Efficacy and prognosis of CT-guided of 125I radioactive seeds implantation brachytherapy as salvage treatment for recurrent nasopharyngeal carcinoma after external beam radiotherapy–A long-term experience at a single institution

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Abstract

Background: To assess the efficacy and prognosis of computed tomography (CT)-guided 125I radioactive seeds implantation brachytherapy (RSI-BT) for recurrent nasopharyngeal carcinoma (NPC) after external beam radiotherapy (EBRT). Methods: Thirty-one patients with recurrent NPC (forty-one lesions) after EBRT from February 2003 to January 2019 were enrolled in this retrospective study. The work-follow of CT-guidance RSI-BT was: indication selection, patient set-up and immobilization on CT couch, CT-simulation, preoperative planning, prescription doses (PD) definition of 110-160Gy, seed implantation, postoperative dosimetric evaluation and postoperative follow-up. Median radioactivity of RSI was 0.43 (range 0.22-0.79, average 0.61) mCi. Median actuarial number of 125I seeds was 24 (range 3-83, average 37). Median value of post-operative D90 was 118.5 (range 62.4-246, average 136.2) Gy. Local control (LC) and overall survival (OS) were investigated for their relationship with the prognosis. The adverse events were evaluated by the Radiation Therapy Oncology Group (RTOG) classification criteria. Results: Median follow-up was 41.9 (range 2.1-60.2, average 44.1) months. Median LC was 35.8 (range 2.1-60.2, average 34.9) months. LC at 1-, 3- and 5-year was 71.3%, 41.9% and 27.9%, respectively. Median OS was 22.6 (range 2.1˜60.2, average 27.1) months. OS at 1-, 3- and 5-years was 57.7%, 23.8% and 11.9%, respectively. Univariate analysis suggested that sex (P=0.037) and frequency of previous EBRT (P=0.001) were prognostic factors influencing LC. Moreover, univariate analysis also suggested that frequency of previous EBRT (P=0.012) was prognostic factors influencing OS. Prevalence of side effects ([?]grade 3) was 6.5%. Conclusion: 125I RSI-BT was a safe and feasible salvage treatment for recurrent NPC after EBRT. Key words: recurrent nasopharyngeal carcinoma; External beam radiotherapy; 125I seed implantation brachytherapy; overall survival; local control; side effects.

Original Article

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Methods : Thirty-one patients with recurrent NPC (forty-one lesions) after EBRT from February 2003 to January 2019 were enrolled in this retrospective study. The work-follow of CT-guidance RSI-BT was:

indication selection, patient set-up and immobilization on CT couch, CT-simulation, preoperative planning, prescription doses (PD) definition of 110-160Gy, seed implantation, postoperative dosimetric evaluation and postoperative follow-up. Median radioactivity of RSI was 0.43 (range 0.22-0.79, average 0.61) mCi. Median actuarial number of ^{125}I seeds was 24 (range 3-83, average 37). Median value of post-operative D90 was 118.5 (range 62.4-246, average 136.2) Gy. Local control (LC) and overall survival (OS) were investigated for their relationship with the prognosis. The adverse events were evaluated by the Radiation Therapy Oncology Group (RTOG) classification criteria.

Results : Median follow-up was 41.9 (range 2.1-60.2, average 44.1) months. Median LC was 35.8 (range 2.1-60.2, average 34.9) months. LC at 1-, 3- and 5-year was 71.3%, 41.9% and 27.9%, respectively. Median OS was 22.6 (range 2.1~60.2, average 27.1) months. OS at 1-, 3- and 5-years was 57.7%, 23.8% and 11.9%, respectively. Univariate analysis suggested that sex (P=0.037) and frequency of previous EBRT (P=0.001) were prognostic factors influencing LC. Moreover, univariate analysis also suggested that frequency of previous EBRT (P=0.012) was prognostic factors influencing OS. Prevalence of side effects ([?]grade 3) was 6.5%.

Conclusion : ^{125}I RSI-BT was a safe and feasible salvage treatment for recurrent NPC after EBRT.

Key words : recurrent nasopharyngeal carcinoma; External beam radiotherapy; ^{125}I seed implantation brachytherapy; overall survival; local control; side effects.

Highlights:

^{125}I RSI-BT was a safe and feasible salvage treatment for recurrent NPC after EBRT.

Frequency of previous EBRT was a prognostic factor influencing LC and OS.

