IMRT using simultaneous integrated boost (66 Gy in 6 weeks) with and without concurrent chemotherapy in head and neck cancer – toxicity evaluation

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Received: 16.11.2007
Accepted: 2.04.2008
Subject: original paper

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Source of support:
Supported by Research Project of the Ministry of Health of Czech Republic MZO 00179906.

SUMMARY:

AIM: To evaluate the toxicity of intensity-modulated radiotherapy with simultaneous integrated boost (SIB-IMRT) in head and neck cancer patients treated using a protocol comprising 66 Gy to the PTV1 (planning target volume; region of macroscopic tumour) and 60 Gy and 54 Gy to the regions with high risk (PTV2) and low risk (PTV3) of subclinical disease in 30 fractions in six weeks.

MATERIAL AND METHODS: Between December 2003 and February 2006, 48 patients (median age 55; range 25–83, performance status 0–1) with evaluable non-metastatic head and neck cancer of various localizations and stages (stages: I–1; II – 8; III – 12; IV – 27 patients, resp.) were irradiated according to the protocol and followed (median follow-up 20 months; range 4–42). Ten patients underwent concurrent chemotherapy (CT) and in 15 patients the regimen was indicated postoperatively because of close or positive margins. In all cases the regimen was used as an alternative to conventional radiotherapy (70 Gy in 7 weeks). The acute and late toxicities were evaluated according to RTOG and RTOG/EORTC toxicity scales, respectively.

RESULTS: All patients finished the treatment without the need for interruption due to acute toxicity. No patient experienced grade 4 toxicity. More severe acute toxicity was observed in patients with CT, but the most severe toxicity was grade 3. Grade 3 toxicity was observed in the skin, mucous membrane, salivary glands, pharynx/oesophagus and larynx in 8.4%, 35.4%, 39.6% and 2.1%, in the CT subgroup in 10%, 100%, 90%, 10%, respectively. The trend of impairment of acute toxicity by concurrent chemotherapy was statistically confirmed by Fisher's exact test (for mucous membranes $p=0.000002$ and pharyngeal/oesophageal toxicity $p=0.0004$). The most severe late toxicity was grade 2 subcutaneous tissue (34.2%), mucous membrane (36.8%) and larynx (11.1%), grade 3 in salivary gland (2.6%) and grade 1 in skin (84.2%) and spinal cord (5.4%). The late toxicity was not increased by chemotherapy.

CONCLUSION: In light of the toxicity profile we consider the presented regimen to be an alternative to conventional radiotherapy 70 Gy in 7 weeks. The addition of CT requires more intensive supportive care.

KEY WORDS: head and neck cancer; intensity-modulated radiotherapy; toxicity

BACKGROUND

In the last few years intensity-modulated radiotherapy (IMRT) has experienced a massive expansion in the radiotherapy of head and neck tumours. IMRT promises highly conformal dose distributions around tumour targets and sparing of the critical organs involved. The possibility to spare eye bulbs, optic nerves and chiasma, brain stem and temporal lobes of brain dosimetrically favours the IMRT techniques in nasopharyngeal, maxillary sinus and nasal cancers [1–3]. The other important advantage of IMRT in head and neck cancer is the possibility of parotid salivary gland sparing. There is already sufficient evidence of the clinical advantage of IMRT parotid-sparing technique after demonstration of a decrease of the risk of late xerostomia [4–7].

IMRT offers a possibility of planned dose inhomogeneity in the planning target volume (PTV). The dose per fraction in the region with high risk of recurrence (region of tumour) is

higher than in other regions of the PTV. This principle is called simultaneous integrated boost (SIB, SIB-IMRT). The advocates of SIB-IMRT techniques emphasize the better conformality of irradiation in comparison to shrinking volumes techniques [8–10]. However, there is no widely accepted SIB-IMRT regimen for head and neck tumours.

