ORIGINAL ARTICLE

IMRT WITH THE USE OF SIMULTANEOUS INTEGRATED BOOST IN TREATMENT OF HEAD AND NECK CANCER: ACUTE TOXICITY EVALUATION

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Summary: Acute toxicity has been evaluated in head and neck cancer patients treated with intensity-modulated radiotherapy using simultaneous integrated boost (SIB-IMRT). The basis of the treatment protocol is an irradiation in 30 fractions with a total dose: 66 Gy to the region of macroscopic tumor, 60 Gy to the region of high-risk subclinical disease and 54 Gy to the region of low-risk subclinical disease. Between December 2003 and September 2005, 38 patients with carcinoma of different locations in the head and neck region were irradiated. Five patients underwent concurrent chemotherapy (weekly cisplatin). Acute toxicity was evaluated according to Radiation Therapy Oncology Group toxicity scale for skin, mucous membrane, salivary glands, pharynx and esophagus and larynx. All 38 patients completed the therapy without urgency of interruption due to acute toxicity of radiotherapy. No patient experienced grade 4 toxicity. More severe toxicity was observed in patients with concurrent chemotherapy. The results confirm that the irradiation according to our SIB-IMRT protocol is a therapy with acceptable toxicity and there is a space for radiobiological enhancement of this regimen by concurrent chemotherapy, e.g. weekly cisplatin.

Key words: *Head and neck cancer; IMRT; Simultaneous integrated boost; Acute toxicity*

Introduction

Radiotherapy (RT) plays an essential role in the management of head and neck cancer. In early stage lesions, radiotherapy can be preferred because it is as effective as surgery in controlling the disease and it has better cosmetic and functional outcome. In advanced stages, RT is used in the postoperative setting or as a primary curative treatment. In most cases, the irradiation should encompass both primary tumor (or tumor bed in postoperative setting) and regional lymphatic nodes.

Radiotherapy treatment planning in head and neck region is more complicated than RT in other regions, mainly due to many critical structures which are necessary to spare (spinal cord, brain stem, brain, optic nerves and chiasma, eyes, salivary glands etc.).

Intensity-modulated radiotherapy (IMRT) is a relatively new radiotherapy technique. It allows highly conformal dose distributions around tumor targets and sparing of the critical organs involved. Cancers in head and neck region became an ideal model for the application of IMRT. The possibility to spare eye bulbs, optic nerves and chiasma, brain stem and temporal lobes of brain dosimetrically favours IMRT in nasopharyngeal, maxillary sinus and nasal cancers (17,25). One of the main advantages of oropharyngeal, hypopharyngeal and laryngeal cancers is the possibility of parotid salivary glands sparing. There is already sufficient evidence of dosimetric and mainly clinical advantage of IMRT parotid sparing technique.

IMRT offers not only critical structures sparing, but also a dose escalation in regions with high risk of local recurrence (primary tumor or tumor bed) in each fraction. This principle is called simultaneous integrated boost (SIB). There are many possible SIB fractionation regimens. Apparently, the most frequent regimen is 66 Gy in 30 fractions to the primary tumor region (2.2 Gy per fraction, biological equivalent 70 Gy in conventional regimen 2 Gy per fraction), 60 Gy to the high-risk subclinical disease region (2.0 Gy per fraction, biological equivalent 60 Gy in conventional regimen) and 54 Gy to the low-risk subclinical disease region (1.8 Gy per fraction, biological equivalent 50 Gy in conventional regimen).

All patients treated at our department by intensity-modulated radiotherapy using simultaneuous integrated boost (SIB-IMRT) and fractionation mentioned above were identified with the aim of acute toxicity evaluation.

Materials and Methods

Patients

Between December 2003 and September 2005, 41 patients started radiotherapy according IMRT-SIB protocol (regimen 66 Gy, 60 Gy and 54 Gy in 30 fractions) at our department. In three patients the treatment was terminated early. In one patient the IMRT was finished after few initial fractions due to necessity of urgent tracheostomy. The patient then completed radiotherapy by conventional technique and the cause of acute suffocation was not interpreted to be in relationship with radiotherapy. The two other patients refused to continue the radiotherapy after completing approximately half of the treatment sessions. Their acute toxicity evaluation did not exceed grade 2 in any organ. All three patients were excluded from acute toxicity evaluation.

