Locoregional Failure Analysis in Head-and-Neck Cancer Patients Treated with IMRT

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Purpose: Analysis of locoregional failure in head-and-neck cancer (HNC) following intensity-modulated radiation therapy (IMRT), with focus on the location of locoregional failures in relation to the chosen planning target volumes (PTVs) and dose distributions.
Patients and Methods: Between January 2002 and May 2006, 280 HNC patients were subjected to IMRT at the authors' institution. Mean follow-up was 23.2 months (3–59.3 months). Definitive IMRT was performed in 75% of all patients. In 71%, simultaneous cisplatin-based chemotherapy was given. 70% of patients presented with T3/4, T1–2 N2c/3 or recurred disease. Locoregional failure patterns were analyzed.
Results: 2-year local, nodal, distant, disease-free, and overall survival rates were 80%, 87%, 87%, 73%, and 82%, respectively. 46 local (16%) and 31 nodal (11%) failures have been observed so far. Local tumor persistence was seen in 23/46 cases (50%), and nodal persistence in 12/31 (39%), respectively. One marginal local failure developed in a patient referred for a recurred oral cavity tumor. Three nodal failures developed outside the PTVs at unexpected locations. All other failures have been confirmed "in field". No failure occurred in level Ib or upper level II. Local failure occurred mainly following definitive IMRT for large tumors, nodal failure only in nodally positive patients with nodal high-risk features.
Conclusion: The dose-volume concept as used here has shown to be adequate, with disease failure developing at the site of the initial gross tumor manifestation inside the boost volume.

Key Words: Locoregional disease control · Outcome in head-and-neck IMRT · Marginal failure in IMRT

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Analyse des lokoregionalen Tumorversagens nach IMRT bei Patienten mit Kopf-Hals-Tumoren

Ziel: Analyse des lokoregionalen Tumorversagens nach intensitätsmodulierter Radiotherapie (IMRT), mit Fokus auf den Ort des Versagens in Bezug auf die konturierten Volumina bzw. die Dosisverteilung.
Patienten und Methodik: Zwischen Januar 2002 und Mai 2006 wurden an der eigenen radioonkologischen Klinik 280 Patienten mit Kopf-Hals-Tumoren einer IMRT unterzogen. Die mittlere Beobachtungszeit beläuft sich auf 23,2 Monate (3–59,3 Monate). Bei 75% der Patienten wurde eine definitive IMRT durchgeführt. 71% der Patienten erhielten eine simultane Chemotherapie mit Cisplatin. 70% wurden mit fortgeschrittenen Stadien T3/4, T1–2 N2c/3 oder einem Rezidiv zugewiesen (Tabelle 2). Das lokoregionale Ereignismuster wurde analysiert.
Ergebnisse: Die Lokal-, Nodal- und Fernkontrollraten nach 2 Jahren beliefen sich auf 80%, 87% und 87%, die krankheitsfreie bzw. Gesamtüberlebensrate betrug 73% und 82% (Tabelle 4). 46 Fälle (16%) lokalen und 31 (11%) nodalen Versagens wurden bislang festgestellt, die in 23/46 Fällen (50%) einer lokalen und in 12/31 Fällen (39%) einer nodalen Tumorpersistenz entsprachen. Nur ein Patient mit einem bereits rezidivierten Mundhöhlentumor entwickelte ein Feldrandrezidiv (Tabelle 1). Dreimal fand sich ein nodales Versagen außerhalb der Planungszielvolumina an unerwarteten Lokalisationen. Alle anderen Fälle von Versagen konnten als „im Feld" befindlich bestätigt werden. Kein Versagen wurde im Lymphknotenlevel I oder kranial im Level II gefunden (Tabellen 5 und 6). Lokales Versagen erfolgte hauptsächlich bei primär bestrahlten Patienten mit großem Tumorvolumen (Abbildungen 1 und 2a); nodales Versagen fand sich ausschließlich bei initial nodal positiven Patienten mit nodalen Risikofaktoren (Tabelle 3, Abbildung 2b).
Schlussfolgerung: Das hier verwendete Dosis-Volumen-Konzept erwies sich als adäquat, da der Großteil der Rückfälle am Ort der initialen Tumormanifestation, innerhalb des Boostvolumens, auftrat.

