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Hyperfractionated accelerated radiotherapy with concomitant integrated boost of 70–75 Gy in 5 weeks for advanced head and neck cancer

A phase I dose escalation study

Although radiotherapy (RT) plays an essential role in the management of locally advanced head and neck squamous cell carcinoma (HNSCC), the results remain poor. Better outcomes could be expected when concomitant chemotherapy [1] or therapy targeted against the epidermal growth factor receptor (EGFR) [12] are applied, but with higher toxicity and low therapeutic ratio [2, 14]. Hyperfractionated and/or accelerated schedules offer better therapeutic ratios [2]; however, severe toxicity has also been recorded quite often in the context of these schedules [3]. Some altered fractionation regimens have an acceptable acute toxicity [5, 6, 8, 10, 13], while other schedules such as CAIR, HARDE, or GORTEC have required modification [7, 15, 16].

Fowler found the total biologically equivalent dose in 2-Gy fractions (EQD_2) to be a strong predictive factor for severe mucositis: if EQD_2 remains <49 Gy, acute and consequential mucosal toxicities are acceptable [11]. An EQD_2 >52.5 Gy indicates an unacceptable risk of acute toxicity and consequential late damage. Between these two values, there is a grey zone in which some reasonable dose escalation might be feasible.

Better irradiation of the target volume while preserving critical surrounding structures can be achieved with intensity-modulated radiotherapy (IMRT), especially when planned as an integrated boost [4]. Although many studies have evaluated different fractionations, the maximum tolerated dose remains unknown, especially when highly conformal radiation techniques are utilized.

Given the above facts, we developed a new regimen of hyperfractionated and accelerated radiotherapy with concomitant integrated boost (HARTCIB).

Methods and materials

Between May 2008 and February 2010, 39 patients with very advanced, bulky, stage IV HNSCC were included in this phase I dose escalation study. Inclusion criteria for this protocol were as follows: inoperable, nonmetastatic, squamous cell carcinoma of the oro/hypopharynx, larynx, or oral cavity; clinical stage IV; bulky primary tumor (minimum gross tumor volume 40 ml); Karnofsky performance status >60; signed informed consent; and contraindication to the concomitant administration of platinum-based chemotherapy because of comorbidity and/or insufficient liver/kidney function.

Patients' characteristics are summarized in **Tab. 1.** The median gross tumor volume (GTV) was 72 ml (range 40–240 ml), which was comprised of median 50 ml (range 20–200 ml) for the primary tumor and median 10 ml (range 0–120 ml) for lymphadenopathy. Percutaneous endoscopic gastrostomy (PEG) was introduced prior to RT in 23 patients (62%) who experienced significant swallowing difficulties or weight loss of ≥10%.

This study was approved by the institutional review board of University Hospital Ostrava. Staging was performed by a multidisciplinary team based on 2002 American Joint Committee on Cancer's TNM Classification of Malignant Tumors, according to a standard procedure. Dental examination and intervention as needed, together with nutritional intervention after screening, were conducted before RT. Positron emission tomography (PET), bone scans, and abdominal or chest CTs were performed in selected cases only.

Simulation and treatment planning

GTV_{tumor} included the primary tumor and involved lymph nodes identified by CT and physical examination or endoscopy. The clinical target volume of the primary tumor plus lymphadenopathy (CTV_{tumor}) was defined as a 4 mm isometric expansion of the GTV_{tumor}. The uninvolved nodal areas ($CTV_{uninvolved}$) included bilateral nodal regions II–V (I–V in oral cavity tumors) in accordance with multi-institu-

Tab. 1 Main patient characteristics

		Number	Percentage
Sex	Male	35	90
	Female	4	10
Age	Median	61	
	Range	40–84	
Sites	Oro/hypopharynx	13	33
	Oral cavity	18	46
	Larynx	8	21
AJCC stage	IV	39	100
T stage	1	0	0
	2	3	8
	3	6	15
	4	30	77
N stage	0	5	13
	1	4	10
	2a	6	15
	2b	16	41
	2c	4	10
	3	5	13
Histology	Squamous	39	100

tional consensus. The CTV–PTV margins were 3 mm for both CTVs. In accordance with our institutional protocol, cone beam CT for image guidance was performed at weekly intervals (more often when set-up errors >3 mm were detected).

