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HEAD AND NECK

Induction chemotherapy with paclitaxel and cisplatin followed by radiotherapy for larynx organ preservation in advanced laryngeal and hypopharyngeal cancer offers moderate late toxicity outcome (DeLOS-I-trial)

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Abstract A prospective multicenter phase-II trial (12 centers) was performed by the German larynx organ preservation group (DeLOS) to evaluate the effect of induction chemotherapy (ICHT) with paclitaxel/cisplatin (TP), followed by accelerated-hyperfractionated (concomitant boost) radiotherapy (RT) in responders. The trial was focused on larynx preservation, tumor control, survival, salvage surgery and late toxicity in patients with advanced larynx/hypopharynx carcinoma eligible for total laryngectomy (LE). Seventy-one patients (40 larynx, 87.5% St. III, IV; 31 hypopharynx, 93.4% St. III, IV) were enrolled into the study and treated with ICHT (200 mg/m^2 paclitaxel, 100 mg/m^2 cisplatin; day 1, 22) according to the DeLOS

This trial was initiated and conducted by the German Larynx Organ Preservation Study Group (DeLOS) which was founded as collaboration between head and neck surgeons and radiation oncologists to focus on the role of multimodality treatment in advanced laryngeal and hypopharyngeal cancer in Germany.

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protocol. Patients with complete or partial tumor response proceeded to RT (69.9 Gy in 5.5 weeks). Non-responders received a LE followed by postoperative RT (56–70 Gy in 5.5–7 weeks). The response rate to ICHT for larynx cancer was 69.6% (7.1% complete, 62.5% partial response) and for hypopharyngeal cancer was 84.3% (6.9% complete, 77.4% partial response). Overall survival after 36 months was 60.3% (95% CI, 48.4–72.2%), after 42 months was 56.5% (95% CI, 44.2–68.8%). Laryngectomy-free survival was as follows: after 36 months, 43.0% (95% CI, 30.9–55.0%); after 42 months, 41.3% (95% CI, 29.3–53.3%). Both parameters did not show different outcomes after distinguishing larynx from hypopharynx. LE was indicated in 15 non-responders after ICHT. Five of the 15 non-responders refused the laryngectomy. Two of the five received RT instead and had no evidence of disease 42 months after RT. Late toxicity (dysphagia III, IV LENT SOMA score in laryngectomy-free survivors: after 6 months, 1.8%; 12 months, 11.4%; 18 months, 14.5%; 24 months, 8.1%; 36 months, 16%) and salvage surgery (4 pharyngocutaneous fistulas in 27 operations) were tolerable. In a large portion of patients eligible for LE, the larynx could be preserved with satisfying functional outcome. Good responders after ICHT had also a good general outcome with relatively rare severe late toxicities. Due to a slight increase of relevant late dysphagia, functional outcome regarding swallowing and tracheotomy free breathing should be more focused in future larynx organ preservation trials.

Keywords Induction chemo · Larynx · Hypopharynx cancer · Organ preservation · Head and neck

Introduction

The term “larynx preservation” has been established in the previous two decades concerning multimodality therapy procedures for advanced carcinomas of the larynx, and/or hypopharynx as alternative treatment for total laryngectomy (LE) [15, 22]. The morphologic definition of the term, “organ preservation” has to be stated more precisely with preservation of “larynx function”, which is of essential importance in the long-term appraisal of life quality beside overall survival [8, 11, 23]. Compared to “swallowing” and “breathing”, the voice has relatively subordinate meaning, even if this is often suggested. In particular in older patients (>70 years), a latent aspiration, under a lowered sensitivity and reduced neural function of the upper esophagus sphincter, can significantly limit the quality of life under recurrent pneumonias, despite the best voice quality. Beyond doubt, larynx preserving surgery of laryngeal and some hypopharyngeal cancers, which covers a wide field of technical options (laser, open procedures) up to T4 stages for high experienced surgeons, is very worthwhile [4, 12]. Nevertheless, the interdisciplinary debate concerning this issue is partly polarizing: some authors suggest, that increasing multimodality treatment of larynx cancer is responsible for decreasing survival of these patients in the last two decades in the USA [13].