Schlüsselwörter: Lokoregionale Tumorkontrolle · Outcome bei Kopf-Hals-Tumoren · Feldrandversagen bei IMRT

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Introduction

Increasing numbers of reports on intensity-modulated radiation therapy (IMRT) in head-and-neck cancer (HNC) are available, most of them on oropharyngeal [4, 7, 8, 21, 29] and nasopharyngeal tumors [13, 16, 17, 28]. To date, there is no generally accepted standard fractionation or technique, and for several HNC subsites like hypopharynx, larynx, or oral cavity, IMRT reports are still scant [25] or missing. Encouraging results have been reached at several IMRT centers, by/despite using different IMRT fractionation schedules and technical solutions like dose painting, serial dose application, pure IMRT, or IMRT combined with conventional three-dimensional conformal radiation therapy (3D-CRT). Published data are concordant with regard to a tendency toward improved locoregional disease control, and confirm a better normal-tissue tolerance compared to 3D-CRT. However, results from prospective randomized multicenter phase III trials are not yet available, outcome data of concurrent chemotherapy and IMRT have been published for only limited numbers of patients (mostly those with nasopharyngeal cancer), and the characteristic advantage of IMRT, a more conformal dose distribution, bares an increased risk of marginal miss [19]. Meanwhile, several anatomic atlases and guidelines are available, providing support in outlining lymphatic pathways in an appropriate, risk-adjusted, standardized way (RTOG website, *www.rtog.org*) [10, 18, 20].

Despite a wide variability of IMRT schedules and planning target volume (PTV) definitions, the majority of locoregional failures – as far as published – are reported to occur at the site of former gross tumor volume (GTV), inside the contour defining the high-dose planning target volume (PTV1), respectively (Table 1, [3, 5, 6, 8, 17, 29]). Consequent follow-up of treated patients and analysis of observed failure patterns are of high importance for every center performing IMRT, in order to realize institutional clinical quality assurance and further progress in IMRT.

This study aimed to evaluate the locoregional failure profile of our single-institution HNC IMRT cohort.

Patients and Methods

Patients

Demographic and tumor characteristics of 280 patients treated between January 2002 and May 2006 are listed in Table 2. The histopathologic diagnoses included 246 squamous cell carcinomas, ten adenocarcinomas, 13 lymphoepithelioid tumors (nasopharyngeal, Schmincke type), three sarcomas, two melanomas, two neuroendocrine tumors, two undifferentiated spindle cell tumors, and two undifferentiated carcinomas (NOS).

Cisplatin-based chemotherapy was given to 229 patients (40 mg cisplatin/m^2/IMRT week); 51 patients did not undergo chemotherapy for several reasons: age > 76 years and/or comorbidity (n = 25), parotid tumors (n = 4), patient's preference (n = 5); also included into this subgroup were 17 patients who tolerated only one to two cisplatin cycles (subjective, or rarely medical reasons).

Methods

Locoregional failures were analyzed with focus on their location in relation to the contoured volumes and the dose distribution of treatment plans, respectively (by two different investigators [G.S., C.G.]). Failures were defined as follows:

- "in-field failure": ≥ 95% of the recurred tumor volume inside the PTV1 (high-dose PTV),
- "marginal failure": 20% to < 95% of the recurred tumor inside the PTV1,
- "outside": < 20% of the recurred tumor volume within the 95% isodose of the PTV1.

In addition, the impact of diagnosis (subsites, Table 4), treatment sequence, UICC TN staging (Figure 1), GTVs (Figures 2a and 2b), and nodal risk factors has been assessed.

For nodal risk feature assessment, we used the same histopathologic risk features as defined by Ang et al. [2] for dissected nodes. This classification has been adjusted for the nonoperated subgroup. The risk factors "extracapsular extension", "resection status" (R0–2), and "perineural invasion" cannot be used in nonoperated individuals, and have been replaced by two additional adverse factors, "central node necrosis", and "recurrence". Risk levels have been defined as follows, based on the risk factors listed in Table 3:

- "low risk": no adverse factor,
- "intermediate risk": only one adverse factor,
- "high risk": two or more adverse factors.

