research article

Induction chemotherapy and concurrent chemoradiotherapy for larynx preservation in laryngeal and hypopharyngeal cancer

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Background. To test the hypothesis that clinical tumor response after a single cycle of induction chemotherapy (ICT) can reliably differentiate between chemo-/radiosensitive and resistant tumors in the larynx preservation setting.

Patients and methods. Treatment consisted of docetaxel/cisplatin/5-fluorouracil (TPF) ICT followed by concurrent chemoradiotherapy (cCRT) with weekly cisplatin. The response of the primary tumor was assessed by transnasal endoscopy after the first ICT cycle.

Results. 37/39 (95%) patients with laryngeal (46%) or hypopharyngeal (54%) carcinoma responded to one cycle of ICT, and two patients were referred for salvage surgery. Laryngectomy-free survival at 2 and 5 years was 87% and 75%, respectively. The corresponding rates for locoregional control (and also for disease-free survival) were 79% and 70% and for overall survival 92% and 82%.

Conclusions. Clinical assessment of tumor response to one cycle of TPF ICT serves as a valid and easy-to-use predictor of tumor sensitivity to platinum-based cCRT.

Key words: induction chemotherapy; response; organ preservation; laryngeal cancer; hypopharyngeal cancer

Introduction

Total laryngectomy with loss of natural voice and permanent tracheostomy is one of the most mutilating surgical procedures in the head and neck region, leaving patients with significant physical impairments and social stigmatization.[1] Therefore, the development of non-surgical treatment strategies that provide comparable survival outcomes and allow preservation of the larynx in almost 60% of cases is an important alternative for patients with locally advanced laryngeal and hypopharyngeal cancer.[2] In this context, it should be emphasized the importance of preserving the larynx functionally and not just anatomically, in order to enable natural speech, swallowing and breathing without the need for permanent tube feeding and/or tracheostomy. According to the RTOG 91-11 trial, patients treated with concurrent chemoradiotherapy (cCRT) with cisplatin have the best chance of laryngeal preservation, albeit with no improvement in survival compared to induction chemotherapy (ICT) followed by radiotherapy (RT) or RT alone.[3,4] However, the impact of the pri-

mary tumor stage, including the mobility status of the vocal cords, and the location of the primary tumor (larynx vs. hypopharynx) must be considered when assessing the prospects for a favorable treatment outcome.

Since not all tumors are equally sensitive to chemotherapeutic agents and radiation, the ability to identify patients with resistant tumors early in the course of non-surgical therapy who should be treated with laryngectomy is crucial. Several studies have confirmed that ICT is a reliable in vivo assay for determining the chemo/bio/radio-sensitivity of tumors.[5,6] In routine clinical practice, after a favorable response to ICT, patients are subsequently treated with RT; the use of a sensitizer concurrently with radiation should be considered investigational.[7] The latter is due to the lack of survival benefit observed in phase 3 clinical trials comparing taxane-based ICT followed by aggressive chemoradiation with chemoradiation alone.[8] In addition, the toxicity of three cycles of taxane-based induction chemotherapy is significant and may seriously compromise the administration of subsequent concurrent chemo/bio-RT.[9]

To mitigate the negative effects of aggressive ICT therapies on subsequent cCRT, the response to a single test cycle of ICT has been proposed as a criterion for selecting patients for non-surgical treatment.[10] Excellent survival results were achieved with this approach, with the larynx being preserved in 66% of patients.[11] In the present study, we retrospectively analyzed the results of larynx-preserving treatment in a prospective cohort of patients with laryngeal and hypopharyngeal cancer who received a limited number of ICT cycles as a chemotherapy response selection strategy prior to platinum-based cCRT. The hypothesis tested was whether the clinical response of the tumor after a single cycle of ICT can be used to differentiate between chemo-/radiosensitive and resistant tumors.

Patients and methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Protocol Review Committee of the Institute of Oncology Ljubljana, Slovenia (ERIDNPVO-0036/2020, 19.11.2020).

