Stereotactic radiotherapy—an approach to improve local control of nasopharyngeal carcinoma

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[Abstract] Radiotherapy is the primary curative treatment of nasopharyngeal carcinoma (NPC) with the dose-response relationship. Local recurrence is one of the major treatment failure patterns. With high accuracy, high tumor dose, high therapeutic enhancement ratio and low normal tissue dose, stereotactic radiotherapy (SRT) is used as boost irradiation for residual lesions and is able to improve the local control rate. Residual lesions involving the carotid artery or cavernous sinus, or with tumor necrosis are treatment contraindications to SRT boost irradiation; while the old patients, patients with hypertension, diabetes mellitus, and severe nasopharyngeal infection are relative treatment contraindications to SRT boost irradiation. Fractionated SRT can spare vessels and nerves better than stereotactic radiosurgery (SRS). SRT can definitely improve the outcome for the boost of NPC residual lesions. Proper patient selection, individualized fractionated regimen, and balance of the benefit of tumor control and the risk of normal tissue damage are of paramount importance to ensure the satisfactory clinical outcome and quality of life.

Key words: Nasopharyngeal neoplasm, residual lesions, stereotactic radiotherapy, boost irradiation

Radiotherapy is the preferred and main treatment of nasopharyngeal carcinoma (NPC), and the control rate is positively correlated with the radiation dose. More than 10% of the NPC patients have nasopharyngeal residue after conventional radiotherapy (CRT) and 30% have local recurrence. In recent years, despite the use of concurrent chemoradiotherapy, intensity-modulated radiotherapy (IMRT) and adjuvant radiosensitization, about 10% of the patients with NPC at UICC stages III and IV still have residual lesions.

Boost with conventional external radiotherapy can obtain a certain effect\(^1\). In the 1990s, Yan et al.\(^2\) reported a randomized study giving boost to residual lesions of NPC after radiotherapy, and the results showed that the 5-year survival rate was 75% and the local recurrence rate was only 6% for the patients treated with boost of 20 Gy after CRT of 70 Gy, and those rates for the patients without boost were only 33% and 36%\(^3\). This clinical study laid the foundation of stereotactic radiotherapy (SRT) as a way to boost. Now the clinically commonly used boost techniques include conventional two-field opposite irradiation, brachytherapy, conformal radiotherapy and SRT. Boost is limited using CRT technique because of normal tissue damage, and the complications after treatment are serious. Brachytherapy is only suitable for superficial residual disease. Surgery requires a good general situation and specific condition of patients, and can only save part of patients\(^4\). IMRT has been carried out in a short time with no long-term results reported.

Advantages of SRS/FSRT

SRT has the characteristics of ‘three highs and one low’: that is, high precision, high dose, high therapeutic gain ratio and low normal tissue dose. It uses three-dimensional framework for positioning, location and treatment, with high-dose region mainly in the target volume that will help to protect the surrounding normal tissue. At the same time, the equivalent biological dose of hypofractionated SRT is higher than CRT, and fractionated radiotherapy is more in line with tumor radiobiological characteristics. In the 1990s, radiation oncologists began to use SRT for extracranial tumors, such as tumors in the head and neck, and body. Multiple medical institutions reported that stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) was used for boost on NPC residual disease after initial radiotherapy.