Table 1. Selected publications on locoregional failure analysis in intensity-modulated radiation therapy. PTV1: high-dose planning target volume.

Tabelle 1. Ausgewählte Publikationen zur lokoregionalen Versagensanalyse nach intensitätsmodulierter Radiotherapy. PTV1: Hochdosis-Planungszielvolumen.

Authors [reference]	Year	Patients (n)	Failures[a] (n)	Site of locoregional failure		
				Inside PTV1 (n)	Marginal (n)	Out of field (n)
Dawson et al. [6]	2000	58	16	10	2	4
Lee et al. [17]	2003	150	10	10	0	0
Chao et al. [5]	2003	165	17	9	3[b]	5
Eisbruch et al. [8]	2004	133	21	17	4	0
Bussels et al. [3]	2004	72	20	15	5[c]	0
Yao et al. [29]	2005	151	11	10	1	0
Own series	2006	280	77	73	1	3
Patients [n (%)]		1,009	172	144 (84)	16 (9)	12 (7)

[a] local and/or nodal events; [b] marginal to clinical target volume CTV1 or CTV2; [c] the bulky mass inside the PTV1, but extending outside

Table 2. Demographic and tumor characteristics of the assessed head-and-neck IMRT cohort. CT: computed tomography; FU: follow-up; IMRT: intensity-modulated radiation therapy; NA: not available.

Tabelle 2. Demographische und tumorbezogene Charakteristika der untersuchten Kohorte mit Kopf-Hals-IMRT. CT: Computertomographie; FU: Nachbeobachtungszeit; IMRT: intensitätsmodulierte Radiotherapie; NA: nicht angebbar.

Factors	Definitive IMRT	Postoperative IMRT
Patients [(n%)]	210 (75)	70 (25)
Gender (male : female)	165 : 45	58 : 12
Age (years)	60 (21–87)	60 (38–85)
Diagnosis		
• Oropharynx	82	23
• Oral cavity	25	19
• Hypopharynx	40	4
• Larynx	24	6
• Nasopharynx	24	0
• Sinus	8	13
• Parotid	0	4
• Others	7	1
T-stages (n)		
• Tx	0	1
• T1	15	15
• T2	69	17
• T3	41	5
• T4	68	19
• Recurrence	17	13
N-stages (n)		
• N0	37	23
• N1	27	7
• N2a/b	60	33
• N2c	66	4
• N3	5	3
• Nodal recurrences	15	0
Concomitant CT [(n%)]	179 (85%)	50 (71%)
Total tumor volume [(n%)]		
• $\leq$ 15 cm^3	42 (20)	NA
• > 15–70 cm^3	124 (59)	NA
• > 70 cm^3	44 (23)	NA
Mean FU (months)	23.6 (3–59.3)	22.3 (5–50.5)

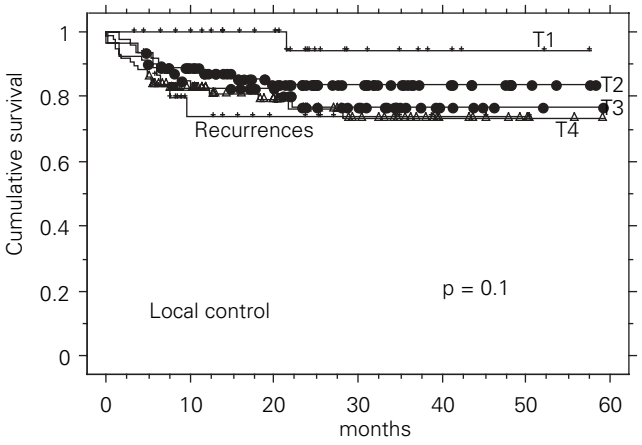


Figure 1. Actuarial 2-year local control according to the T-stage.

Abbildung 1. 2-Jahres-Lokalkontrollraten in Abhängigkeit vom T-Stadium.

