ONKOLOGIE

Onkologie 2000;23:48–53

Postoperative Irradiation for Squamous Cell Carcinoma of Head and Neck: Retrospective Comparison of Accelerated Radiochemotherapy and Standard Radiotherapy

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Key Words
Head and neck tumors · Squamous cell carcinoma · Postoperative radiotherapy · Accelerated fractionation · Chemotherapy

Schlüsselwörter
Kopf-Hals-Tumoren · Plattenepithelkarzinome · Postoperative Radiotherapie · Akzelerierte Fraktionierung · Chemotherapie

Summary

Background: Comparison of accelerated radiochemotherapy (aRCT) and standard radiotherapy (sRT) in postoperative treatment after macroscopically complete resection of squamous cell cancers of head and neck. ***Material and Methods:*** 229 patients treated within the same period had either (no randomization) postoperative radiotherapy with conventional fractionation (60–70 Gy, 2.0 Gy per day) or received 2 fractions of 2.1 Gy per day, 8 times/week, up to a total dose of 56.7 Gy with a treatment split after 2 weeks and simultaneous low dose cisplatin or carboplatin on treatment days (cumulative dose > 66 mg/m^2 or 550 mg/m^2 in 83% of patients). ***Results:*** 65 patients completed their course of twice-daily irradiations within a maximum of 35 days and therefore had aRCT; their 3-year locoregional tumor control (Kaplan-Meier estimate) was 86%, whereas that of 42 patients with prolonged twice-daily radiochemotherapy was 65% (p = 0.0509). After sRT, i.e. 1 fraction daily and treatment time up to 45 days, locoregional tumor control was 67%, this result being significantly inferior to that after aRCT (p = 0.0282). In multivariate analysis, pN stage, tumor site oral cavity/floor of mouth, high/moderate differentiation of squamous cell carcinoma and conventional surgery (versus CO_2-laser surgery) were significantly predictive of locoregional failure. Whereas nodal status, the strongest prognostic factor, was evenly distributed among aRCT and sRT patients, there was a misbalance of 3 risk factors favoring the aRCT collective. Superior tumor control after aRCT was confirmed unilaterally for nearly each subgroup (significant for recurrent tumors, close margins, pN1/2a-b). For pN2c/pN3 nodal stage, the results after aRCT were by tendency worse than after sRT, possibly due to a particularly long interval between surgery and start of radio(chemo)therapy for the patients with aRCT (mean 58.0 days vs. 43.8 days, p = 0.037). Among the total of patients the 3-year hazard for late toxicity III–IV was 31% after twice-daily treatment and 17% after conventionally fractionated radiotherapy (p = 0.083). ***Conclusions:*** This retrospective analysis provides some evidence that accelerated radiotherapy with simultaneous chemotherapy is more potent than standard radiotherapy. However, as multivariate analysis misses significance and the influence of misbalance of some prognostic factors among aRCT and sRT patients remains unclear, only a randomized trial with stratification according to risk factors as well as a defined interval between surgery and initiation of RT can provide more evidence.

