IMRT in Hypopharyngeal Tumors

Gabriela Studer, Urs Martin Lütolf, Jacques Bernard Davis, Christoph Glanzmann[1]

Background and Purpose: Intensity-modulated radiation therapy (IMRT) data on hypopharyngeal cancer (HC) are scant. In this study, the authors report on early results in an own HC patient cohort treated with IMRT. A more favorable outcome as compared to historical data on conventional radiation techniques was expected.
Patients and Methods: 29 consecutive HC patients were treated with simultaneous integrated boost (SIB) IMRT between 01/2002 and 07/2005 (mean follow-up 16 months, range 4–44 months). Doses of 60–71 Gy with 2.0–2.2 Gy/fraction were applied. 26/29 patients were definitively irradiated, 86% received simultaneous cisplatin-based chemotherapy. 60% presented with locally advanced disease (T3/4 Nx, Tx N2c/3). Mean primary tumor volume measured 36.2 cm^3 (4–170 cm^3), mean nodal volume 16.6 cm^3 (0–97 cm^3).
Results: 2-year actuarial local, nodal, distant control, and overall disease-free survival were 90%, 93%, 93%, and 90%, respectively. In 2/4 patients with persistent disease (nodal in one, primary in three), salvage surgery was performed. The mean dose to the spinal cord (extension of > 5–15 mm) was 26 Gy (12–38 Gy); the mean maximum (point) dose was 44.4 Gy (26–58.9 Gy).
One grade (G) 3 dysphagia and two G4 reactions (laryngeal fibrosis, dysphagia), both following the schedule with 2.2 Gy per fraction, have been observed so far. Larynx preservation was achieved in 25/26 of the definitively irradiated patients (one underwent a salvage laryngectomy); 23 had no or minimal dysphagia (G0–1).
Conclusion: Excellent early disease control and high patient satisfaction with swallowing function in HC following SIB IMRT were observed; these results need to be confirmed based on a longer follow-up period. In order to avoid G4 reactions, SIB doses of < 2.2 Gy/fraction are recommended for large tumors involving laryngeal structures.

Key Words: Hypopharyngeal cancer · IMRT · SIB · Radiation-related dysphagia

Strahlenther Onkol 2006;182:331–5
DOI 10.1007/s00066-006-1556-2

IMRT bei Hypopharynxkarzinomen

Hintergrund und Ziel: Daten zur Behandlung des Hypopharynxkarzinoms (HC) mittels intensitätsmodulierter Radiotherapie (IMRT) sind rar. Die Autoren berichten hier über erste eigene Ergebnisse ihres IMRT-Kollektivs konsekutiv behandelter HC-Patienten. Erwartet wurden eine bessere Tumorkontrolle und verbesserte Therapietoleranz bei HC-Patienten nach IMRT gegenüber historischen Kollektiven nach konventioneller Radiotherapietechnik.
Patienten und Methodik: 29 konsekutive HC-Patienten wurden zwischen 01/2002 und 07/2005 mit IMRT mit simultan integriertem Boost (SIB) behandelt. Die mittlere Verlaufsbeobachtung betrug 16 Monate (4–44 Monate). Es wurden Herddosen von 60–71 Gy mit 2,0–2,2 Gy/Sitzung verabreicht. 26/29 Patienten wurden primär definitiv bestrahlt, 86% erhielten eine simultane Cisplatin-basierte Chemotherapie. In gut 60% bestand ein lokal fortgeschrittenes Leiden (T3/4 Nx, Tx N2c/3, Tabelle 1). Das mittlere Tumorvolumen betrug 36,2 cm^3 (4–170 cm^3), das mittlere Lymphknotenvolumen 16,6 cm^3 (0–97 cm^3).
Ergebnisse: Die aktuarischen 2-Jahres-Überlebensraten für die Primärtumor-, Lymphknoten- und Fernkontrolle lagen bei 90%, 93% und 93% (Abbildungen 1a bis 1c); das krankheitsfreie Gesamtüberleben betrug 90%. Vier Patienten zeigten eine Tumorpersistenz; in zwei dieser Fälle konnte eine Salvage-Operation durchgeführt werden. Die mittlere Dosis auf das expandierte Myelon (Sicherheitssaum > 5–15 mm) betrug 26 Gy (12–38 Gy), die durchschnittliche maximale Punktdosis 44,4 Gy (26–58,9 Gy).
Bislang entwickelte ein Patient eine Grad(G)-3-Dysphagie und zwei Patienten G4-Reaktionen (Dysphagie, Larynxfibrose); beide G4-Ereignisse traten nach 2,2 Gy/Fraktion auf. Bei 25/26 primär bestrahlten Patienten konnte eine Organerhaltung erreicht werden; 23 Patienten sind betreffend Dysphagie beschwerdefrei oder minimal symptomatisch (G0–1).
Schlussfolgerung: Sehr gute frühe Ergebnisse hinsichtlich der Krankheitskontrolle und eine hohe Patientenzufriedenheit in Bezug auf die Schluckfunktion wurden beobachtet; diese Resultate müssen mit einer längeren Verlaufsbeobachtung bestätigt werden. Einzeldosen $\geq$ 2,2 Gy werden im Hinblick auf die beobachteten G4-Reaktionen bei ausgedehnten Tumoren mit Befall laryngealer Strukturen empfohlen.