Contouring of GTV and PTV1

When defining the GTV and PTV, we have always taken the findings in diagnostic imaging (computed tomography [CT] and/or magnetic resonance imaging [MRI], and/or fused positron emission tomography-CT (PET-CT, in 97% [11]), as well as clinical examination and the patterns of spread of the tumor into account. In postoperative cases, the pretreatment GTV was drawn in the planning CT.

In definitive as well as postoperative IMRT, the PTV1 included the GTV of the primary and of macroscopic nodal disease with a margin of at least 1.0–1.5 cm in all directions.

Contouring of the Elective Nodal Pathways (PTV2)

The volume definitions have basically been performed using the RTOG lymph node atlas (*www.rtog.org*). The following is a general description of our approach toward the elective nodal pathways' volume definition:

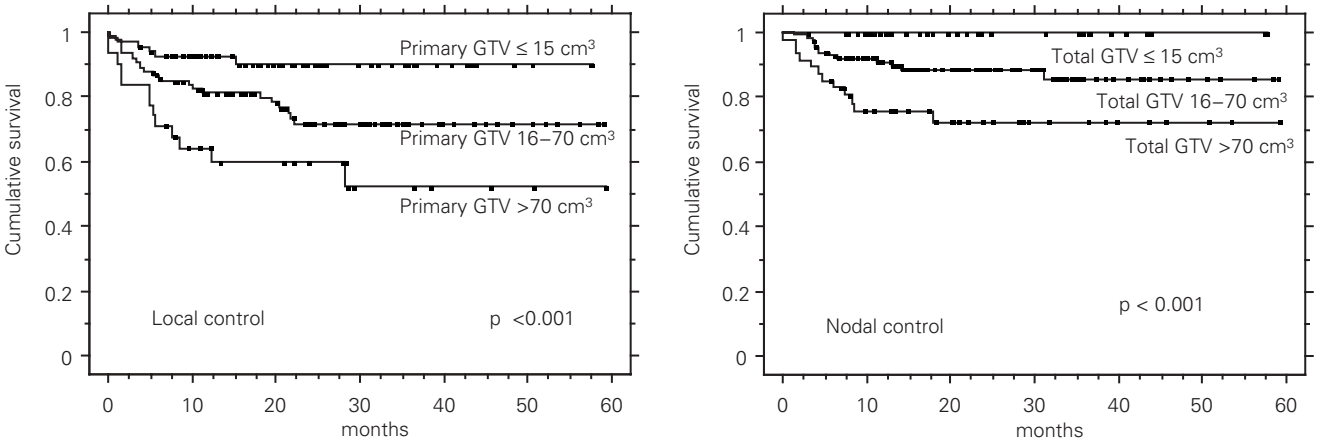
- for nasopharyngeal tumors, levels II–V, the retropharyngeal nodes, and the supraclavicular nodes were routinely covered. When no submandibular nodes were involved, levels Ia and Ib were not included.
- for oropharyngeal tumors without extension into the oral cavity, levels II–V and supraclavicular nodes were covered. When no submandibular nodes were involved, levels Ia and Ib were not routinely included, although often irradiated due to their vicinity to the GTV and PTV1. In lateral oropharyngeal tumors with contralateral N0, the upper part of the contralateral level II was not covered. In early unilateral disease, the contralateral neck was not treated; in oral cavity tumors, level I was included.
- in hypopharyngeal and laryngeal tumors, levels II–VI and supraclavicular nodes were included, without level Ia/b and the upper part of level II in most cases.

In comparison with the RTOG recommendations, no routine coverage of level I nodes was performed but in oral cavity tumors. The ventral level Ib and the cranial part of level II were restrictively treated. PTV2 coverage of the cranial part of level II was divided into three levels: up to the skull base, up to the tip of the dens axis (height of first cervical vertebral body, C1), and up to the base of the dens, respectively.

IMRT Schedules

Simultaneously integrated boost (SIB) was performed in all cases. Details to the use of SIB, planning computerized tomography, planning systems, and linear accelerator used are reported elsewhere [24]. The following schedules were used (five fractions per week each):

- 66 Gy (PTV1, 2.2 Gy/fraction) and 54 Gy (PTV2, 1.8 Gy/fraction) in 30 fractions (n = 40),



Figures 2a and 2b. Volumetric staging system (VS). a) Actuarial 2-year local control rates, based on the primary gross tumor volume (GTV) in definitive IMRT. b) Actuarial 2-year nodal control rates, based on the total GTV. None of the nodally negative patients failed.