Zusammenfassung

Hintergrund: Vergleich von akzelerierter Radiochemotherapie (aRCT) und Standard-Radiotherapie (sRT) postoperativ nach makroskopisch kompletter Resektion von Plattenepithelkarzinomen des Kopf-Hals-Bereichs. ***Material und Methoden:*** 229 Patienten wurden im gleichen Zeitraum therapiert und erhielten entweder (keine Randomisierung) eine postoperative Radiotherapie (N = 122) in konventioneller Fraktionierung (60–70 Gy; 2,0 Gy täglich) oder wurden zweimal täglich (N = 107) mit je 2,1 Gy (8 Fraktionen/Woche) bis 56,7 Gy mit Behandlungspause nach 2 Wochen und simultan mit niedrig dosiertem Cisplatin (6 mg/m^2 KOF) oder Carboplatin (50 mg/m^2), kumulative Dosis > 66 mg/m^2 bzw. 550 mg/m^2 bei 83% der Patienten, behandelt. ***Ergebnisse:*** 65 Patienten beendeten die zweimal tägliche Radiochemotherapie innerhalb von 35 Tagen und erhielten damit aRCT; ihre lokoregionäre 3-Jahres-Tumorfreiheit (nach Kaplan-Meier) betrug 86%, während die von 42 Patienten, deren zweimal tägliche Bestrahlung sich über einen längeren Zeitraum hinzog, 65% betrug (p = 0,0509). Nach sRT, definiert als einmal tägliche Bestrahlung und Behandlungszeit bis 45 Tagen, war die lokoregionäre 3-Jahres-Tumorfreiheit 67%. Dies ist signifikant schlechter (p = 0,0282) als nach aRCT. In der multivariaten Analyse erwies sich das pN-Stadium, Tumorlokalisation in Mundhöhle bzw. -boden, G1- und G2-Differenzierung und konventionelle Chirurgie (im Gegensatz zu Laseroperation) als signifikant ungünstig für die lokoregionäre Tumorfreiheit. Während die pN-Stadien als wichtigster Prognosefaktor gleich verteilt waren unter den sRT- und aRCT-Patienten, begünstigten 3 andere Risikofaktoren das aRCT-Kollektiv. Im univariaten Vergleich zwischen Untergruppen wurde eine bessere lokoregionäre Kontrolle nach aRCT fast immer bestätigt (signifikant für Untergruppen Rezidivbehandlung, knappe Resektionsränder, pN1/2a + b). Beim ungünstigen pN2c/3-Stadium war die lokoregionäre Kontrolle tendenziell schlechter nach aRCT, wobei unter diesen Patienten das Intervall zwischen Operation und Bestrahlungsbeginn besonders lang war (im Mittel 58 Tage vs. 44 Tage bei sRT). Das Risiko, innerhalb von 3 Jahren eine Grad III–IV Toxizität zu entwickeln, betrug nach zweimal täglicher Bestrahlung 31% und nach konventioneller Fraktionierung 17% (p = 0,083). ***Schlußfolgerungen:*** Diese retrospektive Analyse liefert Hinweise, daß postoperativ eine akzelerierte Radiotherapie mit simultaner Chemotherapie wirksamer ist als die Standard-Radiotherapie. Allerdings erreicht die Bestrahlungsmethode in der multivariaten Analyse keine Signifikanz als prognostischer Faktor. Ferner ist der Einfluß dreier nicht gleich verteilter Prognosefaktoren in den Kollektiven schwer abschätzbar. Weitere Klärung brächte eine randomisierte Studie, die Risikofaktoren gleich gewichtet und ein Intervall zwischen Operation und Radiotherapie definiert.

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Introduction

Postoperative radiotherapy (RT) after surgical resection of squamous cell carcinomas of the head and neck is performed with the intention to eradicate residual disease at the former tumor site and the cervical lymphatic pathways. After combined treatment, earlier retrospective studies [1–4] found a risk of locoregional failure of 15–45% which varies in relation to risk factors such as histologic type and extension of nodal disease, resection margins, oral cavity as primary tumor site, etc. The randomized study of Peters et al. [5] compared dose levels of 52.2–54, 57.6, 63, and 68.4 Gy (daily fractions of 1.8 Gy) and established a higher risk of recurrence after doses less than 54 Gy. Dose escalation above 63 Gy did not improve the therapeutic ratio. In order to improve the results especially of high-risk patients, other modes of treatment intensification have to be tested. Simultaneous chemotherapy with mitomycin C [6] or cisplatin [7] resulted in significantly better locoregional control. Recent considerations on tumor biology focus on the time factor [8]. The maximal tumor cell reduction, as achieved by surgery, is hypothesized to be a potent stimulus for tumor cell repopulation. Thus, the postoperative setting appears to be characterized by accelerated tumor repopulation and an adequate answer could be an accelerated fractionation scheme as well as an early initiation of RT. A small randomized study [9] found no overall benefit for accelerated postoperative RT, however, an advantage for tumors with a high [3H]thymidine labeling index, i.e. for fast growing tumors. Preliminary data from an ongoing trial at M.D. Anderson C.C., comparing 63 Gy/1.8 Gy per day with 63 Gy given as a concomitant boost protocol, reveals a benefit for the accelerated treatment as well as for a short-time interval between surgery and the start of RT [10].

