Accelerated Radiotherapy with Concomitant Boost Technique (69.5 Gy/5 weeks)

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Accelerated Radiotherapy with Concomitant Boost Technique (69.5 Gy/5 weeks)

An Alternative in the Treatment of Locally Advanced Head and Neck Cancer

Jiri Kubes[1], Jakub Cvek[2], Vladimir Vondracek[1], Miloslav Pala[1], David Feltl[2]

Background and Purpose: To present the feasibility and results of accelerated radiotherapy with concomitant boost technique (69.5 Gy/5 weeks) in the treatment of locally advanced head and neck cancer.
Patients and Methods: A total of 65 patients were treated between June 2006 and August 2009. The distribution of clinical stages was as follows: II 11%, III 23%, IV 61%, and not defined 5%.
Results: The median follow-up was 30.5 months. The treatment plan was completed in 94% of patients. Patients were treated using the conformal or intensity-modulated radiotherapy (IMRT) technique. The median overall treatment time was 37 days (13–45 days). The mean radiotherapy dose was 68.4 Gy (16–74 Gy). Overall survival was 69% after 2 years. Disease-free survival was 62% after 2 years. Acute toxicity ≥ grade 3(RTOG scale) included mucositis (grade 3: 42.6%), pharynx (grade 3: 42.3%), skin (grade 3: 9.5%), larynx (grade 3: 4%), while late toxicity affected skin (grade 3: 6.25%) and salivary glands (grade 3: 3.7%).
Conclusion: Accelerated radiotherapy with concomitant boost technique is feasible in patients with locally advanced head and neck cancer, has an acceptable toxicity profile, and yields promising treatment results.

Key Words: **Accelerated radiotherapy · Head and neck cancer · Concomitant boost**

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Akzelerierte Strahlentherapie in Concomitant-Boost-Technik (69,5 Gy/5 Wochen) als Therapiealternative für lokal fortgeschrittene Kopf-Hals-Tumoren

Hintergrund und Ziel: Präsentation von Durchführbarkeit und Ergebnissen der Strahlentherapie mit Concomitant-Boost-Technik (69,5 Gy/5 Wochen) bei der Behandlung von lokal fortgeschrittenen Kopf-Hals-Tumoren.
Patienten und Methodik: Im Zeitraum 6/06 bis 8/09 wurden 65 Patienten behandelt. Stadienverteilung: II in 11%, III in 23%, IV in 61% und undefinierbar in 5% der Fälle.
Ergebnisse: Mediane Beoachtungszeit: 30,5 Monate. Die geplante Therapie ließ sich bei 94% der Patienten durchführen. Die Patienten wurden mit 3D-konformaler oder IMRT-Technik bestrahlt. Der Median der Bestrahlungsdauer betrug 37 Tage (13–45 Tage). Die applizierte durchschnittliche Dosis betrug 68,4 Gy (16–74 Gy). Das gesamte 2-Jahres-Überleben betrug 69%, Das krankheitsfreie 2-Jahres-Überleben 62%. Akuttoxizitäten von mindestens Grad 3 (RTOG Skala) betrafen Mukositis (Grad 3: 42%), Pharynx (Grad 3: 42,3%) Haut (Grad 3: 9,5%) und Kehlkopf (Grad 3: 4%). Die Spättoxizitäten betrafen Haut (Grad 3: 9,5%) und Speicheldrüsen (Grad 3: 3,7%).
Schlussfolgerung: Die akzelerierte Strahlentherapie mit der Concomitant-Boost-Technik ist bei Patienten mit Kopf- und Halstumoren durchführbar. Diese Technik hat ein akzeptables Toxizitätprofil und gute Heilungsergebnisse.

Schlüsselwörter: **Akzelerierte Strahlentherapie · Kopf- und Halstumoren · Concomitant-Boost-Technik**

Introduction

The role of the time factor in the radiotherapy of spinal cell head and neck cancer is well known. The prolongation of overall treatment time worsens treatment results and diminishes the effective dose of normofractionated radiotherapy approximately with 0.6–0.8 Gy/day with prolongation of overall time beyond 21 days [14, 18]. This is due to the accelerated repopulation of tumor cells, which occurs between day 21 and 28 following the start of radiotherapy. The optimal overall treatment time should be approximately equal to the time of the

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commencement of accelerated repopulation; the prolongation of overall time may diminish the biological dose due to tumor stem cell repopulation, while shortening of the radiotherapy course can prevent the full effects of reoxygenation and redistribution of tumor cells. The effect of overall treatment time was confirmed in many retrospective analyses and randomized clinical trials [16, 19]. Acceleration of the radiotherapy course is one possibility for intensifying treatment.