Radiobiological analyses

Hyperfractionated schedules and concomitant boost techniques have been used for many years in our department. The IMRT two-plan approach that was initially used has several disadvantages. Therefore, the next step was to adopt the integrated boost to obtain better conformity of irradiation without radiobiological losses. New fractionations would have similar efficacy and lower late toxicity than standard regimes. A higher risk of acute toxicity was allowed in the context of better conformity of integrated-boost IMRT. Calculations based on the linear-quadratic model [9]of standard and new schedules are compared in **Tab. 2.** The following equations and parameters were used to calculate acute mucosal reaction: α/β=10 Gy; α=0.35 Gy^{-1}; Tk=7 days; Tp=2.5 days.

Tab. 2 Comparison of toxicity and efficacy of standard and experimental fractionations

Schedule	70 Gy/35 fractions/NF	CB 72 Gy/6 weeks	CB 69.5 Gy/5 weeks	HFR 81.6 Gy/7 weeks	CIBa (1.4 Gy)	CIBb (1.45 Gy)	CIBc (1.5 Gy)
Total dose (Gy)	70	72	69.5	81.6	70	72.5	75
Morning dose (Gy)	2	1.8	1.8	1.2	1.4	1.45	1.5
Afternoon dose (Gy)	0	1.5	1.5	1.2	1.4	1.45	1.5
Total time (days)	47	40	33	47	33	33	33
Fractions (n)	35	42	40	68	50	50	50
EQD_2 acute (Gy)	42.0	47.0	49.4	48.2	49.8	52.5	55.2
EQD late (Gy)	70.0	68.0	66.2	68.5	61.6	64.5	67.5
EQD tumor (Gy)	70.0	74.4	76.1	76.2	74.5	77.2	79.9

CB concomitant boost, CIB concomitant integrated boost, EQD_2 equivalent dose in 2-Gy fractions (10 Gy/week, 2 Gy/day), HFR hyperfractionation, NF normofractionation.

$$EQD_2 = BED/(1 + 2/\ [\alpha/\beta\,])$$

$$BED = nd(1 + d/\ [\alpha/\beta\,]) - \log 2\,(T - T_k)\,/\alpha T_p$$

For tumor: α/β=10 Gy (D_{repop}=4 Gy/week shorter than 7).

$$EQD_2 = D\frac{d + \alpha/\beta}{2 + \alpha/\beta} + Drepop$$

For late tissues: α/β=3 Gy

$$EQD_2 = D\frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Dose prescription

HARTCIB applies the same plan twice daily with a gap of at least 6 h, totaling 10 fractions/week (50 fractions in 5 weeks). The primary tumor with lymphadenopathy (PTV_{tumor}) received a total dose/dose per fraction of 70 Gy/1.4 Gy in the first cohort of patients. If no dose-limiting toxicity was recorded during the treatment or during the 90-day follow-up period, the dose to the PTV_{tumor} was escalated to 72.5 Gy/1.45 Gy, and then further escalated to 75 Gy/1.5 Gy. $PTV_{uninvolved}$ areas were irradiated at a dose of 55 Gy/1.1 Gy. The prescribed dose in the PTV has been normalized to mean dose (D_{mean}). Inverse planning (Precise PLAN® 2.11, Elekta, Crawley, UK) for 6 MeV photon step-and-shoot IMRT allowed us to keep the maximum dose (D_{max}) to the spinal cord <48 Gy in all cases. If it was possible to protect the parotid glands, the median dose was <26 Gy for at least one parotid. Laryngeal, oral cavitiy, and pharyngeal constrictors were defined as critical structures if tumor infiltration was not detected. In those cases, the median dose was minimized to the lowest possible level without specific dose–volume parameters. Mandible, brainstem, or brachial plexus were delineated as critical structures in specific anatomical situations.

Evaluation of toxicity and response

Acute toxicity was evaluated by the same radiation oncologist during and after RT once weekly until recovery, and was recorded according to the RTOG/EORTC scale. Toxicity was considered acute if it was detected during the RT course or within 90 days after completion of RT. Patients were evaluated during follow-up at 3-month intervals by the otolaryngology specialist and radiation oncologist. Late toxicity was recorded according to the RTOG/EORTC scale for patients in complete remission (CR).