Patients with recurrent NPC after EBRT, especially those treated with re-irradiation might benefit from ^{125}I RSI-BT.

1. Introduction

Nasopharyngeal carcinoma (NPC) was one of the most common head and neck malignancies and was prevalent in southern China. The International Cancer Research Center reported that in 2012 the worldwide incidence of NPC was 12/100,000, whereas new cases of NPC in China accounted for 53.5% of the worldwide incidence[12].

EBRT was first-line treatment modality for NPC. Approximately 20-40% of patients suffered from recurrence after EBRT[3-5]. With the popularity of precise EBRT and comprehensive treatment (EBRT combined with chemotherapy), the efficacy of treatment has improved greatly with a 5-year recurrence-free survival rate of 83.0-91.8%[6-8]. However, advanced NPC carried a poor prognosis if recurrence occurred. Thus, exploring a high efficient treatment for recurrent NPC was necessary.

Over the past few decades, improvement of surgical skills, re-irradiation, chemotherapy and other treatments have contributed to salvage treatment for recurrent NPC. For patients with early-stage recurrence, surgery could be an alternative, which would resect radiation-resistant tumors and avoid reirradiation damage as much as possible. It has been reported that 5-year LC and OS after tumor resection were 43-74% and 47-62% respectively[9-13]. However, most patients recurred with late-stage disease which usually unresectable[14-17].

Reirradiation was one of the most common salvage treatments for recurrent NPC[18]. Previous studies showed that the recurrent NPC patients treated with re-irradiation, LC and OS at 3 years could reach 70-89% and 46-58%, respectively[19-22]. However, about 30-70% of patients were likely to develop severe (grade 3-5) complications [202123-25]. Moreover, some patients might die of fatal complications, such as necrosis of the temporal lobe necrosis or carotid blowout[26].

^{125}I RSI-BT, as a local treatment, was characterized by high local dose, sharp fall-off of dose curve and little unexpected radiation effects on adjacent normal tissues. ^{125}I RSI-BT has been considered as salvage treatment for some types of recurrent cancer, such as rectal cancer[27]. The advantages of CT-guidance punctures were: (1) high resolution of CT scans; (2) high precision for needles into puncture position; (3) minimal invasion and fast recovery. However, few studies of^{125}I RSI-BT against recurrent NPC have reported. In this study we investigated the efficacy and prognosis of^{125}I RSI-BT treatment of recurrent NPC with a long-term follow-up.

2. Materials and Methods

2.1 Patients

There are 31 patients (41 lesions) with recurrent NPC after EBRT from February 2003 to January 2019 reviewed retrospectively, among which 11 patients (35.5%) treated with twice or more times EBRT and the median previous radiation doses were 71.9 (range 60-160) Gy. 17 patients with CT-guided RSI-BT only and 14 of patients with CT-guidance combined with 3D-PT assistant RSI-BT were performed under standard operating procedure in our institution. Informed consent was signed by each patient before the treatment.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) NPC confirmed by pathology; (2) relapse after EBRT and unable or rejecting to undergo surgery or re-irradiation; (3) tumor diameter [?]7cm; (4)pre-plan shown a feasible needle pathway to avoid bones, large blood vessels or organs at risk (OARs); (5) Karnofsky Performance Status (KPS) [?]60; (6) expected survival [?]3 months. The exclusion criteria were as follows: (1) severe bleeding tendency; (2) immunocompromised with acute infection or chronic active infection; (3) patient with conditions intolerant to minimal invasive procedure/surgery such as severe cardiopulmonary insufficiency or liver and kidney; (4) contraindication to anesthesia; (5) uncontrolled multiple metastases.

2.3 ^{125}I RSI-BT

All patients underwent standard RSI-BT procedure (Fig 1). Pre-operative CT scans (slice thickness 2.5-5 mm with contrast) was carried out and images were transmitted to Brachytherapy Treatment Planning System (BT-TPS) (Beijing Astro Technology, Beijing, China). The needle-puncture pathway was designed on BT-TPS. Radioactivity and number of seeds were calculated according to prescription doses (PD) design. Individualized template was made by three-dimensional-printing techniques (3D-PT). Finally, a digital information of needles channels on BT-TPS for pre-operative plan was transferred into 3D-pinting software and reconstruction.