The observation made that induction chemotherapy and following radiotherapy also led to long-term healing, the introduction of adjuvant chemotherapy in multimodality therapy concepts in the late 1970s was performed. Furthermore, this observation led to the conception of two large randomized studies in the 1980s, which compared induction chemotherapy with following radiotherapy with a primary LE and postoperative radiotherapy [15, 22]. Both studies showed for all the world to see, that organ-preserving therapy can lead to 40–60% laryngeal preservation with identical survival rates compared to LE in advanced laryngeal and hypopharyngeal cancer, accounting for several inclusion and exclusion criteria. After this break through, further interest focused in the late 1990s on the improvement of the larynx preservation rate by diversifying treatment protocols. The data showing that concomitant RCT is more effective than sequential RCT [17] led to the conduction of the RTOG 91-11 trial, a large randomized three-arm multicenter study, comparing induction chemotherapy followed by RT, with concomitant RCT or RT alone [9].

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A total of 547 patients with advanced laryngeal cancer were accrued for this study. At a median follow-up of 3.8 years, the larynx preservation rate was significantly higher among patients receiving simultaneous radiochemotherapy with cisplatin (84%) than among those receiving induction chemotherapy followed by definitive radiation (72%) or radiation alone (67%). These results prepared to the next step for larynx organ preservation strategies, which recommended simultaneous chemoradiation as optimal concept. Contemporaneously, observations of late side effects like severe dysphagia, tracheotomy requiring larynx oedema and increasing complications in salvage surgery led to uncertainty and rejection of these organ sparing protocols in many surgery driven centers worldwide [6, 19, 23]. Addressing this important problem, third generation protocols are promoting again induction chemotherapy following radiation alone to avoid concomitant spilling of function limiting late toxicities due to simultaneous chemoradiation. Taxans including protocols showed to be more effective compared to "older" platin based induction chemo regimens [5, 14, 18, 25].

The DeLOS-I-trial presented in this paper was initiated to focus on survival and functional outcome, complications after salvage surgery and late toxicity. The feasibility precursor study has been conducted using a monocenter phase-II design. Data showed encouraging early response rates (chemo-selection), after two cycles taxol/cisplatin (TP) induction chemotherapy, as well as outcome of responders after subsequent radiation [16].

Patients and methods

Patients characteristics

From January 2002 to October 2003, 73 patients were recruited a constant frequency in 12 medical centers all over Germany. The total number of treated patients decreased to 71, because two patients had to be excluded before the start of therapy due to cardio-respiratory disorders. Table 1 shows patient characteristics related to tumor site.

Pre-treatment evaluation included history, physical examination and comprehensive tumor staging. To determine the extent of the disease all patients underwent endoscopy in general anasthesia with multiple biopsies, computed tomography (CT) scan of the head and neck with tumor volume measurement, chest X-ray, pharyngo- and esophagography, cervical/abdominal ultrasound and bone scan. Other studies included quality of voice assessment, audiogram, blood cell count, serum and coagulation tests.

Eligibility criteria included no serious medical condition or illness that would preclude informed consent; performance status, Karnovsky index ≥70; squamous cell carcinoma of the glottis (T3–T4), supraglottis (T2–T4), hypopharynx (T2–T4) feasible for LE (partial resection not possible); neck disease (N0–N3) feasible for complete resection; no metastases M0; tumor volume ≤80 ml; age >18 and <75 years; hemoglobin before start of therapy >13 g/ml; leucocytes ≥4,000/mm^3; granulocyte count ≥2,000/mm^3; platelet count ≥100,000/mm^3; serum bilirubin <2.0 mg/dl; normal SGOT and SGPT activities; creatinine clearance ≥60 ml/min; no other history of active malignancy other than curatively treated basal cell carcinoma of the skin.

Table 1 Characteristics of 71 patients of the DeLOS-1-trial

Localization	Larynx	Hypopharynx
Age (years)	60.9 (Median, min: 37.8, max: 73.2)	
Sex	Female 8 (11.3%), male 63 (88.7%)	
Karnovsky index		
100	22 (30.9%)	
90	37 (52.1%)	
80	8 (11.2%)	
70	4 (5.6%)	
Total number of patients	40 (56.3%)	31 (43.6%)
TNM (UICC 2003)		
T2	5 (12.5%)	6 (19.3%)
T3	20 (50%)	13 (41.9%)
T4	15 (37.5%)	12 (38.7%)
N0	18 (45%)	4 (12.9%)
N1	10 (25%)	6 (19.3%)
N2	0	3 (9.6%)
N2a	0	1 (3.2%)
N2b	5 (12,5%)	14 (45.1%)
N2c	7 (17.5%)	3 (9.6%)
N3	0	0
Stage (UICC 2003)		
I	0	0
II	5 (12.5%)	2 (6.4%)
III	15 (37.5%)	7 (22.5%)
IV	20 (50%)	22 (70.9%)
Demography		
Alone at home	19 (26.7%)	
Sharing home with others	52 (73.2%)	
Education level lower than high school	66 (93%)	

