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Refractory Nasopharyngeal Carcinoma: Positron Emission Tomography Combined with Computed Tomography–Guided $^{125}\text{I}$ Seed Implantation Therapy after Repeated Traditional Radiochemotherapy

Fujun Zhang, MD$^1$*, Ketong Wu, MD$^1$*, Fei Gao, MD$^1$, Weidong Zhang, MD$^1$, Feng Shi, MD$^1$, and Chuanxing Li, MD$^1$

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. To evaluate the feasibility of positron emission tomography combined with computed tomography (PET-CT)—guided $^{125}\text{I}$ seed implantation in the treatment of patients with refractory nasopharyngeal carcinoma after repeated traditional radiochemotherapy.

Study Design. Case series with chart review.

Setting. University medical center.

Subjects and Methods. A total of 26 patients (18 men, 8 women; mean age, 51.3 ± 10.8 years; totaling 53 lesions with an average diameter of 2.86 ± 1.61 cm) were treated by PET-CT-guided $^{125}\text{I}$ seed implantation. All of the patients received a PET-CT scan 2 months after the treatment. Follow-up was conducted for ~2 to 43 months (median, 28.2 months) to observe the local control rate, overall survival rate, and clinical complications.

Results. The local control rates of refractory nasopharyngeal carcinoma after repeated traditional radiochemotherapy after 3, 6, 12, 24, and 36 months were 90.6% (48/53), 79.3% (42/53), 71.7% (38/53), 62.3% (33/53), and 56.6% (30/53), respectively. The overall 1-, 2-, and 3-year survival rates were 87.2%, 71.3%, and 56.5%, respectively, with a median survival time of 28.2 months. Of all patients, 19.2% (5/26) died of local recurrence and 15.4% (4/26) died of metastases. One patient died of hypertensive cerebral hemorrhage, and another patient died from cachexia and infection. The long-term complications included hyperpigmentation at operative sites (n = 5), insensible feeling on the lateral cheek (n = 2), dryness of the oral cavity (n = 1), and headache (n = 1).

Conclusion. PET-CT-guided $^{125}\text{I}$ seed implantation is an acceptable and feasible method for treating refractory nasopharyngeal carcinoma with minimal damage and few complications.

Keywords

$^{125}\text{I}$ seed, nasopharyngeal carcinoma, PET-CT, radiochemotherapy, therapy

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The locoregional control rate for nasopharyngeal carcinoma (NPC) has improved significantly in the past decade due to advances in imaging, radiotherapy techniques, and the use of combined treatments with chemoradiotherapy. Currently, the 5-year local control rates reported for NPC range from 80% to 85%.1,2 Despite improved outcomes in local control, however, local recurrence and metastasis still represent major causes of mortality and morbidity in advanced stages of NPC, while management of local failure also remains a challenge.3-7

The most common sites for local recurrence of NPC include the nasopharynx, the parapharyngeal space, and the carotid sheath.8-10 Disease relapses could still be seen in some recurrent NPC patients after they undergo irradiation and/or chemotherapy. For these cases, traditional radiotherapy and chemotherapy are not expected to be feasible based on the following observations. First, NPC cell sensitivity to radiotherapy has been observed to decrease in patients treated with a third course of radiotherapy.11 Second, after a second course of radiotherapy, the nasopharynx and neck region have been shown to undergo significant structural...
changes, including fibrosis and compromise of the local blood supply, leading to poor radiosensitivity. Moreover, drug concentrations for chemotherapy are difficult to achieve in these regions.12 Third, there are many important structures close to the nasopharynx, such as the brainstem, the temporal lobe, the pituitary gland, the optic chiasm, and the optic nerve, that will have reached their radiation tolerance during an initial radiotherapy treatment course.13 This means that a second round of irradiation would be limited to protect these structures. Finally, surgery performed in this region may be associated with a high risk of complications4,15 and difficulty in controlling the exposure of important blood vessels, nerves, and craniofacial structures adjacent to the nasopharynx to radiation. Therefore, for refractory patients who cannot tolerate surgical removal or reirradiation and chemotherapy after adequate doses of radiotherapy, new and feasible therapeutic techniques are needed to improve the prognosis for refractory NPC.

Previous reports have shown that the implantation of 125I radioactive seeds into tumor tissue provides interstitial irradiation that significantly improves the therapeutic dose of radiation to the targeted area of a tumor while reducing the probability that unnecessary damage will be experienced by surrounding healthy tissue.16-18 In this study, the efficacy and feasibility of 125I seed implantation guided by positron emission tomography combined with computed tomography (PET-CT) for the treatment of refractory NPC after repeated rounds of traditional radiochemotherapy were evaluated.