All patients in the present study were irradiated by SIB-IMRT technique using a uniform fractionation regimen: a dose of 66 Gy to the region of primary tumour and clinical lymphadenopathy or tumour bed with positive or close margins, a dose of 60 Gy to the high-risk region of subclinical disease, and 54 Gy to the low-risk region of subclinical disease in 30 fractions in six weeks. The regimen resembles the fractionation used in the RTOG H-0022 trial (multicentre phase II trial for oropharyngeal cancer T1-2, N0-1M0). The dose of 66 Gy in six weeks is biologically equivalent to 70 Gy in 7 weeks [9]. Concurrent chemotherapy was added based on current practice in conventional radiotherapy. In SIB-IMRT clinical trials published so far there is limited information about the toxicity data for an SIB-IMRT uniform regimen equivalent to 70 Gy in conventional radiotherapy. In comparison with RTOG H-0022 the present trial included patients with cancer sites in the head and neck region other than the oropharynx, as well as patients with locoregionally advanced cancer, who were ineligible for dose escalation or another more toxic treatment approach (SIB-IMRT alone), and patients with concurrent chemotherapy.

AIM

The aim of the present study was to evaluate the acute and late toxicity in head and neck cancer patients treated by SIB-IMRT regimen, comprising 66 Gy to the PTV1 (region of macroscopic tumour) and 60 Gy and 54 Gy to the regions with high risk (PTV2) and low risk (PTV3) of subclinical disease in 30 fractions in six weeks, as well as the experience with concurrent chemotherapy.

MATERIALS AND METHODS

Patients

Between December 2003 and February 2006, 51 patients with head nad neck cancer were irradiated at our department using SIB-IMRT, regimen 66 Gy, 60 Gy and 54 Gy in 30 fractions. In three patients the treatment was terminated prematurely. In one patient the IMRT was interrupted after a few initial fractions because of urgent tracheostomy. The patient then finished the radiotherapy by conventional technique and the cause of acute suffocation was not interpreted in relation with radiotherapy. The two other patients refused to continue the radiotherapy after approximately half of the treatment. The acute toxicity in these patients did not exceed grade 2 in any organ. All three patients were excluded from evaluation.

All 48 evaluable patients were indicated for radiotherapy after histological verification of carcinoma (mostly squamous cell carcinoma) in the head and neck region, and regional lymph node irradiation was indicated in all patients. All patients were primarily examined by an otolaryngologist (including endoscopy), and computer tomography of the head and neck, chest X-ray and liver ultrasound were indicated before treatment in all patients. Magnetic resonance was used in patients with tumours close to the skull base (mainly paranasal sinus and nasopharyngeal cancers).

In all patients the regimen was an alternative to conventional radiotherapy with a dose of 70 Gy alone or with concurrent chemotherapy. Originally, the regimen was indicated only in patients with early head and neck cancer stages, in patients with advanced disease, but unsuitable for dose escalation (age, other diseases) and in nasopharyngeal cancer with concurrent and adjuvant chemotherapy. Later, the regimen with concurrent chemotherapy was indicated in patients with locally and regionally advanced cancer of localizations other than nasopharyngeal in the head and neck region.

Twenty-three patients were irradiated with curative intent. In fifteen cases the radiotherapy was performed postoperatively because of positive or close histological margins. Ten patients were treated by concurrent radiotherapy and chemotherapy (in all cases cisplatin 40 mg/m^2 weekly). Patients with locally or regionally advanced disease treated by radiotherapy alone were assessed as unsuitable for dose escalation or concurrent chemotherapy. Three patients with nasopharyngeal carcinoma were subsequently indicated for adjuvant chemotherapy (3 cycles of cisplatin 80 mg/m^2

on day 1 and continual 5-fluorouracil 1000 mg/m^2 on days 2–5 every four weeks).

One patient was treated by immunosuppressive therapy after kidney transplantation and one patient had chronic therapy by low-dose methotrexate for gout until the first week of radiotherapy. All patient and tumour characteristics are described in Table 1.