Restaging, reassessment and follow-up

The protocol included two cycles of induction chemotherapy and subsequent radiation. Two weeks after induction chemotherapy, restaging by endoscopy and CT-scannning

for early response evaluation were conducted (clinical judgement). Salvage laryngectomy with or without neck dissection was scheduled for patients who had a failure of the primary site and a salvage neck dissection (selective neck dissection levels II–IV or V) for patients who had an isolated failure of the locoregional lymph node region without a tumor of the primary site. After end of radiation, follow-up was conducted by flexible endoscopy and ultrasound every 6 weeks. First reassessment was planned 6 weeks after end of radiation (median 45 days; min., 19; max., 74 days). Follow-up was determined every 6 months after reassessment within 3 years. After 6 months, additional CT or MRI and after 1 year endoscopy in general anasthesia were performed. In the case of recurrent disease, immediate salvage surgery was recommended.

Induction chemotherapy (ICHT)

ICHT was performed with paclitaxel 200 mg/m^2 and cisplatin 100 mg/m^2 at day 1, 22. Dexamethason (20 mg) was administered orally 12 and 6 h and clemastin (2 mg) and ranitidin (50 mg) intravenously 30 min before paclitaxel infusion (applied during 3 h in 250 ml isotonic NaCl solution). After the administration of granisetron (3 mg) for antiemesis and of 100 ml (20%) mannit solution, 100 mg cisplatin/m^2 in 500 ml NaCl solution was given during 2 h. Patients were infused with 2,500 ml isotonic sodium solution during 6 h. Two weeks after the second application of ICHT, endoscopy with biopsies was performed. Tumor volumes were quantified and compared with pre-treatment studies by a CT-based method [18]. Non-responders underwent surgery and postoperative RT, patients with complete or partial response to ICHT were defined for radiotherapy.

Radiation therapy (RT)

Patients with complete or partial tumor response (clinical judgement) proceeded to concomitant boost radiotherapy. The gross tumor received 69.9 Gy in 6.5 weeks and the non-involved locoregional lymph nodes 50.4 Gy. The daily single dose was 1.8 Gy and the concomitant boost dose 1.5 Gy on day 1–5 in week 4 and 5 and day 1–3 in week 6. All patients were treated in a thermoplastic mask for immobilization. Between two daily fractions, there was always a minimum time interval of 6 h. The RT was usually performed with opposed lateral fields for the upper neck and one anterior field for the lower neck using 6-MV photons. Individual blocks were used to spare normal tissue where possible. After a dose of 30 Gy to the isocenter, the spinal cord was spared from the photon fields and the uninvolved posterior neck treated with electrons of selected energy according to CT findings with daily doses of 1.8–2.5 Gy five times a week to a total dose of 50.4–55 Gy. The boost comprising macroscopic tumor was usually delivered by opposed lateral fields. The dose was prescribed to the reference point according to the ICRU 50 report. Target volumes were defined within CT scans and the dose was calculated to midplane. The dose calculation was based on 3D treatment planning [26].

Toxicity assessments

Toxicities were evaluated by laboratory blood cell counts, serum tests, physical examination and history. The systematic toxicities induced by ICHT were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC 2.0) until a period of 6 weeks after end of therapy. The evaluation of radiation induced side effects was based on the grading system for RTOG acute radiation morbidity scoring criteria (RTOG). The grade reported is the worst observed grade of each kind of toxicity that is experienced by the patient. Late toxicities were scored using the LENT SOMA-scoring system. The publication of the Late Effects Normal Tissues (LENT)-Subjective, Objective, Management, Analytic (SOMA) scales by the joint efforts of the EORTC and RTOG in 1995 was an attempt to produce a universal system for measuring and recording the late effects of RT [20].

Statistics

The main target criterion was response to induction chemotherapy (complete or partial response). Secondary target criteria were overall survival, laryngectomy-free survival, early and late toxicity. Ordinal or nominal data are described by absolute and relative frequencies, continuous data by median and range. Survival curves are estimated by Kaplan–Meier with 95% asymptotic confidence intervals at specific points in time. Survival curves are compared by the logrank test. A P value less than 0.05 is considered as significant. Since no adjustments for multiple testing are made, only the result of the main target criterion can be interpreted in a confirmatory sense. The sample size was calculated with respect to the main target criterion ‘response to induction chemotherapy’. Assuming a response rate of 70%, the study should assure that a rate of 50% or less could be excluded with a power of 90% and a significance level of 5% (one-sided). This scenario requires as minimum 58 patients (exact test).

