
T1	0	0	0	0	0	0	0	0	
T2	0	0	6	14.3	1	2.7	7	1.6	NS
T3	205	58.2	17	40.5	24	64.9	246	57.1	
T4	147	41.8	19	45.2	12	32.4	178	41.3	
cN stage									
N0	26	7.4	3	7.1	0	0	29	6.7	
N1	90	25.6	5	11.9	2	5.4	97	22.5	NS
N2	141	40.0	22	52.4	24	64.9	187	43.4	
N3	95	27.0	12	28.6	11	29.7	118	27.4	
cTNM stage									
I	0	0	0	0	0	0	0	0	
II	0	0	3	7.1	1	2.7	4	0.9	<0.05
III	90	33.0	5	11.9	2	5.4	97	22.5	
IV	236	67.0	34	81.0	34	91.9	330	76.6	
Comorbidity									
Yes	18	5.1	12	28.6	3	8.1	43	10.0	<0.01
No	334	94.9	30	71.4	34	91.9	388	90.0	
Reconstruction									
No	352	100	40	95.2	33	89.2	425	98.6	NS
Yes	0	0	2	4.8	4	10.2	6	1.4	
Dissection									
RND	106	30.1	13	31.0	24	64.9	143	33.2	
SND	180	51.1	24	57.1	13	35.1	217	50.3	NS
No	66	18.8	5	11.9	0	0	71	16.5	
Infection									
No	291	82.7	33	78.6	22	59.5	346	80.3	<0.01
Yes	61	17.3	9	21.4	15	40.5	85	19.7	
Fistula									
No	299	85.0	35	83.3	26	70.3	360	83.5	<0.01
Yes	53	15.0	7	16.7	11	29.7	71	16.5	
Swallow dif.									
No	331	94.0	29	69.0	27	73.0	387	89.8	<0.01
Yes	21	6.0	13	31.0	10	27.0	44	10.2	

NS: non significant, c: clinical stage. For other abbreviations see text

months (median 5.2). Surgical mortality rate for both PTL and STL was 0%. The mean length of hospital stay after primary total laryngectomy was 12.4 days, compared to 18.7 days after salvage surgery (p<0.05).

Nasogastric tube was left in place for a median of 16.5 days (range 16-27) after STL.

Selective neck dissection was the most frequent type of dissection for laryngeal cancer (50.3%), while for hypopharyngeal cancer radical neck dissection was predominant (48.6%). The difference between the groups was not sig-

Table 2. Hypopharyngeal carcinoma parameters: status, surgery, and complications

Parameters	*PTL*		*STL-pRT*		*STL-pCTRT*		*Total*		*p value*
	N	%	*N*	%	*N*	%	*N*	%	
Site									
Pyriform	31	59.6	23.7	74.2	17	70.8	71	66.4	
Superior	19	36.5	5	16.1	3	12.5	27	25.2	NS
Postcricoid	2	3.9	3	9.7	4	16.7	9	8.4	
cT stage									
T1	0	0	1	3.2	0	0	1	0.9	
T2	24	46.1	3	9.7	1	4.2	28	26.2	p<0.05
T3	21	40.4	12	38.7	10	41.7	43	40.2	
T4	7	13.5	15	48.4	13	54.1	35	32.7	
cN stage									
N0	0	0	2	6.5	1	4.2	3	2.8	
N1	17	32.7	2	6.5	1	4.2	20	18.7	NS
N2	20	38.5	14	45.2	8	33.3	42	39.2	
N3	15	28.8	13	41.9	14	58.3	42	39.2	
cTNM stage									
I	0	0	1	3.2	0	0	1	0.9	
II	0	0	1	3.2	1	4.2	2	1.8	<0.01
III	17	32.7	2	6.5	1	4.2	20	18.7	
IV	35	67.3	27	87.1	22	91.6	84	78.6	
Comorbidity									
Yes	9	17.3	12	38.7	4	16.7	25	23.4	<0.05
No	43	82.7	19	61.3	20	83.3	82	76.6	
Reconstruction									
No	47	90.4	22	71.0	14	58.3	83	77.6	<0.01
Yes	5	9.6	9	29.0	10	41.7	24	22.4	
Dissection									
RND	25	48.1	15	48.4	12	50.0	52	48.6	
SND	21	40.4	11	35.5	7	29.2	39	36.4	NS
No	6	11.5	5	16.1	5	20.8	16	15.0	
Infection									
No	41	78.8	18	58.1	6	25.0	65	60.7	<0.01
Yes	11	21.2	13	41.9	18	75.0	42	39.3	
Fistula									
No	43	82.7	22	71.0	10	41.7	75	70.1	<0.01
Yes	9	17.3	9	29.0	14	58.3	32	29.9	
Swallow dif.									
No	47	90.4	25	80.6	17	70.8	89	83.2	<0.01
Yes	5	9.6	6	19.4	7	29.2	18	16.8	

NS: non significant. For other abbreviations see footnote of Table 1 and the text

nificant. However, the highest number of radical neck dissections was performed in STL-pCTRT of laryngeal cancer. Neck dissection specimens after radiotherapy were positive for metastatic cancer in 57%, while after chemoradiotherapy in 72% (p<0.01), and this correlated to N stage.

