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REVIEW

Efficacy of intensity-modulated radiotherapy combined with chemotherapy or surgery in locally advanced squamous cell carcinoma of the head-and-neck

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Hua Yang*
Li-Qiong Diao*
Mei Shi
Rui Ma
Jian-Hua Wang
Jian-Ping Li
Feng Xiao
Ying Xue
Man Xu
Bin Zhou

Department of Radiotherapy Oncology, Xijing Hospital, Fourth Military Medical University, Xi'an, People's Republic of China

*These authors contributed equally to this work

Objectives: Long-term locoregional control following intensity-modulated radiotherapy (IMRT) for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN) remains challenging. This study aimed to assess the efficacy and toxicity of IMRT with and without chemotherapy or surgery in locally advanced SCCHN.

Materials and methods: Between January 2007 and January 2011, 61 patients with locally advanced SCCHN were treated with curative IMRT in the Department of Radiation Oncology, Xijing Hospital, Fourth Military Medical University; 28% underwent definitive IMRT and 72% postoperative IMRT, combined with simultaneous cisplatin-based chemotherapy in 58%. The mean doses of definitive and postoperative IMRT were 70.8 Gy (range, 66–74 Gy). Outcomes were analyzed using Kaplan–Meier curves. Acute and late toxicities were graded according to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer radiation morbidity scoring criteria.

Results: At a median follow-up of 35 months, 3-year local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were 83.8%, 86.1%, 82.4%, 53.2%, and 62%, respectively. Postoperative IMRT (n = 44, 72%) had significantly higher LRFS/OS/DMFS than definitive IMRT (n = 17, 28%; $P < 0.05$). IMRT combined with chemotherapy (n = 35, 58%) had significantly higher LRFS/OS/DMFS than IMRT alone (n = 26, 42%; $P < 0.05$). One year after radiotherapy, the incidence of xerostomia of grade 1, 2, or 3 was 13.1%, 19.7%, and 1.6%, respectively. No grade 4 acute or late toxicity was observed.

Conclusion: IMRT combined with surgery or chemotherapy achieved excellent long-term locoregional control and OS in locally advanced SCCHN, with acceptable early toxicity and late side-effects.

Keywords: SCCHN, IMRT, surgery, chemotherapy, prognosis analysis

Introduction

Approximately 560,000 people are diagnosed with squamous cell carcinoma of the head-and-neck (SCCHN) worldwide every year.[1] For patients with locally advanced (stage III, IVa, or IVb) SCCHN, the traditional approach of radical surgery and radiation therapy has resulted in disappointing cure rates.[2–4] In addition, this approach is often associated with significant cosmetic and functional impairment, resulting in decreased quality of life.[5–8] Therefore, active research is exploring combined-modality therapy to improve survival, organ preservation and function in patients with locally advanced SCCHN.[9,10]

Correspondence: Mei Shi
Department of Radiotherapy Oncology, Xijing Hospital, Fourth Military Medical University, 15 West Changle Road, Xi'an 710032, People's Republic of China
Tel +86 29 8477 5425
Fax +86 29 8324 9969
Email mshi82@fmmu.edu.cn

In the past decade, major changes have occurred in the clinical management of locally advanced SCCHN. Intensity-modulated radiotherapy (IMRT) has lower toxicity but retains the antitumor activity of more aggressive treatments, and with the advent of effective drugs, concurrent chemoradiotherapy now plays an important role in locally advanced SCCHN. However, the long-term outcome of locally advanced SCCHN remains unsatisfactory, the main reasons for failure being local recurrence and distant metastasis.[11] Can IMRT improve the efficacy of treatment when combined with surgery or chemotherapy in locally advanced SCCHN? In the present study, we retrospectively and hierarchically analyzed the efficacy and toxicity profile in patients treated for locally advanced SCCHN in our hospital.

Patients and methods

Patient characteristics

This was a retrospective study approved by the Department of Radiotherapy Oncology of Xijing Hospital at the Fourth Military Medical University. Between January 2007 and January 2011, 61 patients with newly diagnosed, biopsy-proven stage III, IVa, or IVb squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, nasal and paranasal sinus, or salivary gland were eligible. The median follow-up time was 35 months (range, 11–58 months), with 36 patients followed for more than 3 years.

The median age at diagnosis was 63 years (range, 33–87 years). The male to female ratio was 4:1 (49:12). The patients were referred for IMRT (26) or chemotherapy combined with IMRT (CIMRT; 35). Forty-four patients received postoperative IMRT and 17 received definitive IMRT. Patient characteristics were hierarchically distributed and are shown in Table 1.