All patients for whom data were available were included in the respective analyses regardless of the actual therapy they received (intention-to-treat). All patients enrolled in the study were included in the analyses of overall and laryngectomy-free survival. Drop-outs were considered as censored information. Toxicity evaluation included all patients for whom data for the respective analyses were available.

Survival time was defined as time from entry into the study until death or date of last observation of the patient. Survival time of patients who were alive at the last date of observation was considered as censored information. Laryngectomy-free survival time was defined as time from entry into the study until the minimum date of laryngectomy, death or date of last observation of the patient. Laryngectomy-free survival time of patients who were alive at the last date of observation with a functionally intact larynx was considered as censored information.

Statistical analysis was done using the Statistical Analysis System SAS, Version 9.1 for Windows (SAS Insitute Inc., Cary, NC, USA).

This protocol was assumed by the German larynx preservation study group (Deutsche Larynxorganerhaltungs Studiengruppe, DeLOS) in a strong acclamation process with the Radiation Oncology Group (ARO) of the German Cancer Society and the Oncology Working Group of the German Society of Otolaryngology, Head and Neck Surgery.

The protocol was approved by the local ethics committees. All patients provided written informed consent according to the Helsinki Declaration II.

Results

Restaging after induction chemotherapy

Sixty-six patients underwent both and five patients only one cycle of ICHT due to renal limitations (one case showed increasing creatinine, four cases developed renal insufficiency after the first cycle). One other patient had only taxol in both cycles, one patient only had taxol in the second cycle and another patient was changed from cisplatinum to carboplatinum in the second cycle due to renal reasons. Restaging after ICHT in 69 of 71 patients showed in 5 cases (7.0%) complete remission (CR) and in 49 cases (69.0%) partial remission (PR). Eleven patients (15.4%) had no change (NC) and four patients (5.6%) progressive disease (PD) (Table 2).

One patient refused further cooperation and dropped out of therapy, and another patient had early salvage surgery before restaging. Early toxicity other than renal insufficiency was limited up to 3 weeks and concentrated on alopecia (12 cases), joint pain at different sides (8 cases), fatigue (5 cases), neuropathy (4 cases) and diarrhea (3 cases). Grade III/IV toxicity according to the CTC grading system has been detected in 8 patients (2 nausea, 2 dysphagia, 1 dyspnoea, 1 infection, 2 others).

In 9 out of 15 patients without remission in restaging, early salvage surgery was performed. Eight patients had LE, and one had partial resection (refused LE) after complete ICHT. In one further case, LE was performed after one cycle of chemotherapy. No salvage surgery-related complications have been monitored, while early salvage surgery after ICHT. Five patients refused salvage surgery and were alternatively treated within of the trial protocol. One patient with restaging resulting in NC was treated like a responder within the trial. One single patient was not operated due to a high risk for surgery (Table 3).

Table 2 Results of restaging 2 weeks after two cycles induction chemotherapy

	CR	PR	NC	PD
Tumor site				
Larynx	2 (5.1%)	25 (64.2%)	10 (25.6%)	2 (5.1%)
Hypopharynx	3 (10%)	24 (80%)	1 (3.3%)	2 (6.7%)
Stage (UICC)				
II	1 (14.2%)	3 (42.9%)	3 (42.9%)	0
III	3 (14.3%)	13 (61.9%)	3 (14.3%)	2 (9.5%)
IV	1 (2.4%)	33 (80.5%)	5 (12.1%)	2 (5%)

69 of 71 patients were available for restaging (details in text)

Endoscopic clinical judgement: *CR* complete remission, *PR* partial remission, *NC* no change, *PD* progressive disease

Reassessment after end of complete therapy

Fifty-three of 54 patients with CR or PR were treated according to the DeLOS-I-protocol with hyperfractionated accelerated radiation. Median interval between ICHT and start of RT was 33.5 days (min. 20, max. 64 days). Accepting an area of tolerance of ±4 Gy for hyperfractionated radiation and ±2 Gy for concomitant boost, no underdose was detected. In one case, dosing of concomitant boost was significantly increased (22 Gy). In three patients, the duration of RT was extended more than 8 days (1 osteomyelitis mandibula, 1 severe stomal mucositis, 1 grade III leucopenia).

Radiation was well tolerated with limited early toxicity. Table 4 shows results of first reassessment 6 weeks after end of complete therapy. The rate of CR (without LE) accounting for all 71 included patients was 57.7% (95% CI, 46.3–69.2%).