While pharyngeal reconstruction was seldom needed for laryngeal cancer, for hypopharyngeal localization it was performed in 22.4% of the patients. Pectoral myocutaneous flap was mainly used in the STL-pCTRT group, and less frequent in the STL-pRT group. This difference was highly

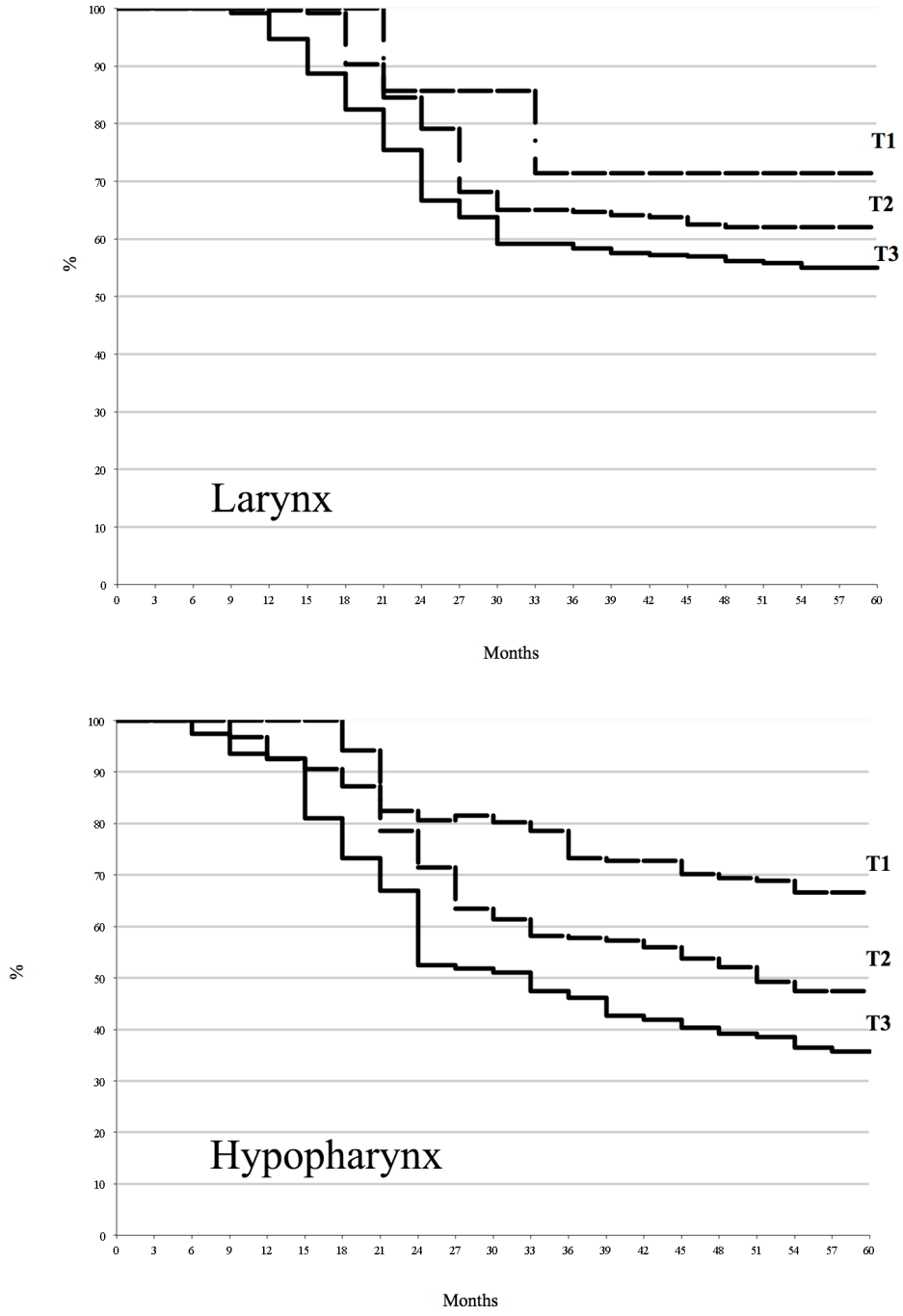

Figure 1. Kaplan-Meier 5-year DFS rate for laryngeal and hypopharyngeal carcinoma after total laryngectomy depending on T stage ($p<0.05$).

significant.