Radiation treatment

In all patients, radiation was delivered in the form of IMRT. Patients were fitted with a customized thermoplastic mask to immobilize the head and neck. The gross tumor volume was specified as the gross extent of tumor as demonstrated by preoperative imaging and physical examination including endoscopy. The clinical target volume (CTV) included areas of macroscopic disease plus a microscopic disease margin. CTV1 covered the CTV and areas at risk of tumor invasion. CTV2 covered lower risk lymphatic levels. Depending on disease site, the planning target volume (PTV), PTV1 and PTV2 contained an automated 0.5 cm expansion of the CTV, CTV1, and CTV2.

Table 1 Patient baseline characteristics and demographics (n = 61)

Factors	CIMRT	IMRT	χ^2	*P*-value	Definitive IMRT	Postop IMRT	χ^2	*P*-value
Gender			3.53	0.06			1.42	0.23
Male	31	18			12	37		
Female	4	8			5	7		
Age (years)			0.37	0.54			0.02	0.88
≤50	6	3			3	6		
>50	29	23			16	36		
Primary site			0.63	0.98			5.57	0.35
Oral	9	7			4	12		
Oropharynx	1	1			1	1		
Hypopharynx	8	5			3	10		
Nasal and paranasal sinus	6	6			3	9		
Larynx	10	6			5	11		
Salivary gland	1	1			1	1		
T stage			2.95	0.23			1.75	0.42
T2	8	8			4	12		
T3	6	7			5	19		
T4	10	11			8	13		
N stage			3.14	0.27			2.05	0.36
N0	20	9			7	22		
N1	8	10			4	14		
N2	7	7			6	8		
UICC stage			0.49	0.48			3.38	0.07
III	18	11			5	24		
IVa	10	12			10	15		
IVb	7	3			2	5		

Abbreviations: CIMRT, chemotherapy combined with intensity-modulated radiation therapy; N, node; Postop IMRT, postoperative IMRT; T, tumor; UICC, International Union Against Cancer; IMRT, intensity-modulated radiation therapy.

Total treatment doses were as follows. For postoperative IMRT, the PTV, PTV1 and PTV2 received 66–70 Gy, 60–68 Gy, and 50–54 Gy, respectively, in 2 Gy per fraction; for definitive IMRT, the PTV, PTV1, and PTV2 received 68–74 Gy, 66–72 Gy, and 50–54 Gy, respectively, in 2 Gy per fraction.

Chemotherapy

Thirty-five patients (57%) with no specific contraindications were simultaneously treated with cisplatin-based chemotherapy. Seven patients received intravenous cisplatin at a dose of 30 mg/m^2 weekly throughout the duration of their radiation therapy; most (28) of the patients received bolus cisplatin (100 mg/m^2) given every 3 weeks on days 1 and 22.

Follow-up

All patients were evaluated weekly during the treatment period. After the completion of their treatment, they were followed-up every 3 months in the first 2 years and every 6 months between 2 and 5 years. Each follow-up visit included a complete examination, basic serum measurements, chest radiograph, and ultrasound of the liver and abdomen. Endoscopy was performed at every visit after treatment. Magnetic resonance imaging of the head and neck area was performed every 6 months. Positron emission tomography was optional in high risk cases. The primary end points were treatment compliance and acute toxicity. The secondary end points were late toxicity, local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS).

Statistics

All statistical analyses involved comparing groups according to a time-to-event end point (survival analysis), using Kaplan–Meier curves and log-rank tests implemented in StatView® (version 4.5; SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant. Acute and late toxicities were observed and scored according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria at each follow-up visit.

Results

Efficacy and outcome of the entire cohort

At median follow-up of 35 months, 1-, 2-, and 3-year LRFS was 84%, 80%, and 72%, respectively; RRFS was 86%, 86%, and 86%; DMFS was 95%, 82%, and 82%; and OS was 73%, 69%, and 62%, respectively, for the entire cohort (Figure 1). Treatment failed in 17 cases; among these, 12 patients had local recurrence, eight had regional recurrence, nine had distant metastasis and five had both recurrence and metastasis. The median time to recurrence or distant metastasis was 9.5 months (range 3–23 months) and 5 months (range 4–23 months), respectively.