All 38 patients included in evaluation had histological verified carcinoma (mostly squamous cell carcinoma) in the head and neck region and all patients had indications for irradiation of regional lymph nodes. Twenty six patients were irradiated with the primary curative intent, in twelve cases the radiotherapy was perfomed postoperatively due to positive or close histological margins. Five patients were treated by concurrent radiotherapy and chemotherapy (cisplatin 40 mg/m^2 weekly). It is necessary to mention accidental treatment of other diseases, which certainly influenced acute toxicity of the patients. One patient was treated by imunosupressive therapy after kidney transplantation and one patient had a chronic therapy with low-dose metotrexate for gout in the first week of the radiotherapy. All patient and tumor characteristics are indicated in Tab. 1.

Treatment planning and radiotherapy

Two planning systems – 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) were used. For defining of planning target volumes and organs at risk planning computer tomography with an application of contrast medium (if no contraindication), in some cases fusion with magnetic resonance, was used. During the treatment planning procedures and radiotherapy head and shoulders of patients were strictly immobilized by thermoplastic masks.

Gross tumor 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 reccommendation. PTV66 encompassed all macroscopic disease (= GTV) with a border (usually 1–2 cm, minimally 0,5 cm) for risk of microscopic spread (CTV) and set-up inaccuracies (PTV). PTV60 and PTV54 encompassed the regions (lymph nodes) with high risk and low risk of subclinical spread of the disease, recpectively. The following structures at risk were defined and contoured: spinal cord, spinal cord + 1 cm margin (for set-up inaccuracies risk), both parotid glands, brain stem and oral cavity and posterior neck region as help structures. In patients with primary tumor localizations near scull base (nasopharyngeal and maxillary sinus carci-

Tab. 1: Patient and tumor characteristics.

Gender (n):	
Male	32
Female	6
Age (y):	
Median	55
Range	25–83
Tumor site (n):	
Oropharynx	13
Hypopharynx	6
Larynx	8
Nasopharynx	5
Maxillary sinus	4
Nasal cavity	2
Histological type	
Squamous cell carcinoma	35
Undifferentiated carcinoma	1
Adenocarcinoma	1
Adenoid cystic carcinoma	1
Tumor stage (n):	
I	1
II	7
III	11
IV	19
Radiotherapy (n):	
RT alone	21
Concurrent RT and CT	5
Postoperative RT	12

Abbreviations: RT = radiotherapy; CT = chemotherapy.

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

Structure	Prescription
	Minimally 95% of prescribed dose to 95% of the volume
PTV66	Maximal dose ≤ 15% of prescribed dose
PTV60	EUD_{PTV66}(a=-8) equivalent to the prescribed dose
PTV54	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.

nomas) eye bulbs, optic nerves and chiasma were also defined. Prescription doses for PTVs and tolerance doses for organs at risk are shown in Tab. 2. It is necessary to point out that not all these demands could be fulfilled in all patients. For example, when macroscopic tumor was close to organ at risk (primary oropharyngeal tumor or lymphadenopathy close to parotid gland etc.), a compromise had to be chosen. The equivalent uniform dose for PTVs was calculated according Niemierko with parametr a=-8 (21).

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

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

Acute toxicity evaluation

The patients were minimally once a week examined by a physician during the treatment. Acute toxicity was evaluated according to the RTOG (Radiation Therapy Oncology Group) toxicity scale for skin, mucous membrane, salivary glands, pharynx and esophagus and larynx (Tab. 3).

Tab. 3: RTOG acute toxicity criteria.

organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamatiom other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste	———	Acute salivary gland necrosis
PHARYNX & ESOPHAGUS	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
LARYNX	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