Materials and Methods

Patient Selection

Between July 2005 and December 2011, 26 patients had a diagnosis of NPC confirmed histopathologically. All of them had previously recurred twice, failed chemoradiation twice, and then considered the 125I seed implantation therapy. Patients were then informed of the potential risks of the proposed PET-CT-guided 125I seed implantation therapy protocol approved by the ethical committee of the Cancer Center of Sun Yat-Sen University and the People’s Hospital of Guangdong Province. All patients who enrolled provided written informed consent before beginning the study.

Study eligibility criteria included the following: (1) diagnosis of NPC was confirmed by needle biopsy; (2) lesions were located in the pharyngeal recess, parapharyngeal space, side of the nasopharynx, retropharyngeal lymph nodes, and neck, distinct from the skull base and not associated with any distant metastases; (3) the patient could not tolerate surgical removal, reirradiation, or chemotherapy after already receiving adequate doses of radiotherapy and chemotherapy; (4) a Karnofsky performance scale score of 70% or greater was received; and (5) no severe, unstable hematogenic parameters and/or active infections were detected.

Patients

A total of 26 patients (18 men and 8 women) with a median age of 54 years (range, 42–68 years) and a mean age of 51.3 ± 10.8 years were treated with 125I seed implantation therapy. The tumor diameter for this cohort varied from 0.5 to 7.8 cm (25 lesions ≤2 cm, 20 lesions 2–5 cm, and 8 lesions ≥5 cm), and all patients were diagnosed using a nasopharyngeal biopsy. Pathological or cytological tests confirmed that 15 of the 26 refractory NPC cases were poorly differentiated squamous cell carcinomas, 4 of 26 were undifferentiated carcinomas, and 7 of 26 were well-differentiated squamous cell carcinomas. The locations of the refractory tumors were as follows: 14 lesions in the pharyngeal recess, 12 lesions in the parapharyngeal space, 8 lesions belonging to retropharyngeal lymph nodes, 10 lesions in the side of the nasopharynx, and 9 lesions belonging to neck lymph nodes. Patients had previously been treated with radiotherapy and chemotherapy. The doses of first process in NPCs were 70 Gy, 35 times, 7 weeks (64–88 Gy, 32~44 times, 6.5~8.5 weeks), while the chemotherapy regimens included cisplatin (100-120 mg m–2, intravenous drip) and 5-fluorouracil (800-1000 mg m–2, for 5 days, intravenous drip) at 3-week intervals. Generally, for the second refractory NPC, chemotherapy will be initially used (DDP +5-Fu 3~4 courses) and then radiotherapy will be performed (68 Gy, 32 times, 7 weeks). To the third refractory NPC, chemotherapy only will be performed as usual, and if it fails, the 125I seed implantation will be performed.

Instruments

A high-speed advantage genesis CT scanner (GE Healthcare) was used. A treatment-planning system (TPS) was developed by the Beijing University of Aeronautics and Astronautics (Beijing, China). Instruments of seed implantation included 18-G implantation needles and a turntable implantation gun. 125I seeds were obtained from Beijing Atom and High Technique Industries Inc Pharmaceuticals Co Ltd (Ningbo, China). The diameter and length of each seed was 0.8 mm and 4.5 mm, respectively. The thickness of the wall of the titanium capsule was 0.05 mm. 125I emits gamma rays (5% of 35.5 keV, 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/h. All of the 125I seeds (6711/BT-125I) were mailed to our hospital in a type-A pack that had passed leak detection and activity series tests (Table 1).

125I Brachytherapy Planning

One to 2 weeks prior to seed implantation, patients underwent a detailed tumor volume study using CT scans with a thickness of 5 mm. The radiation oncologist outlined the gross tumor volume (GTV) and areas at risk for subclinical disease on each transverse image. The planning target volume (PTV) included the entire GTV and 0.5- to 1.0-cm margins. The dose was prescribed as the minimal peripheral dose (MPD) encompassing the PTV. The median MPD was 130 Gy (range, 90-160 Gy). The distribution and MPD of 125I seeds were calculated using a computerized treatment planning system (RT-RSI, Beijing Atom and High Technique Industries Inc, Beijing, China).
**Table 1. Physical characteristics of $^{125}$I seeds.**