Patients were usually positioned supine according to the tumor sites. After the induction of local anesthesia, the operator chose the best layer and angle for needle puncture assisted or not by 3D-PT based on the pre-operative plan and followed by needle insertion. CT scans to verify the needles position and direction, the operator optimized the angle and depth of the needle by real-time CT scan to conform the pre-operative plan. Then, seeds were implanted using a Mick® Applicator (Mick Radio Nuclear Instruments, Mount Vernon, NY, USA) according to pre-plan. Finally, CT was undertaken immediately following seeds implantation to check the actual distribution of 125I seeds and, if necessary, more seeds would be implanted for doses distribution in the targets as pre-plan requirements.

2.4 Follow-up

Patients were followed up every 3-6 months within 5 years after surgery, and once a year thereafter. Follow-up was conducted by telephone, outpatient appointment or hospitalization. Follow-up information included symptoms, physical examination, laboratory-test data and imaging examinations.

2.5 End points and their definition

The first end points included LC. LC was defined as the interval from the date of RSI-BT to the date of local progression. The second end points included OS and treatment-related toxicity. OS was defined as interval from the date of RSI-BT to the date of death for any cause. Treatment-related toxicity was evaluated by the Radiation Therapy Oncology Group (RTOG) classification criteria[28].

2.6 Statistical analyses

Statistical analyses were performed using SPSS v22.0. The Kaplan-Meier method was used to calculate LC and OS. The Cox regression model was used for univariate analysis to analyze correlation between clinical factors with LC and survival.

3. Results

3.1 General information

A total of 41 lesions in 31 patients were assessed. General information of the patients and tumors was shown on Table 1. The median age of the study cohort was 52 (range, 25 – 73, average 52.5) years old. 34.1% lesions (14/41) with RSI-BT were assisted by 3D-PT. The median radioactivity of ^{125}I radioactive seeds was 0.43 (range, 0.22-0.79, average 0.61) mCi. The median number of^{125}I radioactive seeds was 24 (3-83, average 37). The median value of D90 was 118.5 (62.4-246, average 136.2) Gy.

3.2 LC and Survival

Median follow-up was 41.9 (range 2.1-60.2, average 44.0) months. In total, 16 lesions in 11 patients suffered local progression. The median duration of LC was 35.8 (range 2.1-60.2, average 34.9) months (Figure 2). LC at 1, 3 and 5 years was 71.3%, 41.9% and 27.9%, respectively. Twenty patients died: ten (50%) due to local progression, two (10%) due to haemorrhage, four (20%) due to distant metastasis and four (20%) due to non-cancer reasons (two of cachexia, one of transfusion reaction and one of pulmonary infection). The median OS was 22.6 (range, 2.1~60.2, average 27.1) months (Figure 3). OS at 1-, 3- and 5-years was 57.7%, 23.8% and 11.9%, respectively.

3.3 Prognostic factors

Univariate analysis suggested that sex (P=0.037) and frequency of previous EBRT (P=0.001) were prognostic factors influencing LC (Table 3). Moreover, univariate analysis also suggested that frequency of previous EBRT (P=0.012) was prognostic factors influencing OS (Table 4).

For patients who had received only once EBRT, the mean duration of LC was 47.9 (range 5.1-60.2) months. LC at 1, 3 and 5 years was 93.8%, 58.6% and 58.6%, respectively. The median OS was 31.6 (range, 5.1~60.2, average 34.3) months. OS at 1-, 3- and 5-years was 72.3%, 36.3% and 18.1%, respectively. For those who had received EBRT twice or three times, the mean duration of LC was 20.8 (range 2.1-52.2) months. LC at 1, 3 and 5 years was 42.4%, 25.5% and 0%, respectively. The median OS was 9.2 (range, 2.1~33.4, average 13.9) months. OS at 1- and 3-years was 31.2% and 0%, respectively (Figure 4).

The use of 3D-PT might improve LC (P=0.078) though the statistically difference was less significant. For patients who used 3D-PT, the mean duration of LC was 39.1 (range 2.1-41.9) months. LC at 1 and 3 years was 92.9% and 92.9%, respectively. For those who did not use 3D-PT, the mean duration of LC was 29.2 (range 2.1-60.2) months. LC at 1 and 2 years was 61.5% and 29.5%, respectively.