Results

All 38 patients finished the therapy without the need of interruption due to acute toxicity. No patient experienced unacceptable grade 4 toxicity. We registered even acceptable grade 3 toxicity in 2 patients (5.3%) in skin toxicity evaluation, in 11 patients (28.9%) in mucouse membrane toxicity evaluation, in 14 patients (36.8%) in pharyngeal toxicity evaluation, and in 1 patient (2.6%) in laryngeal toxicity evaluation. More severe toxicity was observed in patients with concurrent chemotherapy, in patient treated by imunosupressive therapy and in patient treated with low-dose metotrexate in the first week of the radiotherapy, however grade 3 toxicity at most. Grade 3 acute hypopharyngeal/oesophageal toxicity was classified mainly due to weight loss and severe dysphagia with the necessity of parenteral rehydratation. The mucous mebrane acute reactions grade 3 were higher in subgroup with concurrent chemotherapy as expected: mucous membrane toxicity in 5/5 patients (100%) and pharyngeal/oesophageal toxicity in 4/5 patients (80%), but the number of patients in this subgroup is too small for larger statistical analysis. All acute toxicity data are shown in Tab. 4.

Tab. 4: Acute toxicity evaluation according to RTOG scale – absolute number of patients (in curves – number of patients with concurrent chemotherapy).

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SKIN	0	24 (1)	12 (4)	2 (0)	0
MUCOUS MEMBRANE	0	4 (0)	23 (0)	11 (5)	0
SALIVARY GLAND	0	15 (0)	23 (5)	–	0
PHARYNX & ESOPHAGUS	0	10 (0)	14 (1)	14 (4)	0
LARYNX	0	21 (1)	16 (3)	1 (1)	0

Discussion

The standard of radiotherapy of head and neck cancer is still conventional or conformal radiotherapy with the use of conventional fractionation regimen (2 Gy per fraction). In locally or locoregionally advanced lesions there are two main ways to improve treatment results of RT in curative setting: first is an alteration of fractionation regimen and second is a use of concurrent chemotherapy. The radiobiological enhancement by an alteration of fractionation regimen can be based on a compression of overall treatment time, as e.g. in Dahanca 6,7 trials (22), or a hyperfractionation or a combination of both (accelerated hyperfractionation eventually the use of concomitant boost technique). In all these approaches the locoregional control and survival were significantly improved in comparison to conventional regimen, although there is a higher risk of late effects in some of these regimens (2,5,14).

The second possibility to enhance the effect of radiotherapy is the concurrent chemotherapy (CT). There are many chemotherapy regimens used as concurrent CT, in most cases they are based on cisplatin. In a large meta-analysis reported, Pignon et al analysed data from 10471 patients treated between 1965–1993 in 63 randomised trials. The improvement of overall survival was noted only in concurrent combination of chemotherapy and radiotherapy but not in patients treated with neoadjuvant or adjuvant CT. The absolute survival benefit of concurrent CT was 8% in this meta-analysis (23). The update of the meta-analysis, by adding to the data base the data from the randomized trials performed between 1994 and 2000, was presented in 2004 at ASCO Annual Meeting by Bourhis et al (4). The absolute benefit of concurrent CT was still 8% in overall survival, but the magnitude of the benefit was significantly higher for platinum-based CT than for other CT. The highest benefit was noted in cisplatin alone – 11% (although there was no statistical significance compare to cisplatin poly-CT). The benefit of concurrent CT was noted over the last years in randomized trials with altered regimens of radiotherapy (6) and also in postoperative setting (3,9).

The intensity-modulated radiotherapy has been introduced to the clinical practice approximately in the half of the last decade. IMRT is considered to be very effective and perspective radiotherapy technique, but this method is considered to be still experimental in many cases. The dosimetric advantage of IMRT is a possibility to spare organs at risk better than in conventional and conformal RT, mainly in concavities of PTV. Many authors prefer IMRT in nasopharyngeal cancer due to a concave shape of region of primary tumor. There are also many data about better post-RT parotid gland function (and better quality of life) when parotid glands sparing approach is used (1,8,12,18,26). The sparing of parotids is now one of the main reasons for an IMRT use in head and neck cancer.

Another important advantage of the IMRT is a possibility of planned dose inhomogennity in PTV – a possibility of simultaneous integrated boost. The advocates of SIB-IMRT techniques emphasize a better conformality of irradiation in comparison to shrinking volumes technique (11,20,26). Radiobiological comparison of several SIB-IMRT regimens was elaborated by Mohan et al (20).