Local complications were more often encountered in hypopharyngeal carcinoma compared to laryngeal localization. Wound infection was seen in 39.3 vs 19.7%, and pharyngocutaneous fistula in 29.9 vs 16.5%. Statistically significant increase of local complications in the salvage laryngectomy group was found. Patients with laryngeal cancer receiving chemoradiotherapy developed postlaryngectomy fistula twice more frequently compared to primary laryngectomy. Patients with hypopharyngeal cancer were more prone to fistula formation (58.8% in the STL-pCTRT, and 29.0% in the STL-pRT group). The mean time to spontaneous closure of fistulas was 25± 3 days. In total, 88.4% of fistulas closed spontaneously, with local care and specific antibiotic treatment. Spontaneous closure of fistulas after radiotherapy was verified in 81.4%, while after previous chemoradiothehrapy it was in 69.3% ($p<0.05$). Persistent

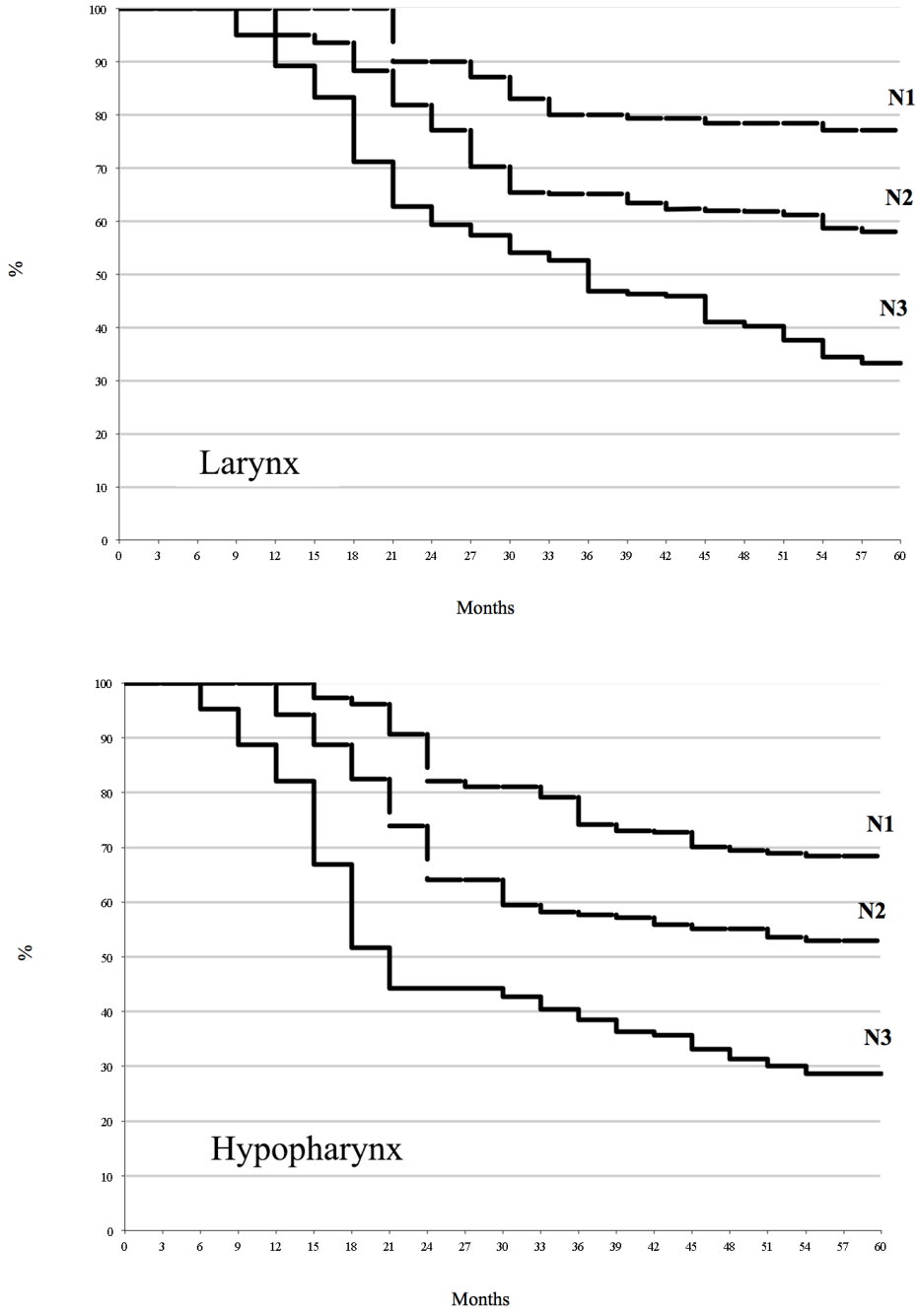

Figure 2. Kaplan-Meier 5-year DFS rate for laryngeal and hypopharyngeal carcinoma after total laryngectomy depending on the N stage ($p<0.01$)