Abbildungen 2a und 2b. Volumetrisches Staging-System (VS). a) 2-Jahres-Lokalkontrollraten, basierend auf dem makroskopischen Primärtumorvolumen (GTV) bei Patienten mit definitiver IMRT. b) 2-Jahres-Nodalkontrollraten, basierend auf dem totalen GTV. Bei den initial nodal negativen Patienten ereigneten sich keine Fälle von nodalem Versagen.

- 69.6 Gy (PTV1, 2.11 Gy/fraction) and 54 Gy (PTV2, 1.64 Gy/fraction) in 33 fractions (n = 155),
- 66–70 Gy (PTV1, 2.0 Gy/fraction) and 54–56 Gy (PTV2, 1.8–1.6 Gy/fraction) in 33–35 fractions (n = 78).

In seven patients, slightly different schedules were used.

Initially, the regimen with 2.2 Gy/fraction was used, according to the RTOG H-0022 pilot series by A. Eisbruch. The dose per session was then changed to a slightly lower SIB dose of 2.11 Gy, as described and analyzed elsewhere [24]. The schedule with 2.0 Gy/fraction was used in postoperative patients, and in definitively irradiated patients with tumors close to central nervous structures (CNS), in order to keep dose/fraction to the CNS ≤ 2.0 Gy, and the total dose ≤ 70 Gy.

Statistics

Actuarial survival data were calculated using Kaplan-Meier curves and log-rank tests implemented in StatView® (Version 4.5). p-values < 0.05 were considered significant.

Table 3. Adverse nodal risk factors used as prognostic indicators for nodal failure in nonoperated patients. OCC: oral cavity cancer.

Tabelle 3. Angewandte ungünstige nodale Risikofaktoren als prognostische Indikatoren für die nodale Versagenswahrscheinlichkeit bei nichtoperierten Patienten. OCC: Mundhöhlenkarzinome.

Adverse factors	n/31 nodal failures
> 1 nodal group	23
≥ 2 positive lymph nodes	29
> 3 cm lymph node	9
OCC	9
Central necrosis	21
Recurrence	5

Results

46 local (LFs, 16%) and 31 nodal failures (NFs, 11%) occurred in 59/280 patients (21%). Distant failures (DFs) developed in 25 (9%), LFs and NFs in 18 (6%), LFs and DFs in six (2%), NFs and DFs in three (1%), and locoregional and DFs in four patients (1.5%), respectively. 90% of LFs were diagnosed in the first 12 months (range 0–29 months), 90% of the NFs in the first 8–9 months (range 0–31 months), and 90% of the DFs in the first 12 months (range 0–34 months) after treatment, respectively. Actuarial 2-year survival rates of the entire population are shown in Table 4.

Patterns of Failure

Local failures (LF) were found "in field" in 45 of 46 cases. One patient presented with a "marginal" failure of a recurred oral cavity cancer. Local persistence was observed in 23/46 cases (50%).

4/46 LFs occurred in postoperative IMRT (6%, [22]), 42 in the 210 definitively irradiated patients (20%). The postoperative subgroup resulted in 94% 2-year local control versus 77% in definitive IMRT (p = 0.004).

Patients with a primary GTV of > 70 cm³ had a > 40% (14/34) risk for local progression, while only 5/67 patients with tumors ≤ 15 cm³ failed [26] (Figures 2a and 2b). There was a 2-year disease control rate of > 90% in small tumors up to 15 cm³, versus ~50% in tumors > 70 cm³.

Subsite analysis showed poorest local outcome in primarily irradiated oral cavity cancer with 33% local control versus 85% local control in operated patients (p < 0.001) [12].

T-stage distribution in failed primaries was as follows: 1/30 T1, 10/86 T2, 8/46 T3, 20/87 T4, and 7/30 patients with a recurrence, respectively (Figure 1; p = 0.1).