Schlüsselwörter: Hypopharynxkarzinom · IMRT · SIB · Strahlentherapie-induzierte Dysphagie

[1] Department of Radiation Oncology, University Hospital, Zurich, Switzerland.

Received: December 13, 2005; accepted: March 17, 2006

Introduction

Locoregional disease control rates of approximately 40–70% [2, 3, 6, 11, 15, 17, 18, 20, 21, 24, 26, 27, 30] or even less [4, 9, 13] are reported for hypopharyngeal cancer (HC) patients receiving three-dimensional conventional radiation therapy (3DCRT) ± chemotherapy, while late-term dysphagia rates range between 40% and 75% in the majority of published articles [1, 6, 19, 20, 28]. The main challenge in conventional irradiation of HC is an appropriate dose coverage mainly to the dorsal aspect of the tumor and the boost planning target volume (PTV1), respectively, which is often close to or overlaps the spinal cord in the lateral-beam projection used for 3DCRT. Dorsal volume compromises in favor of the spinal cord as the organ at highest risk are a frequent consequence of this fact.

For HC patients the feasibility of "horse shoe"-like dose distribution is an advantage that was expected to translate into improved clinical outcome due to uncompromising target volume coverage.

Clinical outcome in HC following intensity-modulated radiation therapy (IMRT) was prospectively assessed.

Patients and Methods

Patients

29 consecutive HC patients received IMRT between January 2002 and July 2005. Mean follow-up time was 16 months (range 4–44 months). Patients' mean age was 60.8 years (34–87 years); the gender ratio was 1 : 5 in favor of men. TN stages are shown in Table 1.

86% of the patients (n = 25) were irradiated definitively, and four postoperatively. 86% (n = 25) received simultaneous cisplatin-based chemotherapy with 40 mg/m^2/week. 21/25 patients (83%) tolerated four to six cisplatin cycles.

Mean primary tumor volume measured 36.2 cm^3 (4–170 cm^3), mean lymph node volume (N+ only) 24.8 cm^3 (1–97 cm^3). Mean total gross tumor volume (GTV) was 52 cm^3 (5–173 cm^3).

Methods

IMRT Schedules

Simultaneous integrated boost (SIB) doses between 60 and 71 Gy (five fractions/week) with 2.0 (n = 8), 2.11 (n = 17), and 2.2 Gy (n = 4)/fraction to the boost volume (planning target volume, PTV1) were applied. Doses to the elective neck areas (PTV2) ranged between 54 and 56 Gy with doses of 1.64–1.8 Gy/session.

Mean total treatment time was 45.4 days (32–58 days).

Table 1. TN stage distribution in 29 hypopharyngeal cancer patients.

