Organ Function and Quality of Life after Transoral Laser Microsurgery and Adjuvant Radiotherapy for Locally Advanced Laryngeal Cancer*

Arno Olthoff[1], Andreas Ewen[2], Hendrik Andreas Wolff[2], Robert Michael Hermann[2], Hilke Vorwerk[2], Andrea Hille[2], Ralph Rödel[3], Clemens F. Hess[1], Wolfgang Steiner[3], Olivier Pradier[4]**, Hans Christiansen[2]**

Background and Purpose: Transoral laser microsurgery (TLM) and adjuvant radiotherapy are an established therapy regimen for locally advanced laryngeal cancer at our institution. Aim of the present study was to assess value of quality of life (QoL) data with special regard to organ function under consideration of treatment efficacy in patients with locally advanced laryngeal cancer treated with larynx-preserving TLM and adjuvant radiotherapy.
Patients and Methods: From 1994 to 2006, 39 patients (ten UICC stage III, 29 UICC stage IVA/B) with locally advanced laryngeal carcinomas were treated with TLM and adjuvant radiotherapy. Data concerning treatment efficacy, QoL (using the VHI [Voice Handicap Index], the EORTC QLQ-C30 and QLQ-H&N35 questionnaires) and organ function (respiration, deglutition, voice quality) were obtained for ten patients still alive after long-term follow-up. Correlations were determined using the Spearman rank test.
Results: After a median follow-up of 80.8 months, the 5-year overall survival rate was 46.8% and the locoregional control rate 76.5%, respectively. The larynx preservation rate was 89.7% for all patients and 100% for patients still alive after follow-up. Despite some verifiable problems in respiration, speech and swallowing, patients showed a subjectively good QoL.
Conclusion: TLM and adjuvant radiotherapy is a curative option for patients with locally advanced laryngeal cancer and an alternative to radical surgery. Even if functional deficits are unavoidable in the treatment of locally advanced laryngeal carcinomas, larynx preservation is associated with a subjectively good QoL.

Key Words: Laser surgery · Radiotherapy · Locally advanced head-and-neck cancer · Quality of life · Organ preservation

Strahlenther Onkol 2009;185:303–9
DOI 10.1007/s00066-009-1967-y

Objektive und subjektive funktionelle Einschränkungen nach organerhaltender lasermikrochirurgischer Resektion und adjuvanter Radiotherapie bei lokal fortgeschrittenen Larynxkarzinomen

Hintergrund und Ziel: Lasermikrochirurgie und adjuvante Strahlentherapie sind in der Klinik der Autoren etablierte Behandlungsmethoden lokal fortgeschrittener Larynxkarzinome mit guten onkologischen Ergebnissen und einer hohe Rate an Organerhalt. Bei organerhaltender Therapie sind funktionelle Einschränkungen oft unvermeidbar. Neben den onkologischen Ergebnissen sollten in dieser Studie das objektive Ausmaß solcher Einschränkungen und deren subjektive Wertung durch die Patienten untersucht werden.
Patienten und Methodik: Von 1994 bis 2006 wurden 39 Patienten (zehn UICC-Stadium III, 29 UICC-Stadium IVA/B) mit lokal fortgeschrittenen Larynxkarzinomen mittels Lasermikrochirurgie und adjuvanter Strahlentherapie behandelt. Bei zehn Patienten erfolgte im Rahmen der Nachsorge in den Jahren 2006/2007 eine Erhebung von Lebensqualitätsdaten. Die Schluckfunktion wurde flexibel endoskopisch überprüft, die Atmung durch eine Bodyplethysmographie. Die Objektivierung der Stimmqualität erfolgte durch das Göttinger Heiserkeitsdiagramm.
Ergebnisse: Nach einer medianen Beobachtungsdauer von 80,8 Monaten betrugen die 5-Jahres-Überlebensrate 46,8% und die lokoregionale Kontrollrate 76,5%. Eine Salvage-Laryngektomie bei Lokalrezidiv erhielten vier Patienten, so dass im Verlauf eine 89,7%ige Rate an Larynxerhalt erreicht werden konnte. Bei der objektiven Untersuchung der Funktionseinschränkungen zeigte

*The study results were reported as oral presentation at the 2008 DEGRO (German Society of Radiooncology) Annual Meeting in Vienna, Austria.
**Olivier Pradier and Hans Christiansen share senior authorship.