Patients

In 2016, a chemoselection program was introduced based on clinical assessment of tumor response after a single cycle of ICT for patients with laryngeal and hypopharyngeal cancer. At the Multidisciplinary Tumor Board, all consecutive patients with newly diagnosed squamous cell carcinoma of the larynx or hypopharynx (cT2–4a, cN0–3resectable, M0) who were suitable for total laryngectomy (with or without partial hypopharyngectomy) as the only possible surgical option were offered this treatment option. Further inclusion criteria were a WHO performance status of 0–1 and adequate laboratory tests. Patients with tracheostomy, feeding tube, recurrent pneumonia (requiring hospitalization within the last 12 months) suggestive of laryngeal dysfunction, or patients with a medical condition that would prevent safe delivery of the planned therapies were considered ineligible.

Treatment protocol and response evaluation

Prior to treatment, the stage of disease was determined by physical, endoscopic and radiologic (CT and/or chest X-ray and/or abdominal US) examination of the upper aero-digestive tract, neck, chest and abdomen. Other tests (PET-CT, bone scan) were performed when clinically indicated.

ICT consisted of two cycles of docetaxel (75 mg/m^2, day 2), cisplatin (75 mg/m^2, day 2) and 5-fluorouracil, 750 mg/m^2/day, days 1–4 in 96-hour infusion). The substitution of cisplatin with carboplatin (AUC 5) and the dosing recommendations in case of toxicity have been as described elsewhere.[12]

Tumor response was assessed clinically and was performed 3 weeks after the start of ICT by transnasal endoscopy (local assessment) and palpation (regional assessment). A complete response (CR) was defined as the disappearance of all evaluable disease within the treatment field, and a partial response (PR) was defined as a decrease of no less than 50% and at least partial recovery of laryngeal mobility (in the case of initial immobility). Patients with CR or PR of the primary tumor received a second cycle of ICT followed by cCRT, and non-responders were referred for surgery (Figure 1). Patients with responding primary tumors who were diagnosed with either T4a or less than PR in the neck after the first ICT cycle were planned for the 3rd cycle of ICT.

RT was scheduled to begin 3-4 weeks after the start of the last cycle of ICT. All patients had CT-based planning and were irradiated with a 6 MV photon beam from a linear accelerator and a concomitant boost intensity modulated radiotherapy/volumetric modulated arc therapy technique. A
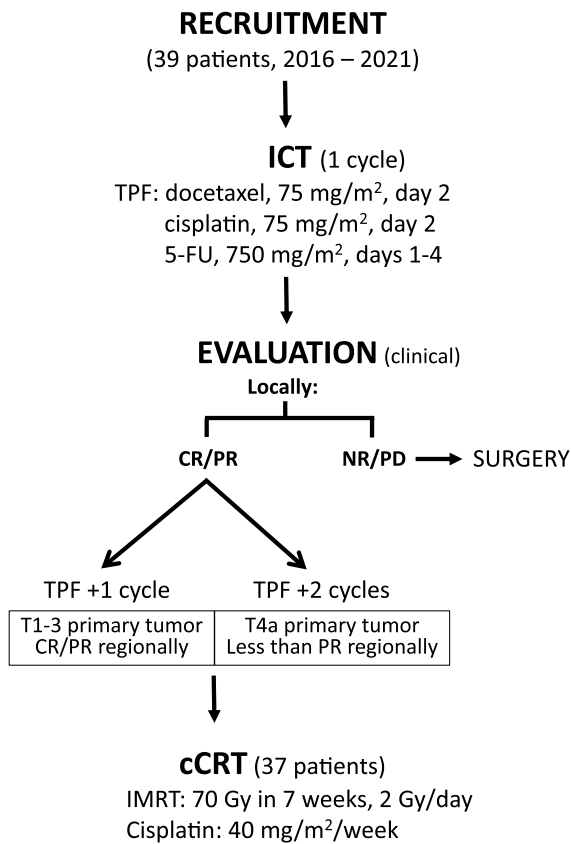
RECRUITMENT
(39 patients, 2016 – 2021)

↓

ICT (1 cycle)
TPF: docetaxel, 75 mg/m^2, day 2
cisplatin, 75 mg/m^2, day 2
5-FU, 750 mg/m^2, days 1-4

↓

EVALUATION (clinical)
Locally:

| CR/PR | NR/PD → SURGERY |

TPF +1 cycle	TPF +2 cycles
T1-3 primary tumor CR/PR regionally	T4a primary tumor Less than PR regionally

↓

cCRT (37 patients)
IMRT: 70 Gy in 7 weeks, 2 Gy/day
Cisplatin: 40 mg/m^2/week

FIGURE 1. Treatment protocol.

