Induction chemotherapy with paclitaxel and cisplatin and CT-based 3D radiotherapy in patients with advanced laryngeal and hypopharyngeal carcinomas—a possibility for organ preservation

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Abstract

Background: To evaluate the effect of paclitaxel/cisplatin induction chemotherapy (ICHT) and CT-based radiotherapy (RT) on larynx preservation, tumor control, and survival in patients with larynx/hypopharynx carcinoma eligible for total laryngectomy (TL) or TL plus partial pharyngectomy (TLPP).

Patients and methods: Fifty patients eligible for TL or TLPP were enrolled onto a prospective study and treated with ICHT (200 mg/m² paclitaxel, 100 mg/m² cisplatin; day 1, 22). In patients with complete or partial tumor response RT (69.9 Gy in 5.5 weeks at the gross tumor, 50.4 Gy in the lymphatic drainage; single dose: 1.8 Gy, concomitant boost: 1.5 Gy) was applied. Non-responders had TL/TLPP and RT with total doses adapted to the radicality of tumor resection (56–70 Gy).

Results: The response rate to ICHT was 88% (10% complete, 78% partial response). At a median follow-up period of 25 months the larynx preservation rate was 84%. The 2-year local-regional control rate was 91% and the 2-year overall survival rate was 72.3%. The 3-year estimate to survive with functional larynx is 60%.

Conclusion: In a large portion of patients eligible for TL or TLPP the larynx was preserved by paclitaxel/cisplatin ICHT and 3D RT.

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Keywords: Larynx preservation; Laryngeal carcinoma; Hypopharyngeal carcinoma; Induction chemotherapy; CT-based radiotherapy

1. Introduction

Treatment of patients with advanced laryngeal/hypopharyngeal carcinomas has involved surgery and radiotherapy for resectable tumors [10,17,22], radiotherapy alone [11,12,16,23,26], or in combination with chemotherapy [1]. Surgical advances [33,34], the improvement of radiotherapy by computerized tomography (CT)-based radiation techniques [2,37] and active chemotherapeutic regimens [14,36] have shifted many paradigms. To avoid removing the entire larynx and, if necessary partially the pharynx, many teams assessed preservation strategies [4,6,7,18,39]. Using paclitaxel/cisplatin chemotherapy as first-line therapy to select candidates for either subsequent surgery or 3D CT-based radiotherapy (RT), a prospective study was initiated. The effects of this protocol in patients with laryngeal/hypopharyngeal carcinomas eligible for total laryngectomy (TL) or TL plus partial pharyngectomy (TLPP) were investigated with special regard to local–regional tumor control, survival and larynx preservation.

2. Patients and methods

2.1. Patient characteristics

From December 1996 to May 2001 50 patients (eight female; age: median 58 years; range: 42–77 years) with primary resectable carcinomas of the glottic (T3–4) and supraglottic larynx/hypopharynx (T2–T4, N0–N3, M0) eligible for TL or TLPP were treated prospectively according to this study.
Pretreatment evaluation included history, physical examination and tumor staging. To determine the extent of the disease all patients underwent multiple biopsies, CT scan of the head and neck with tumor volume measurement, chest X-ray, pharyngo- and esophagography, cervical and abdominal ultrasound, bone scan. Other studies included audiogramm, blood cell count, serum and coagulation tests.

Eligibility criteria included no serious medical condition or illness that would preclude informed consent; performance status: WHO grade 0–2; leucocytes ≥ 4.000/mm³; granulocyte count ≥ 2.000/mm³; platelet count ≥ 100.000/mm³; 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.

Fifty patients (1 T2N0, 14 T3N0, 4 T3N1, 1 T3N2a, 1 T3N2b, 3 T3N2c, 9 T4N0, 5 T4N1, 3 T4N2b, 7 T4N2c, 2 T4N3 stages) received induction chemotherapy (ICHT).

### 2.2. Induction chemotherapy

ICHT was performed with paclitaxel 200 mg/m² and cisplatin 100 mg/m² at day 1, 22. Dexamethason (20 mg) was administered orally 12 and 24 h and clemastin (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 ranitidin (50 mg) intravenously 30 min before paclitaxel administered orally 12 and 6 h and clemastin (2 mg) and dexamethason (20 mg) was given during 2 h. Patients were infused with 2.500 ml isotonic NaCl solution during 6 h.

