JBUON 2013; 18(4): 970-976
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Experience with intensity-modulated radiotherapy in the treatment of head and neck cancer

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Summary

Purpose: *Studies using intensity-modulated radiation therapy (IMRT) in the treatment of head and neck tumors have shown to decrease acute and late radiation toxicity. However, the high conformity of this technique can increase the risk of recurrence due to geographic miss. The aim of this study was to analyze whether the results of IMRT met the theoretical expectations concerning treatment efficacy.*

Methods: *From a total of 185 patients (152 males and 33 females, mean age 58±10.36 years) 176 were evaluable and were studied. Eighty-nine (48.1%) patients had surgical treatment and 50 of them were scheduled for concomitant cisplatin chemotherapy. Irradiation was performed using IMRT, a sliding window with 9 fields in a Varian 2100 C/D linear accelerator, X-ray beam, 6 MeV. The prescribed dose in the planning treatment volume (PTV1), i.e., the area of the primary tumor and nodal area, was 66 Gy/2.2 Gy-70 Gy/2.12 Gy. In the PTV2 (the area at high risk) the dose was 60Gy/2 Gy-59.4 Gy/ 1.8 Gy, and in the PTV 3 (the area treated with prophylactic irradiation) the prescribed dose was 54 Gy/1.8 Gy-50.4 Gy/1.53 Gy.*

Results: *The 3-year overall survival (OS) and relapse-free survival (RFS) of IMRT-treated patients, most of whom were in stages III and IV (158 out of 177), were 50 and 57%, respectively. Using postoperative radiotherapy/chemo-radiotherapy 3-year locoregioncal control was achieved in 75% of the cases as compared with 35% in non-operated patients.*

Conclusions: *The worst outcomes were found in oral cavity and hypopharyngeal tumors, and the best in laryngeal and oropharyngeal tumors. Better results were found in surgically treated patients, and in lower disease stages. Despite the high conformity of dose distribution and efforts to spare healthy tissues, most cases of locoregional relapse occurred in areas receiving the full radiation dose. If dividing relapses into cases of persistence and local recurrence, the former predominated.*

Key words: *head and neck cancer, IMRT, radiotherapy, relapse, survival*

Introduction

IMRT has become one of the most recent additions to the therapeutic options designed to improve the technical parameters of radiotherapy [1]. Use of IMRT in the head and neck area has been recommended based on its ability to provide concave dose distribution and a steep dose gradient in the vicinity of the target volume. A lot of studies have documented high rates of locoregional disease control using IMRT [2-4].

Results of studies designed to assess the efficacy of IMRT have consistently documented a decrease in acute and late radiation toxicity [5].

However, the improved conformity of IMRT is associated with an increased risk of recurrence due to geographic miss. Areas outside the target volumes, yet within the area receiving the full dose in conventional radiotherapy using two opposed contralateral fields, may be affected by subclinical dissemination. This explains why proper selection of target volumes in IMRT is critical for obtaining satisfactory outcomes. Analysis of the

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Received: 13/04/2013; Accepted: 27/05/2013

treatment results is thus a condition sine qua non when adopting this technique.

The aim of our study was to establish whether IMRT efficacy meets the expectations, and to analyse causes of therapeutic failure in a group of IMRT-treated patients with head and neck tumors in a single centre.

Methods

Between 2005 and 2009, IMRT was used to treat a total of 185 patients (152 male, 33 fenale) out of whom 176 were evaluable for follow-up and their data were analysed. Their mean age was 58±10.36 years.

Clinicopathological characteristics are presented in Table 1. While surgery was not performed in 96 (51.9%) patients, 89 (48.1%) had a surgical treatment (44 not radical and 45 radical). All patients provided written informed consent to treatment and data collection. All procedures were in compliance with ethical as well as legal requirements for non-interventional anonymous data collection in the Czech Republic.

