

# An analysis of brachytherapy with computed tomography-guided permanent implantation of Iodine-125 seeds for recurrent nonkeratin nasopharyngeal carcinoma

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**Background:** <sup>125</sup>I seed implantation is a new method in treatment of nasopharyngeal carcinoma (NPC), and it is worthwhile to evaluate its feasibility. In this study, we performed brachytherapy with computed tomography (CT)-guided permanent implantation of <sup>125</sup>I seeds in the treatment of patients with the recurrence of NPC.

**Methods:** A total 30 patients (20 male and ten female) at the median age of 55 (range 25–80) years were diagnosed with recurrent nonkeratin NPC, with a total 38 lesions and a short disease-free interval (median ~11 months) after primary radiotherapy alone or combined with chemotherapy. Patients received CT scan, starting from 2 months after the treatment. Follow-up was conducted for ~2–38 months to observe the local control rate and overall survival rate. We also analyzed the possible correlation between survival periods and the status of recurrent tumors.

**Results:** The local control rates at 6, 12, 24, 30, and 36 months after the procedure of <sup>125</sup>I seed implantation were 86.8%, 73.7%, 26.3%, 15.8%, and 5.3%, respectively. The overall 1-, 2-, and 3-year survival rates were 80.0% (24/30), 30.0% (9/30), and 6.7% (2/30), respectively, with a median survival period of 18 months (17.6±8.6 months). Interestingly, the survival periods of the patients who had primary radiotherapy with or without chemotherapy were 15.8±7.9 and 24.3±7.9 months, respectively. Kaplan–Meier survival analysis demonstrated that  $\chi^2$  (log rank) was 7.555, with very significant difference ( $P<0.01$ ). The survival periods of patients in tumor stages I, II, III, and IV were 25.4±8.7, 19.8±9.4, 16.1±4.5, and 12.8±7.8 months, respectively, with significant differences ( $P<0.05$ ).

**Conclusion:** Our data suggest that the survival period of recurrent NPC patients after <sup>125</sup>I seed implantation is inversely related to the tumor stages of the recurrence but not to chemotherapy after the primary radiotherapy. Therefore, CT-guided <sup>125</sup>I seed implantation can be set for treatment of recurrent NPC, for better survival rate with minimal damage.

**Keywords:** CT-guided <sup>125</sup>I seed, radiochemotherapy, NPC

## Introduction

Nasopharyngeal carcinoma (NPC) caused 65,000 deaths worldwide in 2010.<sup>1</sup> Although it is a relatively uncommon disease in Western countries (0.5–2/100,000/year), nasopharyngeal carcinoma is a common type of head and neck cancers in southern China (30–80/100,000/year).<sup>2</sup> The World Health Organization (WHO) has classified NPC into three histologic types: type I (keratinizing), type II (differentiated nonkeratinizing), and type III (undifferentiated nonkeratinizing). In southern China, 2% of NPC is type I, 3% type II, and 95% type III.<sup>3</sup> Because of their anatomic situation at the base of skull, most nasopharyngeal carcinomas spread early to cervical nodes and are difficult

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to treat with surgical operation. The primary treatment of NPC is radiotherapy, usually combined with chemotherapy.<sup>4</sup> The improvement of therapeutic strategies increased the 5-year survival rate of NPC from ~50% in the 1980s to ~70% in the 1990s and is currently ~80%.<sup>5,6</sup> However, the recurrence rate of NPC following the initial radiotherapy is 15%–58%.<sup>7–10</sup> The recurrence of tumors reduces their sensitivity to radiotherapy and leads to a poor prognosis. Therefore, recurrence becomes a major modality of failure in NPC patients and a challenge to clinicians.