[1]Department of Phoniatrics and Pedaudiology, University of Göttingen, Germany,
[2]Department of Radiotherapy, University of Göttingen, Germany,
[3]Department of Otorhinolaryngology, University of Göttingen, Germany,
[4]Department of Cancerology, CHU Morvan, Brest, France.

Received: October 21, 2008; accepted: October 31, 2008

sich bei fünf Patienten eine gelegentliche Aspiration bei kräftigem Hustenreflex. Die übrigen fünf Patienten wiesen keine Schluckstörung auf. Eine Normalstimme lag bei keinem Patienten vor. Es bestand jedoch keine signifikante Korrelation der objektivierten Funktionsstörungen mit den Lebensqualitätsfunktionsskalen: Subjektiv schätzen die Patienten ihre Lebensqualität als gut ein.
Schlussfolgerung: Lasermikrochirurgie und adjuvante Strahlentherapie sind eine Therapieoption für lokal fortgeschrittene Larynxkarzinome, die neben guten onkologischen Ergebnissen eine hohe Rate an Organerhalt ermöglicht. Die Patienten schätzen ihre Lebensqualität im weiteren Verlauf subjektiv als gut ein. Die tatsächlichen funktionellen Einschränkungen werden durch die Lebensqualitätsdaten allerdings nicht sicher abgebildet. Daher ist zur objektiven Beurteilung posttherapeutischer Funktionsergebnisse die klinische Erhebung funktioneller Befunde erforderlich.

Schlüsselwörter: Laserchirurgie · Radiotherapie · Lokal fortgeschrittene Kopf-Hals-Tumoren · Lebensqualität · Organerhalt

Introduction

Laryngeal cancer is a common malignancy with about 140,000 new cases per year worldwide, approximately 50,000 of them in Europe [9, 27]. In locally advanced stages without distant metastases, surgery followed by radiochemotherapy is a widely accepted curative therapy approach [7]. Radical surgery implementing total laryngectomy implies a permanent tracheostoma and requires tracheoesophageal speech. Since carbon dioxide laser was introduced into clinical otolaryngology, new perspectives for organ preservation in the surgery of head-and-neck squamous cell carcinomas (HNSCC) have been opened up [36]. In the meantime, transoral laser microsurgery (TLM) is an established method in early-stage laryngeal carcinoma with a high level of organ preservation associated with good functional results and quality of life (QoL) [3, 20]. In locally advanced disease, laser surgery combined with postoperative radiotherapy can also be considered as a therapeutic alternative to a more radical open surgery. Recently, we reported on efficacy of adjuvant radiotherapy after TLM for locally advanced both primary and recurrent HNSCC [10, 30].

Due to posttreatment rehabilitation, the preservation of organ function, while maintaining the achievable cure rates, is a major goal of continued clinical cancer research besides the improvement of locoregional control and overall survival. One possible approach is primary radiochemotherapy, which has been shown to offer a chance for organ preservation with acceptable survival rates in locally advanced laryngeal cancer [15]. Here, we present an analysis of 39 patients with locally advanced laryngeal carcinoma treated with organ-preserving TLM and adjuvant radiotherapy in curative intention. The purpose was to evaluate treatment outcome as well as organ function and QoL in cured patients after organ preservation and long-term follow-up.

Patients and Methods

Surgery and Radio(chemo)therapy

39 patients with locally advanced laryngeal carcinoma were treated with postoperative radiotherapy following larynx-preserving TLM (larynx-preserving TLM for the primary tumor, combined with a unilateral or bilateral selective neck dissection). Patient characteristics are summarized in Table 1. Large primary tumors could be removed piece by piece intraoperatively; details of this surgical procedure have been published by Steiner & Ambrosch [36].

Table 1. Patient characteristics. I: patients who underwent transoral laser microsurgery and adjuvant radiotherapy; II: cured patients after long-term follow-up; III: patients analyzed for organ function and quality of life.

Tabelle 1. Patientencharakteristika. I: alle Patienten; II: noch lebende Patienten am Ende der Nachbeobachtungszeit; III: im Rahmen der Studie untersuchte Patienten.