Tabelle 1. TN-Stadien-Verteilung im untersuchten Kollektiv von 29 Patienten mit Hypopharynxkarzinom.

	N0	N1	N2a	N2b	N2c	N3	Total
T1	0	0	1	0	0	1	2
T2	3	0	1	8	2	0	14
T3	1	1	1	2	1	0	6
T4	1	2	0	2	2	0	7
Total	5	3	3	12	5	1	29

Planning Computed Tomography (Planning CT)

Planning CT data (Somatom Plus 4, Siemens, Erlangen, Germany) were acquired with a slice thickness of 2–3 mm and no interslice gap throughout the whole sequentially acquired region of interest. Patients were immobilized in a commercially available thermoplastic mask.

In patients with postoperative irradiation, GTVs were drawn slice by slice in the planning CT, based on diagnostic preoperative magnetic resonance images (MRIs) and positron emission tomography (PET) CTs, which were available for all patients [10]. In the majority of the definitively irradiated patients, fused "PET-planning CTs" (Siemens AG, Erlangen, Germany, and Discovery LS, GE Medical Systems, Waukesha, WI, USA) were performed.

Treatment-Planning Systems

Contouring and plan optimization were performed on a Varian treatment-planning system (Eclipse®, Version 7.3.10, Varian Medical Systems, Hansen Way, Palo Alto CA, USA).

Delineation of Planning Target Volumes (PTVs)

Definitions: GTV with a margin of 10–15 mm was included in the SIB volume (PTV1, 60–71 Gy).

Elective lymph node regions (PTV2, 50–57 Gy) level 2–5 were included bilaterally.

Dose constraints for normal tissues/organs at risk outside PTVs:

- Spinal cord: maximum dose (D_{max}) < 45 Gy, mean dose (D_{mean}) < 35 Gy (cord outlined with a margin > 5–10 mm, with > 10 mm at the ventral aspect).
- Parotid glands were spared to the degree possible without compromising target volume coverage: D_{mean} < 26 Gy (partial volume to be spared was outlined).
- Oral cavity outside the PTV (contouring included the mandible, maxillary bone, and oral vestibulum): D_{mean} < 35 Gy.
- Nuchal tissue: D_{mean} < 45 Gy.

Radiation

Irradiation was done by 6-MV photon beams on a Varian linear accelerator using the sliding-window technique. The technical solution of choice was a five-field equiangular arrangement ("class solution").

Patient alignment was checked by portal imaging; deviations of > 3 mm were corrected before treatment.

The dose homogeneity within the PTV1 was aimed to be in close accordance with the RTOG guidelines:

- The dose was normalized to the mean dose in PTV1 which corresponded, in the majority of cases, approximately to the 95% dose level in that volume.