Three patients died before reassessment caused by tumor-dependent reasons (2 blow-out arterial bleeding following tumor progression; in one case severe bleeding after salvage surgery). Within the first 6 months after reassessment 8 patients died (1 independently of tumor, 1 pulmonary metastases, 1 peritoneal carcinosis, 1 bone metastases, 4 neck bleeding due to progressive disease). Fourteen cases of grade III/IV toxicity according to the CTC grading system have been detected (10 dysphagia, 3 mucositis, 1 laryngitis).

Follow-up

The median follow-up time was 39.5 months (range, 1.1–57.8). Within 3 years of individual follow-up time, 20

Table 3 Early salvage surgery and further treatment options in case of refusal of salvage surgery after induction chemotherapy in non-responders

Tumor site TNM	Overall response	Procedure of salvage surgery	Resection margins	Further adjuvant treatment
H pT4N2b	PD	LE, sel.ND os	R_0	RT
L pT4N0	NC	LE, MRND bs	R_0	RT
L pT2N0	NC	LE, MRND bs	R_0	–
L pT4N2b	PD	LE, MRND bs	R_2	RT
L pT3N0	NC	LE, MRND bs	R_0	–
L pT4N1	NC	LE, MRND os	R_0	RT
L pT3N2b	NC	PR[d], MRND bs	R_0	RCT
L pT3N1	–[a]	LE, MRND bs	R_0	RT, C
L pT3N1	PD	LE, MRND bs	R_0	RT
L pT3N2c	NC	LE, MRND bs	R_0	RT
L T2N2b	NC	Patient refused		RT
L T3N1	NC	Patient refused		RT
H T3N1	PD[c]	High risk for surgery		RCT
H T2N0	NC	Patient refused		RT
H T3N2	PD[c,e]	Patient refused		RCT
L T3N0	NC	Patient refused[b]		RT

pTNM pathology assessed TNM according UICC, *L/H* larynx/hypopharynx, *PD* progressive disease, *NC* no change, *LE* laryngectomy, *SND* selective neck dissection level II–IV, *MRND* modified radical neck dissection levels I–V, *os* one neck side, *bs* both neck sides, R_{0-2} resection margins UICC, *RT* radiation therapy, *RCT* chemoradiation therapy, *C* chemotherapy, *PR* partial larynx resection

[a] Surgery was performed before restaging procedure

[b] Although "NC" the patient was kept in the trial and treated like a responder

[c] Both patients survived after 36 months follow-up with intact larynx

[d] One patient refused LE, so partial vertical resection was done

[e] One patient was categorized in restaging as PD and changed 1 month later in PD, which explains discrepancy of total number of patients with CR/PR in table 3 and 2

Table 4 Reassessment after end of complete therapy according to the DeLOS-I-protocol

	CR	PR	NC	PD
Tumor site				
Larynx	23 (79.4%)	5 (17.2%)	1 (3.4%)	0
Hypopharynx	3 (33.3%)	6 (66.7%)	0	0
Stage (UICC)				
II	2	1	0	0
III	17	1	0	0
IV	22	9	1	0
Sum	41	11	1	0
Not assessable[a]	5			
Death	3			
Drop out	2			
Laryngectomy	8			

CR complete remission, *PR* partial remission, *NC* no change, *PD* progressive disease

[a] Four patients refused first reassessment, two patients were not evaluable due to severe mucositis

patients had salvage LE related to persistent or recurrent disease. Twenty-nine patients died and in 24 cases death was directly related to the tumor disease (5 cases died caused by other reasons: 1 empyema of the lung, 1 suicide, 3 cardiac failure).

A total of 35 patients closed up the trial at final follow-up of 36 months. Remarkably in two patients, the larynx could be preserved, having been treated outside the DeLOS protocol (Table 3). Altogether there were 23 patients with preserved larynx after induction chemotherapy and subsequent to accelerated hyperfractionated radiotherapy, who did not relapse until the end of the study. Of these 23 patients, one patient died 8 months after the 36-month follow-up (reason not tumor-related). Altogether, eight patients were drop-outs (2 had LE and refused follow-up after surgery, 5 refused follow-up investigations at all and 1 patient developed second primary colon cancer and declined further monitoring). After 12 months, the rate of surviving patients with preserved larynx was 65.0% (95% CI, 53.7–76.3%), after 24 months 54.1% (95% CI, 42.1–66.0%), after 36 months 43.0% (95% CI, 30.9–55.0%) and after 42 months 41.3% (95% CI, 29.3–53.3%). No significant differences in survival or laryngectomy-free survival between tumor site (larynx and hypopharynx showed no differences in outcome) or UICC stage were detected (trend for better survival in smaller stages). After 12 months, the overall survival rate was 85.4% (95% CI, 77.0–93.8%),