Hyperfractionation is another confirmed possibility for dose escalation. Application of the higher dose during the same time interval improves treatment results in randomized trials [10, 15]. Moreover, hyperfractionation can be more significant in the second part of the radiotherapy course due to the shortening of the effective doubling time of tumor cells [3].

There are various types of concomitant boost techniques described in literature. The most common variant utilizes a dose of 72 Gy delivered over 6 weeks. This schedule was more effective with respect to local control than normofractionated radiotherapy in the randomized trial [10]. More intensive shortening to 5 weeks with minimal dose reduction resulted in the improvement of local control and overall survival as compared to normofractionated radiotherapy [11]. A similar accelerated schedule with high dose and short treatment time (69.5 Gy/5 weeks) in the treatment of head and neck cancer was applied by Terhaard et al. [21]. They reported excellent treatment results for this schedule in laryngeal tumors, with the majority of patients in stage T2 or T3. We adopted this schedule for the treatment of locally advanced head and neck cancer (in particular stage IV) of various localizations. The aim of our work was to evaluate the feasibility and effectiveness of this technique for the presented group of patients.

Material and Methods

Between January 2006 and June 2009, we used this schedule for the treatment of 65 patients with head and neck cancer (55 men and 10 women; 85% of them with locally advanced tumors, mainly oropharyngeal and laryngeal tumors). Inclusion criteria were histologically verified spinal cell tumor, clinical stage III to IV (unfavorable II), performance status according to WHO scale 0–1. Concomitant chemotherapy was contraindicated in the majority of patients or was refused by the patient. The contraindication for the chemotherapy was mostly due to insufficient renal function rather than to the performance status of patients. The main characteristics of the patient group are outlined in Table 1.

Protocol Compliance

The planned treatment was completed by 58 (89%) of the 65 patients included. The prolongation of treatment due to complications with delivering the prescribed dose was observed in 3 patients. The treatment was stopped prematurely in 4 cases. Reasons for termination of treatment were peritonitis after percutaneous endoscopical gastrostomy and refusal of treatment.

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristika.

		Value (%)
Gender	Male	55 (85%)
	Female	10 (15%)
Age	Mean	58.6 years
	Range	38–78 years
Anatomic sites	Oropharynx	27 (41.5%)
	Larynx	21 (32.3%)
	Hypopharynx	5 (7.7%)
	Oral cavity	7 (10.8%)
	Nasopharynx	1 (1.5%)
	Other	4 (6.15%)
AJCC stage	II	7 (10.7%)
	III	15 (23%)
	IV	40 (61.5%)
	Not defined	3 (4.6%)
T stage	T0	0
	T1	0
	T2	13 (20%)
	T3	21 (32.3%)
	T4	29 (44.5%)
	TX	2 (3.1%)
N stage	N0	25 (38.7%)
	N1	9 (13.8%)
	N2a	8 (12.3%)
	N2b	9 (13.8%)
	N2c	9 (13.8%)
	N3	3 (4.6%)
	NX	2 (3.1%)
Histology	Epidermoid	65 (100%)
Histological grade	Gx	9 (13.8%)
	G1	19 (29.2%)
	G2	31 (47.7%)
	G3	5 (7.7%)
	G4	1 (1.5%)

Radiotherapy Technique

The treatment was performed on linear accelerators with a nominal photon beam energy of 6 MeV. Clinical target volume for the initial phase of treatment included the primary tumor and involved lymph nodes (GTV) with a 10 mm margin for subclinical spreading and neck lymphatic regions according to the institutional protocol for various primary sites (in the majority of cases the Ib–V bilateral and retropharyngeal regions). Boost volume included only the primary tumor and involved nodes with a 10 mm margin for CTV. Critical organs were the spinal cord ($D_{max} \leq 50$ Gy) and parotid glands ($D_{mean} \leq 28$ Gy). IMRT with 5 or 7 fields was usually used. The dose was normalized to the maximum in PTV and the dose was prescribed to the reference isodose (usually 93%). The planned course duration was 5 weeks (optimal being 32 days). A total of 10 fractions of 2 Gy (fractions 1–10) plus 15 fractions of 1.8 Gy (fractions

11–25) for a total dose of 47 Gy were prescribed in the initial volume and 15 fractions of 1.8 Gy (22.5 Gy) (starting from fraction 11) were prescribed in the boost volume. The total dose was 69.5 Gy/5 weeks. The interval between irradiation of the initial and boost volumes was at least 6 hours. The compensatory fractions to the boost volume were applied in the case of treatment interruption lasting longer than 2 days. The majority of patients had percutaneous endoscopic gastrostomy (PEG) introduced during the first 2 weeks of treatment.