CR = complete response; IMRT = intensity-modulated radiotherapy; NR = no response; ICT = induction chemotherapy; PD = disease progression; PR = partial response

dose of 70 Gy was delivered in 35 fractions over 7 weeks (1 fraction/day, 5 days/week) to the original (i.e., pre-ICT) high-risk clinical target volumes (CTV70), taking into account the anatomical barriers to tumor spread. The low-risk CTV56 included areas considered at risk for microscopic disease. The primary tumor and nodal levels were delineated according to the guidelines.[13,14] An isotropic margin of 5 mm was added around the corresponding CTVs to create the planning target volumes (PTVs). During RT, cisplatin was administered intravenously weekly at a dose of 40 mg/m^2 and replaced by carboplatin (1.5 AUC) when creatinine clearance decreased to < 60 mL/min and/or peripheral polyneuropathy or grade >1 hearing impairment was detected. Tumor response was assessed clinically and radiologically 8–14 weeks after cCRT according to RECIST criteria: partial responders and non-responders were referred for surgery if the residual tumor was considered operable.

The acute toxicity of ICT was monitored every 3 weeks and weekly during cCRT. In the first two years, patients were examined at 3-month intervals and later every 4–6 months for toxicity and possible recurrence of the disease or new primary tumors. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria or Adverse Events v5.0.

Statistics

To ensure a potential minimum follow-up period of 2 years, only patients treated between 2016 and 2021 were analyzed. Descriptive statistics were reported with medians, ranges and IQRs for numeric variables and as percentages for categorical variables. Survival curves were calculated using the Kaplan-Meier method and the log-rank test was used to assess the differences between survival curves. All statistical tests were two-sided and a p-value of < 0.05 was considered statistically significant.

The primary study objective was 2-year laryngectomy-free survival (LFS, event: laryngectomy or death from any cause). Additional endpoints were locoregional control (LRC, event: local and/or regional recurrence or death from any cause except distant metastases); disease-free survival (DFS, event: cancer recurrence or death from any cause); overall survival (OS, event: death from any cause); laryngo-esophageal dysfunction-free survival (leDFS, event: local recurrence, total or partial laryngectomy, tracheostomy or feeding tube at 2 years or death) at 2 and 5 years; acute and late toxicities. Survival times were calculated from the first day of treatment. For patients who did not respond to ICT or did not achieve local and/or regional CR after completion of all therapies, the time to event was set to zero months.

Results

Patients and treatment delivered

Between 2016 and 2021, 39 consecutive patients with a median age of 60 years (range 39–72, interquartile range [IQR] 56–64) were treated according to the protocol. The majority (85%) were male, without comorbidities (64%) and had stage T3 primary tumors (72%), of which a comparable proportion originated from the larynx (18, 46%) or hypopharynx (21, 54%). At diagnosis, 14 patients (36%) had vocal cord fixation and 23 (59%) had metastases in the neck nodes. The clinical characteristics of the patients and tumors are listed in Table 1.

The majority, 27 (69%) patients, received 2 cycles of ICT. Five (13%) patients received only one cycle

TABLE 1. Patient, tumor, and treatment characteristics

Sex (female/male)	6/33 (15%/85%)
Age, in years*	60, 39–72 (IQR 56–64)
Comorbidities	14 (36 %)
Cardiovascular	16 events in 10 patients
Diabetes mellitus, tpe 2	3 patients
Gastrointestinal	2 patients
Hypothireosis	1 patient
Depression	1 patient
WHO performance status	
0	27 (69 %)
1	12 (31 %)
Smoking history	
Non-smoker	1 (3%)
Former smoker†	14 (36%)
pack-years*	23, 5–105 (IQR 15–70)
Active smoker	24 (61%)
pack-years*	43, 20–100 (IQR 30–175)
Primary tumor site	
Larynx	18 (46%)
Hypopharynx	21 (54%
T-stage	
T2	8 (20%)
T3	28 (72%)
T4A	3 (8%)
N-stage	
N0	15 (38%)
N1	12 (31%)
N2	10 (26%)
N3	2 (5%)
Overall UICC-TNM stage	
Stage III	25 (64%)
Stage IVA	12 (31%)
Stage IVB	2 (5%)
Induction chemotherapy	
1 cycle	5[3] (13%)
2 cycles	27 (69%)
3 cycles	7 (18%)
Radiotherapy, 70 Gy	39 (100%)
Concurrent chemotherapy (N = 37) ‡	
Number of cycles*	5, 1–7 (IQR 5–6)
Interval ICT – cCRT, in days*	26, 12–48 (IQR 21–28)
Duration of RT, in days*	51, 47–55 (IQR 50–51)
Total duration of treatment, in weeks*	14, 11–25 (IQR 13–15)

