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Original Article

Clinical and dosimetric analyses of acute xerostomia for hypopharynx and larynx carcinoma treated by rotational IMRT

Boning Cai*, Chuanbin Xie*, Wei Yu*, Shouping Xu, Xiaoshen Wang, Jinyuan Wang, Lin Ma

*Department of Radiation Oncology, Chinese PLA General Hospital, Beijing 100853, China. *Equal contributors.*

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Abstract: Objective: To evaluate acute xerostomia in the concurrent chemoradiotherapy of locally advanced squamous cell carcinoma of the hypopharynx and larynx (LA-SCCH/L) realized with Helical tomotherapy (HT) and RapidArc (RA). Methods: Between August 2008 and December 2014, 80 patients with LA-SCCH/L were treated by HT or RA, and combined with concurrent cisplatin-based chemotherapy. The prescription dose was 69~70 Gy to pGTVnx and pGTVnd, 60 Gy to PTV1 and 54 Gy to PTV2, in 30~33 fractions; respectively. The endpoint was ≥ grade 2 (G2) acute xerostomia. The clinical and dosimetric factors were analyzed. Results: Patients treated with HT had lower incidence of G2 xerostomia than RA ($P = 0.025$). Through the limit of parotid Dmean, other parotid parameters were not correlated to the xerostomia. Multivariate analyses showed that ICT was independently associated G2 xerostomia ($P = 0.003$). Both of HT and RA had good protection in parotid gland. However, RA had lower parotid Dmean than HT. Conclusions: In the treatment of LA-SCCH/L, HT and RA are effective in protecting the parotid, without significant difference in acute xerostomia. ICT is the predictor of xerostomia.

Keywords: Helical tomotherapy, rapidArc, xerostomia, parotid gland

Introduction

Locally advanced squamous cell carcinoma of the hypopharynx and larynx (LA-SCCH/L) is sensitivity to radiotherapy, and has a dose-effect relation [1]. Local recurrence is still the main cause of failure, getting enough dose of the target area is the key to the success of the treatment [2, 3]. Intensity modulated radiation therapy (IMRT) is the first choice in treating LA-SCCH/L [4, 5], and has the ability to deliver high doses of radiation to the target structures while sparing adjacent bystander healthy tissues, thus IMRT has the potential to improve local control rate and reduce radiation-related toxicities. Grade 2 or higher xerostomia was significantly less common with IMRT technique than with conventional radiation technique [6].

Static gantry IMRT and rotational IMRT are primary IMRT techniques at present. Dosimetric study showed that there were differences in the homogeneity and conformity of planning target volume (PTV), and protecting nearby organs at risk (OARs), though the rotational IMRT had more dosimetric superiority [7]. However, whether the dosimetric superiority could due to less side effects in actual clinical research is still needed to be further studied. Xerostomia is one of the most common side effects for LA-SCCH/L patients, and the degree of parotid gland dose could display the superiority of the IMRT technique. We used a retrospective analysis in cisplatin-based concurrent chemoradiotherapy (CCRT) of LA-SCCH/L to evaluate the dosimetric differences in clinical practice, analyzed the clinical and dosimetric factors to acute xerostomia. The Helical tomotherapy (HT) and volumetric modulated arc therapy (VMAT) via RapidArc (RA) were applied.

Materials and methods

Patients

Eighty patients were recruited between August 2008 and December 2014, and all patients received rotational IMRT plus cisplatin-based CCRT. Clinical characteristics have been previously described and summarized in **Table 1**.