Statistical analyses

Dose-limiting toxicity was defined as the need for interruption of the RT course due to intolerance or any grade 4 acute toxicity. Other parameters, such as the incidence and duration of acute toxicity, incidence of late toxicity, locoregional pro-

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Hyperfractionated accelerated radiotherapy with concomitant integrated boost of 70–75 Gy in 5 weeks for advanced head and neck cancer. A phase I dose escalation study

Abstract

Background and purpose. The present study was performed to evaluate the feasibility of a new, 5-week regimen of 70–75 Gy hyperfractionated accelerated radiotherapy with concomitant integrated boost (HARTCIB) for locally advanced, inoperable head and neck cancer.

Methods and materials. A total of 39 patients with very advanced, stage IV nonmetastatic head and neck squamous cell carcinoma (median gross tumor volume 72 ml) were included in this phase I dose escalation study. A total of 50 fractions intensity-modulated radiotherapy (IMRT) were administered twice daily over 5 weeks. Prescribed total dose/dose per fraction for planning target volume (PTV_{tumor}) were 70 Gy in 1.4 Gy fractions, 72.5 Gy in 1.45 Gy fractions, and 75 Gy in 1.5 Gy fractions for 10, 13, and 16 patients, respectively. Uninvolved lymphatic nodes ($PTV_{uninvolved}$) were irradiated with 55 Gy in 1.1 Gy fractions using the concomitant integrated boost.

Results. Acute toxicity was evaluated according to the RTOG/EORTC scale; the incidence of grade 3 mucositis was 51% in the oral cavity/pharynx and 0% in skin and the recovery time was ≤9 weeks for all patients. Late toxicity was evaluated in patients in complete remission according to the RTOG/EORTC scale. No grade 3/4 late toxicity was observed. The 1-year locoregional progression-free survival was 50% and overall survival was 55%.

Conclusion. HARTCIB (75 Gy in 5 weeks) is feasible for patients deemed unsuitable for chemoradiation. Acute toxicity was lower than predicted from radiobiological models; duration of dysphagia and confluent mucositis were particularly short. Better conformity of radiotherapy allows the use of more intensive altered fractionation schedules compared with older studies. These results suggest that further dose escalation might be possible when highly conformal techniques (e.g., stereotactic radiotherapy) are used.

Keywords

Altered fractionation · Intensity-modulated radiotherapy · Head and neck neoplasms · Dose fractionation · Survival

Hyperfraktionierte akzelerierte 5-wöchige Strahlentherapie mit simultan integriertem Boost von 70–75 Gy für fortgeschrittene Kopf-Hals-Tumoren. Eine Phase-I-Studie zur Dosiseskalation

Zusammenfassung

Hintergrund. Die Studie untersucht die Machbarkeit eines 5-Wochen-Fraktionierungsschemas der hyperfraktionierten akzelerierten Strahlentherapie mit einem simultan integrierten Boost von 70–75 Gy (HARTCIB) für Patienten mit lokal fortgeschrittenen Kopf-Hals-Tumoren.

Patienten und Methoden. Insgesamt 33 Patienten mit lokal sehr fortgeschrittenen Kopf-Hals-Tumoren im klinischen Stadium vier (mittleres Tumorvolumen von 72 ml) wurden in die Phase-I-Studie aufgenommen. Die Patienten wurden mit 50 IMRT-Fraktionen über 5 Wochen 2-mal tägl. bestrahlt. Die Gesamtdosis/Einzeldosis für PTV_{tumor} betrug 70 Gy/1,4 Gy, 72,5 Gy/1,45 Gy und 75 Gy/1,5 Gy für 10, 13 bzw. 16 Patienten. Unbetroffene Halsregionen ($PTV_{uninvolved}$) bekamen 55 Gy (Einzeldosis 1,1 Gy).

Ergebnisse. Die akute Toxizität wurde anhand der RTOG-Skala beurteilt. Eine Mukositis vom Grad 3 in der Mundhöhle oder im Pharynx trat bei 51% der Patienten auf, eine Grad-3-Hauttoxizität kam nicht vor. Bei allen Patienten war die Heilungszeit kürzer als 9 Wochen. Bei Patienten in kompletter Remission kam es zu keiner gemäß RTOG klassifizierten Spättoxizität vom Grad 3 oder 4. Die progressfreie Überlebensrate nach einem Jahr betrug 50%, die 1-Jahres-Gesamtüberlebensrate 55%.