Two weeks after the second application of ICHT endoscopy with biopsies was performed. Tumor volumes were quantified and compared with pretreatment studies by a CT-based method [38]. Non-responders underwent surgery and postoperative RT, patients with complete or partial response to ICHT were defined for radiotherapy.

### 2.3. Radiation therapy

In responders, tumor invaded head/neck compartments and lymphatic drainages were irradiated with a dose of 50.4 Gy (1.8 Gy/fraction, five fractions/week) with a 5-MV linear accelerator. The gross tumor received a second fraction (1.5 Gy) starting in week 4 of the RT course after an interval of more than 6 h (concomitant boost), resulting in a total dose of 69.9 Gy in 5.5 weeks at the gross tumor and of 50.4 Gy in the lymphatic drainage.

An individualized CT-based target volume concept was used for RT regarding the pretreatment tumor extension and lymph node involvement [27,28]. The planning target volume (PTV) for irradiation of tumor, head/neck compartments and lymphatic drainage (1.8 Gy/fraction) included:

1. For endolaryngeal tumors (N0), the whole larynx and the bilateral upper and mid jugular lymph nodes.
2. For T3/T4 laryngeal and T2–T4 hypopharyngeal carcinomas the larynx and hypopharynx and all jugular and spinal accessory lymph nodes.
3. In tumors involving the posterior pharyngeal wall, the retropharyngeal space up to the skull base in addition.
4. In tumors invading the base of the tongue or the lateral oropharyngeal wall the whole oropharynx in addition.
5. In tumors with pre-epiglottic, prelaryngeal, or sub-glottic/pretracheal extension these compartments in addition.

The PTV for the boost treatment (1.5 Gy/fraction) was adapted to the individual tumor situation:

- in N0-stages the primary tumor including the invaded anatomical compartment(s); and
- in cases of unilateral (N1, N2b, or N3 stages) or bilateral lymph node metastases (N2c, N3 stages) these metastases in addition.

A radiation technique consisting of offset-rotational fields combined with static wedge fields [2] was used for dose homogenization inside the PTV. The maximum spinal cord dose was kept below 45 Gy.

In non-responders to ICHT the dose of postoperative radiotherapy was correlated to the radicality of tumor resection [29].

The PTV of postoperative radiotherapy included the bed of larynx and hypopharynx, the tracheostoma, the bilateral neck and in cases of posterior pharyngeal wall involvement, the retropharyngeal space.

The RT dose in R0-resected patients was 56 Gy (2 Gy/fraction). In patients resected with close margins (<3 mm) or R1-resection a local boost (7 × 2 Gy) was applied to the margin of resection (total dose: 70 Gy). The configuration of the PTV for the boost series corresponded to the assessment of primary tumor and lymph node metastases as shown in pretreatment CT scans.

Using individual masks for patient fixation, a reproducible patient positioning for RT was achieved. During RT simulation all fields were documented by radiographs. For quality control, once weekly all fields were verified by control radiographs taken at the linear accelerator and compared with the radiographs of simulation.

### 2.4. Surgery

Tumor resections had been performed according to the radical concept of head and neck surgery. From six non-responders to ICHT three had R0-resections, two R1-resections histologically and one was resected with close margins. Patients with lymph node residuals after ICHT and RT (n = 4) underwent neck dissection to ensure a complete response. Patients with relapses after ICHT and radiotherapy underwent salvage surgery (n = 2). A lymph node
2.5. 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 [24]. The evaluation of radiation induced side-effects was based on the grading system for RTOG acute radiation morbidity scoring criteria [31]. The grade reported is the worst observed grade of each toxicity that is experienced by the patient.

2.6. Supportive care

Before starting RT the dental status of each patient was supervised by a dentist. Enteral nutrition was ensured by the implantation of a percutaneous endoscopic gastroenterostomy in 24 patients. During treatment, patients were observed by a multidisciplinary team weekly.