This retrospective study compares the results of accelerated radio(chemo)therapy (aRCT) with those of standard radiotherapy (sRT) in patients treated postoperatively at the same institution during the same period.

Materials and Methods

Patients and Radio(chemo)therapy

From 1993 through 1996, 229 patients received RT after macroscopically complete resection of advanced tumors of oral cavity/floor of mouth, oropharynx, larynx, and hypopharynx. 50% of the pT1–2 tumors and 34% of pT3–4 tumors were operated on by CO_2-laser technique using operation microscope. Conventional surgery was significantly more often (chi-square test p = 0.011) performed in advanced tumor stages (66% of pT3–4 tumors; 50% of pT1–2 tumors).

122 patients were treated with once-daily irradiation with a daily dose of 2.0 Gy 5 times per week by opposing fields (lower neck by anterior field, 50 Gy in 3 cm tissue depth). 104 patients (85%) received 60 Gy (or 59.8 Gy) and 18 patients (15%) 62–70 Gy within the opposing fields. The spinal cord was excluded after 36 Gy. 72 of 122 patients finished RT within 45 days and less. This subgroup is addressed as standard radiotherapy (sRT), longer treatment time is addressed as prolonged RT.

107 patients received 2 fractions of 2.1 Gy per day in midline with a time interval of 6 hours by the same irradiation techniques. Irradiation was given on 4 days per week (omitting Wednesdays) with a treatment split of 7–14 days after 2 weeks up to a total dose of 56.7 Gy. First, it was supposed that a 2-week break is needed for complete resolution of acute mucositis, but under optimal supportive measures mucositis healed more quickly in many patients and the therapy-free interval was routinely shortened to 1 week, resulting in an accelerated course of radiochemotherapy (aRCT) in 65 of 107 patients, i.e. 56.7 Gy or 64.7 Gy within 35 days or less. The other patients are addressed as twice-daily RCT without acceleration. On treatment days, most patients received simultaneous cisplatin at a dose of 6 mg/m^2 body surface (57 patients with cumulative dose > 66 mg) or carboplatin at a dose of 50 mg/m^2 body surface (22 patients with cumulative dose > 550 mg). Chemotherapy was infused over 20–30 min immediately before the first RT fraction in the morning. It was withheld in patients with compromised hearing and renal function, with frailness, multimorbidity, subnormal leuko- and thrombocyte counts and those who refused consent.

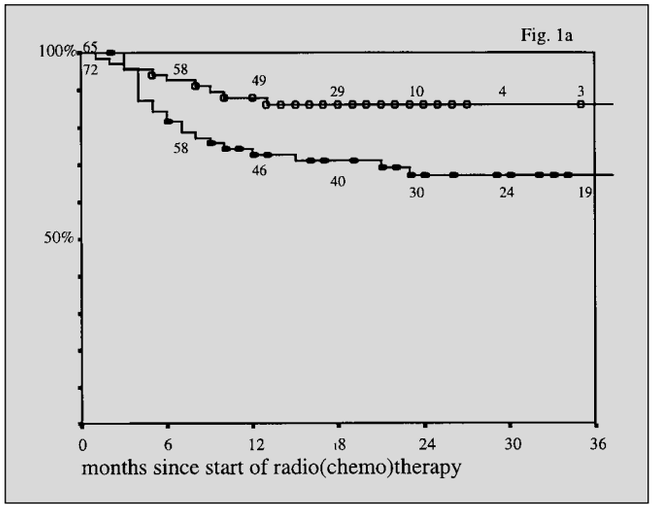
The decision in favor of one of the RT methods was at the discretion of the attending physician responsible for the patient (no randomization). In the course of the observed period, more patients were submitted to accelerated treatment because it was felt that this treatment was more effective. As further analysis will focus on the subgroup of patients receiving sRT (N = 72) and aRCT (N = 65) the distribution of significantly unfavorable factors in both subgroups is given in table 1. There is a balance for nodal status (as well as for other, not significantly influential factors as gender, primary versus secondary treatment, T stage, resection margins). The adverse factors G1–2 grading, oral cavity/floor of mouth tumors and conventional surgery were significantly more prevalent among the sRT patients. On the other hand, aRCT patients had a significantly longer interval between surgery and start of RT (p = 0.000).