Schlussfolgerung. Ein sehr akzeleriertes Fraktionierungsschema von 75 Gy in 5 Wochen mit dem simultanen integrierten Boost ist tolerabel und kann bei Patienten verwendet werden, die mit der Radiochemotherapie nicht behandelt werden können. Die akute Toxizität, vorzugsweise Mukositis und Dysphagie, war niedriger als mit dem aktuellen radiobiologischen Modell kalkuliert. Die hohe Konformität der Bestrahlung macht die Benutzung solcher akzelerierten Schemen möglich. Die Resultate unserer Studie zeigen, dass sogar noch mehr intensive Fraktionierungsschemen ausführbar sein könnten.

Schlüsselwörter

Alternative Fraktionierung · IMRT · Kopf-Hals-Tumoren · Dosisfraktionierung · Überleben

gression-free survival (LR-PFS), and overall survival (OS) were also evaluated.

Patients' characteristics were recorded at the time of initiation of treatment. Response and acute and late toxicity were prospectively evaluated at the above-mentioned intervals. LR-PFS was calculated from the start of RT until the date of first documented disease progression. OS was calculated using the date of death from any cause.

The data cut-off was 31 August 2011. Data were analyzed using GraphPad Prism for Windows 4.0 (GraphPad Software Inc., La Jolla, CA, USA). Cumulative survival and local control were calculated based on the Kaplan–Meier method; intergroup comparisons were performed using the Mann–Whitney test for two groups and the Kruskal–Wallis test for three groups of variables.

Results

Between May 2008 and February 2011, 39 patients with stage IV bulky, nonmetastatic, inoperable HNSCC were treated according to the HARTCIB protocol. Ten patients received the total dose/dose per fraction (70 Gy/1.4 Gy), 13 patients then received 72.5 Gy/1.45 Gy, and 16 patients progressed to the highest dose level (75 Gy/1.5 Gy). Additional dose esca-

Tab. 3 Incidence and duration of confluent mucositis for each dose level (Kruskal–Wallis test)

Dose level	Patients (n)	Incidence (n, %)	Average duration (weeks)	Maximum duration (weeks)	p value
70 Gy	10	5 (50%)	5.3	7	
72.5 Gy	13	7 (54%)	5.2	7	0.98 (NS)
75 Gy	16	8 (50%)	5.3	9	

NS not significant.

lation was not performed because of excessive risk of severe acute toxicity based on radiobiological modeling. All patients were monitored for at least 6 months after therapy or until death. Median follow-up was 10 months (range 6–39 months) for survivors.

Toxicity

All patients completed the treatment course as planned; no excessive toxicity requiring a treatment break was noted. The median doses were 70 Gy (n=10), 72.5 Gy (n=13), and 75 Gy (n=16) for the three dosage groups (**Tab. 3**). The median duration of the RT series was 37 days (range 33–48 days) because of planned and unplanned device shutdowns and/or public holidays. The incidence of grade 3 acute toxicity was 51% for mucosa (oral cavity and/or pharynx) and 0% for skin. No grade 4 or 5 toxicities were recorded. Patients whose treatment time was below median (n=20) had average recovery from grade 3 mucositis of 5.1 weeks, while in those with longer total treatment time (n=19) the average recovery was 4.4 weeks. This result was not statistically significant (Mann–Whitney test, p=0.43).

Parenteral support for severe mucositis was the reason for hospitalization in six cases (15%). As mentioned above, PEG was introduced before treatment in 23 patients (58%); however, 13 patients completed RT with oral nutritional support only, without the use of PEG. Late toxicity was evaluated in patients in CR with a minimum follow-up of 6 months. Grade 1 subcutaneous fibrosis was detected in 64% of patients, and grade 1 xerostomia was detected in 82%. Grade 2 xerostomia was recorded in 18% of patients. Higher degrees of late toxicity were not reported; however, follow-up was short.