Table 4. 2-year survival rates, analyzed according to the assessed tumor subsites.

Tabelle 4. 2-Jahres-Überlebensraten, analysiert nach Diagnosen.

2-year control rates	Oropharnyx (n = 105)	Nasopharynx (n = 24)	Hypopharynx (n = 44)	Oral cavity (n = 44)	Larynx (n = 30)	Sinonasal (n = 21)	All (n = 268)
Local control (%)	88	77	89	60	83	82	80
Nodal control (%)	90	93	93	76	83	95	87
Distant control (%)	92	75	93	88	85	77	87
Disease-free survival (%)	81	66	80	57	71	63	73
Overall survival (%)	91	86	93	52	70	69	82

Local control, disease-free and overall survival rates in patients who underwent three to seven cycles of cisplatin versus zero to two cycles differed significantly, with 85% versus 62% (p = 0.0003), 78% versus 60% (p = 0.001), and 86% versus 70% (p = 0.004), respectively. There was no significant difference in nodal and distant control with 90% versus 82% (p = 0.16) and 90% versus 85% (p = 0.25).

Nodal failure (NF) was observed inside the PTV1 in 26/31 cases, and inside the PTV2 in two cases. Three times, nodal recurrence developed outside of PTV1/2, at atypical locations. Persistence was found in 12/32 cases (39%).

Five NFs occurred following postoperative (7%), 26 following definitive IMRT (12%; p = 0.14). The N-stage distribution in NF patients was 4/34 N1, 9/93 N2a,b, 12/70 N2c, 2/8 N3, and 4/15 patients treated for recurrence, respectively (p = 0.02). All patients with N0 status (n = 60) remained nodally controlled. Of importance, considering the restrictive dose coverage, none of the failed nodes were located in level I or in the cranial part of level II. Doses delivered to level Ib are shown in Table 5, and coverage of the upper level II in Table 6, respectively.

Level II was contoured (PTV2, > 45 Gy) up to the skull base in 75 sides, and up to the tip of the dens (C1) in 41. Nine nodally negative neck sides were only covered up to the basis of the dens axis, respectively. In several nodally positive patients a neck dissection has been performed following IMRT (separate manuscript).

Tolerance

Acute reactions to treatment were mild to moderate and are described in detail in a former analysis [24]. Xerostomia and dysphagia rates in 144 patients with no evidence of disease, assessed at 1 year post treatment, were as follows: grade 0 41% and 80%, grade

Table 5. Coverage of level Ib (distal of the submandibular gland). Hyp: hypopharyngeal carcinoma; NPC: nasopharyngeal carcinoma; Oro: oropharyngeal carcinoma.

Tabelle 5. Dosierung der Lymphabflussregion Ib (distal der Glandula submandibularis). Hyp: Hypopharynxkarzinom; NPC: Nasopharynxkarzinom; Oro: Oropharynxkarzinom.

Diagnosis	Total Ib (n) (= 2× n patiens)	Nodal status (n)	Ib contoured [n (%)]	> 45 Gy	30–45 Gy	< 30 Gy
NPC	48	N0 (13)	0 (0)	0	3	10
		N+ (35)	9 (26)	9	15	11
Hyp	78	N0 (39)	5 (13)	7	18	14
		N+ (39)	6 (15)	6	26	7
Larynx	54	N0 (24)	5 (23)	5	7	12
		N+ (30)	11 (37)	14	11	5
Oro	198	N0 (68)	10 (15)	17	42	9
		N+ (130)	80 (62)	99	27	4
Total	378	N0 (144)	20 (14)	29	70	45
		N+ (234)	108 (46)	128	79	27

Table 6. PTV2 coverage (> 45 Gy) of the cranial aspect of level II (cII) in oropharyngeal tumors (Oro). More than half of the N0 sides were only covered up to the tip or base of the dens, while all N+ sides were covered at least up to the tip of the dens axis. PTV: planning target volume.