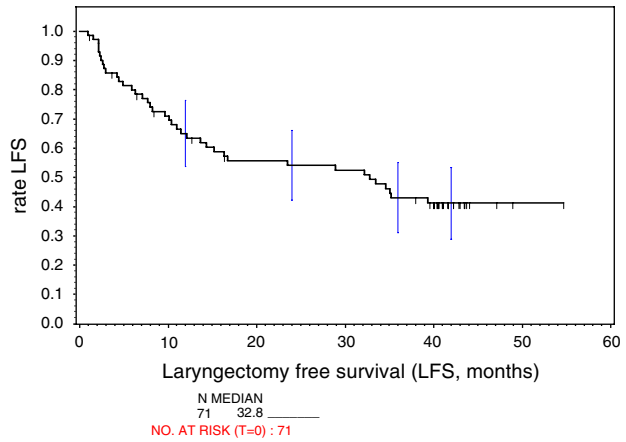

Fig. 1 Laryngectomy-free survival after therapy according to the DeLOS-I-protocol ($n = 71$) (*blue bars* 95% CI)

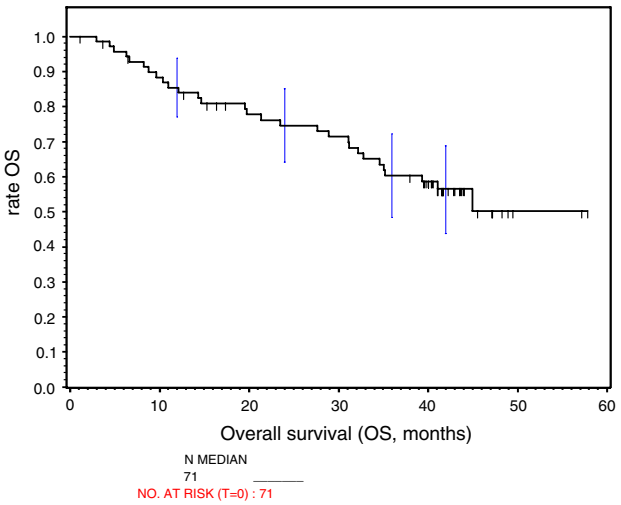

Fig. 2 Overall survival after therapy according to the DeLOS-I-protocol ($n = 71$) (*blue bars* 95% CI)

after 24 months 74.6% (95% CI, 64.1–85.0%), after 36 months 60.3% (95% CI, 48.4–72.2%) and after 42 months 56.5% (95% CI, 44.2–68.8%). None of the patients required a total laryngectomy due to treatment-related complications (Figs. 1, 2).

Late toxicity, salvage complications

Table 5 summarizes the late toxicity developments according to the LENT SOMA-scoring system [20] depending from 6 to 36 months follow-up reports. We observed a slight increase of relevant grade III/IV dysphagia and nearly constant body weight over the time of follow-up. None of the patients had tracheotomy due to late toxicity disorders.

Early salvage LE immediate at restaging after induction chemotherapy is reported in Table 3. Early neck dissections without touching the larynx have been performed in one case after restaging. In all cases, wound healing was not affected, so that no salvage complications in these patients were seen. Later on, another ten patients had salvage surgery procedures within follow-up. Around the date of a 6-months-reassessment, 7 patients had salvage surgery procedures (6 LE plus mod. rad. neck dissections type III both sides; 1 had mod. rad. neck dissection type III one neck site

Table 5 Follow-up reporting of late toxicity according to the LENT SOMA score [25]. Total number and percentages of grade III/IV-toxicities dependent on time of follow-up

	Follow-up after first reassessment					
	6 months ($n = 55$)	12 months ($n = 52$)	18 months ($n = 41$)	24 months ($n = 37$)	30 months ($n = 30$)	36 months ($n = 31$)
Larynx						
Pain	1 (1.8%)	1 (1.9%)	0	0	0	1 (3.2%)
Voice hoarseness	6 (10.9%)	9 (17.3)	4 (9.7%)	6 (16.2%)	2 (6.7%)	3 (10.3%)
Edema	10 (18.1%)	12 (23.0%)	5 (12.1%)	2 (5.4%)	5 (16.7)	2 (6.4%)
Breathing	3 (5.4%)	4 (7.6%)	2 (4.8%)	1 (2.7%)	0	1 (3.2%)
Mucosa oral cavity and pharynx						
Dysphagia	1 (1.8%)	6 (11.4%)	6 (14.5%)	3 (8.1%)	3 (10%)	5 (16.2%)
Pain	1 (1.8%)	3 (5.7%)	2 (4.8%)	1 (2.7%)	0	0
Weight	8 (14.4%)	4 (8.0%)	2 (3.0%)	2 (5.4%)	1 (3.3%)	2 (6.3%)
Ulceration	0	1 (1.9%)	0	0	0	0
Skin						
Rawness	0	1 (1.9%)	0	2 (5.4%)	1 (3.3%)	0
Pigmentation	2 (3.6%)	2 (3.8%)	0	0	0	0
Fibrosis	2 (3.6%)	3 (5.7%)	1 (2.4%)	3 (8.1%)	1 (3.3%)	0
Neuropathy	0	1 (1.9%)	0	0	0	0