fistulas were closed after one month by local flap, mainly for laryngeal cancer, while pectoral myocutaneous flap was needed in 72.0% of persistent fistulas after STL for hypopharyngeal cancer.

Swallowing problems were significantly more frequent in STL groups, both for laryngeal and hypopharyngeal malignancies.

Carotid artery rupture was very rare in laryngeal cancer (0.5%), but present in hypopharyngeal cancer, especially after STL (4.6%) ($p<0.01$). Immediate surgical ligation was performed in cases of carotid artery rupture, and musculocutaneous flaps gave a vascular cover of the exposed vessels.

Complications associated to airway and systemic complications were not significantly different between the groups.

Five-year follow-up was complete in 89.3% of the patients with laryngeal and in 85.0% with hypopharyngeal cancer. The overall DFS rate after total laryngectomy was 59.5% for laryngeal, and

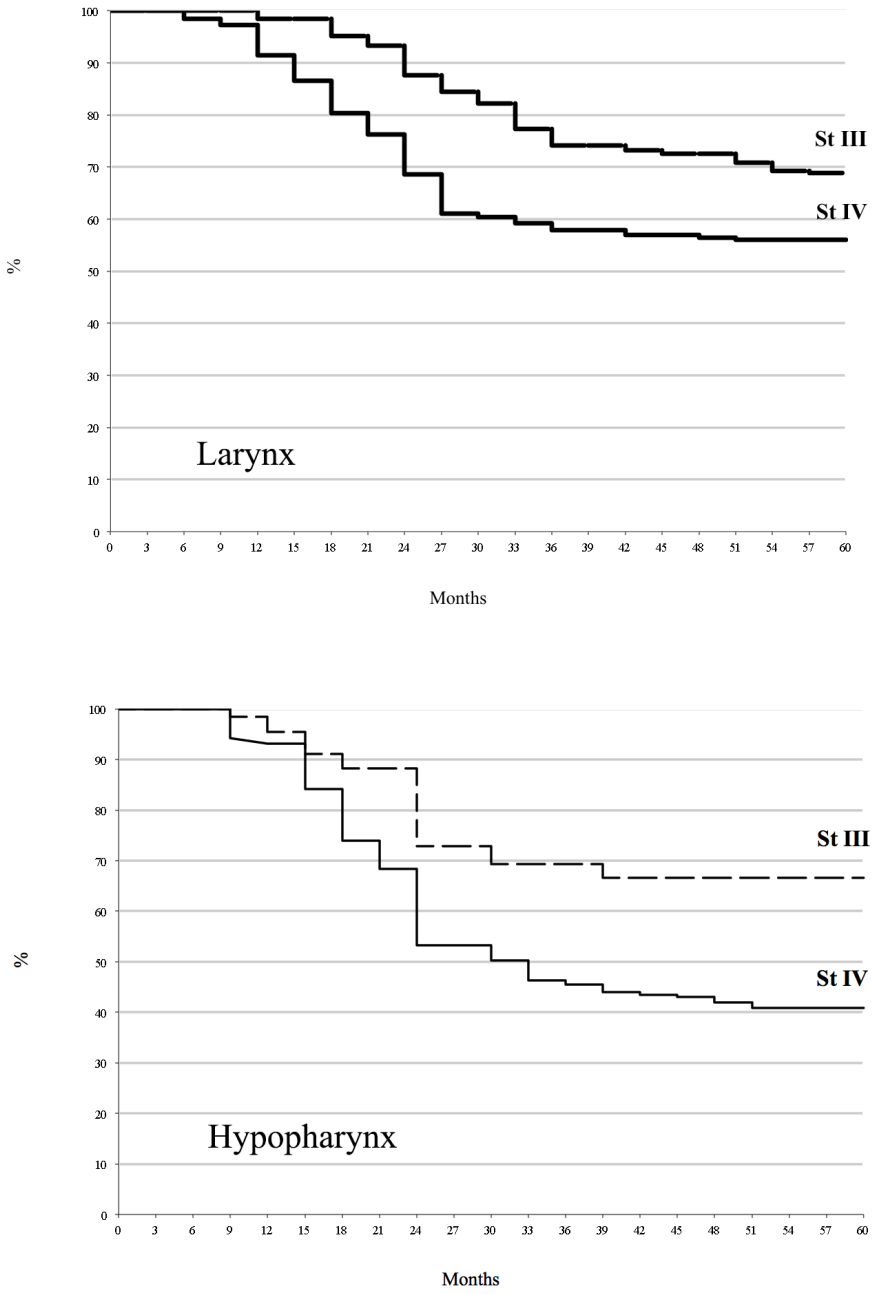

Figure 3. Kaplan-Meier 5-year DFS rate for laryngeal and hypopharyngeal carcinoma after total laryngectomy depending on the stage of disease (p<0.01)