Follow-up data was collected from the records of the Radiooncology or/and the Department for Ear, Nose and Throat Diseases. Patients who did not continue the posttherapeutic control program at our institution were contacted and information were obtained from their private specialists. In this retrospective analysis, dead patients without documentation of

Table 1. Distribution of prognostic factors among patients with standard radiotherapy and patients with accelerated radiochemotherapy

Prognostic factor (unfavorable factors mentioned first)	Patients with				p Value
	standard radiotherapy[a]		accelerated radiochemotherapy[b]		
	n	%	n	%	
pN stage					
pN2c/3	17	24	12	18	0.547[c]
pN1/2a/2b	36	50	35	54	
pN0	19	26	18	28	
Grading					
G1–2	34	47	19	29	0.031[c]
G3	38	53	46	71	
Tumor site					
Oral cavity/floor of mouth	32	44	15	23	0.009[c]
Other localisations	40	56	50	77	
Type of surgery					
Conventional surgery	49	68	32	48	0.025[c]
Laser surgery	23	32	33	52	
	mean	range	mean	range	
Time (days) from surgery to radio(chemo)therapy	40.17	18–112	49.68	24–277	0.000[d]

[a] N = 72.
[b] N = 65.
[c] Pearson chi-square test.
[d] t Test for equality of means.



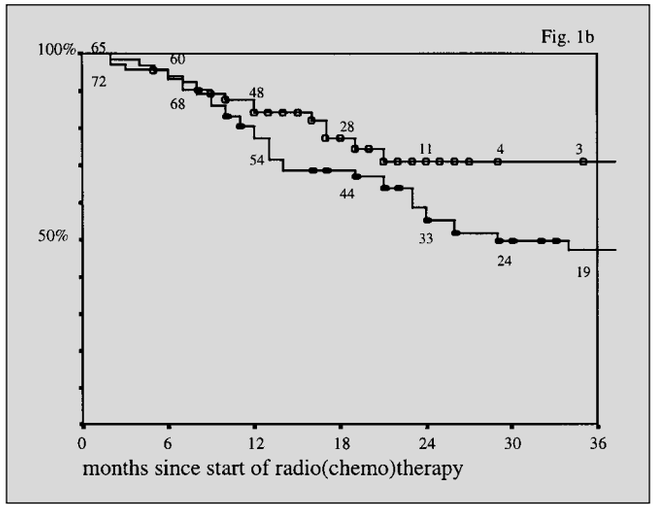


Fig. 1. Actuarial (Kaplan-Meier estimate) locoregional control (**a**) and overall survival (**b**) of patients receiving either postoperative accelerated radiochemotherapy (□; N = 65) or standard radiotherapy (■; N = 78). 3-year locoregional tumor control is 86 and 67%, the difference is significant (p = 0.0282 in log-rank test). 3-year overall survival is 71 and 47% (p = 0.097 in log-rank test).

complications or patients alive with extensive local tumor recurrence were excluded (50 of 229 patients) from the evaluation of chronic side effects. Planned laryngectomy was not evaluated as a side effect, whereas the impossibility of regaining larynx function after temporary tracheostomy was addressed as complication.

Follow-up was calculated from the first day of RT. Actuarial survival and tumor control was estimated by the Kaplan-Meier method. All statistics were computed with the help of SPSS statistics software, version 7.5; the standard error (SE) is indicated in brackets. Survival functions were compared by applying the log-rank test. Prognostic factors (univariate and multivariate) were determined by a time-constant Cox regression model using the forced-entry method and the forward stepwise selection. When both methods yielded the same results, only the data of the forced-entry method is mentioned. It is indicated, if only the forward stepwise selection method yielded significant results. The cut-off value for significance was set at p = 0.05 for all procedures. Prevalence of risk factors in the two treatment groups were calculated by cross-tabs, performing the Pearson chi-square test. Means were compared by t test for equality of means for independent samples.

Results

Survival

Among all observed patients (N = 229), the estimate for 3-year overall survival was 65% (SE 5.3%) for all twice-daily irradiated patients and 53% (SE 4.8%) for all once-daily treated patients (log-rank test p = 0.1751). By comparing the subgroups of patients with short treatment time (aRCT vs. sRT) there was a trend for better survival (fig. 1b) after accelerated treatment, but the difference was not significant (p = 0.097).