There are few publications as single institutions experiences with the use SIB-IMRT technique (16,27). But there is no standard for fractionation scheme, there is no standard for IMRT planning, for normalization of a plan and many other controversies. The multicentric phase II trial RTOG H-0022 uses fractionation scheme 66 Gy – 60 Gy – 54 Gy in 30 fractions for oropharyngeal cancer stage T1–2N0–1M0. The protocol specifies the prescription dose as the dose that encompasses at least 95% of the PTV, no more than 1% of the PTV can recieve < 93% of the prescribed dose and no more than 20% of the PTV can receive > 110% of the presribed dose (28). The phase II RTOG trial 0025 for nasopharyngeal cancer used radiotherapy or con-

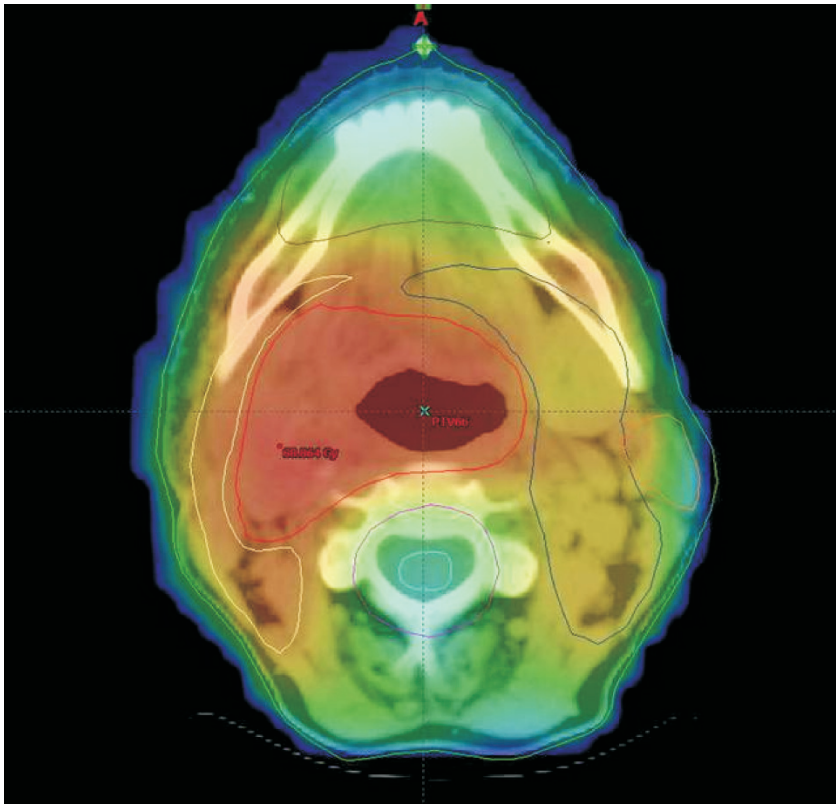

Fig. 1: IMRT-SIB technique (PTV66 – red contour, PTV60 – yellow contour, PTV54 – blue contour).