3.4 Toxicities

Common late adverse effects were mainly skin/mucosal toxicities**.** There were 2 cases of late severe adverse effects (6.5%), including one case of grade 4 mandibular osteonecrosis and one case of grade 3 skin/mucosal toxicity. The patient suffered from mandibular osteonecrosis had received two courses of EBRT before last recurrence, of which the total dose accumulated to 138Gy. Another patient suffered from grade 3 skin/mucosal toxicity had received one course of EBRT for a total dose of 70Gy. Besides, eleven patients (41.9%) suffered from late grade 1-2 adverse effects, including ten cases (32.2%) of skin/mucosal toxicities and one case (3.2%) of pain.

4. Discussion

With the development of treatments, only 10-20% NPC patients would suffer local recurrence after initial treatment[29-31]. Surgery was one of options for recurrent NPC. In most retrospective studies, surgery has been reported to achieve a similar or better result than re-irradiation with a 5-year LC of 43-74% and a 5-year OS of 47-62%[9-13]. Moreover, the advantage of surgery was fewer complications and better quality of life.

However, it might be due to selected patients. The lesions considered resectable included rT1 disease, rT2-3 with limited parapharyngeal space involvement or disease confined to the base of sphenoid sinus. Others, such as involvement of the internal carotid artery, limited invasion to the clivus, posterior maxillary sinus, pterygoid process and petrous apex, might be resectable, which required the careful judgment by surgeon[32]. Therefore, there were still many patients not suitable or willing to receive surgical treatment, especially those with late-stage recurrence.

Reirradiation was the most common salvage treatment for recurrent NPC, especially for those unable to receive surgery[18]. However, previous studies have shown that recurrence usually occurred in high-dose areas with the characteristic of radio-resistance[3334]. Moreover, when finishing the first course of radiation, changes in the microenvironment such as fibrosis and vascular necrosis might exacerbate radio-resistance[35]. Reirradiation became a stuff work because of the balance of high dose needed for radio-resistance tumors and dose limited by accumulation of surrounding organs at risks. Previous studies have shown that the recurrent NPC patients with re-irradiation as a salvage treatment, LC and OS at 3 years can reach 70-89% and 46-58%, respectively[19-22]. However, the side effects of reirradiation remain challenging issues. Virtually most patients with irradiation suffered long-term complications. About 30-70% of patients were likely to develop severe (grade 3-5) complications [202123-25]. Moreover, some patients might die of fatal complications, such as necrosis of the temporal lobe necrosis, carotid blowout, teeth occlusion and mucosal ulcer[26][23,40,41]. Han and colleagues[21]reported that the prevalence of advanced toxicity (grade 3-5) of intensity modulated radiotherapy (IMRT)for treatment of recurrent NPC was 70.3%, and that 69 % of patients died of EBRT-related toxicity. Kong and co-workers[19]reported that 29.3% patients died of radiotherapy-related complications. Of these patients, 23.9% patients died of massive hemorrhage, indicating that massive hemorrhage was the most common cause of death. 75%of patients underwent locally advanced disease. Koutcher and colleagues[36] reported an incidence of 73% that grade III or above complications occurred. Teo and co-workers[37] reported that the incidence of hearing loss or difficulty in opening mouth was approximately 50-70% after reirradiation.

^{125}I RSI-BT, one of the most common brachytherapy, was often chosen as a salvage treatment for recurrent cancers, such as hypopharyngeal carcinoma[38], salivary gland carcinoma[39] or other head and neck squamous cell carcinoma[40]. Because of its sharp dose curve,^{125}I RSI-BT could protect OARs and achieve a higher local dose distribution so as to achieve favorable LC. Many published studies[40-46] have reported RSI-BT as a safe and effective treatment for recurrent NPC, with a local control probability at 1- and 3-years of 52-75.2% and 5.3-73%, respectively, and an overall survival probability at 1- and 3-years of 53-84.6% and 6.7-39%, respectively, as well as a accepted toxicities(Table 4).

In this retrospective analysis, LC of RSI-BT as a salvage treatment for recurrent NPC at 1-, 3- and 5-year was 71.3%, 41.9% and 27.9%, respectively and OS at 1-, 3- and 5-year was 57.7%, 23.8% and 11.9%, respectively, which just the same as published studies.