Table 1. Patient,tumor and clinical characteristics

Characteristic	HT	RA
Age (y), mean (range)	56.6 ± 10.3	58.9 ± 8.2
Gender		
Male	30 (97)	48 (98)
Female	1 (3)	1 (2)
Tumor site		
Hypopharynx	28 (90)	49 (100)
Supraglottic Larynx	3 (10)	0
T stage[1]		
T1	1 (3)	1 (2)
T2	9 (29)	14 (29)
T3	10 (32)	13 (26)
T4a	11 (36)	13 (26)
T4b	0	8 (17)
N stage[2]		
N0	4 (13)	10 (20)
N1	10 (32)	4 (8)
N2a-b	22 (39)	16 (33)
N2c	5 (16)	19 (39)
AJCC Stage		
II	1 (3)	3 (6)
III	9 (29)	8 (16)
IVA	21 (68)	38 (78)
CRT regimen		
CCRT	16 (52)	2 (4)
ICT+CCRT	15 (48)	47 (96)
EGFRI		
No	15 (48)	32 (65)
Yes	16 (52)	17 (35)
Total	31	49

1. The stage of primary tumor; 2. The stage of lymphatic metastasis.

Radiation therapy

The gross tumour volume of primary tumor (GTVnx) and metastatic lymph node (GTVnd), the clinical target volume (CTV) and the nearby OARs were delineated on the Pinnacle 8.0 m planning system. GTVnx and GTVnd were both defined as grossly visible primary tumor and metastatic lymphadenopathy on CT or MRI images. The planning GTVnx (pGTVnx) was obtained by expanding the corresponding GTVnx with a margin of 5 mm. The pGTVnd was the GTVnd with an expansion of 3 mm. CTV included high-risk (CTV1) and low-risk volumes (CTV2). Each CTV was automatically expanded to generate the corresponding PTV with an isotropic 3 mm margin and at least 2 mm from skin surface. The OARs including parotid glands, oral cavity, spinal cord and esophagus-trachea (E-T, ranges from annular cartilage to 1 cm inferior of the PTV2) were also delineated. The prescription dose of pGTVnx, pGTVnd, PTV1 and PTV2 was 69~70, 69~70, 60 and 54 Gy, in 30~33 fractions, 5 fractions per week; respectively. The dose-volume planning constraints for OARs: mean dose (Dmean) below 28 Gy for each gland parotid, percentage of oral cavity volume receiving 40 Gy (V40) below 30%, spinal cord maximum dose (Dmax) below 45 Gy, and the V40 of E-T below 30%.

Treatment planning systems corresponding to different linear accelerators were: Hi Art TomoTherapy 2.2.4.1 for TomoTherapy unit (HT), a field width of 2.5 cm, a maximum modulation factor of 2.8 and a pitch of 0.287 were use. Varian Eclipse 10.0 for RapidArc unit (RA), each plan consisted of two arcs.

Chemotherapy

Of the 80 patients, 18 received cisplatin-based CCRT alone. The other 62 received 2-3 cycles of docetaxel-cisplatin (TP) based ICT (with or without fluorouracil) and CCRT. Twenty-three patients received concurrent epidermal growth factor receptor inhibitor (EGFRI) with CCRT. Eight cases received Cetuximab (Merck KGaA, Darmstadt, Germany), fifteen cases received Nimotuzumab (Biotech, Beijing, China), respectively.

Clinical and dosimetric evaluation

Acute xerostomia was defined and graded according to the established RTOG/EORTC criteria [8].

The volume, Dmean of the ipsilateral parotid gland (I-parotid) with GTVnx and the percentage of gland volume receiving 15 Gy (V15), 20 Gy (V20), 30 Gy (V30),35 Gy (V35), 40 Gy (V40), 45 Gy (V45) and 50 Gy (V50) were calculated using dose volume histograms. These data of the contralateral parotid gland (C-parotid) were also observed. If the tumor is located at the postcricoid area, the ipsilateral was was defined with more or larger metastatic lymph nodes.