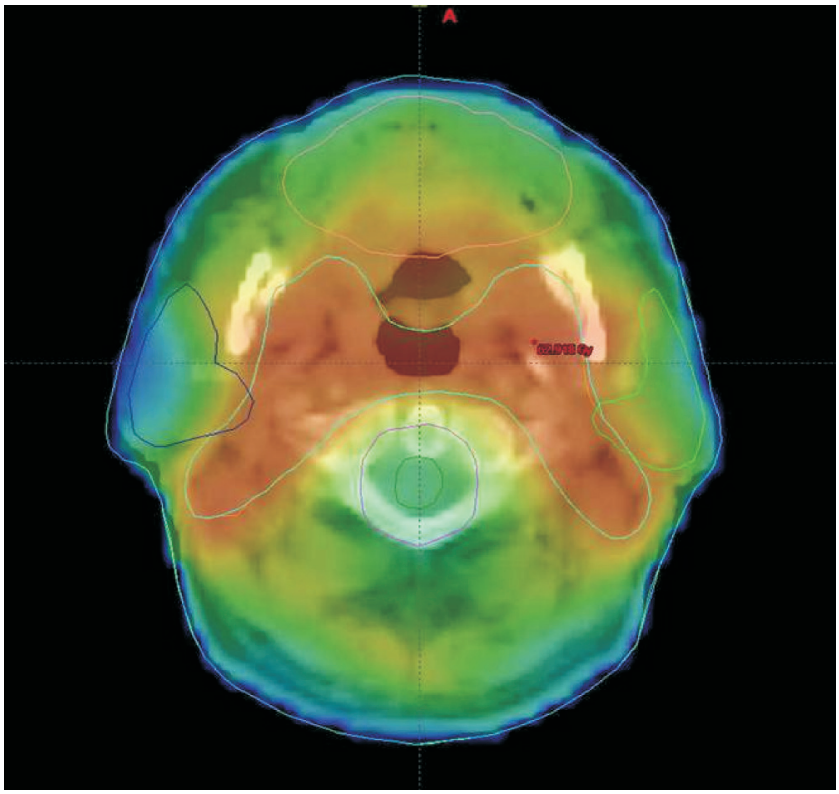

Fig. 2: Sparing of parotid glands by IMRT technique.

current chemoradiotherapy (stage ≥ T2b or node positive) with doses 70 Gy – 59.4 Gy – 50.4 Gy in 33 fractions and similar reccommendations for target coverage (29). In Europe there is a generraly accepted rule that 95% (instead of 100%) of the PTV volume has to recieve 95% of the dose (10). A reason behind this practice is an application of „more real" prescription doses when calculate an equivalent uniform doses according to Niemierko. In the case of the mentioned RTOG studies practice the EUD (PTV) as well as the PTV main dose has to be higher then the prescribed dose. This practice may be considered to be unacceptable because of the dose unequality with convetional plans prepared according to ICRU recommendations.

The present cohort of 38 patients with head and neck cancer with evaluated acute toxicity was treated by SIB-IMRT technique with fractionation regimen 66 Gy – 60 Gy – 54 Gy in 30 fractions. The biological equivalent doses in conventional fractinations are 70 Gy, 60 Gy and 50 Gy (20). Because of this, the regimen cannot be accepted as full-featured for curative RT of locoregionally advanced head and neck cancer. There are three possibilites to enhance effects of radiotherapy. The most common practice is to use a higher dose than 66 Gy in 30 fractions (70 Gy or more) (15,16,27). On the other hand, there are data that dose escalation is tolerability limiting in acute reactions (15), and there is now limited evidence the higher dose per fraction cannot increase the late effect probability. Second option is an alteration of the regimen, e.g. the use of hyperfractionation. At our department we started a clinical trial with hyperfractionated SIB-IMRT regimen. In convetional RT there is now widely accepted standard – the use of concurrent chemotherapy. We suppose the concurrent chemotherapy will become standard also in SIB-IMRT practice.

The risk of acute toxicity grade 3–4 in conventional fractionations is in various studies 25–50% (24). The alteration of fractionation causes higher incidence of mucosal reactions and in some cases the acute toxicity was the cause of discontinuation of clinical studies (13). Similarly, the limit of the chemotherapy enhanced radiotherapy is the acute toxicity, mainly in CT enhanced altered radiotherapy regimens, where grade 3–4 mucosal toxicity can reach 100% (19). There are some data of possible worseness of late toxicity in connection with the concurrent CT (7) but we suppose the late toxicity is in connection with a severe acute mucosal toxicty.

As our department shifts the practice to chemotherapy enhanced SIB-IMRT in locoregionally advanced head and neck cancers in terms of an initiating of a clinical trial we prepared the evaluation of the acute toxicity of head and neck cancer patients treated by the same regimen. Although the cohort is heterogenous group of patients in terms of primary tumor locality, stage of the disease and radiotherapy approach (primary versus postoperative RT, concurrent CT), results of the evaluation confirm a feasibility of this regimen in patients with head and neck cancer, as well as in five patients with concurrent CT. The chronic toxicity evaluation of the cohort will be continously elaborated in next months.

Our results confirm that intensity-modulated radiotherapy with the simultaneous integrated boost and fractionation 66 Gy, 60 Gy and 54 Gy, respectively, in 30 fractions is well-tolerated treatment. Acceptable tolerance of the treatment in patients treated by concurrent administration of weekly ciplatin suggests a potential of this regimen for other tumor localizations in head and neck region then nasopharynx. Complete evaluation of the therapeutic regimen requires longer follow-up and evaluation of chronic toxicity and locoregional control of the disease and overall survivall.

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