2.7. Follow-up

The follow-up routine was every 6 weeks for the first year after finishing the initial treatment. Periodical clinical controls were performed with inspection of the tumor bed by transnasal flexible endoscopy and cervical ultrasound every 6 weeks. Four weeks and 6 months after finishing radiotherapy CT scans were performed. One year after finishing primary therapy a recurrence was excluded by endoscopy under local anesthesia using a 90° rigid or a flexible endoscope. In cases of suspected recurrence CT examination and rigid endoscopy under general anesthesia was indicated. Annually, an X-ray of the chest had been performed. In the second and third year after initial treatment examinations took place every 3 months. At the fourth year the intervals had been prolonged to half a year.

2.8. Statistical methods

The response rates after ICHT with paclitaxel and cisplatin and the combined treatment modalities have been evaluated. For statistical analysis of survival data the software ‘Statistica’ was used, including Kaplan–Meier and log-rank tests. Overall survival, local tumor control and larynx preservation rates were calculated.

3. Results

3.1. Tumor response to induction chemotherapy

Tumor response to ICHT was assessed by video-assisted endoscopy and CT scan in comparison to pretreatment studies. The total tumor volumes (TTV) of the 50 patients before ICHT were 21.4 ml at mean (16.1 ml median, range, 1.1–79.3 ml). ICHT reduced the volumes to 6.1 ml at mean (median 2.8 ml, range, 0–25.4 ml), the reduction was 72% at mean (median 83%). The rates for complete response, partial response and stable disease after ICHT were 10%, 78% and 12%. In three patients with initial cartilage destruction prior to ICHT, the cartilage was restored after chemotherapy. In respect to the function, the quality of voice and former presented dysphagia improved after ICHT.

3.2. Tumor response after radiotherapy

Forty-four responders to ICHT (88%) underwent 3D radiotherapy. Endoscopy and CT scans 4 weeks after finalizing radiotherapy showed a complete response at the primary site in 44/44 patients. In four patients, lymph node residuals were identified, so neck dissection was performed. The pathohistological examination of the specimen (Institute of Pathology, University of Wuerzburg) showed complete necrotic lymph node residuals without vital tumor cells in three cases and small foci of vital tumor cells in necrotic lymph node residuals in one specimen. Six non-responders to ICHT had no evidence of disease after postoperative RT.

3.3. Recurrences

At a median follow-up period of 25 months (range, 7–69.7 months; mean 27.3 months) disease recurred in four patients (8%).

Three out of 44 patients treated with ICHT/RT and one non-responder to ICHT treated with TLPP/RT developed recurrences 9–16 months after primary diagnosis. Recurrences were located at the primary tumor site, in a neck node outside the boost volume, at the margin of the boost volume of radiotherapy, and at the tracheostoma in an area where the built-up effect of the linear accelerator was effective. The overall local-regional control rate at 2 and 3 years was 91% (see Fig. 1).

![Fig. 1. Freedom from local–regional recurrence in patients treated with induction chemotherapy and 3D radiotherapy (+surgery in non-responders).](image-url)
3.4. Distant metastases

Five patients (10%) developed distant metastases (lung: \( n = 2 \), lung/liver: \( n = 1 \), pleura: \( n = 1 \), bone: \( n = 1 \)) 6–29 months after primary diagnosis. In two patients distant metastases have been attributed to recently diagnosed lung cancers.

3.5. Second malignancies

In four patients (8%) second malignancies (three lung cancers, one esophageal carcinoma) were diagnosed during follow-up. Two patients with lung cancer died due to their second malignancies.

3.6. Survival

At a median follow-up of 25 months, 13 patients (26%) had died. The death was not tumor related in eight cases (16%) and was caused by myocardial infarction (\( n = 3 \)), infections, lung abscess and metabolic disorder or intercurrent disease (\( n = 5 \)).

The overall survival rate was 72.3% at 2 years and 66% at 3 years (see Fig. 2).

3.7. Larynx preservation

From 50 ICHT patients, seven were treated with TL/TLPP and ND. As in one patient tumor recurred at the primary site after ICHT and RT the larynx resection rate was 8/50 (16%). At a median follow-up period of 25 months the larynx has been preserved in 84% of the patients. The 3-year estimate for patients to survive with a functional larynx after ICHT is 60% (see Fig. 3).