The value of SRS/FSRT in the boost of NPC

Since Konziolka et al.\(^6\) reported using SRS to treat 1 case of...
recurrent NPC in 1991, a large number of retrospective studies have analyzed the efficacy and complications of SRS or FSRT on residual NPC disease. Tate et al.7 and Le et al.8 used SRS to give boosts to 23 and 45 cases of residual NPC disease after initial radiotherapy respectively, with a single dose of 7–15 Gy, and the 2-year local control rate in the former study and the 3-year local control rate in the latter study were both 100%, with no serious complication in the former, and four cases (8.9%) of cranial nerve injury and three cases (6.7%) of temporal lobe necrosis in the latter. Ahn et al.9 reported using FSRT to give boost to 19 cases of NPC, with the dose of 8–40 Gy by 4–20 fractions, and the 4-year local control rate was 89%, with 1 case of mucosal necrosis. In 2001, Xiao et al.10 reported using FSRT to give boost to 32 cases of residual NPC disease after initial radiotherapy, with the dose of 18–24 Gy by 2–4 fractions in 7–15 days, and two cases of local failure (one recurrent case and one uncontrolled case) occurred. In 2007, Wu et al.11 reported using FSRT to give boost to 34 cases of residual NPC disease after initial radiotherapy, with the dose of 18 Gy by 3 fractions, and the 3-year local control rate was 89.4%, with 3 cases of temporal lobe injury (8.8%). In 2008, Hara et al.12 reported the long-term results of boost by SRS to 82 cases of NPC, in which 66 (80%) were at stages III and IV, with SRS dose of 7–15 Gy and concurrent cisplatin chemotherapy and adjuvant chemotherapy, and the 5-year local recurrence-free survival rate was 98% and the 5-year overall survival rate was 69%. In the recent prospective study by Cancer Hospital, Chinese Academy of Medical Sciences, FSRT was used to give boost to 111 cases of residual NPC disease after initial radiotherapy, in which 84 (76%) were at stages III and IV, with the dose of 12–26 Gy by 2–7 fractions, and the 5-year local control rate was 92.1% and the 5-year overall survival rate was 83.7%, with six cases (5.4%) of cranial nerve injuries and one case (0.9%) of mucosal necrosis.13

The initial stages, residual tumor location, tumor size, dose-fraction mode, followed-up time, physical status, and underlying diseases of the patients and the admitted cases in various medical centers were different, which affected the outcome. Therefore, it is difficult to compare between various centers. However, SRS/FSRT have a certain effect as a method of boost to NPC.

The treatment contraindications and dose-fraction mode of boost by SRS/FSRT

The nasopharyngeal cavity is located in the center of head with small space and is adjacent to vital structures, such as the cranial nerves and blood vessels entering and exiting the skull base, brain stem, spinal cord, eyes, ears and other facial structures, whose functions are particularly critical in the maintenance of patients’ quality of life. Studies have reported bleeding in the nasopharyngeal cavity is the most serious complication of SRS/FSRT. If the residual tumor is located in the pharyngeal recess, parapharyngeal space, petrous apex, or foramen lacerum, especially when the tumor invades the vascular adventitia of cervical internal carotid artery, the patient receiving SRT as boost are prone to have ulcers and infection, and develop life-threatening bleeding once the tumor regresses and the blood vessel perforates. The patients with cavernous sinus invasion should also be on guard against bleeding tendency. If the patients have tumor necrosis accompanied by odor, SRT should not be chose as boost. In addition, it is also reported that for cranial nerve injury of certain degree, especially the posterior cranial nerves at the outside back of the cervical internal carotid artery, the posterior cranial nerves are difficult to be spared in SRT in some cases, therefore, in recent years a small fraction is adopted in this situation to minimize the damage to blood vessels and nerves to protect their functions.13,14,15 At present, the factors need to be considered in determining the dose-fraction plan of SRT include ① target volume location, target volume size, and vital structures surrounding target volume; ② patient’s age, the cleanliness of the nasopharynx, with or without diabetes, hypertension and other complications, as well as the dose of previous radiation and the interval from previous treatment, and so on. Generally, a single dose of 3–6 Gy with a total dose of 15–20 Gy is recommended. The patients should be closely followed up after treatment, and the cleanliness of the nasopharynx and tissue repair should be paid attention to.16

The control of NPC by initial treatment is the key, and FSRS has a certain clinical value in the management of delayed tumor elimination and residual lesions. Select appropriate cases, individualize dose-fraction mode, comprehensively grasp the balance between tumor regression and normal tissue repair, and then satisfactory efficacy and high quality of life can be obtained with improved survival rate of the patients at advanced stage.

References

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