IMRT

Target volumes were defined using the ICRU (International Commission on Radiation Units and Measurements) guidelines in their reports No. 50 and No. 62 [7, 8]. Several clinical target volumes (CTVs) were identified in each patient. With radical irradiation, CTV1 is defined as the gross target volume (GTV) (using either CT or PET/CT) with a 6 mm margin. In cases with an adjacent brain stem, the margin is no greater than 1mm. Involved nodes are defined as those greater than 1cm, alternatively those with central necrosis. The PTV1 included the primary tumor and involved lymph nodes, PTV2 the high risk lymph nodes and PTV3 the low risk lymph nodes. According to our centre's standards, total doses 66 Gy/2.2 Gy-70 Gy/2.12 Gy in PTV1, 60Gy/2 Gy-59.4 Gy/ 1.8 Gy in PTV2, and 54 Gy/1.8 Gy-50.4 Gy/1.53 Gy in PTV3 were prescribed. If indicated, the dose could be complemented with a boost of 6-8 Gy. The irradiation was performed once daily, 5 times a week. The dose was normalized as 100% in the reference point defined as an ICRU point for the volume with the maximum planned dose. The plan was considered acceptable if < 10% of PTV received a 110% dose and at least 95% of PTV received 95% of the reference dose. Postoperative radiotherapy was indicated in post-surgical patients showing positive margins or having negative risk factors.

Radiotherapy and its planning were performed using a TPS Eclipse Varian with a Helios inverse planning module, and a CT GE HiSpeed NX/I Plus simulator. Irradiation was performed using IMRT, a sliding window with a 9 field-shaped multileaf collimator (MLC) in a Varian 2100 C/D linear accelerator, X-ray beam, 6 MeV.

Chemoradiotherapy

Fifty patients with locally advanced tumors and in good general condition were scheduled for concomitant cisplatin chemotherapy with a dose of 100 mg/m^2 on days 1, 22, and 43. Patients received premedication with i.v. setrons and standard hydration as part of the pre and posthydration protocols.

Statistics

Statistical analysis was performed using SPSS 9.0 and SPSS 18.0.1 for Windows software. Standard Kaplan-Meier method was done to determine patient survival, complemented with log-rank test to compare survival rates between patient subgroups. In all tests, statistical significance was set at $p<0.05$.

Results

The median follow-up of the evaluated patients was 3.1 years (range 0.15-5.6). Of the 176 evaluable patients 48 (62.3%) were identified as having persistent and 29 (37.7%) as having recurrent disease.

Relapse-free and overall survival

The 3-year locoregional RFS was 57%. Survival of patients free of locoregional relapse is shown in Figure 1. The 3-year OS reached 50% in the whole patient group (Figure 2). The 3-year RFS reached 49% in stage IV patients and 79% in stage I–III patients (log-rank, p=0.003, Figure 3). The 3-year OS reached 46% and 66% for stage IV and stages I–III patients, respectively (log-rank, p=0.041, Figure 4).

With regard to T stage of the primary tumor the 3-year RFS rates were 39% and 69% in T4 vs T1-3, respectively (log-rank, p=0.001, Figure 5). The 3-year OS reached 40% in T4 tumors and 59% in T1-T3 tumors (log-rank, p=0.002, Figure 6). As for surgery, the 3-year RFS rates in those undergoing and not undergoing surgery regardless of the operational radicality were 75% and 35%, respectively (log-rank, p=0.001, Figure 7), while the 3-year OS rates of operated and non-operated patients, regardless of the operational radicality, were 61% and 39%, respectively (log-rank, p=0.001, Figure 8). Results of univariate analysis are presented in Table 2. When analysing the primary tumor localization, patients were divided into subgroups with tumors involving the hypopharynx, oral cavity, larynx, and oropharynx; the other sites were not evaluated because of the small number of patients. The 3-year relapse-free survival was 62% in laryngeal tumors, 61% in tu-