ICT = induction chemotherapy; cCRT = concurrent chemoradiotherapy; IQR = interquartile range; RT = radiotherapy; UICC = the Union for International Cancer Conrol; WHO = World Health organization

*Median, range (interquartile range)

†Stopped smoking > 6 months before diagnosis

‡Two patients were non-responders at primary tumor site

of ICT. The reasons for this were an unresponsive primary tumor (2), febrile neutropenia with sepsis (2) and the patient's refusal to undergo further ICT after complete tumor disappearance (1). Three ICT cycles were administered in 7 (18%) patients, as 3 patients had a cT4a tumor and 4 patients had less than PR of neck metastases (Table 1).

The median interval between the first day of the last ICT cycle and the start of cCRT was 26 days (range 12–48, IQR 21–28) and the median duration of RT course was 51 days (range 47–55, IQR 50–51). Overall, depending on the number of administered ICT cycles, the duration of treatment was between 11 and 25 weeks (median 14, IQR 13–15).

Response to induction chemotherapy

After the first cycle of ICT, transnasal endoscopy revealed CR and PR locally in 5 and 32 patients, respectively (95% of patients in total) and two patients (5%) were identified as local non-responders and sent for salvage surgery (Table 2). There was no statistically significant difference in the proportion of CR and/or PR between patients with tumors of the larynx and hypopharynx. In 14 patients with initial vocal cord fixation, only partial restoration of hemilarynx mobility was observed in two patients and no change was observed in the patient with transglottic (cT3N0) tumor. The latter and the patient with a non-responding hypopharyngeal cT3N2b tumor were directed to surgery. Regionally, 19 of 23 patients (83%) with cN+ disease responded to the first ICT cycle with at least PR.

Response to concurrent chemotherapy

Tumor response after cCRT was assessed in 37 patients with CT (26), PET-CT (8) or both (3). The median time to assessment after completion of cCRT was 13 weeks (range 7–26, IQR 11–17). Local CR was achieved in all (100%) patients and regional in 19 of 22 N+ patients (86%), resulting in a 92% (34/37) CR rate above the clavicles (Table 2).

Salvage therapies and survival

The three patients with residual disease in the neck underwent unilateral neck dissection. Histopathologic report confirmed residual carcinoma in all three cases. Two of them remained tumor-free and the third patient was diagnosed with local recurrence and lung metastases. Of the 34 patients with CR after cCRT, the disease progressed

TABLE 2. Primary tumor response to induction chemotherapy and concurrent chemoradiotherapy

Primary tumor response	Induction chemotherapy			Concurrent chemoradiotherapy
	Cycle 1 (N = 39)	Cycle 2 (N = 34)	Cycle 3 (N = 7)	(N = 37)
Complete response	5	4	2	37
Larynx	1	0	0	17
Hypopharynx	4	4	2	20
Partial response	32	30	5	0
Larynx	16	16	2	
Hypopharynx	16	14	3	
Less than partial response	2	0	0	0
Larynx	1			
Hypopharynx	1			

N = number of patients

in three patients (Table 3). In seven patients (18%), a new primary tumor developed 6 months to 5 years (median 2.2 years) after treatment (6 non-small cell lung carcinomas and uterine cervix carcinoma), which was the cause of death in 5 of them.