Locoregional Control

For the 107 patients treated by twice-daily treatment, the actuarial 3-year locoregional tumor control (control above clavicles) is 76% (SE 4.6%), for those 122 patients receiving once-daily RT, it amounts to 64% (SE 4.8%). The difference is not significant (log-rank test, p = 0.1207). Among all patients (N = 229), multivariate Cox regression analysis for independent prognostic factors was performed in 2 steps (table 2). First, potential tumor- and patient-related variables were screened. The pathological nodal stage emerged as the most powerful prognostic factor. In a second step, treatment-related variables were tested. Here, the only significant factor was type of surgery. Duration of RT, i. e. sRT or aRCT versus prolonged or not accelerated treatment, failed to reach significance (p = 0.1278).

In univariate analysis, patients with aRCT (N = 65) had a significantly better 3-year locoregional control than those with RCT without acceleration (N = 42) (log-rank test, p = 0.051). There was, however, no difference as to locoregional control between patients with sRT (N = 72) and patients with prolonged RT (N = 50; p = 0.804). Therefore, in order to evaluate the effect of accelerated RCT, further analysis compares the subgroups of patients treated with aRCT and sRT, leaving aside the patients with longer treatment time: Multivariate Cox regression analysis of tumor-related variables revealed the same prognostic factors among the subgroup of 137 patients as the analysis for the total of patients shown in table 2. However, Cox regression analysis for treatment-related variables could not isolate a significant factor, type of surgery being again the strongest factor (p = 0.0834). In bilateral comparison, aRCT results in significantly better 3-year locoregional tumor control than sRT (p = 0.0282; fig. 1a), which was confirmed by univariate Cox regression analysis (p = 0.0278). Most subgroups defined by risk factors profited from aRT (significantly or by tendency) with the exception (by tendency) of high pN stage and R1 resection (table 3). Among the 65 patients receiving aRCT, 3-year locoregional tumor control was 85% (SE 5.6%) for those with simultaneous cisplatin, 100% for those with carboplatin (N = 3) and 83% (SE 8.8%) for those without chemotherapy or low cumulative doses (p = 0.701). Univariate Cox regression analysis revealed no significant influence of interval between surgery and irradiation both in the aRCT group (p = 0.496) and the sRT group (p = 0.4738).

Table 2. Multivariate analysis (Cox regression) of prognostic factors for locoregional tumor control among all observed patients (n = 229)

Prognostic factor (unfavorable characteristic mentioned first)	Rank	p Value[1]
Tumor- and patient-related factors		
Pathological N stage (pN2c/3 vs. pN1/2a/2b vs. pN0)	1	0.0001
Grading (G1–2 vs. G3)	2	0.0026
Tumor site oral cavity/floor of mouth	3	0.0136
Tumor site hypopharynx	4	0.0797
Pathological T-stage (pT4 vs. pT3 vs. pT2 vs. pT1)	5	0.1079
Therapy for recurrent tumor	6	0.1733
Extracapsular nodal disease	7	0.4395
Tumorsite oropharynx	8	0.4841
Patient sex (male vs. female)	9	0.6435
Patient age	10	0.6558
Tumor site larynx	11	0.8612
Treatment-related factors		
Type of surgery (conventional surgery vs. CO_2-Laser-Surgery)	1	0.0014
Prolonged time of radiotherapy	2	0.1278
Resection margins	3	0.2008
Type of radiotherapy (one fraction/day vs. two fractions/day)	4	0.4514
Time between surgery and radiotherapy	5	0.9651

[1] Time constant Cox regression analysis.

Distant Metastasis

Multivariate Cox regression analysis identified pN stage (p = 0.0001), hypopharynx as tumor site (p = 0.0021) and pN0/pN+ without extracapsular nodal disease versus pN+ with extranodal disease (p = 0.0287) as significant predictors for distant metastasis. After aRCT, 3-year freedom from distant metastasis was 84% (SE 5.0%) and 75% (SE 5.9%) after sRT; the difference is not significant.