Evaluation of Treatment Effects

Acute and late toxicities were evaluated according to the RTOG scale. The tumor response was assessed by clinical examination at 3-month intervals and with CT or MRI imaging 3 month after radiotherapy and, thereafter, once a year.

Statistics

Overall survival (OS) and disease free survival (DFS) were calculated using the Kaplan–Meier method. Univariate analysis of predictive factors was undertaken using the Gehan–Wilcoxon test. A p value > 0.05 was considered to be significant.

Results

The median follow-up time in December 2009 was 30.5 months. The treatment was completed successfully in 61 of 65 patients (94%). The treatment was stopped before the planned 69.5 Gy for 4 patients. The planned dose was exceeded in 9 patients due to compensation for treatment interruptions. The mean applied dose was 68.4 Gy (range: 16–74 Gy). The median course duration was 37 days (range: 13–45 days). The acute toxicity grade 3 or 4 was observed in the pharynx and esophagus (42%), skin (10%), mucous membranes (43%), and larynx (4%). Maximal toxicity was observed during weeks 5 and 6 after the start of treatment. There were no toxic deaths as a result of treatment. Late toxicity was scored according to RTOG criteria ≥ 3 or more months after the termination of treatment. Late toxicity grade ≥ 3 was observed in skin (6%) parotid glands (4%), but not in the spinal cord or subcutaneous tissue.

A total of 48 patients were alive and 17 patients died (2 of them without tumor) at the time of evaluation in March 2010. A persistent or recurrent tumor was detected in 22 patients.

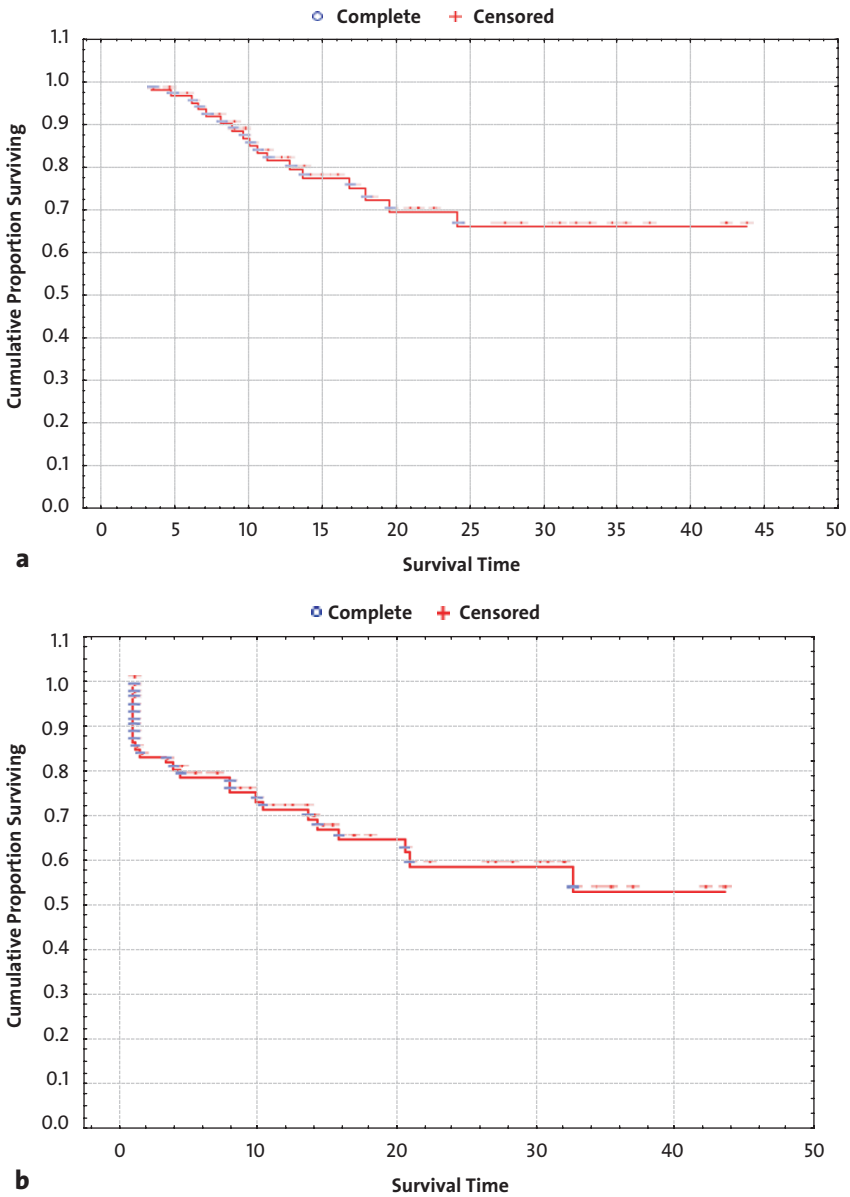

Figure 1. Kaplan–Meier curves for overall (**a**) and disease-free survival (**b**).