On the study close-out date (February 29, 2024), the median follow-up time was 3.8 years (range 1.5–8 years, IQR 3–6.2) and 4.5 years for patients still alive (range 2–8 years, IQR 3.2–6.4). At the last clinical visit, 29 patients were free of treated cancer and one had lung metastases. Two patients died from the treated malignancy (with locoregional recurrence and distant metastases) and seven patients died from intercurrent disease without evidence of index malignancy (second cancer – 5, pulmonary embolism, cardiac arrest). LFS at 2 and 5 years was 87% (95% CI 77–98) and 75% (95% CI 60–89), respectively, and the same rates apply to leDFS. The corresponding 2- and 5-year LRC rates (and also DFS) were 79% (95% CI 67–92) and 70% (95% CI 54–85) and for OS 92% (95% CI 84–100) and 82% (95% CI 69– 95), respectively. There were no statistically significant differences in LFS or other survival outcomes between patients with primary tumors of the larynx and hypopharynx (Figure 2).

Toxicity

In three patients with a history of hearing impairment and impaired renal function, ICT was modified from the outset by replacing cisplatin with carboplatin, and in the second cycle two further patients were switched to carboplatin due to worsening of renal function. In 10 out of 34 patients, the dose of chemotherapeutic agent(s) had to be reduced during the second cycle, and in 2 out of 7 patients during the third cycle. The median change in body weight during ICT was positive (2.5% increase, range -10.2–25.8, IQR 0–5.5). The acute toxicities of the treatment are listed in Table 4.

During cCRT, 5 (14%) patients received less than 5 cycles of chemotherapy due to hematotoxicity (4) or patient refusal (1). Three patients (8%) started concurrent carboplatin treatment (impaired hearing or renal function, chest pain during ICT) and nine (24%) patients were switched to carboplatin

TABLE 3. Disease progression after completion of study therapies

Pt. no.	Sex/ age (yrs)	Primary tumor site	cTNM	No. of ICT cyles	Disease-free interval (mos)	Site of recurrence	Salvage therapy	Outcome, after study therpies
1	M/52	Hypopharynx	T4aN1M0	3	6	Larynx, neck	Tracheostomy, palliative CT	DOD, 1.5 yrs
2	M/70	Supraglottis	T2N2bM0	3	22	Larynx, lungs	Tracheotomy, PEG, CT → ICI	AWD, 6.5 yrs
3	M/59	Hypopharynx	T2N1M0	2	19	Neck, lungs	SURG, RT+CT → ICI	DOD, 6.8 yrs
4	M/53	Glottis	T3N0M0	2	16	Larynx	SURG	NED, 3.4 yrs

AWD = alive with disease; CT = chemotherapy; DOD = death of disease; ICI = immune checkpoint inhibitor; ICT = induction chemotherapy; M = male; NED = no evidence of disease; PEG = percutaneous endoscopic gastrostomy; PT = patient; SURG = surgery; → = followed by
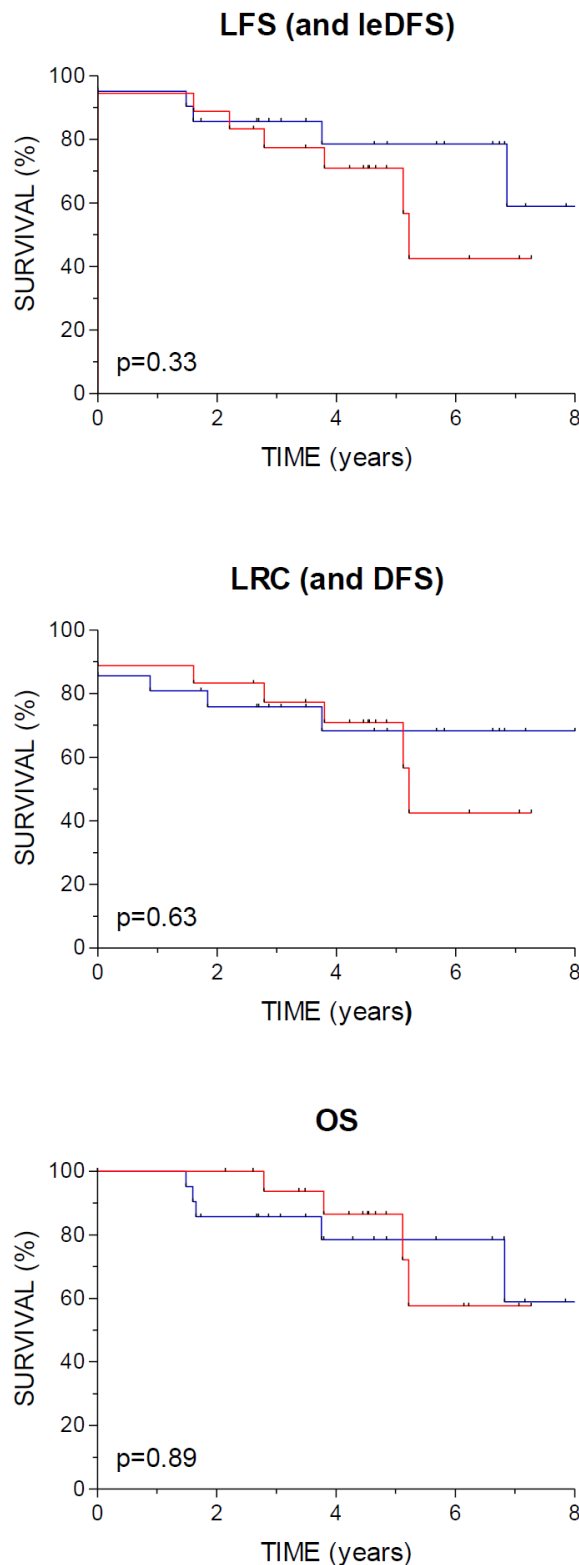
FIGURE 2. Survival outcomes by primary tumor site.