	I (n = 39)	II (n = 16)	III (n = 10)
Sex [n (%)]			
• Male	33 (85)	14 (88)	8 (80)
• Female	6 (15)	2 (12)	2 (20)
Age (years)			
• Median	58	59	56
• Range	26–76	51–73	51–70
UICC stage [n (%)]			
• I	0	0	0
• II	0	0	0
• III	10 (26)	3 (19)	1 (10)
• IVA/B	29 (74)	13 (81)	9 (90)
Tracheotomy [n (%)]	4 (10)[a]	0	0
Concomitant chemotherapy [n (%)]	6 (15)	5 (31)	5 (50)
Follow-up (months)			
• Median	81	64	43
• Range	15–159	15–152	15–119
Acute toxicity grade 3 [n (%)]	17 (44)	7 (44)	3 (30)

[a]laryngectomies as salvage therapy

Adjuvant radiotherapy consisted of 50 Gy to the primary tumor region and cervical/supraclavicular lymph nodes on either side of the neck plus boost to the primary tumor area and sites of extranodal spread to a cumulative dose of 60 Gy (28 patients) or 64 Gy (eleven patients). Conventional fractionated radiotherapy was delivered in treatment fractions of 2.0 Gy per day. The prescribed dose for photons and electrons was defined in accordance with the International Commission on Radiation Units and Measurement report 50 [18]. In six patients, cisplatin-based chemotherapy was given concomitantly.

The differences in cumulative dose, treatment techniques, and concomitant chemotherapy are due to changes in treatment protocols and technical developments over the years. Toxicity during radio(chemo)therapy was scored according to the CTC [Common Toxicity Criteria] Score [38].

QoL and Organ Function in Cured Patients after Long-Term Follow-Up

In ten patients, data concerning QoL and organ function were obtained prospectively after long-term follow-up. For assessment of QoL, we used the EORTC QLQ-C30 and QLQ-H&N35 questionnaires (developed by the European Organization for Research and Treatment of Cancer).

The QLQ-C30 (with a total of 30 items) includes five functional scales (two items cognitive, four items emotional, five items physical, two items role and two items social functioning), three symptom scales (three items fatigue, two items pain, and two items nausea & vomiting), a global QoL scale with two items, and six single items (appetite loss, constipation, diarrhea, dyspnea, financial difficulties, sleep disturbance).

The QLQ-H&N35 with a total of 35 items includes eight items regarding swallowing and social eating, two items with regard to speech, and one item asking for a feeding tube. The remaining 24 items deal with pain, other physical, social and sexual functioning.

Particularly the items of these questionnaires regarding dysphagia, dyspnea and dysphonia were evaluated in order to assess the patient's subjective rating of functional impairments. High values on the 4-point scale (severe, moderate, slight, and no symptoms) indicate high functional deficits. According to the EORTC scoring manuals, the item scores were linearly converted to a 0–100 scale. An assessment of voice-related QoLwas performed using the Voice Handicap Index (VHI) [23]. The answers of this questionnaire were scaled to a 4-point index (0–3), where a high index indicates increased voice disorders. All questionnaires were used in their validated German version.

For the objective measurement of laryngeal functions, the ten patients underwent a clinical examination. During a fiberoptic endoscopic (Wolf, Knittlingen, Germany) evaluation of swallowing (FEES), deficits in bolus transport and aspiration were revealed. A green pudding was used as a bolus and aspiration was classified according to the 5-point scale published by Schröter-Morasch [34]: "0" indicated no and "I" occasional aspiration with reflectory bolus ejection from the airway. "II" indicated permanent aspiration with reflectory and "III" without reflectory but with effort-dependent bolus ejection from the airway. Scale "IV" indicated permanent ("silent") aspiration without reflectory or effort-dependent bolus ejection from the airway. To evaluate the respiratory function, a body plethysmography (Ganshorn, Niederlauer, Germany) was performed to determine the central airway resistance (RAW), which is an effort-independent and therefore objective indicator of laryngeal stenoses [26]. RAW values < 0.3 kPa/l were within the normal range. Voice quality was determined by a perceptive RBH scale (0–3) regarding roughness (R), breathiness (B) and, as a consequence, hoarseness (H). Higher scales indicated increased dysphonia, aphonia was rated as "H4". For objective voice analyses, the Göttingen Hoarseness Diagram (GHD) was used, which is a computerized voice analysis program. Its suitability also for highly irregular voices after partial laryngectomies was shown in a previous study [24]. Reference values of normal voices (n = 116) and of aphonia (n = 60) were measured in a previous study and are shown in Figure 5 [17]. The clinical data were compared to the "single items" of QoL data that represented patient's self-assessments of posttreatment sequelae.

Statistical Analysis

The Kaplan-Meier product-limit method [19] was used to determine overall survical and locoregional control. Possible correlations between subjective and objective measures of organ function as well as the possible influence of side effects on functional skills were statistically proven (Spearman rank test). A significant difference was assumed when $p < 0.05$.

