Initial Experience Of Using Intensity Modulated Radiation Therapy For 49 Cases With Recurrent Nasopharyngeal Carcinoma

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Abstract **Objective** To evaluate the feasibility, toxicity and tumor control of recurrent nasopharyngeal carcinoma (NPC) with intensity modulated radiation therapy (IMRT). **Methods** 49 patients(Karnofsky performance status, KPS≥80) with local-regional recurrent carcinoma in nasopharynx received IMRT from Jan 2001 to Feb 2002 at Cancer Center, Sun Yat-Sen University, Guangzhou, China. Three patients with cervical lymph node metastasis (2 in N1 and 1 in N3) received adjuvant Cisplatin and 5-Fu chemotherapy after IMRT. **Results** The mean dose to covering 95% volume (D95) of gross tumor volume (GTV) in the nasopharynx was 68.09 Gy and the mean volume to GTV (V95) receiving the 95% prescription dose was 98.46%. The mean doses to GTV, clinical target volume CTV1 and CTV2 in the targets were 71.40Gy, 63.63Gy, and 59.81Gy,respectively. With the median follow-up time of 9 months (range 3 to 16 months), the local-regional progression-free survival was 100%. There have 3 patients (6.1%) local-regional residual, but 14 patients (28.6%) were completed with nasopharyngeal mucosa necrosis after IMRT. **Conclusion** IMRT, as a re-treatment option for recurrent NPC, is able to improve the tumor target coverage and spare the adjacent critical structures. As high dose IMRT can result in radio-necrosis of nasopharyngeal mucosa, the prescription dose of GTV should be suitably decreased to 60~65 Gy.

Key Words IMRT; Neoplasm recurrence; Nasopharyngeal neoplasms

The metastasis-free local-recurrence rate of Nasopharyngeal carcinoma (NPC) by conventional radiotherapy was 20.6%[1]; The recurrent rates were 52% under 2 years and 29% from 2 to 5 years as while was 9% over 25 years from those early staging patients [2]. Local recurrence becomes one of the important failure reasons of NPC. It is a challenge for radiation oncologists how to improve the tumor local-regional control and survive of recurrent NPC after reirradiation, and how to at maximum decrease the severe injure of the adjacent sensitive organs for reirradiation and afford a re-treatment chance to the relapsed NPC. Intensity modulated radiation therapy (IMRT) is able to precisely deliver doses to the target volume and sparing the surrounding tissues [3]. We performed the study to demonstrate the feasibility of recurrent NPC treated with the IMRT.

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METHODS AND MATERIALS

Clinical data

From Jan 2001 to Feb 2002, 49 patients (Karnofsky performance status > 80) with local recurrence nasopharyngeal carcinoma, and of them, 3 cases with neck regional recurrent, were treated with IMRT at the Cancer Center, Sun Yat-Sen University, Guangzhou, China. There were 37 males and 12 females with a mean age 49.39 (28~70) years old; the gender ratio is 3.08:1. The pathological features of all cases were diagnosed as poor differential squamous cell carcinoma by biopsy. The average time for recurrent local disease in the nasopharynx was 30.2 months after initial conventional radiotherapy. The median isocenter dose to the nasopharynx was 70.94 Gy (66.0~78.0 Gy).

The disease was re-staged according to the Chinese Fuzhou 92′ staging on NPC. The number of patients with stage Ⅰ, Ⅱ, Ⅲ, Ⅳ were 4, 9, 10

and 26; with T1, T2, T3, and T4 diseases were 4, 9, 11 and 25; and with N0, N1, N2 and N3 diseases were 46, 2, 0 and 1, respectively. Of them, invasion to the nasal cavity, maxillary sinus, ethmoid sinus, sphenoid sinus, cavernous sinus and base skull were found in 8, 1, 3, 8, 15 and 20 cases respectively.

Treatment

The was 68–70 Gy to GTV (gross tumor volume) with conventional fractionation, and the actual delivered mean dose was 68.82Gy and 2.29 daily fraction. Irradiation was delivered with a dynamic multi–vane intensity modulating collimator called MIMiC using a segmental tomotherapy technique (NOMOS Corp., Cranberry Township, PA). The gantry rotation arc was 105° – 255° and beamlet patterns changed every 5°. Patients received irradiation of 3–6 rotation arcs every time. Three patients who had positive lymph nodes metastasis were also treated with 5 to 6 courses of chemotherapy (Cisplatin + 5–FU) after IMRT.

Target definition

According to ICRU 62 guidelines, GTV was defined as the visible tumor, which was shown by CT/MRI imaging studies and was contoured according. Clinical target volume (CTV) was defined as the GTV plus a margin for potential microscopic spread. Two CTVs (CTV 1 and CTV 2) were set–up for the subclinical disease in the nasopharynx. CTV1 was defined as 0.5–1cm away from the border of GTV. CTV2 was defined as 0.5–1cm away from the border of CTV1. The CTV of posterior wall of nasopharynx can reduce down to 2~3mm if the tumor did not expanse to clivus. The surrounding critical normal structures, namely the brainstem, spinal cord, optic nerves, chiasm, pituitary gland, lens, temporal lobes, parotid gland, temporomandibular (T–M) joints, and mandible bone were contoured and the doses to these structures were constrained. All target volumes were outlined on the treatment planning CT images slice by slice.

