3D-Printed Template-Guided $^{125}$I Seed Brachytherapy: A Salvage Approach for Locoregional Refractory Recurrence of Papillary Thyroid Cancer

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Established Facts

- The incidence of thyroid cancer has increased in almost every part of the world. Papillary thyroid carcinoma (PTC) is typically treated with surgical resection, even in recurrent cases. However, it is difficult to remove the tumor completely with resection, and the incidence of recurrent laryngeal injury is high. External irradiation is not routinely used to treat thyroid cancer, as it is difficult to cure the tumor because of the low radiation sensitivity and dose limit of normal tissue. Furthermore, there is no evidence to show that radiotherapy can prolong overall survival. Thus, there is no optimal treatment for refractory recurrence of PTC. As a solution, brachytherapy with $^{198}$Au, $^{192}$Ir, and $^{125}$I seeds has been used to treat recurrent PTC. Furthermore, individualized treatment strategies have been recommended in patients with disease recurrence limited to a local site. $^{125}$I seed permanent brachytherapy has emerged as a promising alternative, but no effective brachytherapy protocol has been reported for tumors with a huge volume, liquefaction, necrosis, and skin invasion.

Novel Insights

- To the best of our knowledge, this is the first reported case in which a large recurrent PTC was effectively treated with $^{125}$I seed brachytherapy.
- The 3D-printed template is a novel invention for brachytherapy. Under its guidance, the needles can be inserted into the tumor more quickly and accurately, resulting in a better dose consistency.

Keywords

Papillary thyroid carcinoma - $^{125}$I seed strand - 3D-printed template - Brachytherapy - Radiation dose

Abstract

Background: Papillary thyroid carcinoma (PTC) is typically treated with surgical resection, even in recurrent cases. However, some cases of recurrent PTC are refractory to the conventionally used locoregional radiotherapy and resection...
methods. $^{125}$I seed permanent brachytherapy has emerged as a promising alternative for such PTCs, but no effective brachytherapy protocol has been reported for tumors with a huge volume, liquefaction, necrosis, and skin invasion. **Case Presentation:** A 47-year-old man presented with recurrence 8 years after 2 thyroidectomy procedures for PTC and recurrent PTC. The tumor measured $6 \times 7 \times 8$ cm$^3$ and exhibited liquefaction, necrosis, and skin invasion. The patient was treated at our hospital from December 2017 to November 2018. He received one round of $^{125}$I seed temporary brachytherapy and 4 rounds of $^{125}$I seed permanent implantation. The activity of the seeds was 0.3–3.0 mCi, and the total dose delivered to the tumor was 145 Gy. The recurrent tumor was successfully removed by $^{125}$I seed brachytherapy guided with a 3D-printed template and ultrasound and CT scanning. The refractory tumor healed uneventfully after $^{125}$I seed brachytherapy without recurrence over the 25-month follow-up. **Conclusions:** To the best of our knowledge, this is the first reported case of a large thyroid carcinoma that was effectively treated by 3D-printed template-guided $^{125}$I seed brachytherapy.

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### Introduction

During the last few decades, the incidence of thyroid cancer has increased in almost every part of the world. Thyroid cancers are mainly classified as papillary, follicular, medullary, and anaplastic thyroid cancers [1, 2]. The most effective method to manage aggressive thyroid cancers is surgical removal of the thyroid gland (thyroidectomy) followed by radioactive iodine ablation and thyroid-stimulating hormone suppression therapy [3, 4]. However, after successful treatment, 35% of patients may experience recurrence [5]. Surgery remains the mainstay of treatment for papillary thyroid cancer (PTC). Most patients with PTC have excellent prognosis, but the study by Zhu et al. [6] showed that the incidence of PTC recurrence has been increasing recently. In PTC patients with locoregional recurrence, locoregional treatment, such as surgical resection and involved-field radiotherapy, is recommended [7]. However, it is difficult to remove the tumor completely with resection, and the incidence of recurrent laryngeal injury is high [8]. External irradiation is not routinely used to treat thyroid cancer, as it is difficult to cure the tumor because of the low radiation sensitivity and dose limit of normal tissue. Furthermore, there is no evidence to show that radiotherapy can prolong overall survival [9]. Thus, there is no optimal treatment for refractory recurrence of PTC. As a solution, brachytherapy with $^{198}$Au, $^{192}$Ir, and $^{125}$I seeds has been used to treat recurrent PTC [10–12]. Furthermore, individualized treatment strategies have been recommended in patients with disease recurrence limited to a local site [4].