DFS = disease-free survival; leDFS = laryngo-esophageal dysfunction-free survival; LFS = laryngectomy-free survival; LRC = locoregional control; OS = overall survival

— larynx, — hypopharynx

during the course of cCRT due to renal toxicity (6), paresthesia (2) and persistent nausea (1). During the course of RT, eight patients (22%) developed grade 3 radiomucositis and 2 patients (8%; in the 5th and 6th week of RT) had a nasogastric tube placed; one of them remained tube-dependent. The median weight loss during cCRT was 7.3% (range 1.1–16.5, IQR 4.1–11.6) (Table 4).

Late treatment-related toxicities are listed in Table 5. Of 32 patients who survived more than 6 months after therapy and had no active disease, four (13%) experienced no treatment-related adverse events and 16 patients (50%) experienced grade ≥ 2 toxicity. No grade 4 or 5 adverse event was recorded. Twelve of these patients (38%) continued to smoke after stopping therapy.

Discussion

The results of the present study confirmed the hypothesis that treatment selection based on response to chemotherapy with clinical evaluation of tumor response after a single cycle of TPF ICT is a valid discriminator between chemo-/radio-sensitive and resistant tumors. The proportion of patients in whom laryngectomy was successfully avoided in the long term (i.e. 5-year LFS) was encouraging and apparently higher than in the most favorable cCRT arm of the pivotal RTOG 91-11 trial, suggesting the superiority of the combination of TPF ICT and platinum-based cCRT over cCRT alone in the larynx preservation setting.[4]

When considering non-surgical treatment options for locally advanced laryngeal and hypopharyngeal tumors, the imperative is to preserve the functional organ without jeopardizing survival. For this reason, the correct selection of candidates is crucial. Any baseline dysfunction of the larynx or major involvement of the laryngeal skeleton by a tumor reduces the possibility of satisfactory restoration of laryngeal function after treatment. Therefore, the selection of patients for non-surgical treatment is usually limited to patients with T2 and T3 tumors who are not suitable for partial surgical procedures, although some patients with T4a tumors can also breathe adequately and swallow solid and liquid food safely and have a usable voice.[7,15] Our patients were only offered larynx preservation after a thorough discussion of all the advantages and disadvantages in the multi-disciplinary tumor board. None of them were dependent on a tracheostomy or feeding tube prior to treatment, and 92% of the primary tumors were

TABLE 4. Acute toxicities of induction chemotherapy and concurrent chemoradiotherapy