Results

Oncologic Results and Acute Toxicity

The median duration of follow-up was 80.8 months. Death occurred in 23 patients, eleven of these died of tumor and twelve of intercurrent disease. The 5-year overall survival rate was 46.8% (Figure 1), the 5-year locoregional control rate 76.5% (Figure 2). In four patients who developed local recurrences at the laryngeal site, laryngectomy as salvage therapy was carried out. However, these patients died of cancer during further follow-up. Thus, larynx preservation was 89.7% for all patients and 100% in patients still alive after follow-up. There were no treatment-related deaths. Grade 3 toxicity (mucositis/dysphagia and/or hematologic toxicity) occurred in 17 pa-

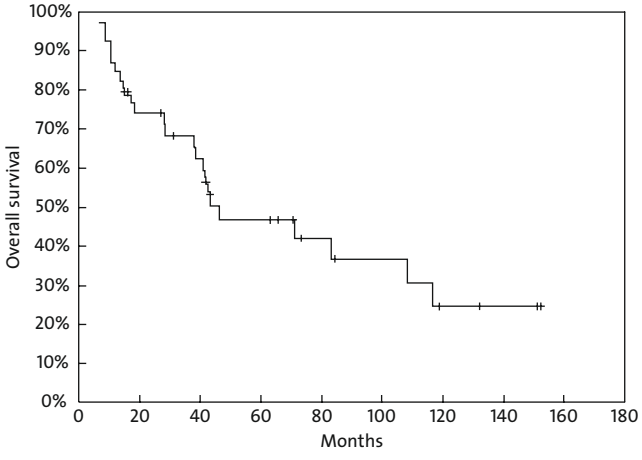

Figure 1. Overall survival (data refer to the total group of 39 patients).
Abbildung 1. Gesamtüberleben (alle Patienten, n = 39).

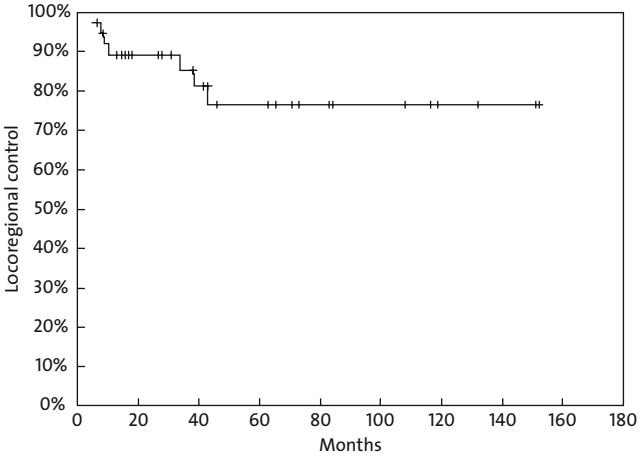

Figure 2. Locoregional control rate (data refer to the total group of 39 patients).

Abbildung 2. Lokoregionale Kontrolle (alle Patienten, n = 39).

tients (43.6%). There was no significant correlation between initial toxic side effects and final organ function or QoL data ($p > 0.05$; Table 2).

QoL and Organ Function in Cured Patients

QoL and organ function were analyzed in ten cured patients after long-term follow-up (median 42.6 months [range 14.9–118.9 months] after diagnosis and treatment). Six other patients still alive at that time were not available for analysis. They either refused the participation in the study or were in poor general condition due to intercurrent diseases and not able to attend our institution. Of the ten patients analyzed, nine had UICC stage IV and one patient UICC stage III. The tumor stages and also the toxicity of radiotherapy did not differ significantly compared to the total collective (n = 39) or compared to the remaining patients still alive (n = 16; $p > 0.05$). Mean age was 61 years (range 53–71 years) and corresponded to the age pattern of the whole (n = 39) and remaining group (n = 16; $p > 0.05$).

The FEES revealed occasional aspirations in two patients (grade "I") and permanent aspirations in three (grade "II"). The reflectory bolus ejection was sufficient in all of these five patients. A total of three patients had percutaneous gastric tubes. One of these patients had no verifiable aspiration during endoscopy, but subjectively suffered from a dysphagia with occasional aspirations of liquids and consecutive coughing. The values from the "single item 'dysphagia'" (QLQ-H&N35) ranged from 1 to 3, with a mean of 1.9. Patient's QLQ item scores did not correlate significantly with the objectified endoscopic findings of swallowing abilities ($p > 0.05$; Table 2, Figure 3).