3.8. Treatment toxicities

3.8.1. Induction chemotherapy toxicity

ICHT toxicity (see Table 1) was tolerable. Paclitaxel-induced alopecia grade 3 was the most frequent side effect (100%). Hemoglobin levels below 11 g/100 ml were observed in 36%, leucocytopenia in 27%, and thrombocytopenia in 8% of the patients. Febrile neutropenia did not occur. Renal toxicity due to cisplatin was diagnosed in 24 patients (48%). All grade 1 renal toxicities (17/24) were reversible.

Non-hematologic toxicities included elevations of serum bilirubin levels (2% grade 3; 34% grade 2) and increased SGOT activities in 42% of the patients. Most frequent gastrointestinal side effects were grade 2 nausea and vomiting. No hypoglycemias or hyperglycemias, no increased amylase activities, or coagulation disorders have been detected. Neurotoxicity included low grade paresthesia, weakness, vertigo, headache, myalgia, and arthralgia grade 1–2. A tendency to hypotension has been noticed.

3.8.2. Radiation toxicity

The acute toxicities in the radiation fields were substantial but tolerable. The degree of radiation induced mucositis and dysphagia in ICHT patients is shown in Table 2.

Most patients required at least 1 month after radiotherapy for resolution of the mucositis to a degree that would allow undisturbed swallowing.

Long-term chronic side effects, noted after 6 months from the initiation of treatment were seen in one patient with a T4N0 hypopharyngeal carcinoma located at the entry of the piriform recess. This patient developed an edema at the base of the tongue and supraglottic larynx, so a protective tracheostoma was necessary. Wound healing problems were observed in one patient who underwent salvage TLPP for a local recurrence after ICHT and RT. A fistula occurred which healed under conservative treatment. Neither chondronecrosis of the thyroid cartilage nor osteoradionecrosis have been observed in the patient population.

Clinical evaluation of patients treated with ICHT and RT revealed that all patients retained intelligible conversational speech during and after treatment including conversation on telephone. Complaints of oral dryness when speaking, clinical symptoms of hoarseness and mild dysarthria were observed in most patients. However, hoarseness was a minor problem and often temporary. Swallowing
complaints also included odynophagia, dysphagia of solids, choking or coughing when eating. PEG tubes were removed after a median of 6 weeks (range, 5–29 weeks) from implantation, but not until the primary site was confirmed to be negative for residual tumor by a post-treatment endoscopy with biopsy.

4. Discussion

In patients with advanced laryngeal and hypopharyngeal carcinoma the functional and cosmetic deformity produced by cancer surgery is very substantial. Any reduction in the need for laryngeal resection and a tracheostoma results in an improvement in quality of life[35].

Several study groups [12,16,23] prefer organ preservation therapy of supraglottic larynx carcinomas by RT alone. After RT, 5-year local control rates of 68% for T3 and 56% for T4 tumors were reported [23]. The cause-specific survival of patients with T3N0 glottic primaries (73% at 2 years) treated with primary RT was identical to the only published report in the surgical literature [20].

A tumor response to chemotherapy is attributed to active chemotherapeutic agents and the presence of an intact blood supply in a neoplasm. As good vascularization of tumor tissues also correlates to a good tumor oxygenation, a major response to chemotherapy appears predictive of a patient’s ability to respond to subsequent radiotherapy [15].

By ICHT two groups of patients can be selected: responding patients amenable to subsequent RT and non-responders, for whom surgery is considered the most appropriate treatment. Two major randomized multicenter studies of ICHT with organ preservation as the treatment goal [18,39] used two cycles of cisplatin/5-fluorouracil followed in responders by a third cycle and radiotherapy.