Current retreatment methods of the locally recurrent NPC include external radiotherapy, stereotactic radiosurgery, and brachytherapy, alone or in combination.<sup>4</sup> Permanent implantation of <sup>125</sup>I seeds has a major advantage of delivering a high dose of irradiation to cancers of the nasopharynx with a very sharp fall off outside the implanted volume.<sup>11–13</sup> Computed tomography (CT)-guided permanent brachytherapy was initially used for treating liver malignancies<sup>14,15</sup> and now is also widely applied in treatment of NPC.<sup>16</sup> The <sup>125</sup>I seeds have an average energy of 27.4–31.4 keV. After implantation of <sup>125</sup>I seeds, the gamma rays are concentrated in the immediate surroundings of the target tissues (valid radius ~1.7 cm).<sup>17</sup> This novel technique delivers high-dose radiation that ensures protracted cancer cell killing over a period of several months.

Many lines of evidence have shown that the implantation of <sup>125</sup>I radioactive seeds into tissues of NPC significantly increases therapeutic doses of radiation in the target area of tumors and as well, probably reduces the unnecessary damage in surrounding healthy tissues. In this study, we have analyzed and evaluated the efficacy of CT-guided <sup>125</sup>I seed implantation in the treatment of recurrent nonkeratin nasopharyngeal carcinoma at Shenzhen People's Hospital. Our results suggest that this therapeutic method can be used for treating the recurrence of NPC after radiotherapy with or without chemotherapy.

## Patients and methods

### Patient selection

Between 2008 and 2014, 30 patients were diagnosed with the recurrence of nonkeratin NPC (Table 1) and selected for the treatment of brachytherapy with permanent implantation of <sup>125</sup>I seeds. The diagnoses were made by needle biopsy. The lesions were located in the pharyngeal recess, parapharyngeal space, nasopharynx side, retropharyngeal lymph nodes, and neck, distinct from the skull base and not associated with any distant metastasis. The enrolled patients were informed of the potential risks of the proposed CT-guided <sup>125</sup>I seed

**Table 1** Patient characteristics (n=30)

Characteristics	Number (%)
Sex	
Male	20 (66.7)
Female	10 (33.3)
Age	51.2±13.9 (years)
Range	25–80
Recurrence	30 (100)
DFI	11.0±3.4 (months)
Histology	
WHO I	0 (0)
WHO II	23 (77.7)
WHO III	7 (23.3)
Tumor stage	
I	5 (16.7)
II	8 (26.7)
III	8 (26.7)
IV	9 (30.0)
Previous radiotherapy	30 (100)
Previous chemotherapy	20 (66.7)

**Notes:** WHO type I, keratinizing; type II, differentiated nonkeratinizing; type III, undifferentiated nonkeratinizing. Tumor stage according to TNM staging: stage I, T1 (confined to nasopharynx, or extension to oropharynx/nasal cavity without posterolateral spread), N0 (no regional metastasis), M0 (no metastasis); stage II, T2 (extension into posterolateral pharyngeal soft tissues), N0, M0, or T2, N1 (unilateral metastasis to cervical nodes, <6 cm size, not level IV/Vb, and/or unilateral or bilateral involvement of retropharyngeal nodes, <6 cm size), M0; stage III, T3 (invasion of bony structures, skull base, and/or sinuses), N0 to N2 (bilateral metastasis to cervical nodes, <6 cm size, not level IV/Vb), M0, or T2, N2, M0; and stage IV, any T (T1, T2, T3, or T4: intracranial extension, cranial nerve involvement, spread to hypopharynx/orbit/infratemporal fossa), any N (N1, N2, or N3: involvement of nodes in levels IV/Vb, supraclavicular fossa), M0.<sup>27</sup>

**Abbreviations:** DFI, disease-free interval; M, metastasis; N, node; T, tumor; WHO, World Health Organization.

implantation therapy, and provided written informed consent before beginning the treatment. The protocol was approved by the ethics committee of Jinan University.