Treatment planning and radiotherapy

Two planning systems were used – CadPlan Treatment Planning System (Varian Medical Systems Inc., Palo Alto, USA) with Helios module for inverse planning, and Eclipse (Varian Medical Systems Inc., Palo Alto, USA). To define planning target volumes and organs at risk we used planning computer tomography (slice gaps of 3–5 mm) with the intravenous application of contrast medium (if no contraindication); fusion with magnetic resonance was performed in some cases (nasopharyngeal, maxillary sinus and nasal cavity cancers). During the treatment planning procedures and radiotherapy, the head and shoulders of patients are strictly immobilized by thermoplastic masks.

Table 1. Patient and tumour characteristics

Gender (n):	
Male	41
Female	7
Age (y):	
Median	55
Range	25–83
Tumour site (n):	
Oropharynx	17
Hypopharynx	11
Larynx	9
Nasopharynx	5
Maxillary sinus	4
Nasal cavity	2
Histological type	
Squamous cell carcinoma	43
Undifferentiated carcinoma	3
Adenocarcinoma	1
Adenoid cystic carcinoma	1
Tumour stage (n):	
I	1
II	8
III	12
IV	27
Radiotherapy (n):	
RT alone	23
Concurrent RT and CT	10
Postoperative RT	15

"Abbreviations: RT = radiotherapy; CT = chemotherapy."

Gross tumour volume (GTV), clinical target volume (CTV) and planning target volumes (PTV) were defined according to the International Commission on Radiation Units and Measurements (ICRU) Report 50 recommendations. PTV1 encompassed all macroscopic disease (= GTV) with a border (usually 1–2 cm, minimally 0.5cm) for risk of microscopic spread (CTV) and set-up inaccuracies (PTV). PTV2 and PTV3 encompassed the regions (lymph nodes) at high risk and low risk of subclinical spread of the disease (CTVs), respectively, with 5mm margin.

The following structures at risk were defined and contoured: spinal cord, spinal cord + 1 cm margin (for set-up inaccuracy risk), both parotid glands, brain stem and oral cavity and posterior neck region as help structures. In patients with primary tumour localizations near the skull base (nasopharyngeal and maxillary sinus carcinomas), eye bulbs, optic nerves and chiasma were defined. Prescription doses for PTVs and tolerance doses for organs at risk are presented in Table 2.

The equivalent uniform dose for PTVs was calculated according to Niemierko with parameter a=–8 [11].

$$EUD = \left(\sum_{i=1}^{N} v_i D_i^a\right)^{1/a} \quad (1)$$

All patients were irradiated on a Clinac 600C linear accelerator (Varian Medical Systems Inc., Palo Alto, USA) with dynamic multileaf collimator (2x26 leafs). The prescribed physical doses (66 Gy, 60 Gy and 54 Gy, respectively) were delivered in 30 equivalent fractions in 6 weeks.

The absolute dose and dose fluences were verified using film dosimetry before treatment. The set-up accuracy was checked minimally once a week by a portal image system. The tolerable set-up error in set-up was 3 mm

in each axis. In case of set-up error of 3–5 mm the portal image was repeated next fraction. In case of set-up error of 3–5mm repeatedly or set-up error > 5mm the patient was resimulated. We did not assess the necessity of re-planning in any patient due to weight loss or tumour shrinkage.

Acute and late toxicity evaluation

All patients were examined by a radiation oncologist minimally once a week during the treatment. Subsequently, the patients were followed every 3 months for the first 3 years by a radiation oncologist and head/neck surgeon. The median follow-up of the whole group of patients was 20 months (4–42 months).

Acute toxicity was evaluated according to the RTOG (Radiation Therapy Oncology Group) toxicity scale for skin, mucous membrane, salivary glands, pharynx/oesophagus and larynx. All toxicity symptoms during the radiotherapy and three months after treatment completion were included in the evaluation. At the beginning of the trial it was not our institution's policy to have prophylactic percutaneous endoscopic gastrostomy (PEG) placement. During the trial we changed the approach to supportive care and the patients who had primary swallowing difficulties or who were planned for concurrent chemotherapy were indicated for prophylactic PEG placement. This non-uniformity in supportive care was the reason not to evaluate the weight loss separately.