In this case report, we describe a valuable salvage technique using image-guided $^{125}$I seed brachytherapy to treat refractory recurrence of PTC after conventional treatment. To the best of our knowledge, this is the first case report in the literature to describe the effective use of this technique on a recurrent, refractory PTC with a large volume, liquefaction, necrosis, and skin invasion.

### Case Report

#### Patient History

A 47-year-old man presented with recurrence of PTC after 2 surgical procedures. Twenty-seven years before he was admitted to our clinic, he had visited a clinic in the vicinity because he had a hard nodule in the thyroid region that had been found during a physical examination. He underwent thyroidectomy and dissection of the central neck compartment. The pathological findings indicated papillary carcinoma. After the surgery, he underwent thyroid-stimulating hormone-suppression therapy with levothyroxine at a dose of 150 μg/day.

Eight years ago, 3 nodules were found during follow-up ultrasound examination. He underwent thyroidectomy again, along with dissection of the cervical lymph nodes. The pathological findings were the same as those obtained after the first procedure, except that metastasis of 3 lymph nodes was found. The patient’s condition remained stable for 8 years, until 2017.

In 2017, a stony hard mass ($3 \times 2 \times 2$ cm$^3$) appeared with severe skin fibrosis in the left neck. No treatment was administered, and the tumor had gradually increased in size to $6 \times 7 \times 8$ cm$^3$ at the time he was admitted to our clinic. The tumor tissue showed liquefaction, necrosis, and skin invasion. The skin of the tumor appeared red and black in some places and showed signs of necrosis (Fig. 1a, b). An enhanced CT scan revealed an area of low density that was approximately $6.5 \times 6.6 \times 8.4$ cm$^3$ in size (Fig. 2a). After a discussion with our multidisciplinary tumor board, palliative resection, $^{131}$I brachytherapy, $^{125}$I seed brachytherapy, and radiotherapy were recommended, and the patient agreed to undergo $^{125}$I brachytherapy.

#### Brachytherapy Procedure

Prior to $^{125}$I seed implantation, the patient was immobilized using a vacuum cushion (size: $120 \times 80 \times 4$ cm$^3$; Tianchen Medical Instruments, China). A line was drawn with the help of a CT laser on the tumor projection surface of the patient skin, and 3 points were marked 3–4 cm away from each other on this line. CT was performed with a slice thickness of 5 mm.

A treatment plan was designed using a treatment planning system (TPS) (Panther Brachy v5.0 TPS; Prowess Inc., Concord, CA, USA) to determine the number, dose, and location of the implanted $^{125}$I seeds. The target volume was delineated carefully according to the CT findings. Clinical target volume was determined by ex-
Expanding the gross target volume by 5 mm and restricted by the volume of critical organs. Dose-volume histogram parameters were applied for the evaluation of target volume and organs at risk (OARs). The clinical target volume edge was covered by an isodose line of 90% of the prescribed dose (PD), and the PD of the seed strands was 60 Gy over a period 30 days. \(D_{\text{max}}\) (the maximum dose) of the spinal cord and left intervertebral vessel and \(D_{\text{mean}}\) (the mean dose) of the larynx and hypopharynx were mainly considered. The

Fig. 1. a The skin of the tumor appeared red and black in some places and showed signs of necrosis before the first procedure. b A stony hard mass (6 × 7 × 8 cm\(^3\)) appeared in the left neck before the first procedure. c At the 8-month follow-up after the first procedure, it was observed that the tumor under the skin surface of the left neck shrank obviously and showed signs of slight radiation-induced skin reaction. d The skin surface showed complete recovery, and the skin on the treatment side had completely healed in the 12th month after the first procedure.