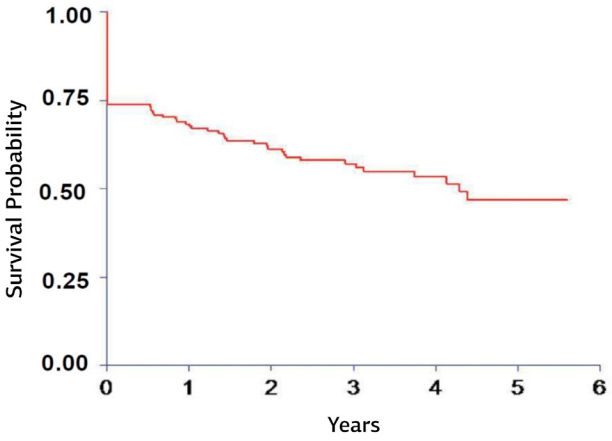

Figure 1. Three-year locoregional relapse-free survival.

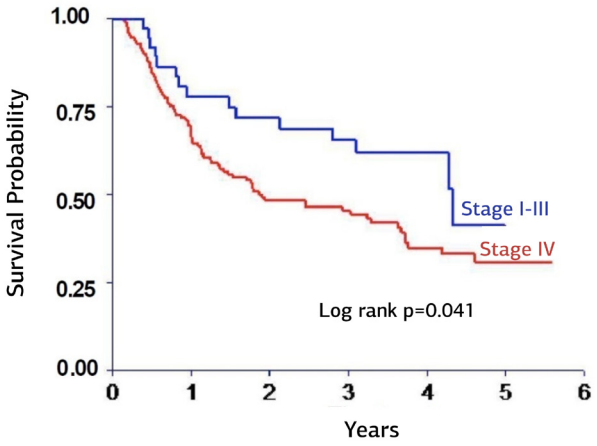

Figure 4. Three-year overall survival by stage (IV vs I–III: 46 vs 66%).

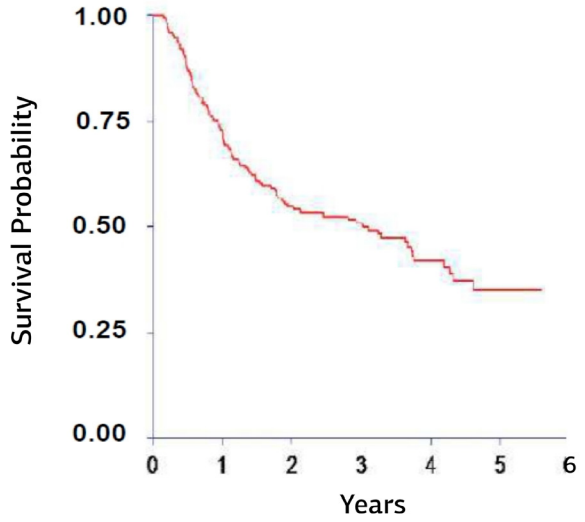

Figure 2. Three-year overall survival.

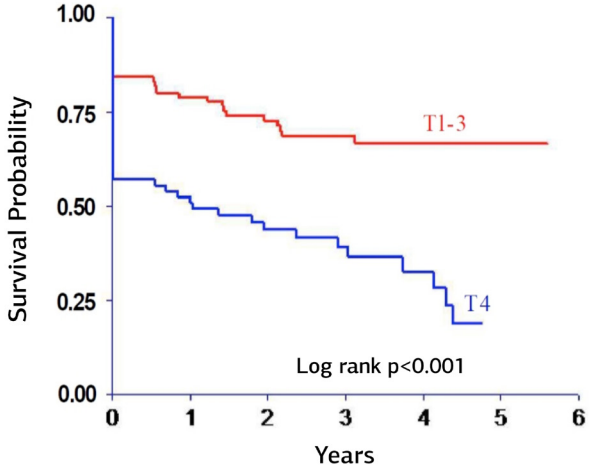

Figure 5. Three-year relapse-free survival by primary tumor stage (T1-3 vs T4: 69 vs 39%).