We found that the total times of previous EBRT was a prognostic factor affecting LC (P=0.001) and OS (P=0.012). For patients those received only once EBRT, LC at 1, 3 and 5 years was 93.8%, 58.6% and 58.6%, respectively and OS at 1-, 3- and 5-years was 72.3%, 36.3% and 18.1%, respectively. However, for those received EBRT twice or three times, LC at 1, 3 and 5 years was 42.4%, 25.5% and 0%, respectively and OS at 1- and 3-years was 31.2% and 0%, respectively. The results were probably due to fibrosis, atrophy and necrosis of local tissue, vascular redistribution, and decreased radio-sensitivity after multiple EBRT. Salvage treatment for local recurrent NPC after previous EBRT was a stuff task especially when the patient experienced twice or more courses of EBRT and RSI-BT might be alternative and promising.

We also found that sex was a key factor affecting LC (P=0.037), which was not reported in previous work. It needs to be further investigated to exclude cause of the patient pool's unbalanced sex ratio males to females and small study cohort.

The use of 3D-PT might improve LC (P=0.078) though the statistically difference was less significant. 3D-PT was creatively designed and introduced into CT-guided RSI technique[47]. With 3D-PT assistance, RSI-BT may be more accurate and have better doses distribution which close to expected preoperative plan[48]. It provided a way of RSI-BT to standardization and normalization. An ideal dose distribution may lead to a better LC, but we can only identify the tendency due to our limited case number and still need more data to confirm it.

KPS was a prognostic factor to LC (P=0.033) and might be a prognostic factor to OS (P=0.075) though the statistically difference was less significant, which might have been due to the small study cohort or confounding factors. However, this prognostic factor needed more data to verify.

Furthermore, safety was another key point needed to be paid attention to. Comparing to EBRT, RSI-BT has the advantage of providing a small radius of radiation, high local radiation dose, sharp fall-off of the radiation dose and few radiation effects on adjacent tissues. These features achieve the goal of Precise EBRT and ^{125}I RSI-BT been recommended for treatment of several types of recurrent or relapsed cancer by the National Comprehensive Cancer Network. In our study, only 2 cases (6.5%) suffered severe radiotoxicity: 1 case with of grade 3 skin/mucosal toxicity and another of mandibular osteonecrosis. Besides, eleven patients (41.9%) suffered from late grade 1-2 adverse effects, including ten cases (32.2%) of skin/mucosal toxicities and one case (3.2%) of pain. The prevalence of severe toxic and side effects observed in our study was obviously lower than that of patients receiving reirradiation for recurrent NPC in other studies, and further demonstrated the safety of ^{125}I RSI-BT for treatment of recurrent NPC.

Conclusion

Our retrospective study demonstrated that ^{125}I seed implantation was a safe, feasible and effective treatment option for treatment of recurrent NPC. The efficacy and safety of this method needs to be verified by randomized controlled studies with large study cohorts.

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Figure legends

Figure 1. Procedure of CT-guided RSI-BT as a salvage treatment for recurrent nasopharyngeal carcinoma after external beam radiotherapy.

OS, overall survival; LC, local control

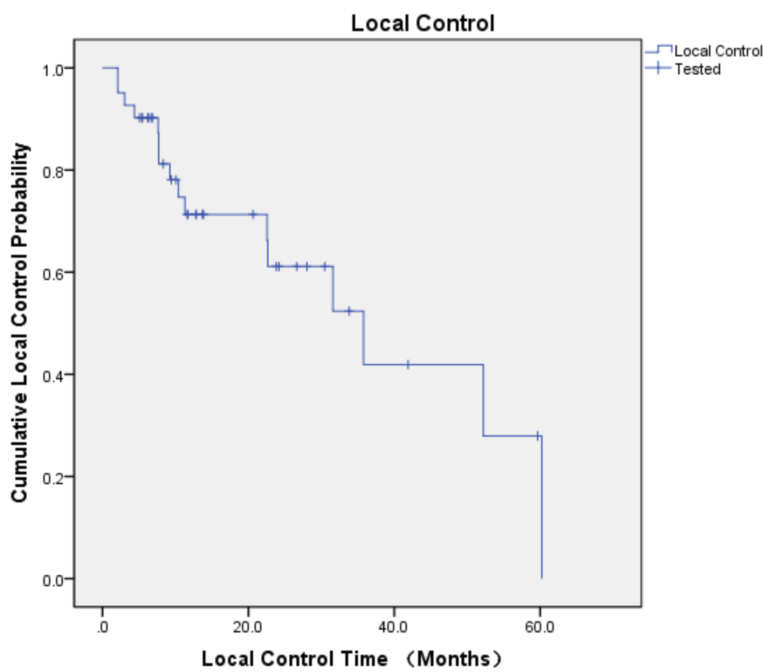

Figure 2. The local control for 41 lesions.