At the Veteran Affairs Hospital 332 patients with laryngeal carcinoma stage III–IV (9% T1/2, 65% T3, 26% T4 tumors) were enrolled into a prospective randomized trial [39]. One-hundred and sixty-six patients received ICHT (arm 1). Patients with complete (31%) or partial tumor response (54%) to ICHT had radiotherapy (+/- salvage surgery), and 48 non-responders underwent TL. Patients of arm 2 underwent primary surgery and postoperative radiotherapy (50–73.8 Gy). The larynx preservation rate in arm 1 was 68% at 2 years, and the survival rate in both arms was 68% at 2 years (median follow-up: 33

<table>
<thead>
<tr>
<th>Grades of toxicities [24] in patients treated with induction chemotherapy (n = 50)</th>
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<tr>
<td>Toxicities</td>
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<tr>
<td>Blood cell toxicity</td>
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<td>Renal toxicity</td>
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<tr>
<td>Circulation</td>
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CTC, common toxicity criteria.

Table 2
Acute radiation toxicities [31] in 49 patients treated with ICHT and RT

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<tr>
<th>Toxicities</th>
<th>Number of patients (% RTOG)</th>
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<tr>
<td>Grade 1</td>
<td>Grade 2</td>
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<tr>
<td>Skin</td>
<td>16 (12)</td>
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<tr>
<td>Mucositis</td>
<td>10 (20)</td>
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<tr>
<td>Xerostomia</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>19 (39)</td>
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</table>
months). In the ICHT arm there were 20% recurrences, in the primary surgery arm 7%.

Lefebvre and co-workers [18] enrolled 192 patients with hypopharyngeal/laryngeal carcinomas (7% stage II, 57% stage III, 37% stage IV, N2c excluded) into a prospective randomized trial. One-hundred patients had ICHT, 94 patients primary surgery and radiotherapy (44–72 Gy, 60 Gy median). In the ICHT arm 54% had a complete, 32% a partial response to ICHT, in 13% of the patients there was no change and in one progressive disease. The larynx preservation rate was 42% at 2 years and 35% at 5 years. The 3-year survival rate in the ICHT arm was 57% and 43% in the primary surgery arm. Local–regional tumor control rates were 83% and 77% in the ICHT arm versus 88% and 81% in the primary surgery arm.

In the RTOG 91-11 trial [21] 547 patients with potentially resectable stage III and low-volume stage IV glottic and supraglottic cancers were randomly assigned to three treatment arms.

Patients in arm 1 received three cycles of induction cisplatin 100 mg/m^2 once and 5-FU 1000 mg/m^2 per day for 5 days every 3 weeks. In responding patients, this treatment was followed by 70 Gy of radiation in 35 fractions for 49 days. Patients in arm 2 received concurrent cisplatin 100 mg/m^2 on days 1, 22 and 43 of radiation treatment (70 Gy/35 fractions for 49 days). Patients in arm 3 received radiation only at 70 Gy/35 fractions for 49 days. After excluding 30 patients from the study, 517 remained for analysis (173 in arm 1, 172 in arm 2, and 172 in arm 3). The laryngectomy-free survival for patients treated with concomitant chemotherapy and radiotherapy was significantly better than for patients treated with radiotherapy alone. The laryngectomy rate at 2 years was 25%, 12%, and 28% for the induction, concomitant and radiotherapy arms retrospectively. Loco-regional control at 2 years for patients in arm 2 (78%) was significantly better than either arm 1 (61%), or arm 3 (56%), \( P < 0.01 \). Ten patients in the study died of treatment toxicity; five died in the ICHT arm, and five in the concomitant chemotherapy and radiation arm. Acute grade 4 and 5 toxicity was 31%, 21%, and 5% in treatment arms 1, 2, and 3 retrospectively (<0.0001). Late grade 4 and 5 toxicity was 9%, 8%, and 10% in the arms (not significant). Overall survival was very similar for the patients in the three treatment arms (about 75% at 2 years).

In the present study the tumor-toxic effects of cisplatin [5] and the synergetic effects of paclitaxel to promote polymerization of microtubules and to arrest tumor cells in the G2- and M-phase of the cell cycle [3] were used for treatment. The toxicity of the chemotherapy protocol was tolerable (see Table 1), and the response rate was 88% in previously untreated larynx/hypopharynx carcinomas.

Patients had a close monitoring by an interdisciplinary team of oncologists to avoid a delay of definitive management, particularly when such therapy included surgical resection. Endoscopical examinations and CT scans were routinely performed to assess tumor volume, tumor extension and response to ICHT and RT, and to achieve transparency for treatment decisions.