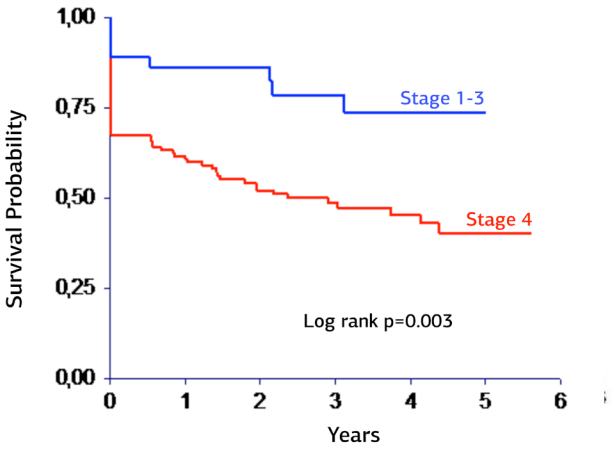

Figure 3. Three-year relapse-free survival by stage (IV vs I–III: 49 vs 79%).

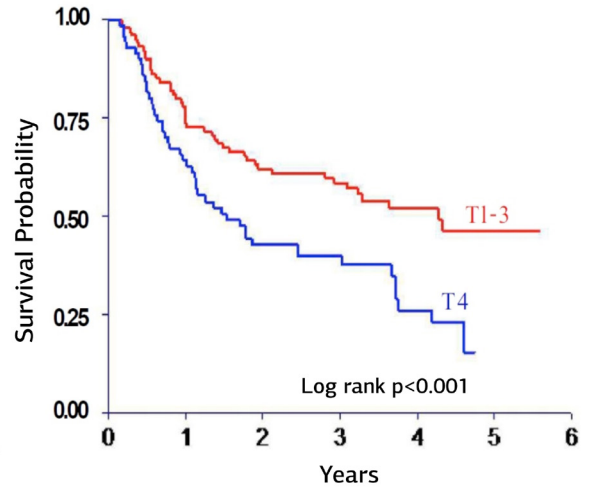

Figure 6. Three-year overall survival by primary tumor stage (T1-3 vs T4: 59 vs 40%).

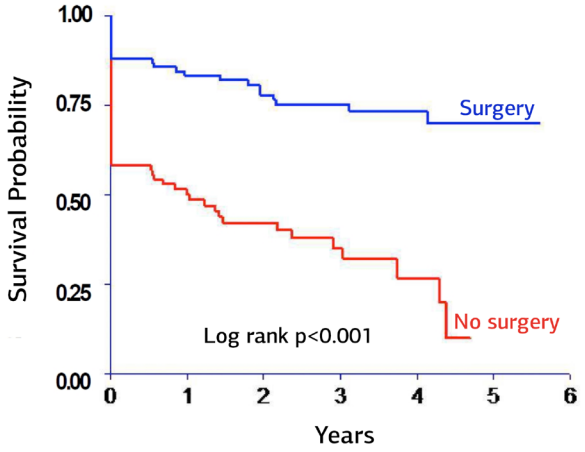

Figure 7. Three-year local relapse-free survival by surgical procedure (non-operated vs operated patients: 35 vs 75%).

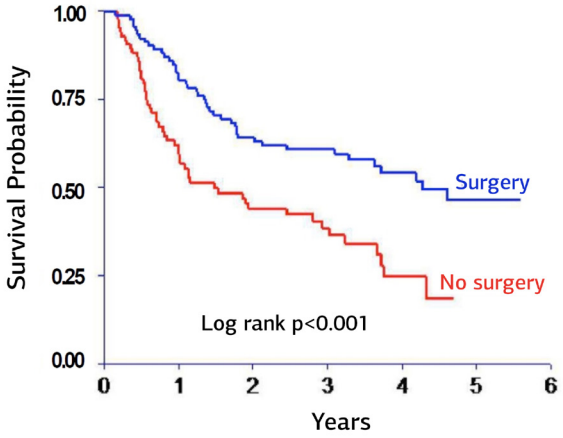

Figure 8. Three-year overall survival by surgical procedure (non-operated vs operated patients: 39 vs 61%).