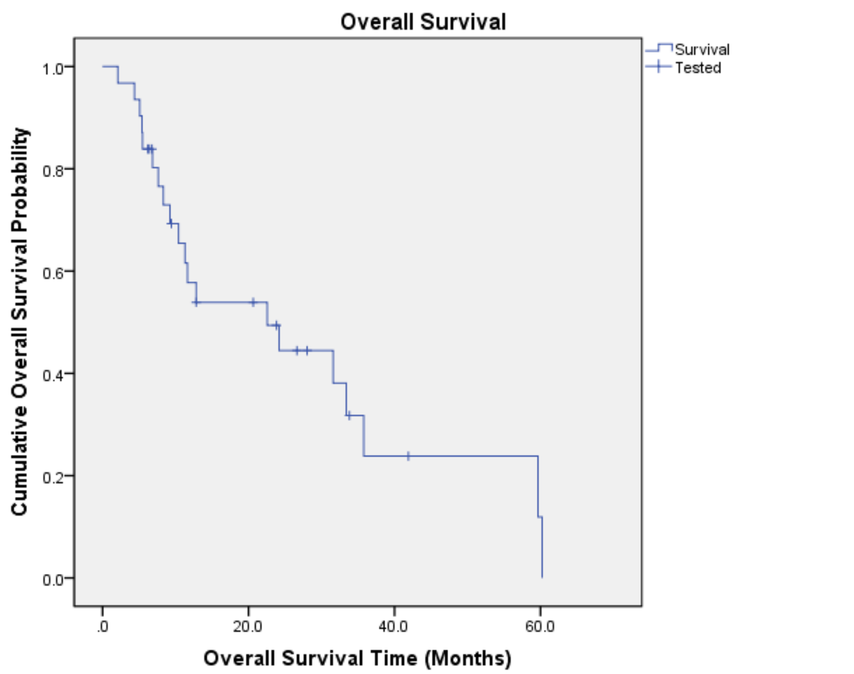

Figure 3. The overall survival for 31 patients.

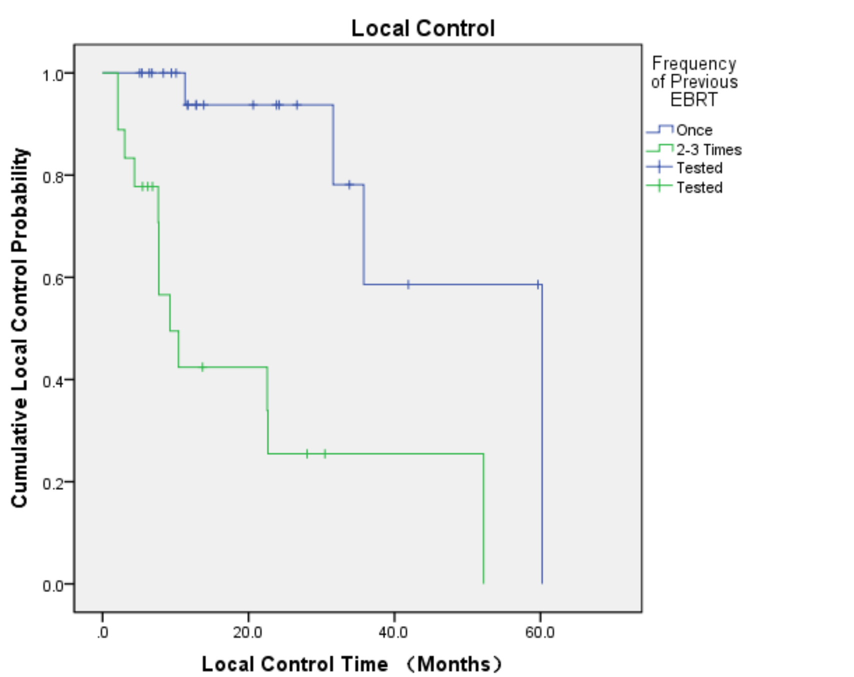

Figure 4. The local control and overall survival for patients treated with EBRT once and 2-3 times.