Fig. 2. a An enhanced CT scan revealed an area of low density that was approximately 6.5 × 6.6 × 8.4 cm\(^3\) in size before the first procedure. b Enhanced CT showed that the target had shrunk in the 4th month after the first procedure. c CT showed that the target had shrunk further in the 5th month after the first procedure. d Enhanced CT showed that the target had shrunk further in the 12th month after the first procedure.
equivalent dose for a 2-Gy fraction schedule was calculated using the EQD2 model: $\alpha/\beta = 3$ (Gy$_{EQD2}$, $\alpha/\beta = 3$) for the OARs and $\alpha/\beta = 10$ (Gy$_{EQD2}$, $\alpha/\beta = 10$) for the target. The established dose parameters are shown in Table 1.

The entry site and path of the needle were determined to avoid vital structures such as bone, unnormal skin, and large vessels. The dose for OARs was set below the tolerance dose. For designing the 3D-printed template, patient skin contour, needle coordinates, and puncture holes in the TPS were reconstructed, and a 3D printing output file was generated. An SLA-600 3D printer was used to print the 3D template (Fig. 3a). One day before the operation, the 3D-printed template was sterilized. A radioactivity meter (RM-905a well-type ionization chamber; National Institute of Metrology, China) was used to measure seed activity and spot check 10% of the seeds. Eight $^{125}$I seed strands were made with 3.0 mCi seeds according to the pre-plan and sterilized.

During the procedure, the patient was fixed with the same vacuum cushion and in the same position as he was during the pre-operative CT. After the patient was disinfected, the 3D-printed template was fixed on the body surface after referring to the points marked and CT laser line (Fig. 3b). Then, 2 or 3 needles were inserted through the hole to stabilize the relative position of the template, skin, and target area. Then, a CT scan was obtained to confirm the location of the template. The treatment was performed under local anesthesia. Electrocardiography and arterial oxygen pressure, respiration, and blood pressure monitoring were performed during the procedure. Eight applicator needles (1.2 mm in external diameter and 10 cm in length) were inserted into the target under the guidance of the 3D-printed template and CT, and an interval of 2.0–3.0 cm was maintained between the needles to ensure adequate dose distribution and target volume coverage (Fig. 3c). After all the needles were inserted into the target according to the pre-plan, $^{125}$I seed strands were delivered into the tumor through the needles. Then, a CT scan was obtained to make sure all the seed strands were in the right place, and then the needles and 3D-printed template were removed. The ends of the seed strands were sutured to the skin, and liquidation of the tumor was treated by incision and drainage (Fig. 3d). The patient stayed in the hospital for 1 month for observation of complications. Twenty days later, the skin on the top of the tumor turned darker and appeared to be breaking. In order to decrease the risk of skin ulcer, 2 seed strands near the skin were removed. One month after the procedure, the $^{125}$I seed strands were removed, and thirty-eight 0.5 mCi $^{125}$I seeds were implanted into the low-dose area permanently near the mucosa of the pharynx at a PD of 60 Gy. No complications were found, and the brachytherapy was well tolerated by the patient. The patient was discharged after 2 days of observation.