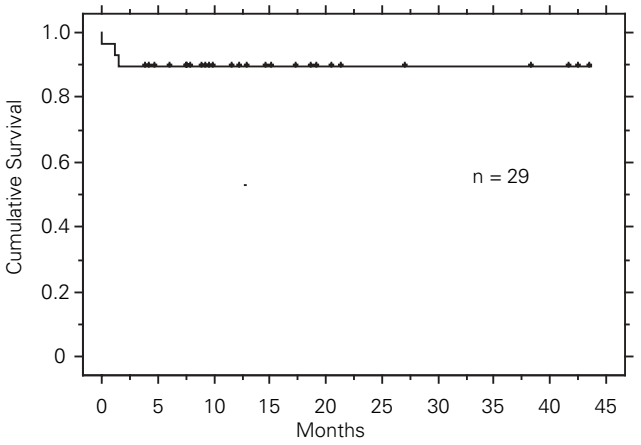

Figure 1a – Abbildung 1a

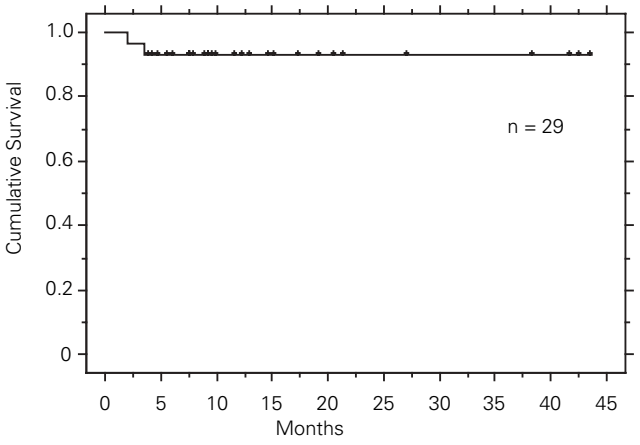

Figure 1b – Abbildung 1b

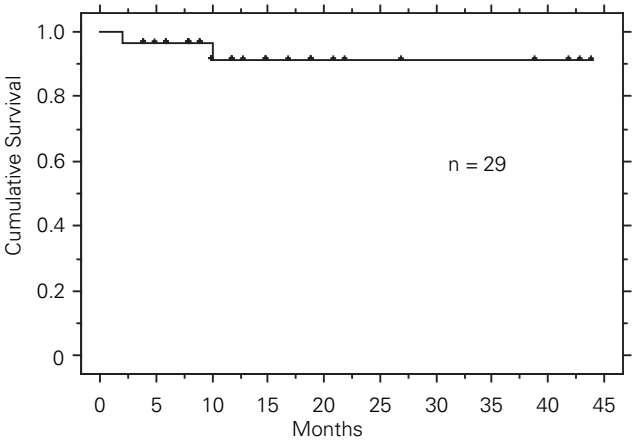

Figure 1c – Abbildung 1c

Figures 1a to 1c. a) Actuarial 2-year local disease-free survival: 90%. b) Actuarial 2-year regional disease-free survival: 93%. c) Actuarial 2-year distant disease-free survival: 93%.

Abbildungen 1a bis 1c. a) Lokale Tumorkontrolle: 90% aktuarisches 2-Jahres-Überleben. b) Nodale Kontrolle: 93% aktuarisches 2-Jahres-Überleben. c) Fernmetastasenkontrolle: 93% aktuarisches 2-Jahres-Überleben.

- The prescription dose was based on the isodose which encompasses at least 95% of the PTV.
- No more than
  - 20% of any PTV received > 110% of its prescribed dose,
  - 1% of the PTV1 received < 93% of its prescribed dose,
  - 1% or 1 cm^3 of the tissue outside the PTV received > 110% of the PTV1 dose.

Clinical Quality Assurance (QA)

Follow-up. Patients under treatment were clinically assessed at weekly intervals, and at 2 weeks and 2 months after completion of treatment.

6 weeks after completion, patients were also seen in the joint clinics of the Department of Head & Neck Surgery, then every 2–3 months in the first 2 years, 3- to 6-monthly in the 3rd year. Suspect findings were substantiated with CT-PET, suspect lymph nodes by needle aspiration and/or biopsy, respectively.

The swallowing function was assessed by semistructured interviews (ability to swallow liquid, soft and solid food, personal comfort [when eating out and whether patients enjoy their food]).

QA with respect to posttreatment events. Isodose plans of patients who experienced grade (G) 3/4 late-term effects were reviewed at the radiation-planning work station, in order to check local dose distributions.

QA with respect to quality of life (QoL). Toxicity was assessed based on SOMA-LENT and RTOG/EORTC Radiation Morbidity Score. For simplification, G3 or 4 late reactions were termed "G3/4" reactions.

Statistics

The StatView® program Version 4.5 was used for calculation of Kaplan-Meier survival curves.

Results

Tumor Response and Survival (Figures 1a to 1c)

After a mean follow-up of 16 months (4–44 months), the actuarial local (LC), nodal (NC), distant control (DC), and overall disease-free survival at 2 years were 90%, 93%, and 93%, respectively. 90% of the patients were alive with no evidence of

disease (ANED) at the time point of data analysis (November 2005). In three patients with definitive IMRT, tumor persistence was observed. In one of these three patients with a large persistent tumor of 115 cm^3, simultaneous metastases occurred a few weeks after treatment completion. The second patient who developed distant disease remained locoregionally controlled. Successful salvage surgery of the primary was feasible in one of these three patients.