Complications

Complications were evaluated for all patients. Acute mucositis RTOG II–III was encountered in all observed patients. Those receiving twice-daily irradiations usually experienced a peak mucosal reaction during the treatment split and again at the end of RCT. Those getting standard treatment had maximal mucositis during the last 2–3 weeks of therapy. Acute mucositis RTOG IV was documented (no standardized records) for 3 of 107 patients receiving twice-daily RCT. With intensive support (antibacterial and antimycotic) the therapy-free interval could be shortened without giving up the principle that mucositis should be healed (allowing receding mucositis RTOG I) before continuing treatment.

The hazard to develop grade III–IV complications was 17% (SE 4.0%) for the once-daily irradiated patients and 31% (SE 4.8%) for the twice-daily treated patients, the difference not being significant (log-rank test, p = 0.1232). The difference for grade IV toxicity was more pronounced (hazard 4%, SE 2.2% vs. 14%, SE 3.6%), but still not significant (log-rank test, p = 0.0834).

More hematologic toxicity was encountered in 22 patients receiving carboplatin 50 mg/m^2 body surface on treatment days than in 65 patients treated with 6 mg/m^2 cisplatin (Leukopenia: CTC grade 3 after carboplatin 4/22 patients, after cisplatin 1/65; CTC grade 4 after carboplatin 1/22; Thrombocytopenia: CTC grade 3 after carboplatin 6/22 patients, after cisplatin 2/65, CTC grade 4 after carboplatin 2/22 patients; elevation of serum urea (double of normal value) 1/22 after carboplatin, 0/65 after cisplatin).

Discussion

The results of postoperative twice-daily radiochemotherapy (split course with therapy-free interval after 2 weeks) were influenced by overall treatment time. Patients having aRCT (56.7 Gy or 64.7 Gy within 5 weeks) did significantly better (in univariate comparison) than those with prolonged treatment time (p = 0.0509; log-rank test). By comparing postoperative sRT (60 Gy and more in up to 6.5 weeks) with aRCT, a significantly better 3-year locoregional tumor control was found with accelerated fractionation and simultaneous low-dose chemotherapy. This benefit does not yet translate into significantly better overall survival. Whereas locoregional recurrences establish themselves early after therapy, a longer time of observation is required before judging definitively the effect on overall survival.

These observations confirm the experiences of Amdur [1] who found significantly worse disease specific and overall survival for patients receiving postoperative RT in standard fractionation with treatment split.

No significant influence was found of the interval between surgery and radiotherapy, which varied widely in this retrospective analysis (table 1). Other authors [2, 5] report likewise about only a tendency for better tumor control if RT is begun within 6 weeks; in the retrospective analysis of Amdur et al. [1] the time interval was not prognostically relevant. We observed better locoregional control within the overall aRCT group, although the mean interval between surgery and initiation of RT had been longer there than in the sRT group.

There are, however, two reports providing conflicting results. These authors [3, 10], both applying accelerated radiotherapy with concomitant boost regimes to exclusively high-risk patients, find a significant influence of the time (4 resp. 6 weeks) between surgery and RT. In our subgroup analysis, the small group of high-risk patients (pN2c/3, R1-resection) did not profit from aRCT. The fact that the high-risk patients of the aRCT collective had been waiting longer for start of adjuvant treatment (mean 58 days) than those of the sRT group (mean 44 days) might have been adverse, and acceleration or simultaneous chemotherapy could not compensate for it. As hypothesized by Peters and Withers [8] and supported by clinical data from Trotti [3], the interval between surgery and radiotherapy is characterized by accelerated repopulation. Locoregional

Table 3. Patients with short treatment time (n = 142): Subgroup analysis of actuarial locoregional 3-year control (Kaplan-Meier-estimate)

Subgroup by risk factor	Locoregional control in patients with				p Value
	standard radiotherapy (N = 72)		accelerated radio-chemotherapy (N = 65)		
	%	SE	%	SE	
pN stage					
pN0	74	10	94	5	n.s.
pN1/2a/2b	63	9	94	4	0.0091
pN2c/3[a]	68	12	49	15	n.s.
Resections margins					
R0	71	11	83	11	n.s.
Close margins	58	9	91	5	0.0006
R1[b]	75	11	71	12	n.s.
Grading					
G1–2	55	9	72	10	n.s.
G3	78	7	91	4	n.s.
Tumor site					
Oral cavity/floor of mouth	57	9	73	12	n.s.
No extension to oral Cavity/floor of mouth	75	8	89	5	n.s.
Timing of treatment					
Primary therapy	70	6	83	6	n.s.
Therapy for recurrent Tumor after surgery alone	54	12	94	6	0.0182