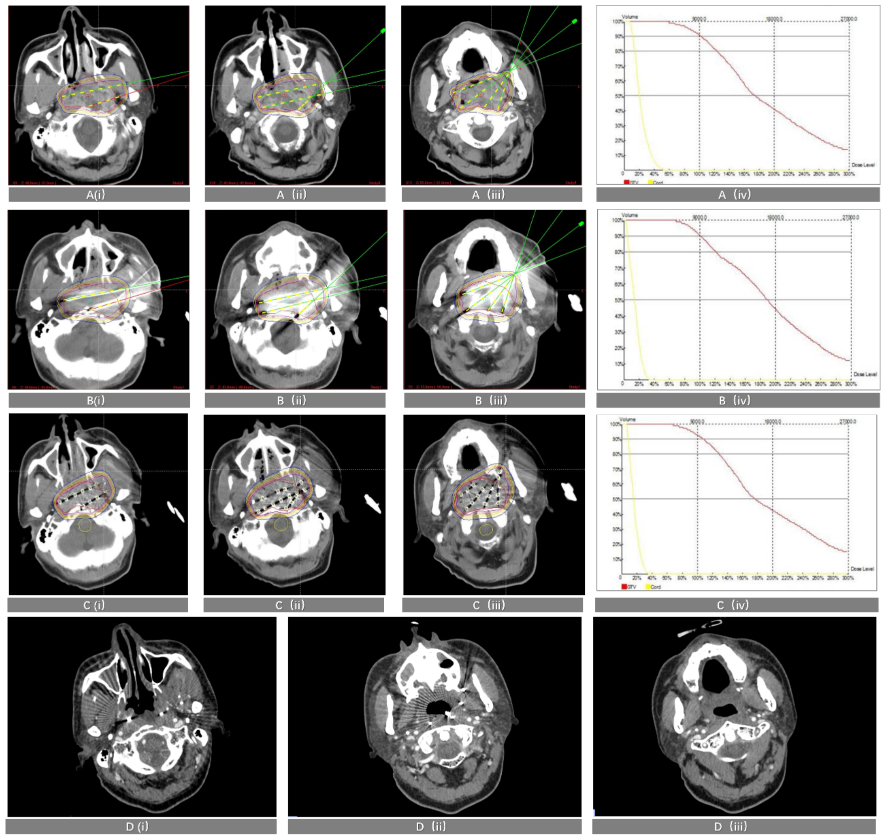

Figure 5. A 52-year-old male with nasopharyngeal undifferentiated non-keratinized carcinoma cT3N2M0 stage III has received sequential chemoradiotherapy, with included 70.4Gy/32fractions of external beam radiotherapy and four cycles of chemotherapy. Ten months after initial treatment, he suffered from recurrence. He decided to receive two cycles of chemotherapy and RSI-BT as a salvage treatment.

A. (i-iii) before RSI-BT, (iv) dose volume histograms (DVH) of RSI-BT; B. (i-iii) intraoperative needle puncture pathway, (iv) dose volume histograms (DVH) of RSI-BT; C. (i-iii) after RSI-BT, (iv) dose volume histograms (DVH) of RSI-BT. D. (i-iii) 2 months after RSI-BT.

Table 1. General information of the study cohort and their tumors

Characteristics	Cases	Percentage
Sex		
Male	20	64.5
Female	11	35.5
Age: years, median (range)	52 (25-73)	
Karnofsky Performance Status: median (range)	80(60-90)	
Pathologic types		
Non-keratinizing	17	54.8
Squamous cell carcinoma	14	45.2
Previous EBRT frequency		
Once	20	64.5
Two times	9	29.0
Three times	2	6.5

Characteristics	Cases	Percentage
Total dose of previous EBRT: Median (Range)	71.9 (60-160)	
Previous surgery		
Yes	7	22.6
No	23	74.2
Not known	1	3.2
Previous chemotherapy		
Yes	23	74.2
No	8	25.8
Previous molecular targeted therapy		
Yes	7	22.6
No	24	77.4
Recurrent sites		
In situ	14	45.2
Lymph node	17	54.8
Time from the initial EBRT to implantation: months, median (range)	19.6(2.1-113.3)	