48.5% for hypopharyngeal malignancies (p<0.05).

TNM stage of disease was very significant factor for DFS. For T4 it was 55.0% for laryngeal and 35.7% for hypopharyngeal disease (Figure 1). Similar results were found when N stage was analyzed (Figure 2). Stage IV disease had 5-year DFS in 56.0% laryngeal, and in 40.8% hypopharyngeal primary site (Figure 3). The worst survival was verified for retrocricoid and subglottic cancer (Figure 4).

Comparison of DFS in primary and salvage laryngectomy showed significantly better results when primary surgery was performed (61.3% for PTL, 54.1% for STL-pCTRT, and 47.6% for STL-pRT), while for hypopharyngeal localization it was 53.3%, 45.0% and 42.3%, respectively (Figure 5).

In this study complete response in the neck after radiotherapy was followed by subsequent neck dissection in 30%, while after chemoradio-

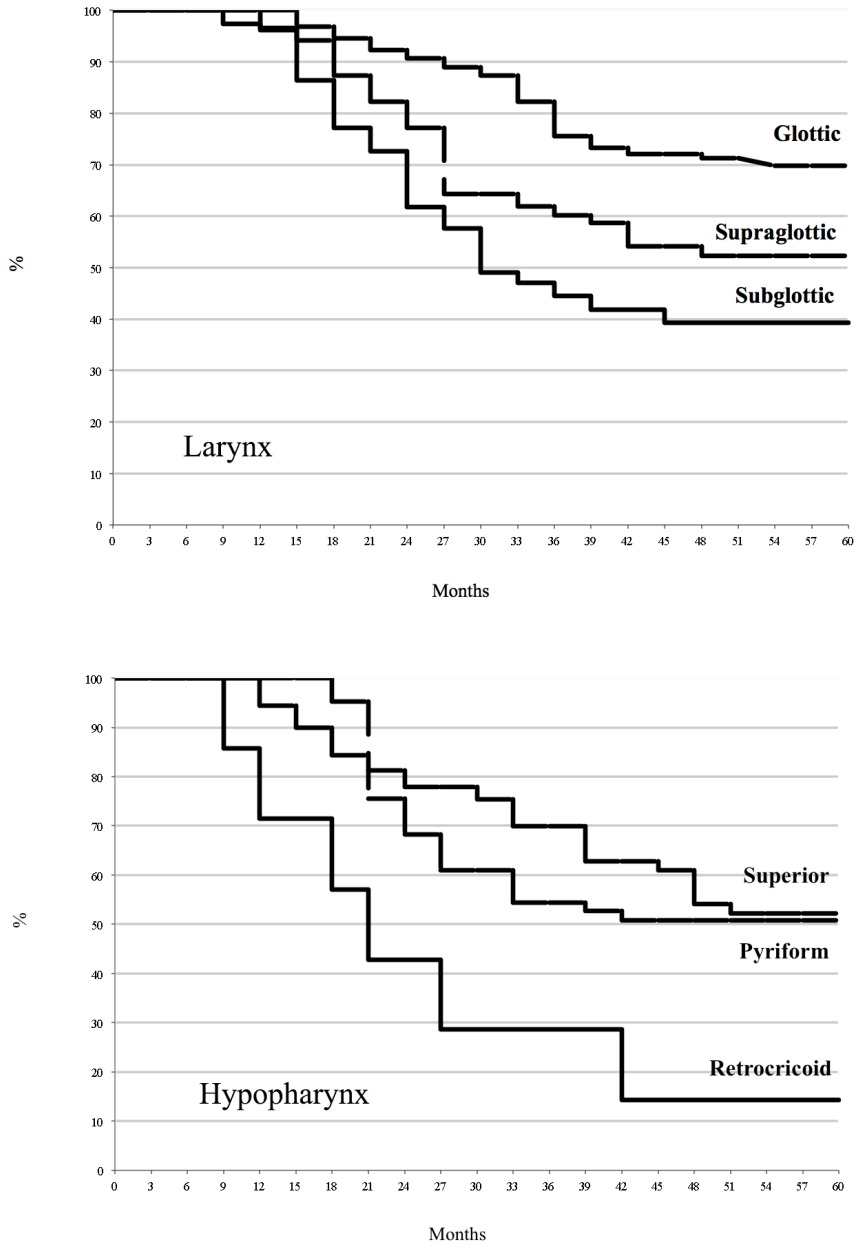

Figure 4. Kaplan-Meier 5-year DFS rate for laryngeal and hypopharyngeal carcinoma after total laryngectomy depending on the localization of the primary tumor ($p<0.01$).