<table>
<thead>
<tr>
<th>Physical Parameter</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal radionuclide</td>
<td>$^{125}$I</td>
</tr>
<tr>
<td>Radionuclide purity</td>
<td>&gt;99.9% for $^{125}$I</td>
</tr>
<tr>
<td>Types of radiation</td>
<td>27.4Kev $\gamma$-ray and 35.5Kev $\gamma$-ray</td>
</tr>
<tr>
<td>Half-life, d, $T_1/2$</td>
<td>Physical $T_1/2$ 60.14</td>
</tr>
<tr>
<td></td>
<td>Biological $T_1/2$ 120-138</td>
</tr>
<tr>
<td></td>
<td>Effective $T_1/2$ 42</td>
</tr>
<tr>
<td>Specific activity</td>
<td>1.73E4 Ci/g max</td>
</tr>
</tbody>
</table>

$^{125}$I Seed Implantation

The patients fasted for 1.0 to 3.0 hours and were given sedatives and local anesthesia before the procedure. Based on the established treatment plan, a 3-mm incision was made on the skin, and a seed implantation applicator was inserted into each tumor under the guidance of CT at a distance. Precautions were taken to avoid puncture of large blood vessels or important organs. For tumors with a thickness of no more than 1.0 cm, interstitial planar (surface) implants were used. $^{125}$I seeds with an activity of 0.8 mCi were implanted into each tumor; these seeds had antitumor activity within a radius of 1.7 cm. After the procedure, the catheters were retracted and incisions were bound and compressed.

The surgeon performed $^{125}$I implantation in a specially designated operating room. At the time of the procedure, medical personnel wore lead gloves, hats, ambinecks, and other protective clothing. After the procedure, a special technician detected the ray dosage in the surroundings in real time to detect any missing seeds or other problems.

Follow-up

Vital signs were monitored for 24 hours after implantation. Any changes from the symptoms seen at presentation were recorded. All patients were hospitalized for at least 3 days. A clinical examination was performed every month postprocedure, and CT was evaluated. Every 2 to 3 months postprocedure, follow-up imaging examinations were performed to evaluate the therapeutic feasibility of $^{125}$I seed implantation therapy. All patients underwent pre- and posttreatment magnetic resonance imaging or CT examination. Based on these examinations, the tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST).\(^{19-21}\)

Evaluation Criteria

Based on RECIST, the feasibility of $^{125}$I seed implantation therapy was evaluated using the following criteria: (1) complete response (CR): disappearance of all target lesions; (2) partial response (PR): a decrease of at least a 30% in the sum of the largest diameter of target lesions, taking as reference the baseline sum of the longest diameter; (3) stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameter since the treatment started; (4) progressive disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of 1 or more new lesions. Total treatment response rate (RR) = (case of CR + case of PR)/case number.

Statistical Analyses

All values are presented as mean ± SD. Overall survival curves were generated using the Kaplan-Meier method using SPSS10.0, and deaths by any cause were scored as events. \( t \) Tests were used to evaluate the significance of differences. \( P \) values less than .05 were considered significant.

Results

Treatment Data

The $^{125}$I seed implantation procedure required 60 to 180 minutes and was guided by PET-CT scan imaging according to the TPS established. The $^{125}$I seeds implanted were distributed with an interval of 1 cm between any 2 seeds, and the radioactive activity per seed was 29.6 MBq to obtain a peripheral dose of 90 to 160 Gy. The median number of seeds implanted per patient was 42 (range, 4-112), and patients underwent 1 to 4 $^{125}$I seed implantation sessions (median, 2). All patients were successfully implanted. The mean follow-up period was 31 months (range, 2-43 months) to monitor the local control rate, overall survival rate, and any clinical complications.

Follow-up Imaging

PET-CT imaging performed prior to $^{125}$I seed implantation revealed abnormal radioactivity concentrations present in all of the tumors imaged. When the same imaging was performed 2 months after $^{125}$I seed implantation, the abnormal radioactivity concentration previously observed had disappeared and was replaced by a cold lesion, which exhibited the size and shape of the inactivated tumor (Figures 1 and 2).