Abbildung 1. Kaplan–Meier-Kurven für Gesamtüberleben (**a**) und krankheitsfreies Überleben (**b**).

There were 21 locoregional failures and 1 synchronous locoregional and distant failure. The 2-year overall survival rate was 69% and the 2-year disease-free survival was 60%. Kaplan–Meier survival curves for overall and disease free survival are shown in Figure 1.

The influence of T stage, N stage, clinical stage, tumor grade, the site of primary tumor, the overall treatment time (with a cut-off of 37 days), and IMRT technique to the overall survival and the disease-free survival were evaluated. Only N stage N0 was significantly better in DFS (p = 0.014) and clinical stage IV was significantly worse in OS (p = 0.028) and DFS

Table 2. The following parameters were used for calculations. Tumor: α/β = 10 Gy; α = 0.35 Gy-1; Tk = 21 d; Tp = 3 days; mucous membrane: α/β = 10 Gy; α = 0.35 Gy-1; Tk = 7 d; Tp = 2.5 days; late tissues: α/β = 3 Gy; α = NA; Tk = ∞; Tp = ∞ [17]. BEDs for the CAIR trial are calculated before dose modification. TD: ((■1)), OT: ((■1)), BED: biologically effective doses.

Tabelle 2. Für die Berechnung wurden folgende Parameter benutzt. Tumor: α/β = 10 Gy; α = 0.35 Gy-1; Tk = 21 d; Tp = 3 Tage; Schleimhaut: α/β = 10 Gy; α = 0.35 Gy-1; Tk = 7 d; Tp = 2.5 Tages; Spät reagierende Gewebe: α/β = 3 Gy; α = NA; Tk = ∞; Tp = ∞ [17]. BEDs für die CAIR Studie wurden vor der Modifikation berechnet. TD: ((■1)), OT: ((■1)), BED: ((■1)).

Regimen	TD	OT	BED tumor	BED late	BED acute
70 Gy/35 fractions (7 weeks)	70	46	67.5	116.7	53.1
HFX 81.6 Gy/68 fractions (1.2 Gy) (7 weeks) [5]	81.6	45	73.0	114.2	61.29
CB 72 Gy/42 fractions (6 weeks) [6]	72	39	72.4	113.0	58.96
CB 69.5 Gy/40 fractions (5 weeks) [9]	69.5	32	74.31	109.8	56.24
CAIR 70 Gy/35 fractions (5 weeks) [4]	70	32	75.7	116.7	62.61

(p = 0.027), which was expected. There was a trend toward better results in shorter overall treatment time and IMRT technique; however, it was not statistically significant.

Discussion

Local control is still the main problem of the treatment of locally advanced head and neck cancer [6], which can be solved by two different methods: (1) using a standard radiation dose (about 70 Gy of normofractionated radiotherapy) in combination with concomitant chemotherapy or biological treatment or (2) using a more effective radiotherapy schedule. Concomitant chemotherapy is a widely accepted schedule, with 4–8% improvement in results as compared to radiotherapy alone [17]. However, the addition of chemotherapy significantly increases the toxicity of treatment and limits radiotherapy dose escalation. Moreover, the higher dose of concomitant chemotherapy may yield poorer results [20] and the combination of chemotherapeutic agents has higher toxicity regardless of the treatment results [22]. Concomitant application of biological treatment is also effective and possibly less toxic [1], but higher than primarily published toxicity of concomitant biological treatment was also described [12].

Radiotherapy alone can be intensified in two ways. The first is total dose escalation and the second is the shortening of overall treatment time. Concomitant boost technique combines the advantages of hyperfractionated and accelerated schedules, i.e., sparing of healthy tissues and preventing the accelerated repopulation of tumor cells.