therapy this rate was 38%. Incomplete response was associated with significantly higher number of salvage dissections and worse survival rate. Five-year survival rate for patients who responded completely to initial treatment was favorable. For laryngeal carcinoma after STL-pCTRT it was 68.4%, and after STL-pRT 63.2%, while for hypopharyngeal carcinoma it was lower: 63.6% after STL-pCTRT, and 50.0% after STL-pRT ($p<0.01$). Only one third of the incomplete responders to initial treatment had 5-year survival: 38.9% and 34.8% for laryngeal and 38.5% and 36.8% for hypopharyngeal cancer (Figure 6).

Discussion

The patient's expectations with laryngopharyngeal cancers are mainly focused on curing the malignancy and achieving longer survival.

Multi-institutional studies in the United States support organ preservation for the management of the primary site in head and neck squamous cell carcinoma. However, larynx pres-

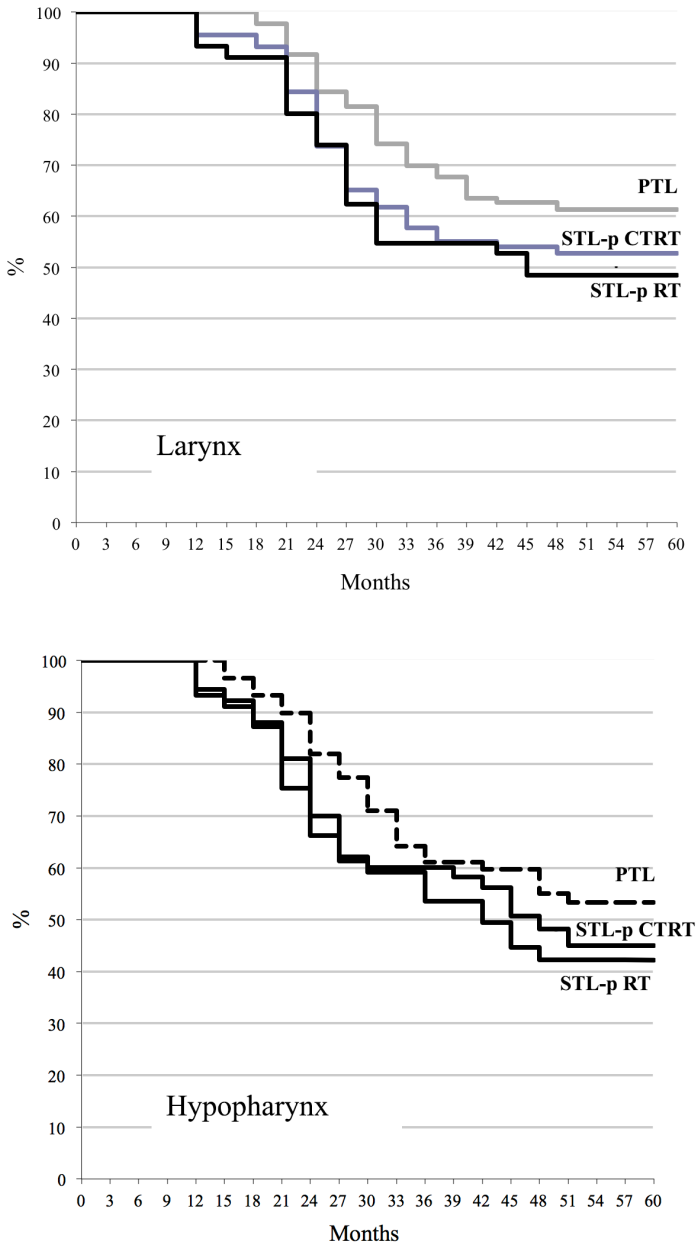

Figure 5. Kaplan-Meier 5-year DFS rate for laryngeal and hypopharyngeal carcinoma after total laryngectomy depending on the previous treatment (PTL: primary total laryngectomy, STL-pRT: salvage total laryngectomy after radiotherapy, STL-pCTRT: salvage total laryngectomy after chemoradiotherapy) ($p<0.05$).

ervation is differently defined in the literature. Preservation means larynx in place, no residual tumor, and also no tracheotomy and no feeding tube. Preservation of function is more important to the patients than just anatomic integrity of the larynx [11-13].