Late toxicity was evaluated according to the RTOG/EORTC (European Organization for Research and Treatment of Cancer) Late Radiation Morbidity Scoring Schema for skin, subcutaneous tissue, mucous membranes, salivary glands, spinal cord and larynx. The function of salivary glands was assessed by quantitative pertechnetate scintigraphy (before radiotherapy, 3–6 months and more than one year after radiotherapy). The patients with persistence or early local recurrence (< 6 months) with subsequent palliative care or death by six months after starting radiotherapy were excluded from the late toxicity evaluation (11 patients) as the local symptoms were distorted by the local progression of the disease. In one patient with persistence of laryngeal cancer where salvage total laryngectomy was performed, laryngeal late toxicity evaluation was not possible. The median follow-up of the subgroup suitable for late toxicity evaluation was 23 months (8–42 months).

Table 2. Prescription doses for planning target volumes and tolerance doses for main organs at risk

Structure	Prescription
PTV66 PTV60 PTV54	Minimally 95% of prescribed dose to 95% of the volume. Maximal dose ≤ 115% of prescribed dose $EUD_{PTV66}(a=-8)$ equivalent to the prescribed dose GTV is in minimally 95% isodose
Spinal cord	Maximum dose <44 Gy
Spinal cord + margin 1 cm	Maximum dose <50 Gy
Brain stem	Maximum dose <54 Gy
Parotid glands	Minimally 50% of gland volume dose <30 Gy or mean dose <28 Gy
Larynx (if it is not a part of PTV)	2/3 below 50 Gy

"Abbreviations: PTV – planning target volume; EUD – equivalent uniform dose; GTV – gross tumor volume."

The overall survival, disease-free survival, locoregional control and distant metastasis-free survival were not the primary aims of the present retrospective study due to heterogeneity in primary tumour site, stage and intent of radiotherapy. In addition, an analysis of local and regional recurrences was made.

Statistical analysis

The chi-square and Fisher's exact test were used for a comparison of subgroups with and without concurrent chemotherapy. Kaplan-Meier curves were calculated for locoregional-free survival, distant-metastasis-free survival, disease-free survival and overall survival.

RESULTS

The mean PTV1 (volume irradiated to dose of 66 Gy) was 289 ccm (range 83–825 ccm). The criteria for dose distribution (Table 2) with sparing of at least one parotid gland were met in 75% of patients. When a macroscopic tumour (primary tumour or lymphadenopathy) was close to the parotid gland, it was not considered advisable to spare it. Higher mean doses in parotid glands were recorded among the first twelve patients who were planned with the Cadplan planning system.

All 48 patients finished the therapy without the need for interruption due to acute toxicity. In patients with concurrent CT, the median number of administered cycles was 4 (range 3–6). The reasons for discontinuation of chemotherapy were leukopenia grade 3 (3 cases), elevation of serum creatinine (1 case), performance status impairment (3 cases, mainly in connection with grade 3 pharyngeal/oesophageal toxicity – loss of weight, parenteral hydration and nutritional support) and acute herpetic infection (1 case with 3 cycles of CT).

No patient experienced unacceptable grade 4 toxicity. We registered grade 3 toxicity in 4 patients (8.4%) in skin toxicity (confluent, moist desquamation), in 17 patients (35.4%) in mucous membrane toxicity (confluent fibrinous mucositis), in 19 patients (39.6%) in pharyngeal toxicity evaluation (weight loss > 15% and severe dysphagia), and in 1 patient (2.1%) in laryngeal toxicity evaluation (whispered speech and marked arytenoid oedema).

More severe toxicity was observed in patients with concurrent chemotherapy, in a patient treated by immunosuppressive therapy and in a patient treated with low-dose methotrexate in the first week of radiotherapy, but grade 3 toxicity at most. Grade 3 acute hypopharyngeal/oesophageal toxicity was classified due to weight loss and severe dysphagia with the necessity of parenteral nutrition and rehydration or PEG usage. The statistical analysis confirmed worse acute toxicity in the subgroup with concurrent chemotherapy in comparison to the subgroup without chemotherapy, mainly in mucous membrane and pharyngeal/oesophageal toxicity. All acute toxicity data are shown in Table 3.