Tabelle 6. Dosisbelegung in PTV2 (> 45 Gy) im kranialen Bereich der Lymphabflussregion II (cII) bei Oropharynxkarzinomen (Oro). Über die Hälfte der N0-Halsseiten wurde nur bis zur Spitze oder Basis des Dens axis bedient, während alle N+-Seiten mindestens bis zur Höhe der Spitze des Dens behandelt wurden. PTV: Planungszielvolumen.

Daignosis	Nodal status (n)	Skull base (n)	Upper border PTV2 Tip of dens (n)	Basis of dens (n)	Level cII (n)	Total cII (n)
Oro	N0	29	25	10	64	184
	N+	87	33	0	120	

1 35% and 13%, and grade 2 15% and 3%, respectively. Grade 3/4 persistent late reactions (according to the EORTC/RTOG toxicity criteria) included four patients with xerostomia, three with dysphagia, one with a laryngeal fibrosis, and one with impaired visual function of the optic nerve that was exposed to 70 Gy (3% persistent late-term effects). Eight of these nine grade 3/4 events occurred in the 229 patients who underwent combined radiochemotherapy.

Treatment tolerance data related to the used radiation schedules (2.0 vs. 2.11 vs. 2.2 Gy/session) are published elsewhere [23, 24].

Discussion

This study aimed to assess the locoregional failure profile of our IMRT cohort, with focus on the location of the observed failures in relation to the PTVs.

Our results are in concordance with reported patterns of failure from other centers [3, 5, 6, 8, 17, 29], describing a low number of marginally failed cases (~10% of all reported failures), with the majority (~83%) of relapses at the site of former GTV, inside the boost area, respectively (Table 1). This key information confirms PTVs have been adequately chosen. The variety of diagnoses and stages of the assessed cohort does not impair this result. PTV margin definitions as described seem to be appropriate likewise for all assessed tumor entities and volumes, respectively.

The dose-volume concept has shown to be very satisfying for small tumors, while larger GTVs may profit from a mild dose escalation.

Most patients were subjected to combined IMRT and chemotherapy. Combined-modality treatment was well tolerated, with a G3/4 late effect rate of 3.5% [23, 24]. The little number of events and the unbalanced sample size of 229 patients with chemotherapy versus 51 without, however, do not allow reliable statistical analysis on differences in the tolerance of IMRT with or without chemotherapy. Similarly, the highly significant local control, disease-free and overall survival differences shown in favor of the combined IMRT and chemotherapy subgroup should be taken with caution, given the different, retrospectively built subgroups, with mainly comorbid elderly patients characterizing the IMRT-alone subgroup.

In definitively irradiated patients, the failure probability was well predicted by the tumor volume ([26], Figure 2a), the presence of large macroscopic nodal disease with high-risk features, and the diagnosis of an oral cavity cancer as statistically significant prognostic criteria.

The outcome in the more favorable postoperative subgroup (positive selection in terms of locoregional tumor extent) was superior compared to definitively irradiated patients [22].

The restrictive coverage of level I/upper level II (Tables 5 and 6) eases sparing mucosal, parotid gland, and mandible bone tissue [1, 14, 15, 27]. None of the patients failed in these areas. Of 250 Ib levels not intended to treat, only 72 (19%) received < 30 Gy. In contrast to the upper level II, level Ib areas which had not been included into the PTV2 often received doses between 30–45 Gy (in 149 of 378 Ib areas, of whom only 128 were defined as PTV2, Table 5), due to the vicinity to the GTV/PTV1. Together with chemotherapy, this low dose coverage represents still an effective treatment of microscopic disease. Fletcher et al. ([9], p. 194, Table 2-17) reported a 60–70% eradication of occult nodal neck disease following 3,000–4,000 rads alone (50 patients), and of > 90% when 5,000 rads were delivered (356 patients), respectively.

Conclusion

The dose-volume concept as described has shown to be adequate, with disease failure developing at the site of large GTVs, inside the high-dose area in the majority of cases. This may indicate a need for higher doses in locally advanced tumors, and planned postoperative neck dissection in N+ patients with high-risk features, in order to further improve locoregional disease control.