### Patient information

A total of 30 patients (20 male and ten female) at the age of 51.2±13.9 years (median 55, range 25–80 years) were treated with <sup>125</sup>I seed implantation. All tumors were recurrent nonkeratin NPC. The interval time from the end of the first course of radiotherapy to diagnosis of recurrence (disease-free interval [DFI]) was 11.0±3.4 months (median 11, range 6–20 months). The tumor diameters were 2.5±1.2 cm and varied from 1.0 to 5.9 cm (16 lesions ≤2 cm, 20 lesions 2–5 cm, and two lesions ≥5 cm). Patients had previously been treated with radiotherapy alone or followed with chemotherapy (Table 1). The doses of the first radiotherapy were 70 Gy, 35 times, 7 weeks (64–88 Gy, 32–44 times, 6.5–8.5 weeks). After radiotherapy, 20 patients were further treated with the chemotherapy regimens, which included cisplatin (100–120 mg·m<sup>-2</sup>, intravenous drip) and 5-fluorouracil (800–1,000 mg·m<sup>-2</sup>, for 5 days, intravenous drip) at 3-week

intervals. No patients received chemotherapy after <sup>125</sup>I seed implantation.

## Instruments

For <sup>125</sup>I seed implantation, we used a HiSpeed Advantage Genesis CT scanner (GE Healthcare, Little Chalfont, UK) and a treatment-planning system (Beijing University of Aeronautics and Astronautics, Beijing, People's Republic of China), and the instruments of seed implantation included 18G implantation needles and a turntable implantation gun. The diameter and length of each <sup>125</sup>I seed (Beijing Atom and High Technique Industries Inc. Pharmaceuticals Co Ltd, Ningbo, People's Republic of China) was 0.8 mm and 4.5 mm, respectively. The thickness of the wall of the titanium capsule was 0.05 mm. The <sup>125</sup>I emits gamma rays (5% of 35.5 keV and 95% of 28 keV) with a half-life of 59.4 days, half-value thickness of 0.025 mm of lead, penetration of 17 mm, and incipient rate of 7 cGy/hour. All <sup>125</sup>I seeds (6,711/BT-<sup>125</sup>I) were delivered in a type-A pack that had passed leak detection and activity series tests.

## Patient preparation

At 1–2 weeks prior to the procedure, patients were examined, using CT scans with a thickness of 5 mm, for the detailed tumor volumes. The planning target volume included the entire gross tumor volume and 0.5–1.0 cm margins, and was prescribed the minimal peripheral dose of <sup>125</sup>I seeds (median 130 Gy, range 90–160 Gy).

## <sup>125</sup>I seed implantation

Before <sup>125</sup>I seed implantation, patients fasted for 1 to 3 hours. In a specially designated operating room patients were given sedatives and local anesthesia. The procedure included making a 3 mm incision on the skin and inserting a seed implantation applicator into each tumor under the guidance of CT with caution in avoiding puncture of large blood vessels or important organs. The <sup>125</sup>I seeds (0.8 mCi)

were implanted into each tumor, and then, the catheters were retracted and incisions were bound and compressed. Medical personal were protected by wearing lead gloves, hats, and other protective clothing. A special measurement of the ray dosage was performed to detect any missing radioactive seeds after the procedure.

## Patient assessment and follow-up

After the implantation of <sup>125</sup>I seeds was completed, vital signs were monitored and recorded for 24 hours. Patients were hospitalized for at least 3 days. A clinical examination and CT scan were performed every 2–3 months until death. To evaluate the therapeutic feasibility of <sup>125</sup>I seed implantation, we used criteria according to the Response Evaluation Criteria in Solid Tumors (RECIST), which include: complete response (CR), defined as the disappearance of all target lesions; partial response (PR), defined as a decrease of at least 30% in the sum of the largest diameter of target lesions; stable disease (SD), defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD); PD, defined as at least a 20% increase in the sum of the longest diameter of target lesions; and total treatment response rate (RR), defined as CR cases + PR cases/case number (Table 2).

## Statistical analyses

All values are presented as mean ± standard deviation. Student's *t*-test, analysis of variance (ANOVA) test, and Kaplan–Meier survival analysis were used to evaluate the significance of differences. *P* < 0.05 was considered significant and *P* < 0.01, very significant.