The mean RAW was 0.57 kPa/l (SD [standard deviation] ± 0.56). Increased RAW values (> 0.3 kPa/l) were found in seven patients. In two patients, the RAW was twice as high as normal, but both patients denied dyspnea. Regarding the "single item 'dyspnea'" (QLQ-C30), only two patients mentioned severe dyspnea, both had an RAW > 0.5 kPas/l. However, there was no significant correlation between "single-item" scores and body plethysmographic measures ($p > 0.05$; Figure 4). No patient had a tracheostoma.

Voice quality was subjectively evaluated using the VHI. The index ranged between 0 and 3 (mean 1.8). The single item

Table 2. Influence of tumor stages, acute side effects and functional outcome on QLQ scales. Correlation analyses are shown. (+): significant (Spearman rank test; $p < 0.05$). CTC: Common Toxicity Criteria Score "mucositis" [38]; EORTC: European Organization for Research and Treatment of Cancer; FEES: fiberoptic endoscopic evaluation of swallowing; GHD: Göttingen Hoarseness Diagram; NS: not significant; QLQ-C30 and QLQ-H&N35: quality-of-life questionnaires; RAW: central airway resistance; UICC: tumor classification (I–IV) of the International Union Against Cancer [35]; VHI: Voice Handicap Index.

Tabelle 2. Einfluss der Tumorstadien, akuter Nebenwirkungen und der objektiven Funktionseinschränkungen auf die subjektive Lebensqualität (QLQ). (+): signifikant (Spearman-Rank-Test; $p < 0{,}05$). CTC: Common Toxicity Criteria Score „Mukositis" [38]; EORTC: European Organization for Research and Treatment of Cancer; FEES: „fiberoptic endoscopic evaluation of swallowing"; GHD: Göttingen Hoarseness Diagram; NS: nicht signifikant; QLQ-C30 and QLQ-H&N35: „quality-of-life questionnaires"; RAW: „central airway resistance"; UICC: Tumorstadien (I–IV) der International Union Against Cancer [35]; VHI: Voice Handicap Index.

	UICC	CTC	FEES	RAW	GHD
EORTC QLQ-C30					
Functional scales					
• Cognitive functioning	NS	NS	NS	NS	NS
• Emotional functioning	NS	NS	NS	NS	NS
• Physical functioning	NS	NS	NS	NS	NS
• Role functioning	NS	NS	NS	NS	NS
• Social functioning	NS	NS	NS	NS	NS
Symptom scales					
• Fatigue	NS	NS	NS	NS	NS
• Pain	NS	NS	NS	NS	NS
• Nausea & vomiting	NS	NS	NS	NS	NS
Single items					
• Appetite loss	NS	NS	NS	NS	NS
• Constipation	(+)	NS	NS	NS	NS
• Diarrhea	NS	NS	NS	NS	(+)
• Dyspnea	NS	NS	NS	NS	NS
• Financial difficulties	NS	NS	NS	NS	NS
• Sleep disturbance	NS	NS	NS	NS	NS
• Global quality of life	NS	NS	NS	NS	NS
EORTC QLQ-H&N35					
• Swallowing	NS	NS	NS	NS	(+)
• Social eating	NS	NS	NS	NS	NS
• Speech	NS	NS	NS	NS	NS
• Feeding tube	NS	NS	NS	NS	NS
VHI	NS	NS	NS	NS	NS

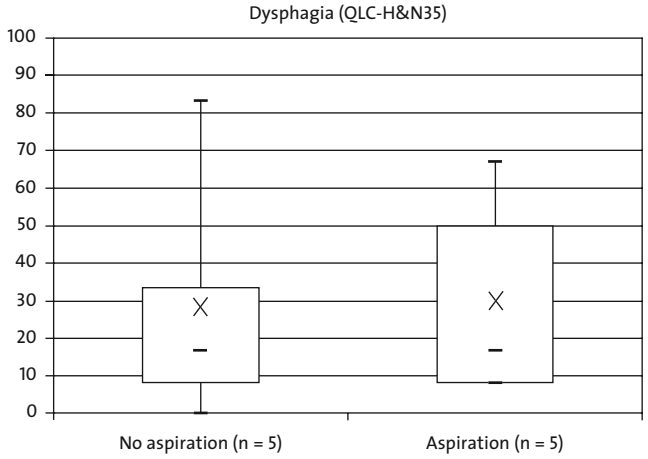

Figure 3. Score of dysphagia (QLQ-H&N35). Boxplot graphs reflect minimum, 25th, 50th, 75th percentiles and maximum, the cross reflects mean. Higher scores represent a lower level of functioning. The difference between both groups (patients with and without aspiration during endoscopy) was not significant ($p > 0.05$).