Dosimetric research

We designed a treatment plans study to compare the dosimetric results between dosimetric

Table 2. Dose-volume histogram analysis of Parotid Dmean (Gy)

DVH	HT (Dmean ± SD)	RA (Dmean ± SD)	*p*	*t*
Clinical research				
Ipsilateral	26.90 ± 5.59	20.86 ± 4.09	0.002	5.566
Contralateral	27.04 ± 5.04	20.58 ± 3.75	0.000	6.549
Dosimetric research				
Left	22.51 ± 5.04	22.99 ± 4.41	0.459	0.77
Right	22.50 ± 4.99	23.31 ± 4.47	0.192	1.44

Table 3. Univariate analysis of xerostomia

Parotid gland	Dmean ± SD	*P*	95% CI
Ipsilateral			
Dmean (Gy)	23.20 ± 5.55	0.228	0.999~1.000
V15 (%)	50.11 ± 14.70	0.486	0.930~1.020
V20 (%)	41.62 ± 12.26	0.986	0.964~1.036
V25 (%)	36.06 ± 10.65	0.967	0.960~1.043
V30 (%)	31.34 ± 9.30	0.968	0.955~1.050
V35 (%)	26.89 ± 8.20	0.976	0.947~1.054
V40 (%)	23.18 ± 7.54	0.901	0.940~1.056
V45 (%)	19.71 ± 7.00	0.870	0.934~1.060
V50 (%)	16.32 ± 6.49	0.726	0.923~1.058
Contralateral			
Dmean (Gy)	23.08 ± 5.31	0.578	0.999~1.001
V15 (%)	51.30 ± 15.28	0.140	0.948~1.008
V20 (%)	42.24 ± 11.87	0.221	0.940~1.014
V25 (%)	35.77 ± 9.98	0.492	0.942~1.029
V30 (%)	30.73 ± 8.70	0.556	0.936~1.036
V35 (%)	26.54 ± 7.84	0.783	0.938~1.050
V40 (%)	22.57 ± 7.17	0.735	0.930~1.052
V45 (%)	18.87 ± 6.78	0.655	0.923~1.052
V50 (%)	15.24 ± 6.28	0.619	0.915~1.054

Table 4. Distribution of xerostomia

Factor	G0	G1	G2	Total
T stage				
T1+2	1	6	18	25
T3	0	10	13	23
T4a+4b	2	20	10	32
IMRT technique				
HT	0	20	11	31
RA	3	16	30	49
CRT regimen				
CCRT alone	0	14	4	18
ICT+CCRT	3	22	37	62

research and clinical research. Ten patients with LA-SCCH/L received postoperative radiotherapy between August 2008 and August 2014 were selected, 6 with hypopharynx carcinoma, and 4 with supraglottic larynx. The dose volume parameters of the high-risk (CTV1) and low-risk volumes (CTV2), and the OARs were consistent with the clinical research. We used left and right parotid gland to differentiate bilateral parotid gland. The prescription dose of PTV1 and PTV2 was 60 and 54 Gy, in 30 fractions, 5 fractions per week, respectively. The parameters with relevance to xerostomia founded in the clinical research would be evaluated.

Statistical analysis

All data analyses were performed using IBM SPSS (Statistical Package for Social Sciences, version 19.0). Pearson's chi square test was used in bivariate analysis and t test for continuous variables. Logistic regression was performed to analyze correlations between clinical parameters (only the parameters with $P < 0.15$ in the univariate analysis were analyzed to exclude those with weak correlation) and acute xerostomia. P values < 0.05 were considered as statistically significant.

Results

Clinical research results

36/80 (45%) patients developed Grade 1 xerostomia, 41/80 (51%) developed Grade 2, and 3/80 (4%) without xerostomia. There were no Grade 3 xerostomia occurred.

The mean volume of I-protid and C-parotid was 35.56 cm^3 (14.23~75.89 cm^3) and 34.56 cm^3 (8.76~84.52 cm^3), respectively. The Dmean was 23.20 Gy (11.87~40.34 Gy) and 23.08 Gy (10.40~36.81 Gy), respectively. No differences between the ipsilateral and contralateral parotid gland (P = 0.077 and 0.712, respectively). The Dmean of HT plans were higher than RA plans, both the results had statistical significance (P = 0.002 and 0.000, respectively). The results shows in **Table 2**.