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References

1. Al-Nawas B, Al-Nawas K, Kunkel M, et al. Quantifying radioxerostomia: salivary flow rate, examiner's score, and quality of life questionnaire. Strahlenther Onkol 2006;182:336–41.
2. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–8.
3. Bussels B, Maes A, Hermans R, et al. Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer. Radiother Oncol 2004; 72:119–27.
4. Chao KS, Ozyigit G, Blanco AI, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol Phys 2004;59:43–50.
5. Chao KS, Ozyigit G, Tren BN, et al. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2003;55:312–21.
6. Dawson LA, Anzai Y, Marsh L, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2000; 46:1117–26.
7. De Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of orophyryngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 2006;64:363–73.
8. 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 an for parotid gland sparing. Int J Radiat Oncol Biol Phys 2004;59:28–42.
9. Fletcher G, Basic clinical parameters. In: Fletcher G, ed. Textbook of radiotherapy. Philadelphia: Lea & Febiger, 1980:194.
10. Gregoire V, Eisbruch A, Hamoir M, et al. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol 2006;79:15–20.
11. Grosu AL, Piert M, Weber WA, et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181:483–99.
12. Hoeller U, Biertz I, Flinzberg S, et al. Hyperfractionated-accelerated radiotherapy followed by radical surgery in locally advanced tumors of the oral cavity. Strahlenther Onkol 2006;182:157–63.

13. Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. Int J Radiat Oncol Biol Phys 2004;60:1440–50.
14. Kuhnt T, Janich M, Gotz U, et al. [Presentation of a 3D conformal radiotherapy technique for head-and-neck tumors resulting in substantial protection of the parotid glands.] Strahlenther Onkol 2006;182:325–30.
15. 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.
16. Kwong DL, Pow EH, Shams JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. Cancer 2004;101:1584–93.
17. Lee N, Xia P, Fischbein NJ, et al. Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. Int J Radiat Oncol Biol Phys 2003;57:49–60.
18. Martinez-Monge R, Fernandes PS, Gupta N, et al. Cross-sectional nodal atlas: a tool for the definition of clinical target volumes in three-dimensional radiation therapy planning. Radiology 1992;211:815–28.
19. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. J Clin Oncol 2006;24:2618–23.
20. Poon I, Fischbein N, Lee N, et al. A population-based atlas and clinical target volume for the head-and-neck lymph nodes. Int J Radiat Oncol Biol Phys 2004;59:1301–11.
21. Puri DR, Chou W, Lee N. Intensity-modulated radiation therapy in head and neck cancers: dosimetric advantages and update of clinical results. Am J Clin Oncol 2005;28:415–23.
22. Studer G, Furrer K, Davis BJ, et al. Postoperative IMRT in head and neck cancer. Radiat Oncol 2006;1:40 (DOI 10.1186/1748-717X-1-40).
23. Studer G, Glanzmann C. Letter to the Editor in reply to Drs AS Garden et al (Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma, Int J Radiat Oncol Biol Phys 2006, Dec 1 [ahead of print]). Int J Radiat Oncol Biol Phys 2007:68:313–4.
24. Studer G, Huguenin P, Davis J, et al. IMRT using simultaneously integrated boost (SIB) in head and neck cancer patients. Radiat Oncol 2006;1:7 (DOI 10.1186/1748-717X-1-7).
25. Studer G, Lütolf UM, Davis JB, et al. IMRT in hypopharyngeal tumors. Strahlenther Onkol 2006;182:331–5.
26. Studer G, Lütolf UM, El-Bassiouni M, et al. Volumetric staging (VS) is superior to TNM and AJCC staging in predicting outcome of head and neck cancer treated with IMRT. Acta Oncol 2006;19:386–94.
27. Studer G, Studer SP, Zwahlen RA, et al. Osteoradionecrosis of the mandible: Minimized risk profile following intensity-modulated radiation therapy (IMRT). Strahlenther Onkol 2006;182:283–8.
28. Wolden SL, Chen WC, Pfister DG, et al. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 2006;64:57–62.
29. Yao M, Dornfeld KJ, Buatti JM, et al. Intensity-modulated radiation treatment for head-and-neck squamous cell carcinoma – the University of Iowa experience. Int J Radiat Oncol Biol Phys 2005;63:410–21.

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