Local Control and Survival

Local control rates for recurrent NPC treated with $^{125}$I seed implantation 3, 6, 12, 24, and 36 months after the procedure were 90.6% (48/53), 79.3% (42/53), 71.7% (38/53), 62.3% (33/53), and 56.6% (30/53), respectively. For tumors ≤2 cm in diameter, $^{125}$I seed implantation treatment achieved a CR rate of 84.0% (21/25) and PR in 16.0% (4/25) of cases. For tumors ≥5 cm in diameter, $^{125}$I seed implantation treatment achieved a CR in 25.0% (2/8) of cases, PR in 37.5% (3/8) of cases, and PD in 37.5% (3/8) of cases. For tumors of 2 to 5 cm in diameter, $^{125}$I seed implantation treatment achieved a CR in 65.0% (13/20) of cases, a PR in 15.0% (3/20) of cases, and SD in 20.0% (4/20) of cases (Table 2). The overall 1-, 2-, and 3-year survival rates were 87.2%, 71.3%, and 56.5%, respectively. The median survival time was 28.2 months (Figure 3). For this cohort, 19.2% (5/26) of patients died of local recurrence,
and 15.4% (4/26) died of metastases. In addition, 1 patient died of hypertensive cerebral hemorrhage, while another patient died from cachexia and infection.

Complications
Several complications were related to the implantation of $^{125}\text{I}$ seeds in this study. During the procedure, 3 patients presented with minimal bleeding from the applicator route, and 1 presented with syncope for 1 min and then recovered after the operation was immediately stopped. During patient follow-up, the long-term complications experienced included hyperpigmentation at the operative sites ($n = 5$), insensible feeling on the lateral cheek ($n = 2$), dryness of the oral cavity ($n = 1$), and headache ($n = 1$). None of the patients reported nasopharyngeal bleeding, infection, bone marrow suppression, or ectopic embolization.

Discussion
Currently, the reported 5-year local control rates for NPC range from 80% to 85%. However, despite improved outcomes in the local control of NPC, local recurrence still represents a major cause of mortality and morbidity for cases of advanced stage NPC. In addition, management of local failure remains a challenge. Lee et al and others reported a recurrence rate of 8.2% for lymph nodes of the nasopharynx and neck during the first 5 years following the completion of radiotherapy for NPC. In 70% to 90% of these cases, tumor recurrence was diagnosed within 2 to 3

Figure 1. A refractory nasopharyngeal carcinoma patient. (A) Abnormal radioactivity concentration in the left retropharyngeal lymph nodes. (B) Absence of abnormal radioactivity concentration and a cold lesion.

Figure 2. A 47-year-old patient with tumors of metastatic malignant melanoma after surgery excision for primary lesion.
years, and the recurrent sites were focused in the nasopharynx, the nasal pharyngeal space, and the carotid sheath.\textsuperscript{23-26}

Because of the damage that is induced in the neck skin, subcutaneous tissue, muscles, nerves, and blood vessels as a result of definitive radiotherapy, it is difficult to further treat recurrent cases with radiotherapy.\textsuperscript{27-29} In cases in which radiotherapy was still performed as a second round of treatment, stiffening and contracture of the neck tissue fibers was reported. In comparison, surgical removal is associated with narrow indications and frequent complications such as postoperative wound infections, necrosis, effusions, and poor wound healing.\textsuperscript{30-32} These complications largely reduce the quality of life and survival time of patients. As a result, the treatment of recurrent NPC located in the nasopharynx and neck following radical radiotherapy is difficult, especially for patients who have undergone multiple radiotherapy and chemotherapy treatments.\textsuperscript{33-35}

The implantation of radioactive \textsuperscript{125}I seeds represents a localized, precise, and minimally invasive technique that is currently extensively used for the treatment of tumors. By using a stereotactic guidance device, \textsuperscript{125}I seeds are able to be positioned directly in the target tissue of the affected site, thereby providing a continuous application of high-intensity radiation directly to the cancer present. In addition, a much lower dose of radiation is delivered to adjacent normal structures because of the drop off in radiation with distance.\textsuperscript{36,37} As previously demonstrated, the implantation of low-energy radioactive seeds directly into a malignant tumor improves the distribution of radiation in local tumors and leads to a decrease in the mitosis of tumor cells. An induction of a hypoxic environment in the tumor due to irradiation also increases the sensitivity of tumor cells to radiation.\textsuperscript{38} In combination with the low risk of serious adverse side effects associated with the low energy and weak penetration of the \textsuperscript{125}I seeds used, minimal damage to surrounding vital organs can be achieved.\textsuperscript{39,40}

Radioactive \textsuperscript{125}I seed implantation is associated with another important advantage in that the low-energy \textgreek{y}-rays, x-rays, and ionizing radiation of all energies that are released from the \textsuperscript{125}I seeds have a dose that is inversely proportional to the square of the distance from the seeds. Therefore, while the cancer tissue in close proximity to the seeds will receive high-intensity irradiation, surrounding tissues will receive a much lower intensity of irradiation. As a result, local control is achieved, complications are reduced, and survival time of patients is prolonged. Moreover, the repopulation of tumors decreases significantly because of the persistent radiation exposure experienced in proximity to the seeds, and continuous low-dose irradiation can induce hypoxic cells to reoxidize, which increases the sensitivity of tumor cells to radiation.