The highest grade of late toxicity according to the RTOG/EORTC scale was grade 3 in salivary gland toxicity in one patient. In this patient with oropharyngeal cancer (but also with hepatic cirrhosis after hepatitis type C treated by interferon alpha) treated by radiotherapy alone, and followed for 25 months, both parotids were spared according to the protocol, but there was noted severe mucous acute toxicity grade 3 during radiotherapy. The majority of patients reported an improvement of xerostomia approximately one year after the radiotherapy. The subjective feeling of xerostomia in all patients corresponded to the results of quantitative pertechnetate scintigraphy of salivary glands.

The late toxicity in any other organ did not exceed grade 3. In comparison of subgroups with and without concurrent chemotherapy there were not noticed statistical significances except spinal cord toxicity. Two patients with nasopharyngeal cancer and multiple lymphadenopathy with concurrent chemotherapy presented transient Lhermitte's sign (approximately 4–12 months after radiotherapy). Both patients were young (36 and 42 years old) and they were treated by adjuvant chemotherapy because of nasopharyngeal primary localisation. The IMRT plans and portal images of these patients were checked (maximal set-up error 3.4 mm and 3.1mm, respectively), the

Table 3. Acute toxicity evaluation according to RTOG scale – absolute and relative numbers of patients (parenthesis – number of patients with concurrent chemotherapy)

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	p*	p⁺
SKIN	0	26 (1) 54.2% (10.0%)	18 (8) 37.5% (80.0%)	4 (1) 8.4% (10.0%)	0	0.005	1.0
MUCOUS MEMBRANE	0	4 (0) 8.4% (0.0%)	27 (0) 56.2% (0.0%)	17 (10) 35.4% (100.0%)	0	0.00001	0.000002
SALIVARY GLANDS	0	19 (0) 39.6% (0.0%)	29 (10) 60.4% (100.0%)	-	0	0.004	-
PHARYNX & ESOPHAGUS	0	11 (0) 22.9% (0.0%)	18 (1) 37.5% (10.0%)	19 (9) 39.6% (90.0%)	0	0.001	0.0004
LARYNX	0	25 (1) 52.1% (10.0%)	22 (8) 45.9% (80.0%)	1 (1) 2.1% (10.0%)	0	0.003	0.2

* p values of the chi-square test for radiotherapy vs. radiotherapy plus concurrent chemotherapy.
⁺p values of the Fisher exact test (RTOG Grade < 3 versus ≥ 3) for radiotherapy vs. radiotherapy plus concurrent chemotherapy

tolerance doses in spinal cord region were not exceeded (maximum spinal cord dose 38.9 and 39.0 Gy, maximum spinal cord + 1cm margin dose 47.7. and 48.0 Gy, respectively), and no other cause of myelotoxicity was observed. In one patient a trismus persisted and in one patient normal swallowing was not restored. These patients are partly dependent on PEG intake. Observed late toxicity data are shown in Table 4.

To complete the information, the locoregional-free survival, distant-metastasis-free survival, disease-free survival and overall survival of the cohort were evaluated using Kaplan-Meier method (Figure 1). A subanalysis of local recurrences according to site of primary tumour, tumour stage and modality combination was made (Table 5). All local recurrences were in the region of the primary tumour (PTV1) except one, which was considered to be a marginal miss (in a patient with postoperative IMRT of maxillary sinus carcinoma, the recurrence was close to the spared optic nerve in the orbital apex).

DISCUSSION

The present study evaluated the toxicity of SIB-IMRT fractionation regimen 66 Gy – 60 Gy – 54 Gy in 30 fractions in head and neck cancer patients. In the view of biological equivalency to conventional doses of 70 Gy, 60 Gy and 50 Gy, respectively [9], the regimen was used as an alternative to conventional 70 Gy in all patients.