Abbildung 3. Subjektives Maß an Schluckbeschwerden (QLQ-H&N35). Die Boxplots zeigen jeweils das Minimum, die 25., 50. und 75. Perzentile sowie das Maximum, das Kreuz ist der Mittelwert. Je höher der Score, desto geringer die Funktion. Zwischen den Gruppen mit und ohne objektive Aspiration bestand kein statistisch signifikanter Unterschied ($p > 0{,}05$).

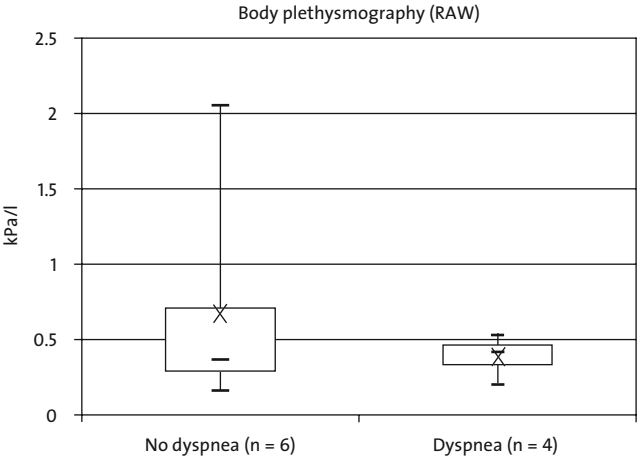

Figure 4. Body plethysmography. Boxplot graphs reflect minimum, 25th, 50th, 75th percentiles and maximum, the cross reflects mean. An abnormally increased central airway resistance (RAW [kPa/l]) is defined as > 0.3 kPa/l. The difference between both groups (patients with and without dyspnea according to the EORTC QLQ-C30 questionnaire) was not significant ($p > 0.05$).

Abbildung 4. Body-Plethysmographie. Die Boxplots zeigen jeweils das Minimum, die 25., 50. und 75. Perzentile sowie das Maximum, das Kreuz ist der Mittelwert. Ein pathologisch erhöhter Atemwiderstand ist definiert ab einem Wert von > 0,3 kPa/l. Zwischen den Gruppen mit und ohne subjektive Dyspnoe (gemäß EORTC QLQ-C30) bestand kein statistisch signifikanter Unterschied ($p > 0{,}05$).

"speech" (QLQ-H&N35) ranged from 1.33 to 3.66 (mean 2.4). The perceptive scales to evaluate hoarseness revealed 1 as minimal, 4 (aphonia) as maximal, and 2.7 as the mean value. The objective determination of voice quality, the GHD, revealed a mean of 7.6 (SD 0.7) for the "irregularity" and 2.7 (SD 0.57) for the "noise component". Details are shown in Figure 5.

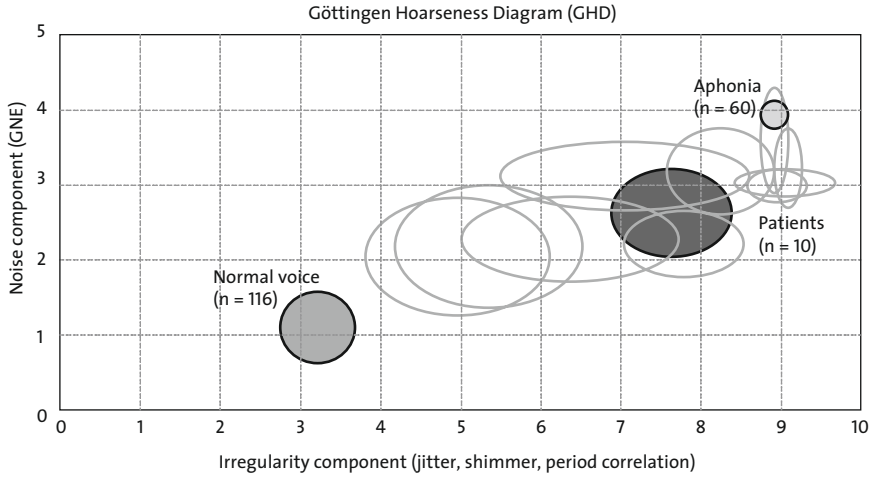

Figure 5. Göttingen Hoarseness Diagram. Ellipses reflect mean (center) and standard deviation (half axes) of individuals (gray lines) and particular groups (gray-scaled fill ins). GNE: glottal-to-noise excitation ratio.