The procedure of IMRT See to reference[4].

RESULTS

The irradiated doses and volumes of target

The results of treatment planning showed that the percentage of GTV receiving 95% of the prescribed dose (V95) was 98.46%, and the dose encompassing 95% of GTV (D95) was 68.09 Gy in the nasopharynx. The mean doses of GTV, CTV1 and CTV2 were 71.40Gy, 63.63Gy and 59.81Gy respectively.

The irradiated doses and volumes of critical structures

The average doses and volumes of critical structures in these 49 patients are shown in Table1.

Acute toxicity of irradiation

Acute toxicity in 49 patients was evaluated according to the acute radiation morbidity scoring criteria of USA radiation therapy oncology group (RTOG), 29, 19 and 1 patients had grades 0, 1 and 2 skin toxicity respectively; 16, 10, 21 and 2 patients had grades 0, 1, 2 and 3 toxicity in oral mucosa were respectively; 26,18 and 5 patients had grades 1, 2 and 3 xerostomia respectively.

Clinical follow–up

At a median follow–up of 9 months (range 3 to 16 months), the local–regional progression–free survival was 100%. Three (6.1 %) of 49 patients were found out local residual lesion at the end of IMRT. Tumor necrosis was seen in 14 patients (28.6%) toward the completion of IMRT. Three patients have developed metastases at a distant site: 2 in the bone, 1 in the liver and lung, at the 16 months after the IMRT.

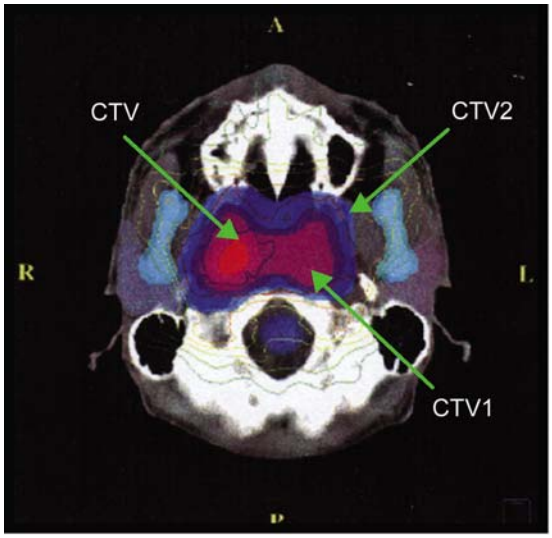

Fig.1. 100%dose curves surrounding GTV(bright red); 90%dose curves surrounding CTV1(dark red); 80%dose curves surrounding CTV2(blue); Spinal cord and bilateral parotid is under the lower dose curves.

Table 1. The IMRT doses and the volume of critical structures were delivered by IMRT in 49 patients with recurrent nasopharyngeal carcinoma

Critical structures	Mean dose (Gy)	Range of dose (Gy)	Volume (cc)	Range of volume (cc)
Brain Stem	28.51	9.09–55.30	23.04	6.77–34.69
Spinal Cord	20.19	5.54–38.71	5.44	2.96–7.53
Optical Chiasm	21.56	12.41–32.95	0.87	0.39–1.26
Pituitary	32.59	23.52–43.44	0.21	0.06–0.44
Lens				
L	3.91	2.28–6.35	0.20	0.18–0.22
R	4.10	3.00–6.50	0.20	0.15–0.23
Optical Nerves				
L	19.56	10.06–34.14	0.60	0.45–0.79
R	19.20	10.08–32.62	0.62	0.39–1.36
Temporal Lobes				
L	20.98	4.48–60.98	40.46	28.98–64.80
R	22.14	4.89–60.85	39.22	29.66–65.24
Parotids				
L	20.97	9.19–39.81	10.98	3.35–23.13
R	18.44	7.60–35.29	14.24	3.84–27.06
T–M Joints				
L	27.89	19.35–43.28	1.77	1.45–1.93
R	28.84	19.68–43.59	1.85	1.39–2.09
Mandible Bone				
L	20.19	5.38–50.95	36.30	22.50–47.34
R	19.71	4.86–48.48	35.79	29.16–46.89

L = left side, R = right side

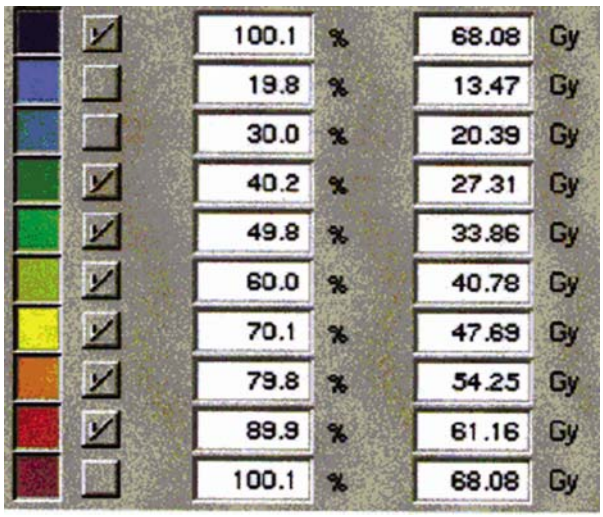

Fig.2. The various colors show the dose curves at differential level (%)