## Results

### Treatment and follow-up

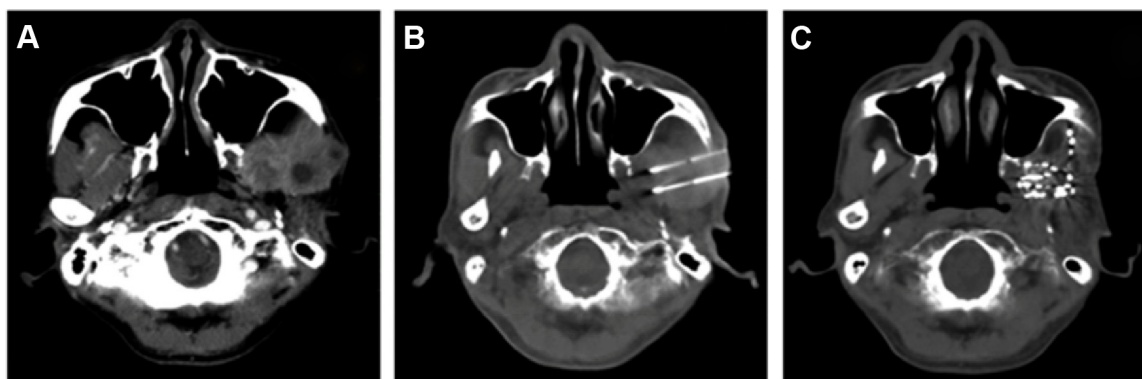
The <sup>125</sup>I seed implantation procedure required 60 to 180 minutes and was guided by CT scan imaging according to the treatment-planning system established (Figure 1). The

**Table 2** Clinical efficacy of recurrent NPC with <sup>125</sup>I seed implantation therapy

Tumor Dia (cm)	Local control efficacy (%)				RR
	CR	PR	SD	PD	
≤2	13 (81.3)	3 (18.8)	0 (0.0)	0 (0.0)	16/16 (100.0)
2–5	14 (70.0)	4 (20.0)	2 (10.0)	0 (0.0)	16/20 (80.0)
>5	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	1/2 (50.0)
Total					35/38 (92.1)

**Notes:** CR, disappearance of all target lesions; PR, a decrease of at least 30% in the sum of the largest diameter of target lesions; SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; PD, at least a 20% increase in the sum of the longest diameter of target lesions; RR, (cases of CR + cases of PR)/number of NPC cases.

**Abbreviations:** CR, complete response; Dia, diameter; NPC, nasopharyngeal carcinoma; PD, progressive disease; PR, partial response; RR, total treatment response rate; SD, stable disease.



**Figure 1** CT images of a recurrent NPC patient.

**Notes:** (A) A recurrent enhancing mass with NPC following initial radiochemotherapy. (B) CT-guided  $^{125}\text{I}$  seed implantation. (C) Resolution of the tumor mass at 2 months post- $^{125}\text{I}$  brachytherapy.

**Abbreviations:** CT, computed tomography; NPC, nasopharyngeal carcinoma.

$^{125}\text{I}$  seeds implanted were distributed with an interval of 1 cm between any two seeds, and the radioactive activity per seed was 29.6 MBq to obtain a peripheral dose of 90–160 Gy. The median number of seeds implanted per patient was 42 (range 4–112), and patients underwent one to four  $^{125}\text{I}$  seed implantation sessions (median of two). All patients were successfully implanted. The range of follow-up period was from 2 to 38 months for monitoring the local control rate, overall survival rate, and any clinical complications.

CT imaging performed prior to  $^{125}\text{I}$  seed implantation revealed images of all the tumors. When the same imaging was performed 2 months after  $^{125}\text{I}$  seed implantation, CT showed resolution of the tumor mass, which exhibited the size and shape of the inactivated tumor (Figure 1 and 2).