The early results of the RTOG H-0022 trial with the same fractionation regimen in early

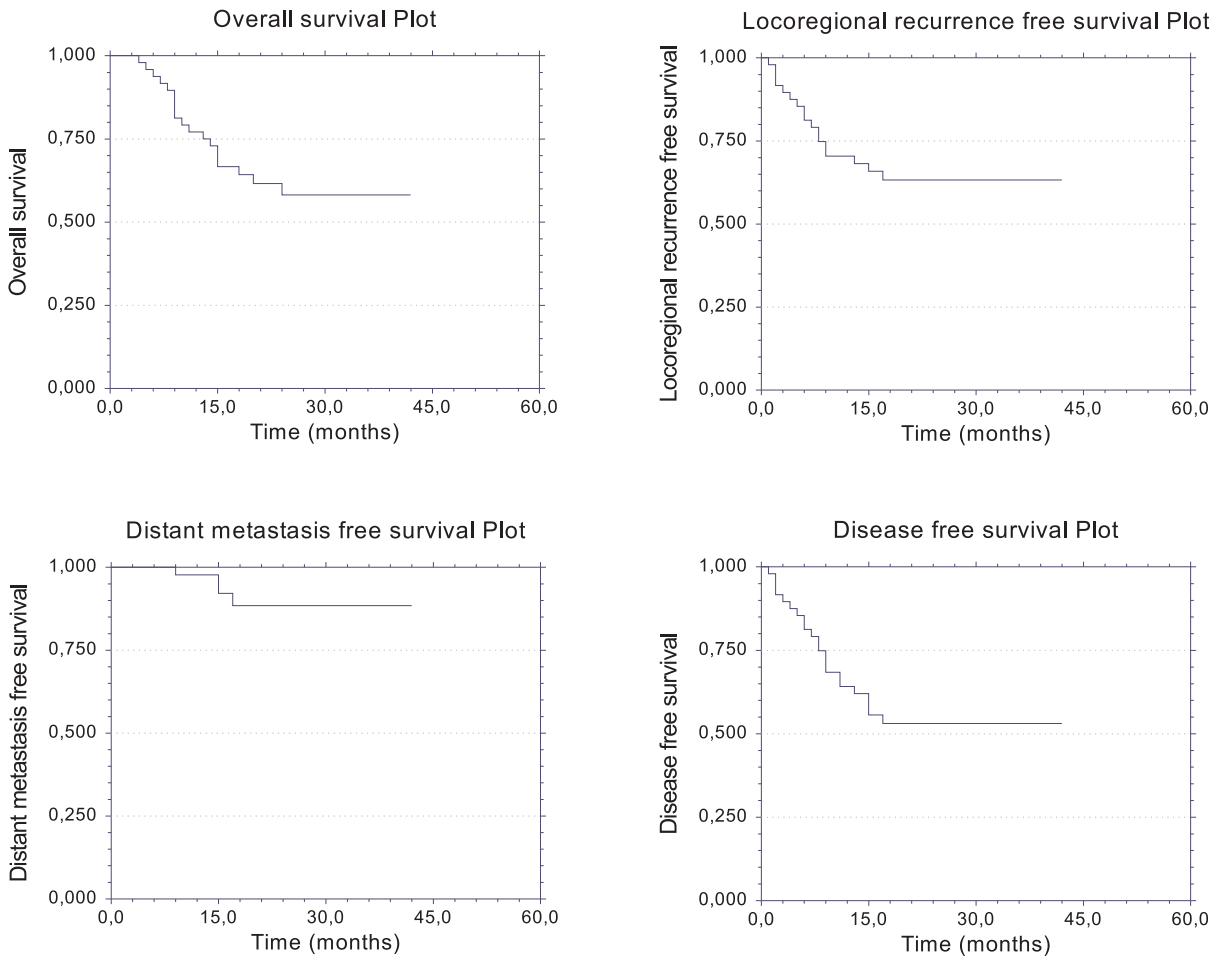

Fig. 1. Kaplan-Meier curves of overall survival, distant metastasis free surival, locoregional recurrence free survival and disease free survival.