Toxicity	Toxicity grade							
	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Induction chemotherapy (N = 39, 80 cycles)								
Anemia	28	72	4	10	0	0	0	0
Neutropenia	1	3	1	3	1	3	5	13
Thrombocytopenia	5	13	0	0	0	0	0	0
Febrile neutropenia	-	-	-	-	5	13	1	3
Vomiting	0	0	1	3	0	0	0	0
Diarrhea	0	0	3	8	4	10	0	0
Hearing impairment	0	0	1	3	0	0	0	0
Chest pain	0	0	0	0	1	3	-	-
Weight loss	2	5	1	3	0	0	-	-
Any adverse event (no. of patients)	32	82	10	26	8	21	5	13
Concurrent chemoradiotherapy (N=37)								
Anemia	14	38	23	62	0	0	0	0
Neutropenia	8	22	8	22	6	16	1	3
Thrombocytopenia	23	62	8	22	2	5	0	0
Febrile neutropenia	-	-	-	-	1	3	0	0
Nausea	0	0	0	0	3	8	0	0
Dysphagia	13	35	16	43	5	14	0	0
Weight loss	15	41	11	30	0	0	0	0
Radiomucositis	6	16	23	62	8	22	0	0
Radiodermatitis	22	59	11	30	4	11	0	0
Any adverse event (no. of patients)	36	97	35	95	21	57	1	3

stage T2 or T3. In addition, the relatively low median age and low comorbidity burden assured the best possible adherence to the planned oncological treatment.

Although a meta-analysis has confirmed the association between poor response to ICT and subsequent (cC)RT in larynx preservation trials, the optimal number of ICT cycles to reliably identify tumors suitable for non-surgical treatment scenarios is not known. According to the Larynx Preservation Consensus Panel, assessment should be performed after two cycles of ICT.[16] However, Urba *et al*. showed in their phase II study that after a single cycle of cisplatin/5FU ICT, 75% of laryngeal cancer patients achieved at least a partial response at the primary site; after cCRT in responders or surgery in non-responders, DFS was 80% and 78% after 2 and 3 years, respectively.[10] These results compare favorably to the larynx preser-

vation trials, which used more than one cycle of ICT, and underscore the prognostic importance of tumor shrinkage dynamics during ICT.[5] Several other authors later confirmed the prognostic value of tumor shrinkage after the first cycle of ICT.[17,18] Furthermore, tumor assessment using flexible endoscopy appears to be reliable given the survival results presented and the fact that it correlates well with volumetric CT measurements but has a higher interobserver reliability.[19,20] Moreover, it is easy to perform even in the context of a busy clinical routine. Alternative methods of assessing tumor response to ICT using modern imaging techniques, blood biomarkers or a specific gene signature are either much more complex or less validated, but do not appear to be more reliable.[21-23]

Since we used the TPF ICT regimen, the proportion of responders in our series was, as expected, higher (95%) than in the previously mentioned

TABLE 5. Late toxicities in 32 patients surviving > 6 months after therapy and without active disease (median observation time 4.5 years, range 2–8, interquartile range 3.5–6)

Toxicity	Toxicity grade					
	Grade 1		Grade 2		Grade 3	
	No.	%	No.	%	No.	%
Voice changes	15	47	1	3	0	0
Laryngeal edema	9	28	0	0	0	0
Dysphagia	4	13	2	6	0	0
Alteration of taste	2	6	1	3	0	0
Xerostomia	15	47	5	16	0	0
Skin fibrosis	9	28	2	6	1	3
Altered skin pigmentation	15	47	0	0	0	0
Chronic neuropathy, sensory	2	6	1	3	0	0
Thyroid dysfunction	1	3	15	47	0	0
Any adverse event (no. of patients)	26	81	16	50	1	3