Response

Seventeen progressions were recorded during the follow-up, of which one was a case of distant metastasis. The remaining 16 progressions were in areas that had received a high dose of radiation (GTV_{tumor}). Local, regional, and combined locoregional progression were observed in 5, 4, and 7 patients, respectively. The 1-year LR-PFS at 12 months was 50%. The expected OS at 12 months was 55%.

Discussion

Although standard treatment of nonmetastatic, locoregional, advanced, head and neck cancers is concomitant radiochemotherapy [17], many patients are ineligible for this treatment because of comorbidities and/or global performance status. While concomitant anti-EGFR therapy may be an alternative [12], it has also been associated with excessive toxicity [14]. Although better outcomes may be expected when hyperfractionated accelerated RT is used [3], severe acute toxicity has been reported as the limiting factor in several studies in which the fractionations required modification [7, 15, 16]. Highly conformal techniques, such as IMRT, have the potential to reduce toxicity, as reported in RTOG 00–22 [18]. Some available radiobiological predictions based on the linear-quadratic model define the risk of excessive acute toxicity [11]; however, there is a grey zone that remains to be clarified. To the best our knowledge, only one study has evaluated the feasibility of hyperfractionated accelerated RT with integrated-boost IMRT [19]. The present dose-escalation study contributes to the search for the maximum tolerated dose when single modality RT is used in the era of highly conformal techniques.

Because severe acute toxicity was not recorded at dose levels of 70 Gy or 72.5 Gy, it was reasonable to proceed to the next level despite the high radiobiological probability of unacceptable acute toxicity. At the 75-Gy dose, the incidence of grade 3 acute mucositis was 50%, median duration of toxicity was 5.3 weeks, and maximum duration of toxicity was 9 weeks. No toxicity-related treatment break was recorded, and there were no grade 3 skin toxicities. Tolerance was considered acceptable given the large volume of PTV, and according to our definition the maximum tolerated dose was not reached. However, additional dose escalation was not performed because there were cases of longer recovery from confluent mucositis. The real acute toxicity was much lower than expected from radiobiological calculations.

The linear-quadratic model predicts that using a smaller dose per fraction will have a positive effect on late toxicity, which corresponds with our results. Dependence on PEG 3 months after RT was recorded in patients with persistent or progressive tumor only; no PEG-dependence was observed in patients with CR. There was no osteonecrosis, which may be the result of very good interdisciplinary cooperation with the dental surgeon; however, longer follow-up is needed to determine the real incidence of this rather rare toxicity. Subcutaneous fibrosis was mild in all cases and xerostomia varied between grades 1 and 2. Given that no other late toxicities were observed, there is no evidence that this regimen has significant sequelae; however, this information must be confirmed in a longer follow-up period.

The 1-year LR-PFS and OS were 50% and 55%, respectively (**Fig. 1**). Although these results appear disappointing, they were predictable in bulky tumors with a median tumor volume of 72 ml. Moreover, most tumors were located in the oral cavity, and therefore carry worse prognosis [20, 21], and patients had contraindications to concomitant chemotherapy because of comorbidities. The very low incidence of distant relapse was an interesting finding, and underscores the importance of local control for OS in HNSCC. Because all locoregional relaps-

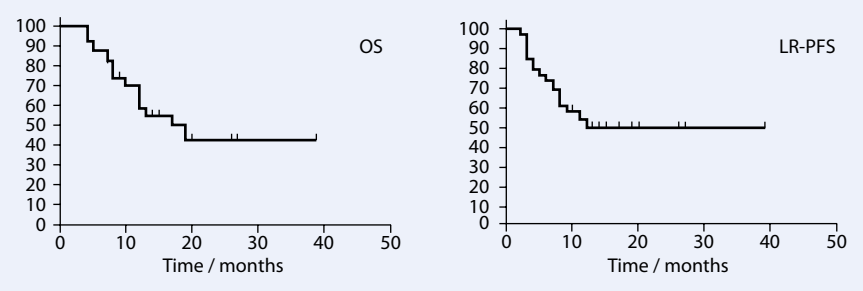

Fig. 1 ▲ Kaplan–Meier curves for overall survival (*OS*) and locoregional progression-free survival (*LR-PFS*)

es were detected within the GTV_{tumor}, further treatment intensification is needed. We recently started to add a stereotactic boost of 5 Gy with a CyberKnife (Cyberboost) for GTV at the end of fractionated irradiation, analogous to the intraluminal brachytherapy boost that is used for nasopharyngeal carcinomas. Finally, given the absence of progression outside the GTV, we hypothesize that the elective dose may be decreased or elective irradiation might even be omitted in some very advanced cases.