Table 4. Late toxicity evaluation according to RTOG/EORTC scale – absolute and relative numbers of patients (parenthesis - number of patients with concurrent chemotherapy)

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	p*	p+
SKIN	6 (0) 15.8% (0.0%)	32 (8) 84.2% (100.0%)	0	0	0	0.2	-
SUBCUTANEOUS TISSUE	0	25 (4) 65.8% (50.0%)	13 (4) 34.2% (50.0%)	0	0	0.3	0.4
MUCOUS MEMBRANE	3 (0) 7.9% (0.0%)	21 (5) 55.3% (62.5%)	14 (3) 36.8% (37.5%)	0	0	0.6	1.0
SALIVARY GLANDS	9 (1) 23.7% (12.5%)	23 (6) 60.5% (75.0%)	5 (1) 13.1% (12.5%)	1 (0) 2.6% (0%)	0	0.8	1.0
SPINAL CORD	36 (6) 94.6% (75.0%)	2 (2) 5.4% (25.0%)	0	0	0	0.005	-
LARYNX	8 (1) 22.2% (12.5%)	24 (6) 66.7% (75.0%)	4 (1) 11.1% (12.5%)	0	0	0.7	1.0

* p values of the chi-square test for radiotherapy vs. radiotherapy plus concurrent chemotherapy.
+p values of the Fisher exact test (RTOG Grade < 2 versus ≥ 2) for radiotherapy vs. radiotherapy plus concurrent chemotherapy

Table 5. Analysis of locoregional recurrences according to primary tumour site, stage of the disease, intent of radiotherapy and age.

Group	Locoregional recurrence	%
Tumour site:		
Oropharynx	2/17	11.8
Hypopharynx	7/11	63.6
Larynx	3/9	33.3
Nasopharynx	1/5	20.0
Maxilary sinus	3/4	75.0
Nasal cavity	1/2	50.0
Stage:		
I	0/1	0.0
II	3/8	37.5
III	2/12	16.6
IV	12/27	44.4
Intent of radiotherapy:		
Radiotherapy alone	10/23	43.5
Chemoradiotherapy	3/10	30.0
Postoperative radiotherapy	4/15	26.7
Age (years):		
< 70	12/41	29.3
≥ 70	5/7	71.4
Total:	**17/48**	**35.4**

stages of oropharyngeal cancer were published at the American Society for Therapeutic Radiology and Oncology Annual Meeting in 2006. Eisbruch et al. [12] reported results in 67 evaluable patients: acute xerostomia grade 2 and 3 in 49% and 1.5%, mucositis grade 3 and 4 in 25% and 1.5% and skin toxicity grade 3 and 4 in 10% and 0% of patients, respectively. The frequencies for late xerostomia at median follow-up of 13.3 months after treatment started were 20% and 1.5% for grade 2 and 3, respectively.

However, at the same time this fractionation scheme has to be considered inadequate for locally and regionally advanced head and neck cancers, as well as for postoperative radiotherapy in patients with positive margins and extracapsular spread of the disease. There are three possible approaches to enhance the radiobiological effect of radiotherapy on the tumour in locally and regionally advanced disease. The most common practice is the use of a higher dose than 66 Gy in 30 fractions (70 Gy or more) [13–15]. On the other hand, there are data showing that dose escalation has limits in acute reactions. Lauve et al. [13] concluded that the "maximal tolerable dose" is 70.8 Gy in 30 fractions (dose per fraction 2.36 Gy). The acute toxicity in two patients irradiated to a dose of 73.8 Gy (dose

per fraction 2.46 Gy) required a treatment break and dose reduction. Butler et al. [16] earlier referred 20 patients irradiated in 25 fractions in five weeks to a total dose of 60 Gy and 50 Gy, respectively (dose per fraction 2.4 Gy and 2.0 Gy, respectively). 80% of patients developed RTOG grade 3 acute mucositis and 50% grade 3 pharyngitis. The high number of grade 3 acute side effects corresponds to the escalation of dose per fraction. Furthermore, there is still limited evidence that the higher dose per fraction cannot increase the late effect probability.