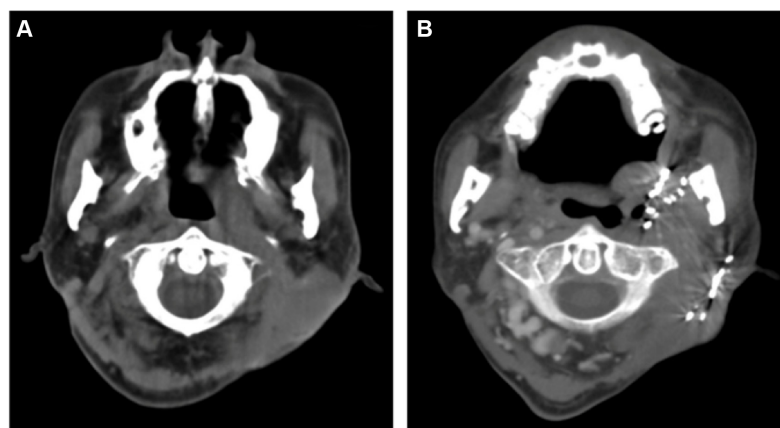
## Local control

Local control rates for the recurrent NPC treated with  $^{125}\text{I}$  seed implantation at 3, 6, 12, 18, 24, 30, and 36 months after the

procedure were 92.1% (35/38), 86.8% (33/38), 73.7% (28/38), 44.7% (17/38), 26.3% (10/38), 15.8% (6/38), and 5.3% (2/38), respectively. For tumors  $\leq 2$  cm in diameter,  $^{125}\text{I}$  seed implantation treatment achieved a CR rate of 81.3% (13/16), a PR rate of 18.8% (3/16), and a RR of 100% (16/16); for tumors of 2–5 cm in diameter, the CR rate was 70.0% (12/20), PR was 20.0% (4/20), SD rate was 20.0% (2/20), and RR was 80% (16/20); for tumors  $> 5$  cm in diameter, the PR was 50.0% (1/2), SD was 50.0% (1/2), and the RR was 50% (1/2). The overall RR was 92.1% (35/38) in all cases (Table 2).

## Survival rates

After the  $^{125}\text{I}$  seed implantation, the overall 1-, 2-, and 3-year survival rates were 80.0% (24/30), 30.0% (9/30), and 6.7% (2/30), respectively, with a median survival period of 18 months ( $17.6 \pm 8.6$  months). Furthermore, the 1-, 2-, and 3-year survival rates of  $^{125}\text{I}$  seed implantation-treated patients with or without previous chemotherapy after radiotherapy



**Figure 2** Metastasis of nasopharyngeal carcinoma.

**Notes:** (A) Lymph node metastasis of NPC behind the ear. (B) CT-image of resolution of tumor mass at 6 months post- $^{125}\text{I}$  brachytherapy.

**Abbreviations:** CT, computed tomography; NPC, nasopharyngeal carcinoma.



were 70.0% (14/20) and 100% (10/10), 20% (4/20) and 50% (5/10), and 5% (1/20) and 10% (1/10), respectively. After <sup>125</sup>I seed implantation, the survival period of patients with primary radiotherapy alone was 24.3±7.9 months, longer than that of patients with primary radio- and chemotherapy, 15.8±7.9 months. Kaplan–Meier survival analysis demonstrated that  $\chi^2$  (log rank) was 7.555 ( $P<0.001$ ), with very significant difference (Figure 3).