In one patient with nodal persistence, salvage surgery was successfully performed 1 year earlier.

No locoregional tumor recurrences were observed up to now.

Toxicity

Acute Reactions

No G4 acute toxicity occurred, and no interruptions of radiotherapy were required due to radiation-related side effects (elongated total treatment time due to radiotherapy-independent intercurrent events in two patients). Skin and mucosal acute reactions were mild to moderate and limited to the high-dose area (six G3, 13 G2 mucositis).

A feeding tube was inserted in nine patients (30%). The average body weight loss from initial pretreatment value to the end of irradiation was 7% (19% loss up to 11% gain); mean loss was 3% in patients with a feeding tube and 9% in the subgroup without tube, respectively.

Late Reactions

In three patients G3/4 late-term effects were observed: one laryngeal fibrosis G4 (no increased dose was delivered to the laryngeal region), one G4 dysphagia (good voice, but unable to swallow liquids). In both cases laryngeal and infralaryngeal structures were infiltrated by the tumor. One patient developed dysphagia G3 following $SIB^{2.11}$ to 69.6 Gy.

Laryngeal preservation was maintained in all 23 locally controlled patients who underwent definitive IMRT, an ultimate organ preservation in 96% (26/27). 24/27 controlled patients had no or minimal dysphagia (G0–1) at the time of last visit, two had a persisting G3 and G4 dysphagia, respectively.

The mean body weight loss 1 year after treatment completion was 3.3% (+11% to –11%).

The mean dose to the (expanded) spinal cord was 26.4 Gy (12–38 Gy); mean maximum (point) dose was 44.4 Gy (26–57 Gy). No spinal cord toxicity is expected.

Dose-Volume Coverage

Doses of > 110% of prescribed total dose were delivered to a mean of 0.3% (0–2%) of PTV1. A mean of 8.2% (0–13%) of PTV1 received < 95% of the prescribed dose.

All treatment plans were analyzed with respect to the dose-volume compromises which would have been made, if 3DCRT techniques had been performed. In this technique, a "compromise" was made, if the photon-electron field matching line across primary or nodal GTV in order to spare the spinal cord, or if the GTV/PTV1 was not adequately covered, or if the deep aspect of large nodal disease was insufficiently covered by electrons. In 9/29 cases such a "compromise" could be avoided with IMRT [16, 25].

Discussion

To our knowledge this is the first analysis of a single-institution HC series irradiated with IMRT.

Improved early outcome in HC following IMRT compared to 3DCRT, with high locoregional control and disease-free survival rates of 90% each, was found in a cohort with definitive IMRT in the majority of cases. All four locoregional failures presented as tumor persistence inside the high-dose PTV1. However, the follow-up is still too short to draw final conclusions from presented disease outcome.

There is a single report on outcome in HC after IMRT by Eisbruch et al., who described a 3-year locoregional control rate of ~ 77% in twelve HC patients [5].

In historical HC series, the 3- to 5-year disease-specific survival rates range from ~ 40 up to 70% [2, 3, 6, 11, 15, 17, 18, 20, 21, 24, 26, 27, 30]; Garden et al. [8] found a 2-year LC of 89% and 77% for HC stage T1 and T2, respectively, in 82 HC patients; Nakamura et al. [23] reported a 5-year disease-specific survival of 90% in 43 stage I/II HC patients.

Our early results confirm earlier data on 3DCRT of pharyngeal wall tumors published by Fein et al. back in 1993 [7]. These authors found an improved outcome in 49 patients in whom the dorsal field border of the boost fields was placed at the anterior aspect of the spinal cord, versus 50 patients in whom the dorsal boost field border was halfway across the vertebral bodies (equal 2-year LC of 100% in T1 stages, statistically significant difference in T2 stages with 100% vs. 57%, 73% vs. 46% in T3, and 75% vs. 29% in T4, respectively).