The prolongation of treatment course duration over 4 weeks may lead to the loss of the applied dose (about 0.6–0.8 Gy/day)[14, 18]. Prolongation of overall treatment time is a negative prognostic factor for local control of the disease [16, 19]. In contrast, shortening treatment time to less than 3 or 4 weeks increases the toxicity without effecting local control, as was described in the CHART trial [4]. Optimal radiotherapy treatment time for head and neck cancer is most likely the same as the kick-off time of accelerated repopulation, which is about 28 days after treatment start [7].

The risk of alternative fractionated schedules is increased toxicity, both acute and late. For example, acceleration in the CAIR trial caused strong acute toxicity with "consequential" late effects necessitating a change to the fractionation schedule [19]. Acute reaction is the main problem of all regimens with significant acceleration and high total dose [2]. Mathematic modeling of fractionation for tumor, acute, and late tissues is necessary. Such a model was described by Fowler using the LQ model approach with consideration of the time factor. Biologically effective doses (BED) for tumor, acute, and late tissues can be determined using Equation 1. A BED lower than 117 Gy is considered acceptable for late effects (derived from BED for 70 Gy of normofractionated radiotherapy) [8]. Dose limits for acute reaction of mucous membranes are approximately 59–63 Gy [9]. Table 2 shows that the concomitant boost regimen has the best ratio of BED for tumor, late tissues, and acute tissues as compared to most widely used regimens.

$$BED = nd(1 + (d/(\alpha/\beta))) - ((\log_e 2(T - Tk)/\alpha \cdot Tp) \quad (1)$$

Concomitant boost schedules in the treatment of head and neck cancer are described in literature and their effectiveness and safety were verified in randomized trials. The most frequently used regimen is 72 Gy in 6 weeks [10]. Overall treatment time for this regimen is 40 days, which is still much longer than the presumed optimal treatment time with regard to accelerated repopulation of tumor cells. This regimen is more effective than normofractionated radiotherapy in locoregional control with a mild increase of acute, but not late toxicity. Concomitant boost technique with the shortening of treatment time to 5 weeks (33 days) and a total dose 69.5 Gy was published by Terhaard et al. [21]. The authors reported excellent effectiveness and an acceptable toxicity profile for this technique. This technique was used primarily for the treatment of localized laryngeal cancer with the majority of T2 or T3 and N0 stages. The paper did not present volumes of GTV, but based on the stages it can be inferred that tumors were smaller than in our group of patients. The simultaneous integrated boost IMRT technique with the shortening of overall treatment time is also highly effective, as was described. However, this technique was used on intermediate T stage tumors [13]. Our work shows that this regimen can be safely used for the treatment of locally advanced head and neck cancer in localizations other than the larynx, with large boost volumes.

Overall survival and disease-free survival are better than the results in the majority of published series. This may be due to selection bias as this kind of treatment is offered to patients with better treatment compliance. On the other hand, a significant number of patients were treated with accelerated

radiotherapy due to contraindication for chemotherapy, so it can be inferred that they had substantial comorbidities.

The presented results demonstrate that the acute toxicity of the regime is comparable with the toxicity of normofractionated chemoradiotherapy. The percentage of mucositis and dermatitis grade 3 is slightly higher than during chemoradiotherapy (70 Gy/35 fractions/7 weeks with weekly cisplatinum 40 mg/m^2; data not published) at our institution, but the time of severe mucositis is shorter. Every patient was provided with percutaneous gastrostomy (PEG) before the treatment. We strongly recommend this with respect to mucosal reaction grade. The absence of hematological and renal toxicity is one of the main advantages of the presented schedule. Another indispensable advantage is limited nausea and emesis, which contributes to the weight loss and deterioration of patients during concomitant chemoradiotherapy. The late toxicity is acceptable and is not different from chemoradiotherapy.

A remarkable fact is that the number of distant metastatic recurrences is very low, which may be a result of a small number of patients with high grade (grade 3 or 4) tumors that have higher metastatic potential. A high number of low grade tumors may also contribute to the high effectiveness of the schedule. Epidermoid tumors with good or intermediate differentiation have higher dependency on overall treatment time [5].

Conclusion

Accelerated radiotherapy with concomitant boost (69.5 Gy/5 weeks) is a safe and highly effective technique for patients with locally advanced head and neck cancer. This schedule appears to be optimal with respect to the ratio of antitumor effectiveness and acute and late toxicities, based on both clinical results and mathematical modeling. It can be recommended as an alternative in the case of a contraindication to concomitant chemoradiotherapy and possible as a first choice treatment for grade 1 or 2 epidermoid tumors, where the effect of the acceleration will be most prominent. Additional dose escalation, especially to the GTV, is possible with careful radiobiological modeling.

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