### Survival periods and status of tumors

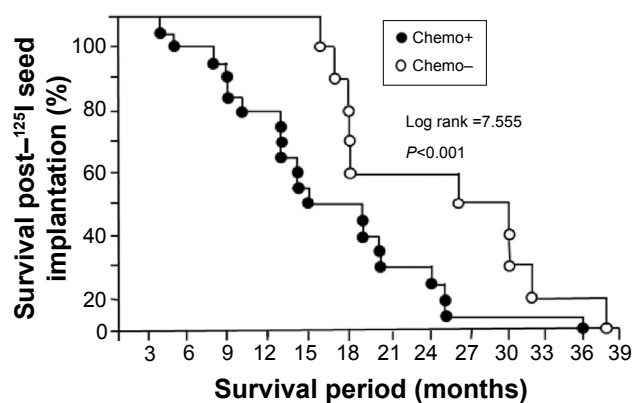
The survival period of all 30 patients after <sup>125</sup>I seed implantation was 17.6±8.6 months (n=30) (Figure 3). The survival periods of patients with the tumor size ≤2 cm and >2 cm were 10.1±2.9 (n=7) and 11.3±3.6 months (n=23), respectively, without significant difference ( $P>0.05$ ) (Figure 4A). The survival periods of patients with differentiated and undifferentiated nonkeratin NPC were 16.9±8.4 (n=23) and 24.1±8.1 months (n=7), respectively, without significant difference ( $P>0.05$ ) (Figure 4B). In contrast, the survival periods of patients with the tumor stages I, II, III, and IV were 25.4±8.7 (n=5), 19.8±9.4 (n=8), 16.1±4.5 (n=8), and 12.8±7.8 (n=9) months, respectively, with significant differences ( $P<0.05$ , ANOVA tests) (Figure 4D). These data suggest that the survival period of NPC patients after <sup>125</sup>I seed implantation is inversely related to the tumor stage. We also analyzed survival periods of 13 patients with stage III recurrent NPC after <sup>125</sup>I seed implantation therapy. The survival period of five patients with the primary

radiotherapy alone was 18.6±4.7 months, longer than that of eight patients with the primary combined radiochemotherapy, 12.0±1.9 months, with very significant difference ( $P<0.01$ ) (Figure 4C). The interesting results question the effect of radio- and chemotherapy in primary NPC.

### Discussion

An extremely poor prognosis has been observed in patients with the local recurrence of NPC. For example, one analysis of 219 cases in the 1980s reported a 5-year survival rate was less than 1% if the patients were without any treatment.<sup>18</sup> Another analysis of 891 patients with locally recurrent NPC showed a 5-year survival rate of 14%, although 79% (706/891) of patients had been reirradiated with various techniques and doses.<sup>19</sup> Accordingly, the local recurrence of NPC is 8%–58% (median 34%).<sup>19</sup> Therefore, the high frequency of the recurrence is a major cause of the mortality in NPC. To develop efficient methods for treatment of the recurrent disease is still a challenge in NPC treatment. Several techniques have been used to treat the recurrent NPC, including external radiotherapy, stereotactic radiosurgery, nasopharyngectomy, and brachytherapy, alone or combined with further chemotherapy.<sup>20–23</sup> Among these therapies, brachytherapy with <sup>125</sup>I seed implantation has been used widely in salvage treatment of the NPC recurrence.<sup>4</sup>