A large study of treatment of laryngeal cancer in the United States confirmed higher survival when patients had primary laryngectomy [1,4]. Other authors also concluded that none of the nonsurgical approaches to treatment of laryngopharyngeal cancer provided a better survival than initial radical surgery [13-15].

Salvage total laryngectomy is indicated after induction chemotherapy, after irradiation, and after concurrent chemoradiotherapy in case of residual disease, or during follow-up in case of relapse. There are insufficient data on salvage laryngeal surgery after chemoradiotherapy. Difficulties in proper tumor detection, determination of surgical margins, adequate resection, complication rate, and survival cause problems in salvage total lar-

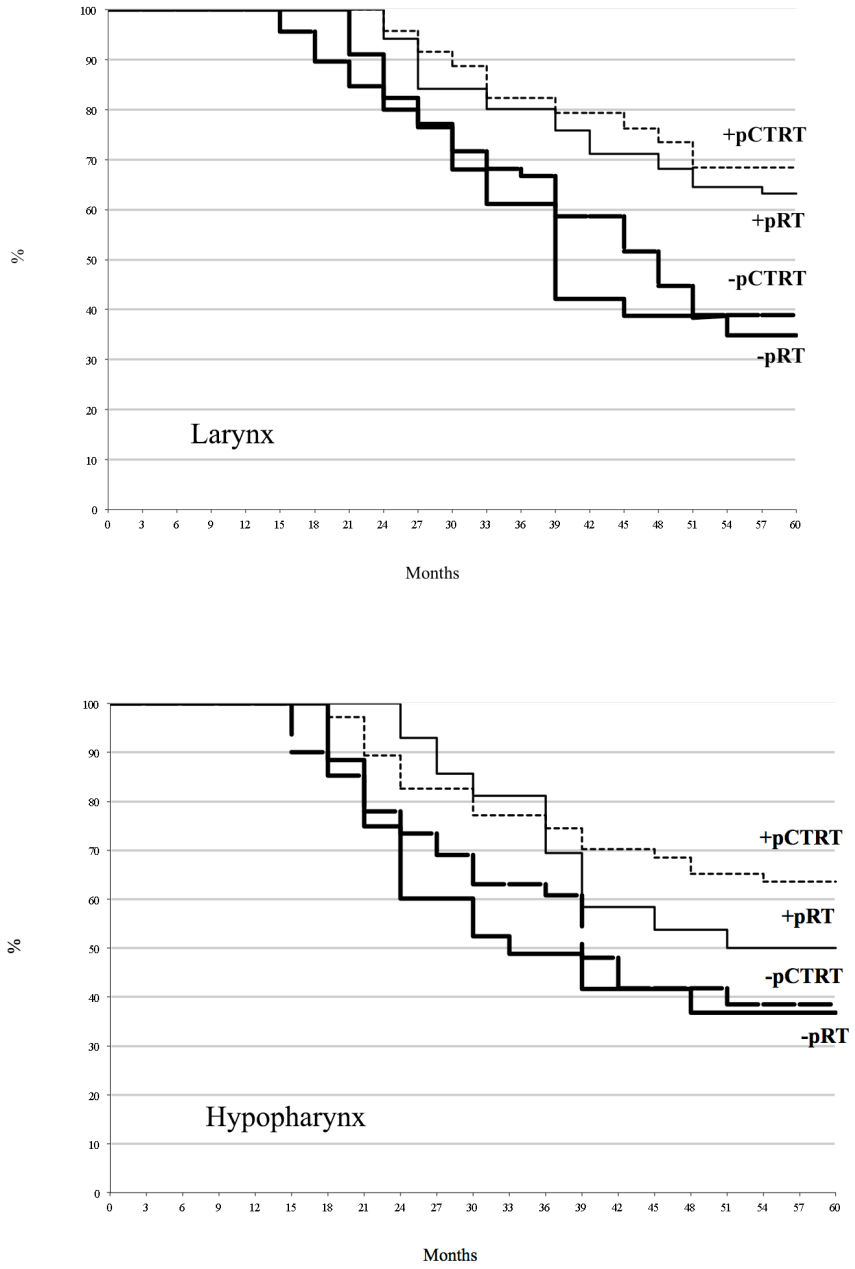

Figure 6. Kaplan-Meier 5-year DFS rate for laryngeal and hypopharyngeal carcinoma after total laryngectomy depending on the response to initial therapy (+pRT:complete response after radiotherapy, -pRT:incomplete response after radiotherapy, +pCTRT:complete response after chemoradiotherapy, -pCTRT: incomplete response after chemoradiotherapy) ($p<0.05$).

yngectomy. Since salvage surgery in aerodigestive areas is usually contaminated, proper dissection and hemostasis, as well as antibiotic therapy are very important [11,16,17].