Abbildung 5. Göttinger Heiserkeitsdiagramm. Die Ellipsen zeigen den Mittelwert (Zentrum) und die Standardabweichung (Halbachsen) der untersuchten Patienten (graue Linien) sowie der Referenzgruppen (grau hinterlegte Ellipsen). GNE: glottal-to-noise excitation ratio.

Comparing QLQ item scales with clinical measures and objective laryngeal functions, only the correlation between "swallowing" (EORTC QLQ-H&N35) and voice quality (GHD) was significant ($p < 0.05$; Table 2).

Discussion

The treatment results of the present study confirm our previous work [10, 30], in which we showed that the outcome after organ-preserving TLM and adjuvant radiotherapy for locally advanced HNSCC is comparable to the results of radical surgery with adjuvant radio(chemo)therapy [4–6, 8, 11, 12, 16, 28, 29, 31, 32, 37, 39], primary radio(chemo)therapy [1–3, 11, 13, 15, 21, 22, 31, 33, 37] or neoadjuvant treatment setting [14]. Only Forastiere et al. [15] reported similar data concerning organ preservation. However, different patient selection is crucial when compar-

ing the results of different studies. In our Department of Otorhinolaryngology, all patients with stage III/IV head-and-neck cancers are evaluated to determine whether a total tumor resection can be performed by TLM. If function-preserving TLM is not deemed feasible, either radical surgery or primary radiochemotherapy is carried out. Comparing our data with the study by Forastiere et al., one must consider as well that there was also a patient selection by Forastiere et al., because large-volume T4 disease was excluded [15]. In addition to oncologic safety, organ preservation first implies preserved vital "primary" functions of the larynx (opening and protection of the airway) and includes rehabilitation of the "secondary" phonatory function. Particularly in the treatment of advanced laryngeal tumors, however, functional deficits are not avoidable. None of the ten patients who underwent evaluation of organ function had a normal voice and one patient was aphonic. Three patients suffered from permanent aspirations (while preserved reflectory bolus ejection from the airway) compensated by supraglottic swallowing maneuvers. In two patients, RAW was twice as high as normal, which was clinically equivalent to an exertional dyspnea under physiological stress [26]. No patient required a tracheotomy. However, a correlating impact of functional disorders on QoL data was not evident. The significant correlation between "swallowing" (EORTC QLQ-H&N35) and voice quality (GHD) might indicate the degree of laryngeal incompetence. However, patients who showed aspirations in FEES denied dysphagia in the questionnaires. The evaluation of health-related QoL did not reflect the functional outcome, but showed the impact of functional deficits on health-related QoL. In a previous study, even verified functional restrictions after total laryngectomy (compared to organ preservation in locally advanced stages) revealed less impact on QoL data than presumed and the need for objective clinical evaluations of functional skills was emphasized [25].

Conclusion

In the current study, clinical evaluations were mandatory to detect and to grade disorders like dysphagia, dyspnea, or dysphonia. Objective measures were preferred to perceptive scales. In our study, no patient suffered from sequelae that speak against the organ-preserving treatment. In spite of post-treatment handicaps in laryngeal functions (deglutition, respiration, voice), patients rated their health-related QoL as being positive.