Outcome according to treatment modality

Postoperative IMRT patients (n = 44, 72%) had significantly higher LRFS/OS/DMFS than those who underwent definitive IMRT (n = 17, 28%; $P < 0.05$). Comparing the postoperative IMRT subgroup with the definitive IMRT subgroup (n = 30), 1-, 2-, and 3-year LRFS was 95%, 87%, and 80% versus 75%, 68%, and 60% ($\chi^2 = 12.02$, $P = 0.011$); 1-, 2-, and 3-year OS was 85%, 81%, and 81% versus 76%, 61%, and 47% ($\chi^2 = 18.49$, $P = 0.0019$); and 1-, 2-, and 3-year DMFS was 93%, 83%, and 83% versus 75%, 72%, and 65% ($\chi^2 = 8.07$, $P = 0.038$), respectively (Figure 2 and Table 2).

Outcome according to chemotherapy

CIMRT patients (n = 35, 58%) had significantly higher LRFS/OS/DMFS than IMRT patients (n = 26, 42%; $P < 0.05$). Comparing the CIMRT subgroup with the IMRT subgroup, 1-, 2-, and 3-year LRFS was 95%, 87%, and 84% versus 85%, 78%, and 67% ($\chi^2 = 5.25$, $P = 0.042$); 1-, 2-, and 3-year OS was 83%, 74%, and 74% versus 68%, 60%, and 60% ($\chi^2 = 5.52$, $P = 0.035$); and 1-, 2-, and 3-year DMFS was 93%, 83% and 79% versus 75%, 75%, and 65% ($\chi^2 = 10.07$, $P = 0.015$), respectively (Figure 3 and Table 2).

Toxicity

IMRT was well tolerated with respect to early toxicity as well as late side-effects. No patient had his or her radiation therapy interrupted due to treatment-related effects. No grade 4 acute or late toxicity was observed in the cohort. The incidence of acute skin reaction of grade 0, 1, 2, or 3 was 3.3%, 65.6%, 29.5%, and 1.6%, respectively. The incidence of acute mucositis of grade 0, 1, 2, or 3 was 13.1%, 57.4%, 26.2%, and 1.6%, respectively. One year after radiotherapy, the incidence of xerostomia of grade 1, 2, or 3 was 13.1%, 19.7%, and 1.6%, respectively. Disturbance of hearing, neck skin fibrosis, restriction of mouth opening, and dysphagia occurred in 13.1%, 6.5%, 4.8%, and 1.6% of cases, respectively (Table 3).

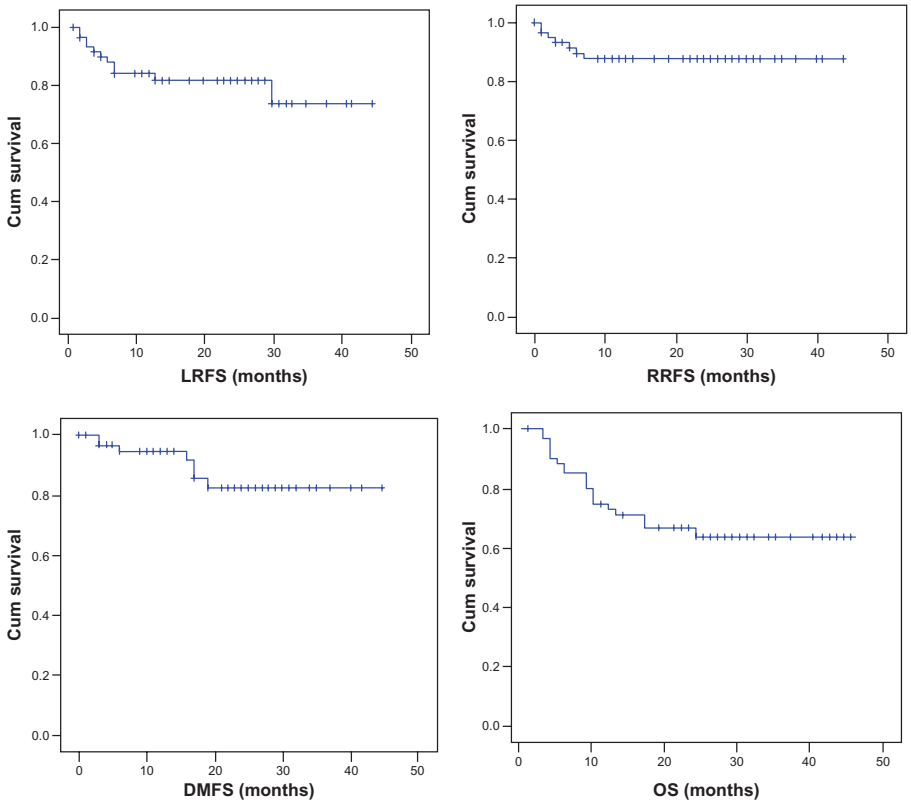

Figure 1 Local recurrence-free, regional recurrence-free, distant metastasis-free, and overall survival rates in 61 patients treated with intensity-modulated radiotherapy with or without chemotherapy.
Abbreviations: Cum, cumulative; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; OS, overall survival; RRFS, regional recurrence-free survival.