With average doses to the expanded spinal cord of mean/maximum 26/44 Gy in our cohort, no increased cord risk was taken.

Johansson et al. [14] performed plan comparisons for protons, IMRT, and 3DCRT in five HC patients. They reported that 3.6%, 10.9%, and 70.3% of the spinal cord volume received > 50% of prescribed doses, and cord maximum doses of approximately 43, 46, and 44 Gy, respectively. In addition to the absolute mean dose reduction with IMRT technique, spinal cord exposure (as most organs [20, 22, 29]) in IMRT is also reduced from a radiobiological point of view, as the dose/fraction is about one quarter to one third of the prescribed dose.

Laryngopharyngeal organ preservation and organ function in our cohort were excellent with > 90%.

Organ preservation following definitive conventional radiochemotherapy has been reported by several groups and ranges between about 40% and up to 75% [1, 6, 12, 19, 20, 28, 30]. Huguenin et al. reported dysphagia and laryngitis G3/4 late reaction rates of ~ 22% and 3%, respectively, in a pro-

spective study of 224 patients with 25% hypopharyngeal and ~ 16% laryngeal tumors [12].

Samant et al. [26] evaluated 25 patients following radiochemotherapy for advanced pyriform sinus carcinoma and found an organ preservation rate of 88%, with 90% of patients having a satisfactory voice and 70% being able to swallow 1 year after treatment.

The two relevant late-term effects observed in our series developed after an exposure of 66–68 Gy with 2.2 Gy per session ($SIB^{2.2}$) to a large GTV involving the larynx and cranial esophagus.

Conclusion

Improved early locoregional outcome with excellent preservation of swallowing function was found in HC patients treated with IMRT compared to historical reports; these results need to be confirmed based on a longer observation time.

SIB using 2.2 Gy per fraction is not recommended for HC involving laryngoesophageal structures.

Acknowledgment

This work is in part sponsored by a credit of the "Zürcher Krebsliga".