Conclusion

In patients with advanced, bulky HNSCC deemed unsuitable for chemoradiation, 75 Gy HARTCIB administered in 5 weeks is feasible with acceptable acute toxicity, especially because it is associated with short duration of dysphagia and confluent mucositis. Better conformity of RT allows the use of more intensive altered schedules than indicated by radiobiological considerations and older clinical data. The prognosis of patients with very advanced disease remains poor, elective irradiation of uninvolved lymph nodes is questionable, and additional dose intensification for the GTV (e.g., with the stereotactic boost) is necessary.

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Conflict of interest . On behalf of all authors, the corresponding author states that there are no conflicts of interest. Parts of the contribution were presented at the ASTRO annual meeting 2010.

References

1. Pignon JP, Bourhis J, Domenge C et al (2000) Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 355:949–955
2. Corvo R (2007) Evedence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol 85:156–170
3. Bourhis J, Overgaard J, Audry H et al (2006) Hyperfractionated or accelerated radiotherapy in head and neck cancer: a metaanalysis. Lancet 368:843–854
4. Mohan R et al (2000) Radiobiological considerations in the design of fractionation strategies for intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 46:619–630
5. Fu KK, Pajak TF, Trotti A et al (2000) A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 48:7–16
6. Overgaard J, Hansen HS, Specht L et al (2003) Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 362:933–940
7. Skladowski K, Maciejewski B, Golen M et al (2006) Continuous accelerated 7-days-a-week radiotherapy for head-and-neck cancer: long-term results of phase III clinical trial. Int J Radiat Oncol Biol Phys 66:706–713
8. Kubes J, Cvek J, Vondracek V et al (2011) Accelerated radiotherapy with concomitant boost technique (69,5 Gy/5 weeks). Strahlenther Onkol 187:651–655
9. Stell G (2002) Basic clincal radiobiology. 3rd ed. Hodder Arnold, London
10. Horiot JC, LeFur R, N'Guyen T et al (1992) Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 25:231–241
11. Fowler JF, Harari PM, Leborgne F et al (2003) Acute radiation reactions in oral and pharyngeal mucosa: tolerable levels in altered fractionation schedules. Radiother Oncol 69:161–168
12. Bonner JA, Harari PM, Giralt J (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567–578
13. Dische S, Saunders M, Barrett A et al (1997) A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol 44:123–136
14. Giro C, Berger B, Bölke E et al (2009) High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: results of a survey in EORTC institutes. Radiother Oncol 90:166–171
15. McGinn CJ, Harari PM, Fowler JF et al (1993) Dose intensification in curative head and neck cancer radiotherapy-linear quadratic analysis and preliminary assessment of clinical results. Int J Radiat Oncol Biol Phys 27(2):363–369
16. Bourhis J, Lapeyre M, Tortochaux J et al (2006) Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. J Clin Oncol 24:2873–2878
17. Tribius S, Kronemann S, Kilic Y et al (2009) Radiochemotherapy including cisplatin alone versus cisplatin +5-fluorouracil for locally advanced unresectable stage IV squamous cell carcinoma of the head and neck. Strahlenther Onkol 185:675–681
18. Eisbruch A, Harris J, Garden AS et al (2010) Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00–22). Int J Radiat Oncol Biol Phys 76:1333–1338
19. Gunn GB, Endres EJ, Parker B et al (2010) A phase I/II study of altered fractionated IMRT alone for intermediate T-stage oropharyngeal carcinoma. Strahlenther Onkol 186:489–495
20. Harrison LB, Ferlito A, Shaha AR et al (2003) Current philosophy on the management of cancer of the base of the tongue. Oral Oncol 39:101–105
21. Rades D, Seibold ND, Gebhard MP et al (2011) Prognostic factors (including HPV status) for irradiation of locally advanced squamous cell carcinoma of head and neck (SCCHN). Strahlenther Onkol 187:626–632