Table 1. Clinicopathological characteristics

Diagnosis	*Patients N*	*%*
Localization		
Oral cavity	31	16.8
Oropharynx	66	35.7
Nasopharynx	14	7.6
Larynx	37	20.0
Salivary glands	7	3.8
Unknown primary	3	1.6
Nasal cavity and paranasal sinuses	9	4.9
Hypopharynx	18	9.7
Histology		
Squamous cell carcinoma	166	89.7
Other	19	10.3
TNM stage		
I	1	0.5
II	9	4.9
III	27	14.6
IV	131	70.8
Unknown stage	17	9.2

Table 2. Univariate analysis

	Relapse-free survival %	*Overall survival %*
TNM stage IV	49	46
TNM stage I - III	79 (p=0.003)	66 (p=0.041)
T4	39	40
T 1-3	69 (p=0.001)	59 (p=0.002)
Surgery	75	61
No surgery	35 (p=0.001)	39 (p=0.001)

Table 3. Multivariate analysis

Overall survival	
Surgery vs no surgery	RR 0.50; 95% CI 0.30 - 0.73; p < 0.001
Relapse-free survival	
TNM stage IV vs I - III	RR 2.33; 95% CI 1.03 - 5.27; p = 0.043
Surgery vs no surgery	RR 0.26; 95% CI 0.15 - 0.44; p < 0.001

mors of the oropharynx, 47% in tumors in the oral cavity, and 0% of hypopharyngeal tumors. Adding chemotherapy to radiation had no impact on RFS and OS. Nevertheless, reliable comparison of patients with vs without chemotherapy was restricted due to the heterogeneity of these subgroups (various disease sites and stages).

Multivariate analysis of stage, T classification and surgery revealed that the only significant parameter for overall survival was surgery vs non surgery (RR 0.50; 95% CI 0.30–0.73; p<0.001). Regarding the 3-year relapse-free survival, the following two parameters were identified as significant: stage IV vs stages I–III (RR 2.33; 95% CI 1.03–5.27; p=0.043), and surgery vs non surgery (RR 0.26; 95% CI 0.15–0.44; p<0.001) (Table 3). In terms of locoregional recurrence localization and irradiation plan, most recurrent cases were localized in areas treated with the full dose (68 cases), and a minority in areas receiving lower radiation doses (6 cases), with unidentifiable localization in 3 cases. A summary of locoregional control and number of disseminated cases divided according to tumor localization is shown in Table 4.

Table 4. Proportion of complete remissions, persistent disease, relapses and disseminations according to primary tumor localisation

Diagnosis	*Locoregional control %*				*Dissemination %*	
	Complete remission	*Persistent disease*	*Relapse*	*Not evaluable patients*	*Yes*	*No*
Oral cavity	42	42	13	3	3	97
Oropharynx	62	23	12	3	6	94
Nasopharynx	79	0	21	0	21	79
Larynx	59	19	19	3	5	95
Salivary glands	43	43	14	0	14	86
Unknown primary	100	0	0	0	0	100
Nasal cavity and paranasal sinuses	45	22	33	0	0	100
Hypopharynx	39	44	17	0	22	78

Discussion

Currently, the outcomes of treatment of advanced head and neck tumors are not satisfactory. Literature reports suggest that, within 2 years, approximately 50-60% stage III and IV patients with head and neck tumors will develop locoregional recurrence and 20-30% disease dissemination [8].

The rates of 3-year overall survival and relapse-free survival in our group of IMRT-treated patients, most of whom were in stages III and IV (158 out of 177), were 50 and 57%, respectively; these rates are consistent with data reported for patients with advanced head and neck tumors treated with conventional radiotherapy techniques without concomitant chemotherapy [9].