Discussion

Radiotherapy, which is one of the most effective means of cancer treatment, plays a crucial role in combined-modality therapies for patients with locally advanced SCCHN.[12,13] Due to its advantages in terms of greater dose conformity for complex tumor targets and better protection of adjacent critical normal structures, IMRT is increasingly widely used in the treatment of this disease.

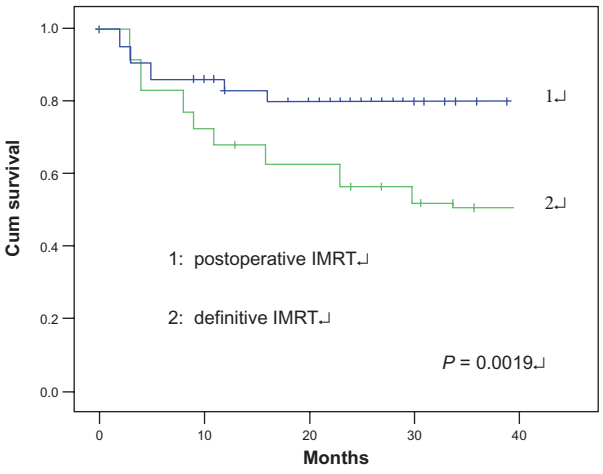

Figure 2 Overall survival of all patients was analyzed according to treatment modality. Postoperative IMRT had a superior OS compared with definitive IMRT ($P = 0.019$).
Abbreviations: Cum, cumulative; IMRT, intensity-modulated radiation therapy; OS, overall survival.

In recent years, many investigators have demonstrated IMRT to have a better therapeutic effect and achieve greater local or regional control than conventional techniques or three-dimensional conformal radiation therapy.[14–16] The clinical outcomes of IMRT are excellent for the treatment of locally advanced SCCHN; the latest randomized study showed that IMRT with or without chemotherapy achieved excellent local progression-free survival and OS in locally advanced SCCHN according to 3-year estimates,[17] and excellent 2-year clinical outcome and less toxicity was reported by Yao et al.[18] Maguire et al[19] reported 3-year LRFS and OS of 87% and 80%, respectively, in 39 patients, and Habl et al[20] reported 2-year LRFS and OS of 82% and 65%, respectively, in 43 SCCHN patients. The excellent results and lower toxicity reported in these studies could be largely due to the use of IMRT. The results achieved in the present study in our department are similar to those reported from other centers. Three-year LRFS, RRFS, DMFS, DFS and OS were 83.8%, 86.1%, 82.4%, 53.2%, and 62%, respectively. The RRFS was similar to that in other trials, but the OS was

Table 2 Outcomes in 61 IMRT patients were analyzed according to use of chemotherapy and treatment modality

Factor	3-year OS (%)	χ^2	*P*-value	3-year LC (%)	χ^2	*P*-value	3-year DMFS (%)	χ^2	*P*-value
Chemotherapy		5.52	0.035		5.25	0.042		10.07	0.015
IMRT	59.7			67.0			65.3		
CIMRT	74.1			83.8			79.0		
Treatment modality		18.49	0.0019		12.02	0.011		8.07	0.038
Definitive IMRT	46.5			60.0			65.0		
Postoperative IMRT	81.1			79.6			82.5		

Abbreviations: CIMRT, chemotherapy combined with intensity-modulated radiation therapy; DMFS, distant metastasis-free survival; IMRT, intensity-modulated radiation therapy; LC, local control; OS, overall survival.

slightly lower than that reported by Maguire et al. The most likely reason for this discrepancy is that the percentage of our patients who underwent concurrent chemoradiotherapy (CCRT) was significantly lower (57%) than in Maguire's center (>90%).

In the treatment of locally advanced SCCHN, radiotherapy alone cannot achieve a definitive cure. Multidisciplinary collaboration such as surgery combined with radiotherapy or surgery combined with chemoradiotherapy has become the standard treatment for most patients. There are two possible advantages to this approach. First, complete or subtotal resection may reduce the area that needs to be irradiated and decreases the incidence of acute and late complications. Second, regardless of whether the surgical margins are positive, appropriate target outlines may be delineated and dose designs created. The advantages of multidisciplinary collaboration were obvious in our patients. Postoperative IMRT patients (n = 44, 72%) had significantly higher LRFS/RRFS/DMFS/OS than those who underwent definitive IMRT (n = 17, 28%; $P < 0.05$).