Univariate analysis of clinal characteristics showed that the T stage, IMRT technique and CRT regimens were influence factors of xerostomia (P = 0.008, 0.025, 0.005, respectively).

Table 5. Comparison of between clinical and dosimetric researches

	Tumor type	Number of cases	Prescription dose	IMRT techniques	Average of Parotid Dmean (Gy)
Wiezorek (2011) [7]	Oropharynx/hypopharynx/larynx	10	PTV1 60.9/65.1 Gy PTV2 52.2/55.8 Gy	HT	14.1
				RA	26.5
Van Gestel (2013) [14]	Oropharynx	5	PTV1 69 Gy PTV2 56Gy	HT	21.7~24.1
				RA	25.6~32.0
Broggi(2014) [17]	Nasopharynx/oropharynx/hypopharynx	18	PTV1 66 Gy PTV2 54 Gy	HT	24.7
				RA	34.8
Lee(2014) [18]	Nasopharynx	10	PTV1 70 Gy PTV2 60 Gy	HT	40.6
				RA	42.3
Current clinical study	Hypopharynx/larynx	80	pGTV/pGTVnd 69-70 Gy PTV1 60 Gy PTV2 54 Gy	HT	26.9-27
				RA	20.58-20.86
Current dosimetric study	Hypopharynx/larynx	10	PTV1 60 Gy PTV2 54 Gy	HT	22.51
				RA	22.99-23.31

The incidence of G2 xerostomia in patients with HT was lower than RA plans (35.5% vs 61.2%), and it was significantly higher in patients received ICT (37/62, 59.7%). However, the N stage, AJCC stage and EGFRI treatment were not influence factors (P = 0.315, 0.241, 0.396, respectively). **Table 3** shows the distribution of xerostomia.

Univariate analysis of dose parameters showed that there was no influence factors. The results are showed in **Table 4**. In our actual clinical research, the I-parotid Dmean in 17 patients were above 28 Gy, and 13 for C-parotid, respectively (all these were HT plans). The parotid Dmean above 25 Gy of I-parotid and C-parotid were happened in 25 and 27 patients, respectively. Used the parotid Dmean above 25, 26, 28 Gy as risk factors to univariate analysis, the results showed that the C-parotid Dmean above 28 Gy was correlated to G2 xerostomia (P = 0.027), the C-parotid Dmean above 25 Gy, 26 Gy were not influence factors (P = 0.388 and 0.370, respectively). The I-parotid Dmean above 28 Gy, 25 Gy, 26 Gy were not influence factors, either. (P = 0.141, 0.177 and 0.377, respectively).

The results of multivariate analyses the parameters with $P < 0.15$ showed that T stage and ICT was independently associated G2 xerostomia (B = -0.044, P = 0.001 and B = 2.032, P = 0.003, respectively).

Dosimetric research results

In the clinical research, parotid parameters were not correlated to G2 xerostomia, only the parotid Dmean above 28 Gy showed correlation in univariate analysis. **Table 2** showed the results of dosimetric research, there were no significant differences between the parotid Dmean of HT and RA plans.

Discussion

Parotid glands are the major salivary glands, generally believed that the dose parameters would be correlated to the xerostomia, and had to be limited in radiotherapy plan design. Eisbruch et al. [9] reported the Dmean, V15, V30, V45 of stimulated parotid were correlated to the xerostomia. The quantitative analysis of normal tissue effects in the clinic (QUANTEC) [10] and Milano et al. [11] prompted that control the parotid Dmean could reduce the degree of xerostomia. They suggested the Dmean should be limited below 25 Gy or 26 Gy, respectively. The high-risk volumes in LA-SCCH/L contains upper cervical lymphatic drainage area, bilateral parotid glands would be irradiated, and the parotid would change during irradiation [12, 13], it is hardly defined stimulated or unstimulated parotid. We consider the ipsilateral and contralateral parotid to the GTV should be appropriate to observe.