|                | D80, Gy | D90, Gy | D100, Gy | V90, % | V150, % | $D_{\text{max}}$, Gy | $D_{\text{mean}}$, Gy |
|----------------|---------|---------|----------|--------|---------|----------------------|----------------------|
| CTV            | 64      | 52.2    | 22.0     | 94.5   | 70.1    | –                    | –                    |
| Spinal cord    | –       | –       | –        | –      | 7.9     | 7.9                  | 7.9                  |
| Left intervertebral vessel | –   | –       | –        | –      | 21.8    | –                    | –                    |
| Larynx         | –       | –       | –        | –      | –       | –                    | 7.2                  |
| Hypopharynx    | –       | –       | –        | –      | –       | 12.1                 | –                    |

CTV, clinical target volume.
Two months after the first procedure, the tumor was stable compared to its preoperative state. The target irradiated by the seed strands did not exhibit any radioactivity. Therefore, twenty-nine 0.8 mCi $^{125}$I seeds were implanted into the target permanently at a PD of 40 Gy. Two months later, enhanced CT showed that the target had shrunk (Fig. 2b). One month later, CT showed that the target had shrunk further (Fig. 2c). The dose was verified, and some low-dose areas were found in the target. Therefore, forty-seven 0.6 mCi seeds were implanted into the target at a PD of 45 Gy. One year after the first procedure, PET-CT was used to evaluate the concentration of radioactivity in the tumor near the pharynx (Fig. 4a). As some low-dose areas were found, twenty-eight 0.3 mCi seeds were implanted into the target at a PD of 67 Gy. The patient is regularly followed up at our clinic. For this procedure, a coplanar needle can be used to puncture a specific site corresponding to the area with insufficient dose. The 3D-printing templates were not required. The treatment course and characteristics are shown in Table 2.

Before each of the treatment modalities was administered, informed consent was obtained from the patient. Treatments were performed with standard institutional approval.

Follow-Up Findings

At the 8-month follow-up after the first procedure, it was observed that the tumor under the skin surface of the left neck shrank obviously and showed signs of slight radiation-induced skin reaction (grade I) (Fig. 1c), as characterized by redness and pigmentation. During the follow-up examination in the 12th month after the first procedure, the skin surface showed complete recovery, and the skin on the treatment side had completely healed (Fig. 1d). Enhanced CT showed that the target had shrunk further (Fig. 2d). The patient has been followed up for 25 months, and there are no

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Table 2. Treatment course and characteristics

| Activity, mCi | Dose, Gy | Seed number | Implantation method | Permanent or temporary implantation |
|--------------|----------|-------------|---------------------|------------------------------------|
| 1            | 3.0      | 60          | 35                  | 3D-printed template and CT guidance Temporary implantation Two seed strands were removed after 20 days, and the others were removed after 1 month |
| 2            | 0.5      | 60          | 38                  | CT guidance                        | Permanent implantation |
| 3            | 0.8      | 40          | 29                  | CT guidance                        | Permanent implantation |
| 4            | 0.6      | 45          | 47                  | CT guidance                        | Permanent implantation |
| 5            | 0.3      | 67          | 28                  | CT guidance                        | Permanent implantation |

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Fig. 4. a One year after the first procedure, PET-CT was used to evaluate the concentration of radioactivity in the tumor near the pharynx. b Two years after the first procedure, PET-CT showed that there was only a small area of concentrated radioactivity near the site of brachytherapy.
signs or symptoms of complications. The most recent PET-CT showed that there was only a small area of concentrated radioactivity near the site of brachytherapy (Fig. 4b).

### Discussion

The present study describes a case of refractory PTC that was treated with image-guided $^{125}$I seed brachytherapy as salvage treatment. A literature search of PubMed shows that there is only one other study on the use of $^{125}$I seed implantation for the treatment of recurrent PTC. In this previous study by Parker et al. [13], a patient with cerebral metastasis of PTC was treated with craniotomy followed by postoperative external cerebral radiotherapy and $^{125}$I seed implantation in the tumor bed, and complete recovery was achieved. This study by Parker et al. [13] was the first to use $^{125}$I to treat cerebral metastasis of PTC. However, this study only studied tumor bed implantation for the treatment of cerebral metastasis after surgery.