In conventional RT guidelines there is now a widely accepted standard – the use of concurrent chemotherapy. The analogical CT schemes can be considered to be useful in SIB-IMRT techniques, but there is a necessity to confirm it in clinical trials. Concurrent CT usually belongs to IMRT protocols for nasopharyngeal cancer [2,17]. The toxicity profile in these trials was acceptable. Lee et al. [18] recently published a study with SIB-IMRT regimen with dose 70 Gy, 59.4 Gy and 54 Gy in 33 fractions and concurrent CT (mostly two cycles of cisplatin 100 mg/m^2 every 3–4 weeks) in 41 patients with locally advanced oropharyngeal cancer. Acute grade 3–4 mucous toxicity was reported in 66% of patients, and late xerostomia grade ≥ 2 was reported in 12% of cases.

The last option consists in a further alteration of the regimen – hyperfractionation. However, there is only limited experience with the use of hyperfractionated SIB-IMRT in head and neck cancer [19].

The present trial confirms the feasibility and very good tolerance of this regimen without concurrent chemotherapy in head and neck cancer. The addition of chemotherapy is supposed to be related to an increase in acute toxicity severity. Our acute toxicity data are in accordance with this hypothesis. The risk of acute toxicity grade ≥ 3 in conventional fractionation was reported at generally less than 25%, but in some studies up to 50% [20]. The alteration of fractionation causes higher incidence of mucosal reactions (≥ 66%) [20] and in some cases the acute toxicity was the cause of discontinuation of clinical studies [21]. Similarly, the limit of chemotherapy enhanced radiotherapy is acute toxicity, mainly in CT enhanced altered radiotherapy regimens, where grade 3–4 mucosal toxicity can reach 100% [22]. The acute toxicity data in the present study are not different from estimated values experienced from conventional radiotherapy of 70 Gy in seven weeks.

Concurrent CT shifts the acute toxicity to the levels of dose escalation trials. Similarly to conventional chemoradiotherapy, the administration of concurrent chemotherapy in IMRT techniques requires intensive supportive care, mainly nutrition support. Inadequate supportive care may be the reason for administration of an incomplete number of CT cycles in some patients.

The late toxicity was not unambiguously increased by concurrent chemotherapy (Table 4). The two cases of transient Lhermitte's sign (grade 1 of late myelopathy) in the chemoradiotherapy group cannot be explained simply by the addition of concurrent cisplatin. The exact cause of the myelopathy in these patients is not clear, but the occurrence of Lhermitte's sign is not unusual in nasopharyngeal cancer patients [23, 24]. All late toxicity data correspond to data from previously published head and neck cancer IMRT trials. The use of quantitative pertechnetate scintigraphy has shown advantages in late xerostomia evaluation.

Disease control was not the primary endpoint of this retrospective evaluation. The analysis of local recurrences noticed an unexpected low local control in the hypopharyngeal cancer subgroup. Histologically confirmed persistence of the disease was detected in three patients in stage II of hypopharyngeal cancer after radiotherapy alone (age 55, 76 and 83 years, respectively), although the expected local control in early stages of hypopharyngeal cancer is 68–79% [25]. In other patients with local persistence or recurrence of hypopharyngeal cancer, radiotherapy was indicated for extensive inoperable disease.

CONCLUSIONS

Although the cohort is a heterogeneous group of patients in terms of primary tumour location, stage of the disease and radiotherapy approach (primary versus postoperative RT, concurrent CT), the present data confirm the feasibility of this regimen in patients with head and neck cancer. The regimen without CT can be used in patients unable to receive a more intensive regimen (dose escalation,

chemoradiotherapy). Concurrent CT increases the acute toxicity similarly to conventional radiotherapy and there are similar demands on supportive care as in conventional radiotherapy with concurrent chemotherapy (mainly nutritional support). In light of the acute and late toxicity profiles we consider the presented regimen to be a possible alternative to conventional radiotherapy (70 Gy / 7 weeks), although there is a necessity to confirm the regimen with or without concurrent chemotherapy for each primary tumour localization and stage. It could be an alternative to conventional radiotherapy also in view of local control and overall survival.

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