Several studies outline the role of the tumor volume as the strongest independent predictor of failure in patients treated with radiotherapy [13,23,38]. By cisplatin/paclitaxel ICHT the total tumor volume was reduced to 28% at mean of the pretherapeutic volume. Hermans and co-workers [13] reviewed the pretreatment CT studies of patients with supraglottic carcinoma for tumoral involvement of anatomic subsites and extralaryngeal tumor spread. They performed statistical analysis of outcome for each covariates. The degree of involvement of the paraglottic space at the level of the true vocal cord \( (P < 0.001) \) and subglottic extension \( (P < 0.01) \) were significantly correlated with local recurrence rate. In the multivariate analysis, the degree of involvement of the pre-epiglottic space \( (P < 0.01) \) and subglottic extension \( (P < 0.01) \) were found to be independent predictors of local recurrence.

To minimize the recurrence rate a radiation technique based on risk adapted target volume concepts regarding the individual tumor invasion of head/neck compartments and the lymphatic tumor spread [28,29] has been used. Therefore, pretreatment CT studies were analyzed. In case of tumor invasion of the pre-epiglottic, prelaryngeal, and subglottic space moulds were used to correct the built-up effect of the linear accelerator. For dose homogenization inside the PTV special field arrangements were applied [2]. By this technique the spinal chord dose could be kept below 45 Gy even in N2c stages, which are excluded from the E.O.R.T.C. Trial 24 954 [8]. CT-based 3D radiotherapy was performed in a concomitant boost technique reducing the total treatment time, which is a predictor for local control [9]. Less toxic side effects as reported in studies [19,21] using concomitantly applied radiochemotherapy were observed in the present study with the sequential application of chemotherapy and radiotherapy.

If lymph node residuals had been detected in routinely performed CT studies 4 weeks after radiotherapy, patients underwent neck dissection to increase local control and disease-free survival. This treatment approach has been recommended after organ preserving radiotherapy [25]. With the described treatment modalities a local control rate of 91% at 2 years for patients treated with ICHT was achieved.

Patients of the present study died for reasons often not related to their initial cancer, but very often caused by the abuse of tobacco and alcohol. This is typical in head and neck cancer and may be one of the reasons why in randomized trials significant differences in overall survival are often not noticed. Despite the lack of an indentifiable survival benefit from neoadjuvant treatment in the present study as well as in previous trials for laryngeal cancer [18, 21,39], it is important to recognize that organ preservation represents a valid assessment for the therapeutic goal.

A meta-analysis [30] of three randomized trials including laryngeal and hypopharyngeal tumors treated with ICHT
presented updated overall survival and disease-free survival results of 602 patients, with a median follow-up of 5.7 years. The overall survival in the ICHT regimen was 39% at 5 years and 45% in the control group (\( P = 0.1 \)) and the disease-free survival 34% in the ICHT regimen and 40% in the control group (\( P = 0.1 \)). Recurrences occurred in 35% in the ICHT vs. 20% in the control, but less metastases or second primaries (38%) vs. the control (54%). The reduction in distant metastases did not translate into an improvement in survival. Similar rates of death not due to cancer have been observed (27% vs. 28%). In conclusion no significant differences in overall and disease-free survival were observed between the ICHT and the control group. But we have to notice that in the metaanalysis there was a significant heterogeneity between the three trials (\( P = 0.05 \)). In one trial [32] only 68 patients were enrolled and CT scans were not routinely performed to assess the tumor extension nor the tumor response to chemotherapy or after radiotherapy.

In the present study using CT-based 3D radiotherapy the 2-year survival rate was 72.3%, the larynx preservation rate 84%, and the 2-year local–regional control rate was 91%. Deaths not related to the initial cancer reduced the laryngectomy-free survival rates of patients treated with ICHT to 60% at 3 years. The high rates of larynx preservation, local–regional tumor control, and the acceptable treatment toxicity of our treatment approach encouraged us to continue our treatment protocol in a multicenter trial of the German Larynx Organ Preservation Study Group (http://www.delos.de.vu).

Acknowledgements

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