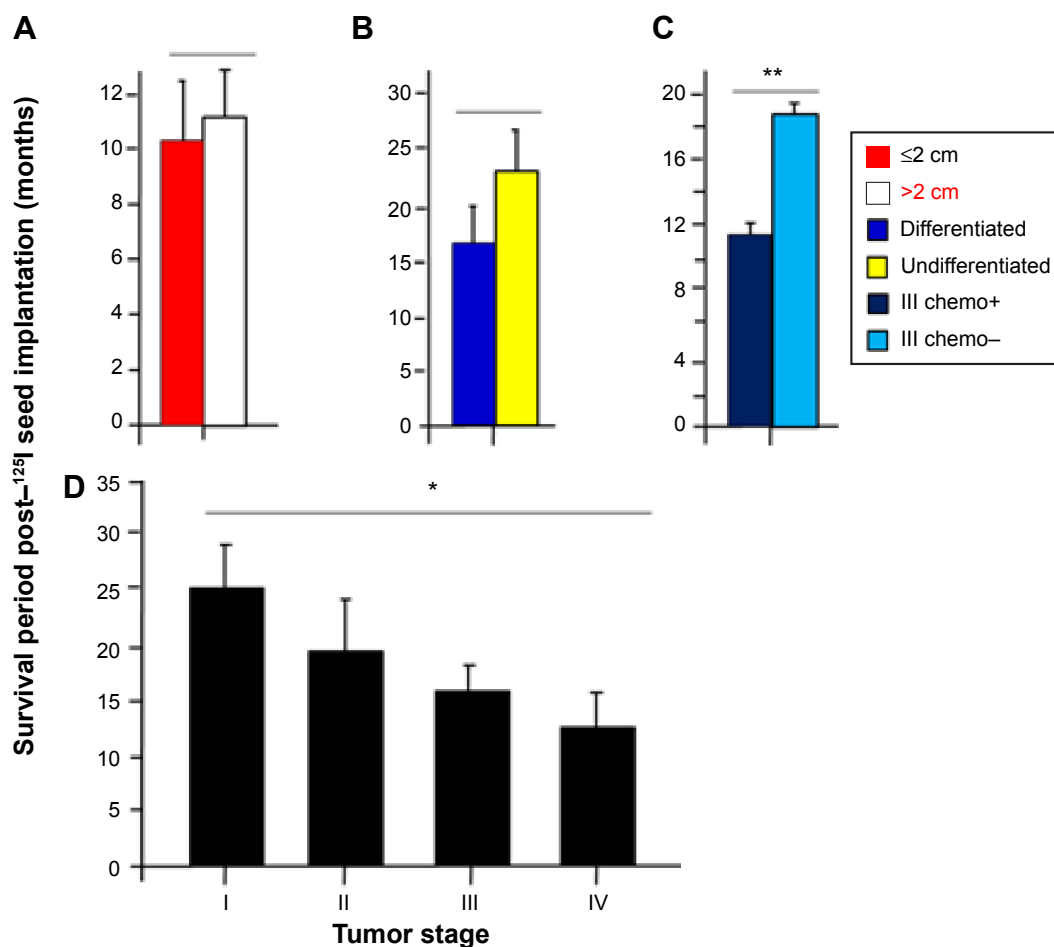
To estimate the efficacy of <sup>125</sup>I seed implantation therapy in certain NPC types, we selected 30 patients with the recurrence of differentiated or undifferentiated nonkeratinizing cancers (WHO type II or III) (Figures 1 and 2). All patients had a short DFI, representing the interval time from the end of first course of radiotherapy to diagnosis of recurrence (6–12 months in 23 patients and 13–20 months in seven patients). The median interval of recurrence after the primary radiotherapy was only about 11 months (Table 1), much shorter than 24–26 months, the median interval of recurrence of NPC in prior reports.<sup>8,24,25</sup> After <sup>125</sup>I seed implantation therapy, the total treatment response rate reached 92.1%, and 1-, 2-, and 3-year survival rates were 80.0%, 30.0%, and 6.7%, respectively, with a median survival period of 18 months (Figure 3). In this study, we did not set up a control group because we could not leave recurrent NPC patients with no treatment. Our therapeutic efficacy is similar to a previous study using <sup>125</sup>I seed implantation therapies, although recurrent NPC patients had a shorter DFI. For example, a recent report has shown that the 1-, 2-, and 3-year survival rates of a total of 19 patients with recurrent NPC after surgery and radiotherapy were 53.0%, 18.2%, and 18.2%, respectively, with a median survival period of 13 months.<sup>26</sup>



**Figure 3** Kaplan–Meier survival curves of patients with the recurrent NPC post-<sup>125</sup>I seed implantation therapy.

**Notes:** Survival rates post-<sup>125</sup>I seed implantation therapy, for NPC patients who received primary radiotherapy with or without chemotherapy. The 1-, 2-, and 3-year survival rates of <sup>125</sup>I seed implantation-treated patients with or without previous chemotherapy, after radiotherapy were 70.0% and 100%, 20% and 50%, and 5% and 10%, respectively. The survival periods of patients with and without chemotherapy were 15.8±7.9 and 24.3±7.9 months, respectively. Kaplan–Meier survival analysis demonstrated that  $\chi^2$  (log rank) was 7.555, with very significant difference ( $P<0.001$ ). After <sup>125</sup>I seed implantation therapy, 1-, 2-, and 3-year survival rates of all 30 recurrent NPC patients were 80.0%, 30.0%, and 6.7%, respectively, with a median survival period of 18 months.