and selective neck dissection on the other site) due to residual persistent or recurrent disease. Three had LE and modified radical neck dissection both sides after 12 months and one after 18 months. Severe salvage complications like pharynx fistulas with need for revision surgery and repeated intake of salivary tubes took place in one case after 12 months after surgery. Altogether 4 (14%) pharyngocutaneous fistula after salvage LE have been detected. Fourteen of 28 patients, who had salvage surgery, died during follow-up; 1 immediately died after restaging, 5 around 6 months, 3 up to 12 months, 1 up to18 months, 3 up to 24 months and 1 up to 36 months follow-up. Depending on the individual handling of pretherapeutic PEG application, 35% of patients had PEGs before start of treatment. Except in three cases, PEG was removed within 6 weeks after the end of radiotherapy (all 3 cases died within the first 2 years of follow-up due to tumor reasons and had their PEGs until date of death).

Discussion

The term "organ preservation" has become a synonym for nonsurgical treatment of laryngeal cancer based on chemo and radiation multimodality therapy. Recently, the American Society of Clinical Oncology published clinical practice guidelines for the use of larynx preservation strategies in the treatment of laryngeal cancer and declared combined modality treatment worldwide as a legal alternative option to LE in most T3, T4 laryngeal cancer cases [3]. The goals of organ preservation strategies are cancer control with preservation of function. Swallowing ability after treatment represents a combination of pre-treatment tumor-related dysfunction, treatment-related dysfunction, and the patient's ability to compensate spontaneously or with therapy. Patients who cannot swallow adequately before treatment are at higher risk for chronic dysphagia after treatment, and at high risk for permanent feeding-tube dependence. This underscores the observation that conservation of structure and function do not necessarily go hand in hand [10, 19]. The international scene of head and neck oncologists is currently under consideration, that late toxicities after programs focusing on organ preservation are usually underestimated [23]. Even head and neck surgeons, who are sensitized due to facing augmented late toxicity-related problems and salvage surgery complications, increasingly suffer from discomfort regarding multimodality treatment in a principally well standardized and safe surgically manageable disease [4].

It is clear from randomized trials comparing chemoradiotherapy with radiotherapy alone that chemotherapy substantially increases acute toxicity. There is a natural tendency to increase the intensity of treatment modalities under the belief that more will achieve better results. Head and neck cancer has not been an exception to this practice, and thus, the adverse effects of current chemo radiotherapy regimens have generally reached the limits of toxicity [10]. Nevertheless, there are only few detailed data in literature about late toxicity outcome with an obvious lack of consistent grading systems regarding simultaneous and induction chemoradiation protocols. Exemplary data of a well-known randomized German trial (which was attended by many DeLOS centers), in which effectiveness of simultaneous chemoradiation (5FU/carboplatin) versus radiation alone was checked, show that 52% of the patients still having a feeding tube due to stage IV dysphagia after 2 years (vs. 25% in the radiation arm) [21]. The GORTEC study group reported on the end of a large phase III study of a 56% risk of severe toxicities after 5 years in the simultaneous chemoradiation group, compared to 30% in the radiotherapy group [1, 2]. The other long-term effects of chemoradiation regimens, such as dysphagia, aspiration, and laryngeal immobility caused by fibrosis, are just beginning to be studied and need to be more adequately assessed [4]. The call for uniform and accurate documentation of late function and late toxicities is increasingly resounding, because their immense influence on the quality of life is becoming more prevalent [23].