Direct implantation of radioactive particles is difficult because of the complex anatomy of the head and neck region, particularly the rich neurovascular supply in this region. Therefore, a PET-CT-guided device was used to implant the \textsuperscript{125}I radioactive seeds into the refractory NPC. Moreover, a seed-implanting tumor TPS was used as a reference to ensure the accuracy of seed positioning, to achieve a reasonable dose distribution, to provide a simple procedure, and to minimize trauma. Based on these conditions, and the results obtained in this study, PET-CT–guided \textsuperscript{125}I seed implantation appears to represent a feasible method for the treatment of patients with recurrent NPC. Furthermore, seed implantation has been shown to be acceptable in preventing the recurrence of NPC while reducing the risk of damage to neighboring healthy tissues, organs, or structures in proximity of the targeted tumor.\textsuperscript{41-43}

<table>
<thead>
<tr>
<th>Tumor Diameter, cm</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Total Response Rate: (CR + PR)/Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>21/25 (84.0)</td>
<td>4/25 (16.0)</td>
<td>0</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>2−5</td>
<td>13/20 (65.0)</td>
<td>3/20 (15.0)</td>
<td>4/20 (20.0)</td>
<td>0</td>
<td>80.0</td>
</tr>
<tr>
<td>≥5</td>
<td>2/8 (25.0)</td>
<td>3/8 (37.5)</td>
<td>0</td>
<td>3/8 (37.5)</td>
<td>62.5</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 3. Kaplan-Meier curve shows overall survival rates for 26 patients with refractory nasopharyngeal carcinomas after \textsuperscript{125}I seed implantation therapy.

Table 2. Clinical efficacy of refractory nasopharyngeal carcinomas with \textsuperscript{125}I seed implantation therapy.
From the implantation procedures performed, the following observations regarding the techniques of the procedure were made. For example, by adjusting the direction of the needle toward the front lower part of the temporomandibular joint, damage of important neural and vascular structures could be avoided. Second, it is currently recommended that the number and distribution of $^{125}$I seeds in the target area be imaged with CT within 24 hours of the procedure to facilitate timely replanting. According to the requirements of the 3-dimensional TPS, the goal is to have an even distribution of seeds and for the radiation to be emitted in parallel lines. However, it is difficult to achieve a multiplane needle entrance in practice because of the location of skull base lesions, puncture path, vascular structures, and other factors. Therefore, to ensure that the total dose and number of $^{125}$I seeds meet the requirements of the TPS, it is necessary to implant $^{125}$I seeds in 1 trail continuously. However, for residual tumors in patients with NPC who have accepted radiotherapy by carrying out a CT examination, the focus is too small (the diameter is about 8 mm) and is located in the pharyngeal recess. As a result, it is difficult to carry out multiplane or continuous single-plane implantations. Therefore, to supply the necessary radiation dose, it is recommended that 2 seeds be implanted unilaterally in a single plane.

The results indicated that $^{125}$I seed implantation as a conformal radiotherapy has the characteristics of continuous low-dose rate and local accumulated high-dose rate. Furthermore, the ability to precisely position $^{125}$I seeds enabled a high dose of targeted radiation to be delivered to the tumor area while minimizing radiation exposure to adjacent tissues and organs. Based on these data, the use of $^{125}$I seed implantation in previously irradiated regions appears to be a feasible short-term treatment option for the treatment of NPC that is refractory to radiotherapy. However, further studies are needed to confirm these observations with a larger number of patients and a longer follow-up period.

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Author Contributions

Fujun Zhang, conception and design, analysis and interpretation of data, drafting of the manuscript; Ketong Wu, conception and design, drafting of the manuscript; Fei Gao, acquisition of data, drafting of the manuscript; Weidong Zhang, acquisition of data, drafting of the manuscript, Feng Shi, acquisition of data, drafting of the manuscript; Chuanxing Li, conception and design, analysis and interpretation of data, drafting of the manuscript.

Disclosures

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