There is little doubt that IMRT has advantages in the local control of SCCHN.[21,22] Thus, IMRT combined with concurrent chemotherapy can further improve OS, and this has become the standard treatment for most patients with locally advanced SCCHN. In the meta-analysis undertaken by the MACH-NC (Meta-Analysis of Chemotherapy in Head and Neck Cancer) Group, the survival benefit was 8% at 5 years when chemotherapy was applied concomitantly with radiotherapy, compared to radiotherapy alone.[23]

Another meta-analysis has shown that concurrent chemoradiotherapy achieves a smaller but still significant survival benefit of 4.5%, a locoregional benefit of 9.3%, and a distant metastasis-free benefit of 2.5% according to 5-year estimates.[24] Multiple phase III trials have obtained the same results; compared to radiotherapy alone, CCRT can significantly improve locoregional control and OS.[17,25,26] Maguire et al[19] have moved to weekly cisplatin dosing (30 mg/m^2) in their CCRT regimens for patients with locally advanced SCCHN, with 3-year LRFS and OS of 87% and 80%, respectively. Theoretical benefits include improved radiosensitization and decreased toxicity compared with the current RTOG standard (100 mg/m^2 every 3 weeks). In our department, CIMRT patients (n = 99, 62%) had significantly higher LRFS/RRFS/DMFS/OS than IMRT patients (n = 61, 62%; $P < 0.05$). The present study implies that concurrent chemotherapy has a significant additive effect on LRFS, RRFS, DMFS, and OS in locally advanced SCCHN patients.

In radiotherapy for head and neck cancer, the major salivary glands often receive a high radiation dose. This may lead to xerostomia, which is cited by patients as a major cause of decreased quality of life.[27] However, parotid-sparing

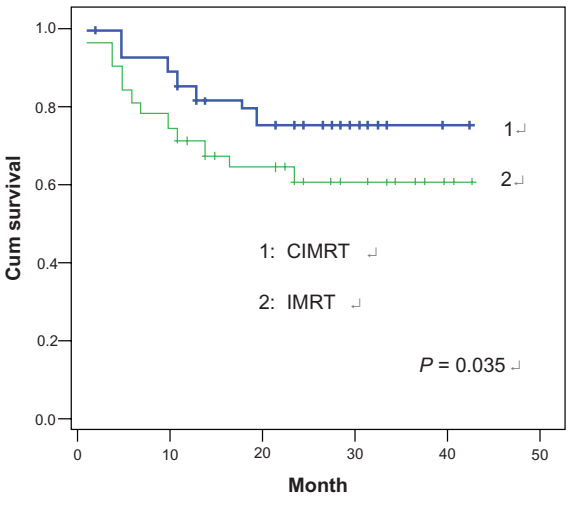

Figure 3 Overall survival (OS) of all patients was analyzed according to use of chemotherapy. Chemotherapy combined with intensity-modulated radiation therapy (CIMRT) had a superior OS compared to IMRT ($P = 0.035$).
Abbreviations: Cum, cumulative; OS, overall survival; IMRT, intensity-modulated radiation therapy.

Table 3 Acute and late toxicities observed in 61 patients with locally advanced squamous cell carcinoma of the head and neck (number [%])

Adverse effect	Grade 1	Grade 2	Grade 3	Grade 4
Skin reaction	40 (65.6)	18 (29.5)	1 (1.6)	0
Mucositis	35 (57.4)	16 (26.2)	1 (1.6)	0
Xerostomia	8 (13.1)	12 (19.7)	1 (1.6)	0
Disturbance of hearing	2 (3.2)	5 (8.0)	1 (1.6)	0
Dysphagia	0	1 (1.6)	0	0
Neck skin fibrosis	1 (1.6)	3 (4.8)	0	0

IMRT can significantly reduce the incidence of xerostomia compared to conventional radiotherapy.[28,29] In our study, 1-year after radiotherapy, the incidence of xerostomia of grade 1, 2, or 3 was 13.1%, 19.7%, and 1.6%, respectively. The clinical outcomes of IMRT are promising.

In summary, the present study showed that IMRT combined with surgery or chemotherapy achieved excellent long-term locoregional control and OS in locally advanced SCCHN, with acceptable early toxicity and late side-effects.

Disclosure

The authors report no conflicts of interest in this work.

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