The management of neck metastases is controversial in head and neck cancer. Neck failure after previous radiotherapy renders prognosis poor. Because of this, planned neck dissection after chemoradiotherapy was proposed in stages N2 and N3 [12].

Postlaryngectomy pharyngocutaneous fistula is reported in the range from 3 to 65%. One study on postlaryngectomy fistula indicated the significance of preoperative hemoglobin, prior trache-

otomy, previous radiotherapy and neck dissection [18]. There are insufficient data to confirm the importance of suture material, antibiotics, positive surgical margins, pharyngeal myotomy, blood transfusion and type of radiotherapy [18-22].

Supraglottic tumor location and extended laryngectomy were associated with increased number of fistulas, probably because of wider resection needed. When a tumor invades hypopharynx, fistulas are twice as common [20]. The influence of neck dissection on fistula formation is unequally reported. The same is valid for flap reconstruction. Prolonged wound drainage caused more complications. Delayed oral feeding is now not considered necessary. Some authors do not place nasogastric tubes, and start oral feeding after 3 days from the operation [23-26].

Earlier studies documented more frequent fistulas after radiotherapy, especially when bigger fields and doses were used. Radiotherapy can cause acute toxic effects. In chronic phase, irradiated tissue becomes hypovascular, hypocellular, and hypoxic. So, it seems obvious that the longer the period from the completion of irradiation to salvage surgery the 2-3 times higher the risk of fistula formation. Nowadays, the reported rate is slightly less, probably because of advances in radiotherapy and surgery, as well [4,17,27].

Chemotherapy was a single factor that increased wound complications in treated patients, and the rate is even higher when radiotherapy is added. This leads to impaired healing, infection, dehiscence and fistula. Bad nutrition and immune depletion are potential reasons for fistulas in chemoradiotherapy groups [28,29].

The most important analyzed parameter of this study was the 5-year survival rate. Independent risk factors for survival were: advanced clinical disease stage, tumor localization, incomplete response to initial therapy and previous therapy. Stage IV caused low survival in both groups of the patients. Retrocricoid and subglottic localization were particularly associated with low survival, that is caused by local propagation and advanced neck stage. Salvage total laryngectomy caused worse results than primary surgery, both for laryngeal and hypopharyngeal tumor sites. The addition of chemotherapy to radiotherapy significantly improved the outcome. Since the differences in the stage of disease between the groups were not significant for laryngeal cancer, these results imply the advantage of primary surgery. The extrapolation of data for hypopharyngeal cancer is more difficult, since the number of cases was much smaller, and the disease was more advanced in the salvage laryngectomy group. Also, this data shows that when response to initial therapy is not complete survival is much worse. Since a great number of these patients will be dependent on permanent tracheotomy and the voice quality will be bad, the purpose of initial organ preservation with worse results and increased complications with salvage surgery is in question.

Diagnosis of squamous cell carcinoma of the upper aerodigestive tract is usually made at advanced clinical stages. The risk of locoregional recurrence is high causing the prognosis poor in such cases. CT, MRI and ultrasound have limitations in detecting recurrent carcinoma, especially after salvage surgery. So, selection of patients for salvage surgery is sometimes difficult. This selection would reduce the interval from initial therapy to salvage surgery, and improve the survival rate [30-33].

Conclusion

1. Primary total laryngectomy (PTL) for laryngeal carcinoma is associated with pharyngocutaneous fistula in 15.0% of the cases, while salvage total laryngectomy after previous radiotherapy (STL-pRT) leads to fistula formation in 26.2%, and after chemoradiotherapy (STL-pCTRT) in 29.7% of the cases.
2. Five-year DFS rate is significantly influenced by TNM stage and the localization of the primary laryngeal tumor. For laryngeal cancer is 61.3% for PTL, 54.1% for STL-pCTRT, and 47.6% for STL-pRT.
3. Survival of incomplete responders to initial treatment was only 38.9% after chemoradiotherapy and 34.8% after radiotherapy.
4. Primary total laryngectomy for hypopharyngeal carcinoma resulted in significantly more local and general complications and swallowing problems. Salvage laryngectomy, especially after chemoradiotherapy, was associated with more frequent local complications.
5. Primary total laryngectomy still offers the best survival rate with low complications in advanced laryngeal and pharyngeal squamous cell carcinoma patients.

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