EBRT, external beam radiotherapy

Table 2. Univariate analysis of LC for recurrent NPC

		Univariate analysis	Univariate analysis	Univari
Variables	**Categories**	**HR**	**95%CI**	**p-value**
Sex	Male	0.316	0.107-0.935	0.037
	Female			
Age (years)	[?]50	1.828	0.648-5.157	0.255
	¿50			
Pathology	Non-keratinizing	0.840	0.502-1.405	0.507
	Squamous			
Previous EBRT times	1	0.115	0.032-0.415	0.001
	2-3			
Time from EBRT to RSI-BT (months)	[?]18	1.733	0.573-5.243	0.330
	¿18			
KPS	[?]80	0.261	0.076-0.900	0.033
	¡80			
Implantation Sites	In situ	2.517	0.782-8.108	0.122
	Lymph nodes			
D90 (Gy)	¡120	1.126	0.383-3.314	0.829
	[?]120			
RSI-BT assistance	Without 3D-PT	6.242	0.814-47.867	0.078
	3D-PT			
Short-term efficacy	CR+PR	0.785	0.167-3.683	0.759
	SD+PD			

EBRT, external beam radiotherapy; HR, hazard ratio; CI, confidence interval; LC, local control; NPC, nasopharyngeal carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Univariate analysis of OS for NPC

		Univariate analysis	Univariate analysis	Univar
Variables	**Categories**	**HR**	**95%CI**	**p-value**
Sex	Male	0.730	0.285-1.871	0.512
	Female			
Age (years)	[?]50	0.742	0.277-1.984	0.552
	¿50			
Pathology	Non-keratinizing	0.813	0.321-2.062	0.663
	Squamous			
Previous EBRT times	1	0.288	0.109-0.756	0.012
	2-3			
Time from EBRT to RSI-BT (months)	[?]18	0.899	0.348-2.322	0.826
	¿18			
KPS	[?]80	0.367	0.122-1.108	0.075
	¡80			
Implantation Sites	In situ	0.993	0.389-2.533	0.988
	Lymph nodes			
D90 (Gy)	¡120	0.837	0.299-2.346	0.735
	[?]120			
RSI-BT assistance	Without 3D-PT	1.509	0.535-4.252	0.437
	3D-PT			
Short-term efficacy	CR+PR	0.579	0.181-1.854	0.357
	SD+PD			

EBRT, external beam radiotherapy; HR, hazard ratio; CI, confidence interval; OS, overall survival; NPC, nasopharyngeal carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Outcomes of published retrospective studies on RSI-BT as treatment for NPC

Author	**No. of patients**	**Tumor Volume**	**Dose (Gy)**	**Median follow up (Months)**	**Local Control (%)**	**Overall Survival (%)**	**Toxicity**
Yuliang Jiang (2010)[41]	14 (3 NPC)	32(9.1-290.4)	157.5(90-218)	12(3-60)	Median 18mo 1y 52% 3y 39% 5y 39%	Median 20mo 1y 65% 3y 39% 5y 39%	1 case mucosal reaction
Lihong Zhu (2013)[42]	19 (1 NPC)	20(1-270)	131(90-160)	11(3-44)	Median 24mo 1y 73.3% 2y 27.5% 3y 27.5%	Median 13mo 1y 53.0% 2y 18.2% 3y 18.2%	1 case skin reaction
Xinying Shen (2015)[43]	30	Diameter 2.5±1.2cm (1.0-5.9)	130 (90-160)	2-38	1y 73.7% 2y 26.3% 3y 5.3%	1y 80.0% 2y 30.0% 3y 6.7%	NR
Hai Huang (2016)[44]	31 (9 NPC)	Mean 21.23 ± 8.83 cm2	Mean 101.03 ± 8.54 (90–125)	Range 6-38	1y 64.51% 2y 45.16%	1y 67.74% 2y 45.16%	3 cases G1 2 cases G2
Huzheng Yan (2017)[45]	81 (39 RSI-BT)	NR	120(100-140)	30(5-68)	1y 71.7% 2y 41.0% 3y 23.1%	1y 84.6% 2y 51.3% 3y 30.7%	[?]G3 25.6% No G5

Author	No. of patients	Tumor Volume	Dose (Gy)	Median follow up (Months)	Local Control (%)	Overall Survival (%)	Toxicity
Zhe Ji (2018)[40]	101 (28 NPC)	15.5(2.4-99.4)	117 (44-246)	12.2(2.9-73.2)	5y 26.6%	5y 15.5%	7.9% G3 2% G4
Ping Jiang (2019)[46]	64 (12 NPC)	Mean 8cc(2.5-320)	130(90-160)	14(1-103.5)	1y 75.2% 3y 73.0% 5y 69.1%	1y 57.4% 3y 31% 5y 26.6%	2 cases of G4 skin reaction; 17% G1-2 skin reaction

NR, not reported.

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