In the present case, the tumor was large in size, with liquidation, blood vessel invasion, and local skin necrosis. It is very difficult to treat such a large tumor with simultaneous surgery and radiotherapy and avoid complications such as skin ulcer, tumor necrosis, mucosa, and blood vessel injury. Furthermore, according to our experience, permanent implantation of $^{125}$I seeds in a large tumor such as this one is highly likely to lead to loss of control or complications. The preprocedure enhanced CT showed enriched blood supply of the tumor, and this might explain the high growth rate of the tumor. To control the tumor, $^{125}$I seeds needed to be administered in pulses. The tumor was large and required short-term control. But to prevent complications such as tumor rupture, we used seeds with higher activity for temporary implantation so that the dose could be more controllable. So, a dose of 60 Gy was delivered over 1 month with temporary 3.0 mCi $^{125}$I seed strands. In order to lower the risk of skin injury, all the needles were inserted into the tumor via normal skin. Therefore, it was not possible to use coplanar needles. Noncoplanar needles are needed, but difficult to control under CT guidance. This problem was resolved by using a 3D-printed template to guide noncoplanar needles. With this method, the tumor could be punctured accurately, according to the pre-plan, while avoiding harm to the blood vessels and bones. Thus, with this method, the room for error was significantly reduced, and the dose distribution was much better.

Then, we treated the low-dose area stepwise with permanent implantation of low-activity (0.3–0.8 mCi) $^{125}$I seeds over the 1-year follow-up. The purpose of this method is to prevent complications induced by tumor overdose. Low-activity seeds (0.3–0.5 mCi) were implanted into the tumor near the pharynx to avoiding mucosal complications. During the entire procedure, the target was covered with high-dose radiation (145–200 Gy), but the dosage delivered to the spinal cord, left intervertebral vessel, larynx, and hypopharynx was relatively low. During the procedure, tumor liquefaction necrosis caused by local high-dose points can be solved by local drainage with tube placement. However, the occurrence of liquefaction necrosis after particle implantation is rare, as long as the tumor dose is well controlled and the dose is within the tolerance limit of the organs, and most large tumors gradually shrink, according to clinical observation. The shrinkage may be caused by the elimination of necrotic tumor cells by immune cells.

Although the radiosensitivity of PTC is not high, the outcome of $^{125}$I seed brachytherapy was remarkable. Obvious shrinkage of the tumor was observed from 4 months after the first procedure, and no serious complications were found over the 25-month follow-up period after interstitial brachytherapy with $^{125}$I seeds. Thus, the low-dose-rate $^{125}$I seed interstitial brachytherapy method used here provided a superior therapeutic rate and enabled curative dose treatment with prominent therapeutic enhancement. In the future, the long-term results of this treatment need to be monitored and evaluated.

### Conclusion

Although there are ongoing discussions about the best management and/or optimal treatment option for recurrence of PTC, the use of a 3D-printed template and CT-guided $^{125}$I seed brachytherapy may be safe and practical. The main benefit of $^{125}$I interstitial brachytherapy is that a high dose of radiation can be precisely applied to the tumor while simultaneously sparing radiation to healthy tissues. Thus, in select patients, image-guided $^{125}$I seed interstitial brachytherapy may be a valuable salvage treatment approach for refractory recurrence of PTC.

### Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. There was no need for institutional review board approval, as it is only a case report with a review and did not involve a study protocol.
Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this study.

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Author Contributions

Zhen Gao and Hongtao Zhang drafted the manuscript and conducted the literature review. Lijuan Zhang was involved in the idea of the study and provided relevant information about the case. Huimin Yu and Xuemin Di provided images and relevant information about the case. Juan Wang and Zeyang Wang suggested that this case be reported and revised the manuscript by making the required corrections, and Aixia Sui is the oncologist who currently follows the patient. Zezhou Liu and Gaofeng Shi designed the pre-plan and the 3D-printed template.

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