References

1. Adelstein DJ, Lavertu P, Saxton JP, et al. Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. Cancer 2000;88:876–83.
2. Adelstein DJ, Saxton JP, Lavertu P, et al. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. Head Neck 1997;19:567–75.
3. Ambrosch P. The role of laser microsurgery in the treatment of laryngeal cancer. Curr Opin Otolaryngol Head Neck Surg 2007;15:82–8.
4. Amdur RJ, Parsons JT, Mendenhall WM, et al. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:25–36.
5. Amdur RJ, Parsons JT, Mendenhall WM, et al. Split-course versus continuous-course irradiation in the postoperative setting for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1989;17: 279–85.
6. Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys 1996;36:999–1004.
7. Bernier J, Cooper JS. Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? Oncologist 2005;10: 215–24.
8. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.
9. Bray F, Sankila R, Ferlay J, et al. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002;38:99–166.
10. Christiansen H, Hermann RM, Martin A, et al. Long-term follow-up after transoral laser microsurgery and adjuvant radiotherapy for advanced recurrent squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2006;65:1067–74.
11. Christiansen H, Hess CF. Comment on Studer G, et al. Locoregional failure analysis in head-and-neck cancer patients treated with IMRT, in Strahlenther Onkol 2007;183:417–23. Strahlenther Onkol 2007;183:424–5.
12. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
13. Department of Veterans' Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans' Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685–90.
14. Eich HT, Löschcke M, Scheer M, et al. Neoadjuvant radiochemotherapy and radical resection for advanced squamous cell carcinoma of the oral cavity. Outcome of 134 patients. Strahlenther Onkol 2008;184:23–9.
15. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–8.
16. Fortin A, Allard J, Albert M, et al. Outcome of patients treated with cobalt and 6 MV in head and neck cancers. Head Neck 2001;23:181–8.
17. Fröhlich M, Michaelis D, Strube HW, et al. Acoustic voice analysis by means of the hoarseness diagram. J Speech Lang Hear Res 2000;43:706–20.
18. International Commission on Radiation Units and Measurements. ICRU report 50: prescribing, recording, and reporting photon beam therapy. Washington: International Commission on Radiation Units and Measurements; 1993.
19. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;58:457–81.
20. Kennedy JT, Paddle PM, Cook BJ, et al. Voice outcomes following transoral lasermicrosurgery for early glottic squamous cell carcinoma. J Laryngol Otol 2007;20:1–5.
21. Kessler P, Grabenbauer G, Leher A, et al. Five year survival of patients with primary oral squamous cell carcinoma. Comparison of two treatment protocols in a prospective study. Strahlenther Onkol 2007;183:184–9.
22. Lefebvre JL, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–9.
23. Nawka T, Wiesmann U, Gonnermann U. Validation of the German version of the Voice Handicap Index. HNO 2003;51:921–30.
24. Olthoff A, Mrugalla S, Laskawi R, et al. Assessment of irregular voices after total and laser surgical laryngectomy. Arch Otolaryngol Head Neck Surg 2003;129:994–9.
25. Olthoff A, Steuer-Vogt MK, Licht K, et al. Quality of life after treatment for laryngeal carcinomas. ORL J Otorhinolaryngol Relat Spec 2006;68:253–8.
26. Olthoff A, Zeiss D, Laskawi R, et al. Laser microsurgical bilateral posterior cordectomy for the treatment of bilateral vocal fold paralysis. Ann Otol Rhinol Laryngol 2005;114:599–604.

27. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
28. Parsons JT, Mendenhall WM, Stringer SP, et al. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997;39:137–48.
29. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys 1993;26:3–11.
30. Pradier O, Christiansen H, Schmidberger H, et al. Adjuvant radiotherapy after transoral microlasersurgery for advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2005;63:1368–77.
31. Rades D, Stoehr M, Meyners T, et al. Evaluation of prognostic factors and two radiation techniques in patients treated with surgery followed by radio(chemo)therapy or definitive radio(chemo)therapy for locally advanced head-and-neck cancer. Strahlenther Onkol 2008;184:198–205.
32. Regine WF, Valentino J, Sloan DA, et al. Postoperative radiation therapy for primary vs. recurrent squamous cell carcinoma of the head and neck: results of a comparative analysis. Head Neck 1999;21:554–9.
33. Richard JM, Sancho-Garnier H, Pessey JJ, et al. Randomized trial of induction chemotherapy in larynx carcinoma. Oral Oncol 1998;34:224–8.
34. Schröter-Morasch H. Klinische Untersuchung des Oropharynx und videoendoskopische Untersuchung der Schluckfunktion. In: Bartolome G., Schröter-Morasch H., Hrsg. Schluckstörungen, Diagnostik und Rehabilitation, 2 Aufl. München–Jena: Urban & Fischer, 1999:132.
35. Sobin LH, Wittekind C. TNM classification of malignant tumours. New York Toronto: Wiley-Liss, 6th edition 2002.
36. Steiner W, Ambrosch P. Endoscopic laser surgery of the upper aerodigestive tract. With special emphasis on cancer surgery. Stuttgart–New York: Thieme, 2000.
37. Studer G, Luetolf UM, Glanzmann C. Locoregional failure analysis in head-and-neck cancer patients treated with IMRT. Strahlenther Onkol 2007;183:417–23, discussion 424–5.
38. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.
39. Tupchong L, Scott CB, Blitzer PH, et al. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. Int J Radiat Oncol Biol Phys 1991;20:21–8.

Address for Correspondence
PD Dr. Hans Christiansen
Klinik und Poliklinik
für Strahlentherapie und Radioonkologie
Universitätsmedizin Göttingen
Robert-Koch-Straße 40
37075 Göttingen
Germany
Phone (+49/551) 39-8866, Fax -6192
e-mail: hchrist@gwdg.de