Using postoperative chemoradiotherapy, 3-year locoregional control was achieved in 75% of the cases as compared with 35% in non-operated patients, regardless of the degree of radicality of the surgical procedure. A study by Chen et al. presented results comparing postoperative treatment of head and neck tumors using IMRT and conventional irradiation with two opposite fields. Their group included 130 patients, out of which 78 (60%) were treated conventionally and 52 (40%) with IMRT. Three-year locoregional control was 70 and 73% in conventionally and IMRT-treated patients, respectively (p=0.33) [10]. It can be thus reasonably concluded that locoregional control in our operated patients is nearly identical with the data reported above.

The favorable results of local control in the larynx and oropharyngeal area and the unfavorable ones in hypopharyngeal and oral cavity carcinomas are consistent with data reported by other authors [11,12]. Studer et al. when reporting poor outcomes of radiotherapy using IMRT alone in the oral cavity, found outcomes of postoperative radiotherapy favorable even in this localization [13]. Comparing postoperative radiotherapy with radiotherapy alone, Yao et al. reported better outcomes with oropharyngeal tumors compared with oral tumors [14]. Similarly, Schoenfeld et al., using chemoradiotherapy alone, obtained more favorable results with oropharyngeal tumors compared with nasopharyngeal, hypopharyngeal, and laryngeal tumors [15].

Concerning the primary tumor stage, the 3-year RFS rates for T4 and T1–3 groups were 39 and 69%, respectively (p=0.001), and the 3-year OS rates were 40% with T4 tumors and 59% with T1–3 tumors (p=0.002). Similar differences were found when comparing outcomes in TNM stages IV vs I–III. It is thus evident that the stage of disease and extent of the primary tumor play a major role in the prognosis of patients with head and neck tumors, even in the era of IMRT-based radiotherapy [16,17]. One can speculate that factors contributing to the better outcomes in surgically-treated patients include lower disease stages and better general health status. However, it can be said that the results presented in our study support the importance of surgery in the multidisciplinary treatment of head and neck tumors.

Use of IMRT is associated with a risk of increased recurrence rates due to geographic miss, whereby shielding of critical organs may result in marginal recurrence [3]. In an effort to assess the role of underdosing through geographic miss, we analyzed the recurrence distribution pattern with respect to tumor localization. Sixty-eight cases of relapse occurred in areas receiving the full radiation dose, there were 6 cases of marginal recurrence (in areas receiving prophylactic irradiation), with no locoregional recurrence shown outside the irradiated area. The site of recurrence could

not be identified in 3 cases.

It is clear from the aforementioned results and published reports that the overwhelming majority of relapsed cases do occur in areas receiving the full radiation dose [2]. Our data suggest that, if dividing relapses into cases of persistence and local recurrence, the former predominate. Temporary complete remission is not obtained in many patients even when delivering maximum tolerable radiation doses. The cause of relapse was due to the extent of tumor and not the result of improper target volume identification.

The potential benefit of IMRT in the treatment of head and neck tumors is a widely debated topic [18]. Therapeutic outcomes published to date suggest that, compared with conventional techniques, use of IMRT in head and neck cancer reduces the severity of acute and late toxicity, particularly xerostomia [2].

Extensive analysis designed to compare various techniques of radiotherapy for head and neck tumors in terms of their efficacy and toxicity concluded that IMRT is associated with disease control rates comparable with those obtained with the current techniques of radiotherapy [19]. Although the results of all studies are inconsistent, most of them showed a significant decrease in the side effects of radiotherapy, particularly late xerostomia as a major clinical complication deteriorating the quality of life of patients. Use of IMRT in this clinical indication can thus be considered medically unavoidable.

In conclusion the outcomes in IMRT-treated group of patients were significantly affected by the decision to perform surgery, with better results obtained in surgically-treated patients. Likewise, a major role was indentified for the primary tumor stage classification, as longer survival rates were reported with T1–3 tumors vs T4 tumors. Most cases with locoregional relapse occurred in areas receiving the high radiotherapy dose.

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