In this context, data of the DeLOS-I-trial showed a slight increase of dysphagia over the years after finishing therapy. Starting with 1.8% grade III/IV dysphagia at 6 months follow-up, the group of patients with severe dysfunction in this field after 3 years was 16.2%. In the RTOG 91-11 trial, the incidence of grade 3 or 4 late toxic effects after 1 year was 30% in the group that received simultaneous RCT, and 24% in the group that had induction chemotherapy followed by RT. Two questionnaires, to be completed by the patients, were used to evaluate quality of life: the Functional Assessment of Cancer Therapy—Head and Neck Scale, version 2, 4 and the University of Washington Quality of Life instrument [9]. In contrast, we used the LENT SOMA system, thus our data are comparable only in superficial lines with the 91-11 trial (Table 5). Furthermore, the percentage of stage IV diseases in the 91-11 trial (33–36%) is lower than in the DeLOS-I-trial (50–70%) and also hypopharyngeal carcinoma was excluded. The comparably lower laryngectomy-free survival rates in the DeLOS-I-trial (41.3% after 42 months vs. 45% after 60 months) could be explained by more advanced tumor stages. However, the 24-months overall survival of both trials was equal (91-11, 74.6%; DeLOS-I, 74%; 60 months data, 91-11, 54%; 42 months data DeLOS-I, 56.5%). Furthermore, the rate of therapy-caused late edema was low in our trial. After 36 months, only 6.4% of the patients had grade III/IV larynx oedema without need for toxicity-related tracheotomy. This observation is not self-evident due to late toxicity data

of simultaneous chemotherapy trials correlating with increasing late toxic edema-related tracheotomies after 3 years up to 25% [7].

Induction chemotherapy seems to be of advantage due to several reasons. First, newer regiments are highly effective and improve overall survival and preservation rates [1, 18, 25]. Preliminary results of the GORTEC 2000–2001 trial, which was designed for organ preservation in advanced laryngeal and hypopharyngeal cancer suggest that taxan (docetaxel) based induction chemotherapy in combination with cisplatin and 5-fluorouracil (TPF) may be more effective than PF, followed by sequential radiation alone [5]. Calais et al. conclude, that larynx preservation was offered for 80% of patients in the TPF versus 57.6% in the PF group. TPF was better tolerated and preliminary results suggest that larynx preservation could be achieved for a higher proportion of patients. There are no specific data to late toxicity outcome yet.

However, the possibility of chemo-selection of responders after induction chemotherapy to avoid dispensable complications related to salvage LEs seems to be another relevant reason [24]. In our trial, early salvage surgery was recommended after two cycles of induction with TP. The response rate (CR/PR) after chemotherapy was 69.6% for larynx and 84.3% for hypopharyngeal carcinomas. Unexpectedly, response of larynx cancer was worse, which cannot be explained by different tumor stages. Anyway, this led to a recommendation for early salvage LE in at least 16 cases. Five patients refused LE and had consecutive alternative treatment. This high rate (33%) of patients, who refused the recommended salvage LE after induction and so accepted an inferior outcome has to be taken seriously. This also emphasizes that comprehensive priming of the patients and clarification of acceptance of the whole concept before the start of the program is of high importance. In two of these five cases, alternative chemoradiation was successful and both patients survived with good functional outcome without the need for surgery. This observation does not discount the advantages of chemo-selection due to 4 of 6 non-responders without early LE did not survive the first year after treatment. It is a hint that chemo-response cannot cover all the complicated molecular mechanisms of radio-response, which are still a strong target of many investigative groups all over the world. Nevertheless, we think that induction chemotherapy is a feasible and a practicable tool for early selection of a high rate of responders and gives some convincing arguments for early salvage surgery.

Remarkably, in spite of significantly inferior induction chemo-response of the larynx cancer group, laryngectomy-free and overall survival was equal in both larynx and hypoharynx cancer groups during the follow-up time period. Accounting for the fact that some groups separated these localizations due to expected better outcome of larynx cancer (i.e., RTOG 91–11), no difference in our study sample has been observed.

Conclusion

In conclusion, we think the DeLOS-I-program is feasible for organ preservation in advanced laryngeal and hypopharyngeal cancer and shows a low late toxicity profile with a satisfying rate of larynx organ preservation in the investigated high-stage sample of non-partially resectable disease. Induction chemotherapy gives an important opportunity for the treating team, to early select non-responders before radiation for salvage surgery, and might help to reduce disasters related to late surgery following relapse after chemoradiation. Future trials should focus on improvement of induction chemotherapy (TPF, in combination with EGFR targeting), and effective reduction of quality of life-threatening late toxicities due to sequential chemotherapy and radiotherapy. Concomitant chemoradiation seems to increase late toxicity, which is the main counterproductive factor for successful larynx preservation in well resectable disease. To come to the central point, successful functional larynx preservation is more a question of late functional outcome, including safe salvage surgery procedures than of early response. Due to this consideration, larynx organ preservation concepts have to be strongly differentiated from concepts for non-resectable disease.

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