DISCUSSION

There are many factors resulting in recurrence after primary radiotherapy in NPC, such as irradiation techniques, irradiation dose and the difference of individual. Although most of the recurrence patients were received the re–irradiation, decrease of the overall survival rate and the increase of the irradiation injury would obviously result in increase of the mortality rate and decrease of the quality of life (QOF) in these patients[5]. Because of the inaccuracy of irradiation technique, some tumors can relapse at the edge of the primary irradiation field. If the recurrent tumors expand to the adjacent critical organs, such as brainstem, cerebellum, cavernous sinus and orbits, re–irradiation will be very difficult, even be unacceptable. In these 49 patients, 36 (73.5%) cases were re–staged as local advanced lesion (stage Ⅲ, Ⅳ). It´s quite refractory by conventional re–irradiation that 55 lesions invaded nasal cavity, maxilla sinus, ethmoid sinus, sphenoid sinus, cavernous sinus, base of skull, brain stem and middle cranial fossa. Both tumor cover of irradiation targets and spared of adjacent normal tissues in IMRT plans of this study are perfect idealization. It showed that IMRT is a new predominant method as rescuable treatment to recurrent NPC patients.

For recurrent NPC patients with re–irradiation, there are few salvage options on radiation, include stereotactic radiosurgery (SRS), three dimensions

conformal radiotherapy (3D−CRT) and IMRT. All of these methods can diminish the doses and volumes of critical organs that surround tumor. The indication of SRS is very narrow, it is difficult to treat the large mansions lesion. IMRT plans are able to deliver the different dose or dose rate to the tumor target and adjacent sensitive organs respectively. Thereby the aim of irradiation is either validly enhanced the tumor control rate or furthest reduced the dose of sensitive critical normal tissues[6]. Compared the NPC treatment plans to 3D−CRT, IMRT techniques was predominance according to clinical study reports of European and American countries in recent years[7].

The effectiveness of radiotherapy in NPC is correlation with the volume of target coverage, the dose of target and the homogeneity of target dose. The IMRT of relapse NPC is isomorphous. If GTV in the inverse plans didn´t be covered the all target or didn´t receive the radical dose, the recurrent tumors were easy to become insuppressible. If the homogeneity of target doses weren´t satisfied, there would result in overlow or overhigh dose distribution in the GTV, and finally occur the reduction of tumor control rate and the occurrence of the nasopharynx mucosa necrosis. Our results show that the mean cover volume in GTV at 95% (GTV V_{95}) prescription dose reach at 98.46%, and the mean dose of 95% volume (GTV D_{95}) is 68.09 Gy. According to the character of nasopharyngeal anatomy and NPC biological behavior, in order to deliver a dose gradient from GTV to normal tissues and organs, we set two CTVs (CTV1 and CTV2) around GTV target. The results in our inverse plans showed that the mean doses of GTV, CTV1 and CTV2 were 71.40Gy, 63.63Gy and 59.81Gy respectively (Figure 1 and Figure 2).

After primary radiotherapy, the critical organs surround nasopharynx had received considerable irradiated doses. Reirradiation will further induce the irradiation damage. IMRT was able to reduce this damage to minimum. Although most of the recurrent NPC patients (73.5%) were stage Ⅲ and Ⅳa (Table1), our results revealed that all the mean doses of normal organs adjacent nasopharynx were lower than their prescription limited doses. All patients´ maximum irradiation dose and volume were under the normal tissues tolerance dose that recommend by Emami[8]. In these 49 recurrent NPC patients, 14cases emerged nasopharyngeal mucosa irradiation necrosis, but the antibiotics could control the progress of the necrosis and mucositis. The reasons of the complications may be as follow: (1) IMRT delivered higher dose and fractionation size to the nasopharynx. The mean fractionation dose was 2.29Gy and the total treat time was 42d. The equivalent biological dosage is higher than the dose of conventional radiotherapy; and (2) the recurrent tumor in nasopharynx has poorer blood supply than the primary, and its mucosa tolerance dose is lower than initial radiotherapy.

Our initial therapeutic results showed that IMRT as a re−treatment option for recurrent NPC is an effective method. IMRT is able to precisely conformal radiotherapy to the local tumor target while synchronously sparing the surrounding normal tissues. Irradiation induced the skin and mucosa injure didn´t aggravate during the course of IMRT, and the patients are tolerable. The further therapeutic outcome need to longer−term follow−up of a larger cohort of patients to evaluate late toxicity and to confirm the early promising treatment outcome.

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