study by Urba *et al.* (75%) or in other studies using a platinum-based/5FU combination.[3,10] However, it was comparable to the reported experience with TPF ICT, although tumor response assessment in these studies occurred later in the course of ICT.[9,24] Another observation in our study is that both primary laryngeal and hypopharyngeal tumors responded to TCF ICT, with no statistically significant differences in the proportion of CRs and PRs between the two groups. The reliability of early assessment of tumor response during the ICT phase of treatment, as applied in our study, was confirmed by the low rate of local and/or regional recurrence (in 4 patients, 10%), half of which were cured after timely salvage surgery. Only two patients died of the disease and the third is still alive with the lung metastases 5.8 years after the treatment. In addition, the 2- and especially the 5-year LFS (and leDFS) of 87% and 75%, respectively, in our patients compares favorably with the results of the RTOG 91-11 study, despite a significant proportion of prognostically less favorable hypopharyngeal primary tumors in our group.[3,4] Exactly the same applies to the comparison with other prospective randomized trials and nonrandomized cohort studies that included patients with both laryngeal and hypopharyngeal cancer.[9,17,24,25] The encouraging results suggest the efficacy of the approach tested and emphasize the importance of treating such patients in an experienced multidisciplinary team that provides a balanced assessment of each case, therapeutic expertise, follow-up and timely surgical salvage.[26] In addition, the number of systemic progressions was low (2/39) and most deaths were due to smoking-related metachronous cancers (5/9 deaths). The latter reflects the high proportion of smokers (97%) among our patients, 62% of whom were active smokers at the time of diagnosis and half of whom did not stop smoking after treatment.

The majority of our patients received only two cycles of ICT and the cumulative doses of chemotherapeutic agents were significantly lower than in the pivotal TAX 323 and TAX 324 trials, in which TPF was compared with the PF ICT regimen.[27,28] Still, toxicity was significant: the median interval between the start of the last ICT cycle and the start of cCRT was 26 days, and grade 3 and 4 adverse events were observed in 21% and 13% of patients, respectively, so that a second cycle could not be performed in two (5%) patients. Furthermore, it is questionable whether the third ICT cycle contributed to the efficacy of the treatment, as the disease recurred in 2 of these 7 patients. On the other hand, all three responders who had received only one ICT cycle were free of malignant disease at the last follow-up. Considering the aggressiveness of subsequent cCRT, it seems reasonable to limit ICT to the smallest number of cycles that is still safe. In fact, the proportion of patients with cCRT-related toxicities of grade ≥ 3 was 57%. Although this is within the expected range, it requires optimization of the induction phase of treatment.[12] The role of immune checkpoint inhibitors in the induction

phase of larynx preservation therapy is currently the subject of intensive clinical research.[29]

Despite the significant proportion (54%) of prognostically unfavorable hypopharyngeal cancers in our group, the calculated DFS and OS rates were high, suggesting that treatment intensification by combining ICT and cCRT is important in larynx preservation setting. This has also been noted by other authors.[10,11] However, the results of randomized trials investigating the role of the addition of TPF ICT to cCRT in head and neck cancers contradict our observation of a positive contribution of ICT to treatment efficacy.[8] The reason for this could be the difference in tumor burden, which is generally lower in the larynx preservation setting than in the reported studies.

Our study has limitations primarily related to the small sample size, the retrospective design, and the inclusion of laryngeal and hypopharyngeal cancers, which differ significantly in terms of prognosis.[30] However, in our group, no difference in survival was found between patients with primary laryngeal and hypopharyngeal tumors, and the same was found in the TREMPLIN trial.[31] Furthermore, the study was not originally designed to answer the question of the optimal number of ICT cycles required for reliable identification of chemo-/radiosensitive tumors, nor to test the contribution of ICT to the efficacy of a particular treatment scenario. However, given the toxicity of TPF ICT and the lack of a clear benefit of a third ICT cycle for prognosis, two applications of ICT appear to be sufficient. Whether a single "chemoselector" cycle of TPF ICT followed by platinum-based cCRT would lead to an equally favorable outcome remains to be determined.

We conclude that clinical assessment of tumor response to one cycle of TPF ICT serves as a valid and easy-to-use predictor of tumor sensitivity to platinum-based cCRT. The tested combination of two cycles of ICT and cCRT resulted in a favorable larynx preservation rate and survival outcomes, with no difference between laryngeal and hypopharyngeal primary tumors. However, due to the toxicity of combination therapy, further de-intensification of the ICT component to a single chemoselector cycle with possible optimization of the drug combination appears to be justified.

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AI disclosure

During the preparation of this paper, the author(s) used InstaText in the writing process to improve the readability and language of the manuscript. After using this tool/service, the author(s) have reviewed and edited the content as required and take full responsibility for the content of the publication.

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