There are many dosimetric differences between HT and RA. Wiezorek et al. [7] selected 10 patients with head-and-neck tumours (oropharynx, hypopharynx and larynx), showed that HT and RA resulted in better target dose homogeneity and protection of OARs, and HT seemed to be better than the other. Van Gestel et al. [14] dosimetric study of oropharynx carcinoma showed that HT gived most homogeneous target coverage with more sparing of parotids,

brainstem and spinal cord. HT was also showed better target dose homogeneity in study of Ronget al. [15]. However, the focus of dosimetric research and clinical research is not the same. In dosimetric study of IMRT techniques, researchers usually select a limited number of cases with target areas close to each other, but also more stringent requirements on the dose parameters. The actual clinical research observes more cases, due to the diversity of the primary tumor and metastasis of lymph nodes, and more complex target areas, which leads to changes of the final statistical results. Smet et al. [16]. reported clinical and dosimetric evaluation of RA versus standard sliding window IMRT (swIMRT). RA had better target coverage and better sparing of the OARs, and the grade of acute toxicity was lower for RA than for swIMRT. But more grade 3 dermatitis was observed for RA, and more grade 3 mucositis and dysphagia for swIMRT.

Parotid Dmean is one obvious example to evaluate. In Wiezorek et al. [7] study, the average of Dmean was relatively low, 14.1 Gy for HT against 26.5 Gy for RA, respectively. In Van Gestel et al. [14]. study of five patients, the parotid Dmean ranged from 21.7 Gy to 24.1 Gy in HT plans, and from 25.6 to 32.0 Gy in RA plans, respectively. The average of Dmean was relatively higher in Broggi et al. [17] study, 24.7 Gy for HT against 34.8G for RA, respectively. These three studies showed that parotid Dmean was significantly lower in HT plans than RA , and the results were statistically significant. Lee et al. [18] reprted a dosimetry research in nasopharyngeal carcinoma, HT reduced the parotid Dmean compared to RA, but the Dmean was 40.6 ± 8.7 Gy, which was much higher than our previous actual clinical research. The parotid Dmean of nasopharyngeal carcinoma treated by HT was around 30 Gy in our experience [19]. In current study, HT and RA had good protection of parotid either in clinical or in dosimetric research. However, RA had lower parotid Dmean than HT in clinical research, and no statistically significant in dosimetric research. **Table 5** showed the differences of parotid Dmean between clinical and dosimetric researches.

CCRT has become the main choice of non-surgical treatment of LA-SCCH/L [20, 21]. The common modality is cisplatin-based CCRT, or with 2-3 cycles of ICT before CCRT [22, 23]. CCRT does not increase the incidence of acute or late xerostomia relative to IMRT alone [24], but from Takácsi-Nagy et al. [23] study, the addition of ICT to CRT increased the incidence of grade 2-3 xerostomia compared with standard CCRT. In our study, ICT was an independent factor.

However, due to the evaluation of xerostomia mainly in accordance with the subjective feelings of patients, researchers in determining the grade of xerostomia may produce certain deviation; meanwhile, submandibular gland sparing could reduce the risk of both stimulated and unstimulated xerostomia [25, 26], but it was not one of OARs in our study. Probably because of the above reasons, we got a negative correlation result between T stage and G2 xerostomia.

Conclusions

In conclusion, HT and RA are effective in protecting the parotid, without significant difference in acute xerostomia in this actual treatment of LA-SCCH/L. The observed parotid dose parameters were not correlated to the xerostomia, ICT was an independent factor, we consider that with a limit of the parotid Dmean at smaller values, the grade of xerostomia was unaffected by dose parameters changes or IMRT techniques.

Disclosure of conflict of interest

None.

Address correspondence to: Lin Ma, Department of Radiation Oncology, Chinese PLA General Hospital, Beijing 100853, China. E-mail: mlingg93@sina.com

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