**Abbreviations:** chemo, chemotherapy; NPC, nasopharyngeal carcinoma.



**Figure 4** Analyses of survival periods post-<sup>125</sup>I seed implantation therapy and status of NPC.

**Notes:** (A) The survival period for tumor size  $\leq 2$  cm was  $10.1 \pm 2.9$  months ( $n=7$ ) and for tumor size  $>2$  cm was  $11.3 \pm 3.6$  months ( $n=23$ ), without significant difference ( $P>0.05$ ). (B) The survival period for differentiated tumor was  $16.9 \pm 8.4$  months ( $n=23$ ) and for undifferentiated tumor was  $24.1 \pm 8.1$  months ( $n=7$ ), without significant difference ( $P>0.05$ ). (C) The survival period among 13 patients with stage III recurrent NPC was  $18.6 \pm 4.7$  months for five patients treated with the primary radiotherapy alone, and was  $12.0 \pm 1.9$  months for eight treated with combined radio- and chemotherapy (\*\* $P<0.01$ ). (D) The survival period for stage I was  $25.4 \pm 8.7$  months ( $n=5$ ), for stage II was  $19.8 \pm 9.4$  months ( $n=8$ ), for stage III was  $16.1 \pm 4.5$  months ( $n=8$ ), and for stage IV was  $12.8 \pm 7.8$  months ( $n=9$ ), with significant differences (\* $P<0.05$ , ANOVA test).

**Abbreviations:** ANOVA, analysis of variance; chemo, chemotherapy; NPC, nasopharyngeal carcinoma.

After <sup>125</sup>I seed implantation, the RR of selected NPC patients was 92.1% (Table 2). The survival periods post-<sup>125</sup>I seed implantation were 4–38 months (Figure 3). Based on the results, we analyzed the possible factors affecting the prognosis. In 30 cases, before recurrence, ten patients had received the primary radiotherapy alone and 20 had received the primary radiotherapy combined with chemotherapy. After <sup>125</sup>I seed implantation, the survival period of patients with primary radiotherapy alone was  $24.3 \pm 7.9$  months, longer than that of patients with the radio- and chemotherapy combination ( $15.8 \pm 7.9$  months). Kaplan–Meier survival analysis demonstrated that  $\chi^2$  (log rank) was 7.555 ( $P<0.001$ ), with very significant difference (Figure 3). Among a total 13 patients with stage III recurrent NPC, after <sup>125</sup>I seed implantation therapy, the survival period of five patients with the primary radiotherapy alone was  $18.6 \pm 4.7$  months,

longer than that of eight patients with the primary combined radiochemotherapy,  $12.0 \pm 1.9$  months, with very significant difference ( $P<0.01$ ) (Figure 4C). These unexpected results were probably caused by a small sample volume but may also be worth investigating for the effects of chemotherapy in the NPC treatment. Our further analyses demonstrated no significant correlation between the survival period and tumor size (Figure 4A) or differentiated and undifferentiated statuses (Figure 4B). By performing ANOVA, we found there were significant differences ( $P<0.05$ ) between survival periods post-<sup>125</sup>I seed implantation and stages (I, II, III, IV) of recurrent NPC (Figure 4D), suggesting that tumor stage is the most important prognostic factor, which agrees with most results of NPC treatment reports.

Because of the complex anatomy and the rich neurovascular supply in the nasopharynx region, direct implantation

of radioactive particles is difficult. The <sup>125</sup>I seed implantation brachytherapy has been extensively performed in NPC treatment in recent years. CT image guidance improves <sup>125</sup>I seed deposition accuracy and delivers a sufficiently high dose to the tumor target, especially for the recurrent carcinoma after radiotherapy. In addition, the <sup>125</sup>I radioactivity decreases very rapidly with distance, which reduces the risk of damage to neighboring healthy tissues, organs, or structures in proximity of the targeted tumors. Based on our results and other reports, CT-guided <sup>125</sup>I seed implantation appears to be a feasible method for the treatment of patients with the recurrent NPC.

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## Disclosure

The authors report no conflicts of interest in this work.

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