[a] In this subgroup the mean intervall between surgery and radiotherapy was 43.8 days for patients with standard treatment and 58.0 days for patients with accelerated treatment (t test; p value 0.037).
[b] In this subgroup the mean interval between surgery and radiotherapy was 42.5 days for patients with standard treatment and 46.9 days for patients with accelerated treatment (t test; p value 0.518).

control in high-risk patients might be more dependant on the time elapsed since surgery, maybe due to higher tumor load.
Interestingly, high or moderate differentiation of squamous cell carcinoma appeared as a significant adverse factor. The ability to accelerated repopulation seems to be more developed in well and moderately differentiated tumors than in poorly differentiated ones [11]. Therefore treatment time should be particularly influential in better differentiated tumors, affecting G3 tumors less. Although G3 tumors were prevailing among the twice-daily irradiated patients, locoregional control was significantly dependent on treatment time. Our regimen is a split-course regimen and long treatment interruptions might be detrimental even to G3 tumors. In subgroup comparison between aRCT and sRT, we found a nonsignificant trend for better locoregional control after aRCT both for G1/2 and G3 tumors. Again, this observation does not appear to be consistent with a different ability for accelerated repopulation in G2 and G3 tumors. However, the differences did not reach significance and other factors might have also influenced the results.
Our data reconfirms earlier observations which find tumor features to be strong prognostic factors in postoperative RT.
The aRCT and sRT collectives differ in the distribution of risk factors (table 1) with a preponderance of three unfavorable factors in the sRT group, but a balance as to the most influential factor, which was nodal stage.
The data do not allow us to analyze the effect of simultaneous low-dose chemotherapy. More toxicity was encountered after carboplatin than after cisplatin, maybe due to a relatively higher dosage. Other authors [12] applied also 6 mg/m^2 cisplatin 5 times per week up to a cumulative dose of 270 mg/m^2 versus carboplatin 25 mg/m^2, which is half of dose applied by us, and found an equivalent effect in simultaneous radiochemotherapy for inoperable head and neck tumors. Their third treatment arm consisted of RT alone and resulted in significantly worse locoregional control. In postoperative therapy Bachaud [7] found a significant benefit for simultaneous cisplatin given once per week up to a cumulative dose of 350–450 mg absolute.
For patients with high nodal stage, the risk to develop distant metastasis was impressively high (60% after 4 years for pN2c and pN3). Tumor site hypopharynx and extracapsular extension of nodal disease were also predictive of distant metastasis. Whereas the recurrence pattern after primary radio(chemo)-

therapy for inoperable head and neck tumors is dominated by locoregional failures [13], at least within this subgroup of patients, distant metastases became a frequent cause of death. The efficacy of adjuvant chemotherapy to prevent distant metastasis in combination with postoperative RT is not established yet [14, 15] and currently tested in a German multicenter trial (ARO-96-3).

Severe chronic toxicity was more often encountered after twice-daily RCT than after once-daily RT (difference not significant), although most patients received a lower total dose than with standard fractionation. Other trials applying accelerated fractionation for head and neck tumors found significantly worse toxicity [overview 8] than after standard fractionation or hyperfractionation. We gave twice-daily single doses of 2.1 Gy in midline 8 fractions per week (weekly dose 16.8 Gy) according to a previously developed protocol [16]. As the reaction of late responding tissues is related to the size of dose per fraction, decreasing single dose to 1.8 Gy (9 fractions per week), as meanwhile implemented, might reduce late complications.

The retrospective data presented seems to support the hypothesis that postoperative aRCT results in better locoregional control. However, multivariate analysis misses significance and the influence of misbalance of prognostic factors among aRCT and sRT patients remains unclear. Further evidence must be expected from a randomized trial with stratification according to risk factors as well as a constant interval between surgery and initiation of RT.

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