References

1. Altundag O, Gullu I, Altundag K, et al. Induction chemotherapy with cisplatin and 5-fluorouracil followed by chemoradiotherapy or radiotherapy alone in the treatment of locoregionally advanced resectable cancers of the larynx and hypopharynx: results of single-center study of 45 patients. Head Neck 2005;27:15–21.
2. Bahadur S, Thakar A, Mohanti BK, et al. Results of radiotherapy with, or without, salvage surgery versus combined surgery and radiotherapy in advanced carcinoma of the hypopharynx. J Laryngol Otol 2002;116:29–32.
3. Chu PY, Wang LW, Chang SY. Surgical treatment of squamous cell carcinoma of the hypopharynx: analysis of treatment results, failure patterns, and prognostic factors. J Laryngol Otol 2004;118:443–9.
4. During A, Sauer R, Steiner W, et al. [Combined treatment of hypopharyngeal carcinoma.] Strahlenther Onkol 1987;163:764–73.
5. Eisbruch A, Marsh LH, Dawson LA, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys 2004;59: 28–42.
6. Featherstone CJ, Clarke S, Jackson MA, et al. Treatment of advanced cancer of the larynx and hypopharynx with chemoradiation. Aust N Z J Surg 2004; 74:554–8.
7. Fein DA, Mendenhall WM, Parsons JT, et al. Pharyngeal wall carcinoma treated with radiotherapy: impact of treatment technique and fractionation. Int J Radiat Oncol Biol Phys 1993;26:751–7.
8. Garden AS, Morrison WH, Clayman GL, et al. Early squamous cell carcinoma of the hypopharynx: outcomes of treatment with radiation alone to the primary disease. Head Neck 1996;18:317–22.
9. Godballe C, Jorgensen K, Hansen O, et al. Hypopharyngeal cancer: results of treatment based on radiation therapy and salvage surgery. Laryngoscope 2002;112:834–8.
10. Grosu AL, Piert M, Weber WA, et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181:483–99.
11. Hamoir M, Ledeghen S, Rombaux P, et al. Conservation surgery for laryngeal and hypopharyngeal cancer. Acta Otorhinolaryngol Belg 1999;53:207–13.
12. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 2004;22:4665–73.
13. Johansen LV, Grau C, Overgaard J. Hypopharyngeal squamous cell carcinoma – treatment results in 138 consecutively admitted patients. Acta Oncol 2000;39:529–36.
14. Johansson J, Blomquist E, Montelius A, et al. Potential outcomes of modalities and techniques in radiotherapy for patients with hypopharyngeal carcinoma. Radiother Oncol 2004;72:129–38.
15. Kim S, Wu HG, Heo DS, et al. Advanced hypopharyngeal carcinoma treatment results according to treatment modalities. Head Neck 2001;23:713–7.
16. Kuhnt T, Jirsak N, Muller AC, et al. [Quantitative and qualitative investigations of salivary gland function in dependence on irradiation dose and volume for reduction of xerostomia in patients with head-and-neck cancer.] Strahlenther Onkol 2005;181:520–8.
17. Kurek R, Kalogera-Fountzila A, Muskalla K, et al. Usefulness of tumor volumetry as a prognostic factor of survival in head and neck cancer. Strahlenther Onkol 2003;179:292–7.
18. Layland MK, Sessions DG, Lenox J. The influence of lymph node metastasis in the treatment of squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx: N0 versus N+. Laryngoscope 2005;115:629–39.
19. Lefebvre JL. Larynx preservation: the discussion is not closed. Otolaryngol Head Neck Surg 1998;118:389–93.
20. 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.
21. Luukkaa M, Minn H, Aitasalo K, et al. Treatment of squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx – an analysis of 174 patients in south western Finland. Acta Oncol 2003;42:756–62.
22. Momm F, Volegova-Neher NJ, Schulte-Monting J, et al. Different saliva substitutes for treatment of xerostomia following radiotherapy. A prospective crossover study. Strahlenther Onkol 2005;181:231–6.
23. Nakamura K, Shioyama Y, Sasaki T, et al. Chemoradiation therapy with or without salvage surgery for early squamous cell carcinoma of the hypopharynx. Int J Radiat Oncol Biol Phys 2005;62:680–3.
24. Rudert HH, Hoft S. Transoral carbon-dioxide laser resection of hypopharyngeal carcinoma. Eur Arch Otorhinolaryngol 2003;260:198–206.
25. Salz H, Wiezorek T, Scheithauer M, et al. IMRT with compensators for head-and-neck cancers. Treatment technique, dosimetric accuracy, and practical experiences. Strahlenther Onkol 2005;181:665–72.
26. Samant S, Kumar P, Wan J, et al. Concomitant radiation therapy and targeted cisplatin chemotherapy for the treatment of advanced pyriform sinus carcinoma: disease control and preservation of organ function. Head Neck 1999;21:595–601.
27. Stuschke M, Budach V, Dinges S, et al. [Accelerated hyperfractionated radiotherapy combined with simultaneous chemotherapy in locally advanced pharyngeal and oral carcinomas.] Strahlenther Onkol 1994;170:689–99.
28. Urba SG, Wolf GT, Bradford CR, et al. Neoadjuvant therapy for organ preservation in head and neck cancer. Laryngoscope 2000;110:2074–80.
29. Wiggenraad R, Mast M, van Santvoort J, et al. ConPas: a 3-D conformal parotid gland-sparing irradiation technique for bilateral neck treatment as an alternative to IMRT. Strahlenther Onkol 2005;181:673–82.
30. Zelefsky MJ, Kraus DH, Pfister DG, et al. Combined chemotherapy and radiotherapy versus surgery and postoperative radiotherapy for advanced hypopharyngeal cancer. Head Neck 1996;18:405–11.

Address for Correspondence
Dr. Gabriela Studer
Radiotherapie, USZ
Universitätsspital Zürich
Rämistraße 100
8091 Zürich
Switzerland
Phone (+41/44) 255-2931, Fax -4547
e-mail: gabriela.studer@usz.ch