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Original Article

Clinical efficacy of iodine-125 (^{125}I) seed implantation in patients with iodine-refractory differentiated thyroid cancer

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Abstract: Patients with radioactive iodine refractory differentiated thyroid cancer (RAIR-DTC) are resistant to radioactive iodine-131(^{131}I) treatment, and the clinical treatment for these patients is complex. The implantation of iodine-125 (^{125}I) seeds in the lesion has been successfully applied to treat malignant tumors, but there are few reports on using ^{125}I particles in the treatment of RAIR-DTC. This retrospective study collected data of 92 patients with RAIR-DTC. Patients treated with sorafenib were included in a control group (50 cases with 72 lesions) and patients treated with ^{125}I implantation were included in an observation group (42 cases with 68 lesions). The results showed that compared with those in the control group, the lesion volume was lower and the VVR was higher in the observation group (P<0.05). The Tg and Tg-Ab levels 6 months after treatment were lower than those before treatment in both groups, and the post-treatment Tg and Tg-Ab levels of the observation group were lower than those of the control group (P<0.05). The efficacy, disease control rate, and objective remission rate were not significantly different between the observation group and the control group (P>0.05). Overall survival of patients in the observation group was longer than that in the control group, χ^2 = 4.430, P = 0.035. The incidence of total adverse reactions in the observation group was lower than that in the control group (P<0.05). In conclusion, ^{125}I seed implantation is effective in RAIR-DTC treatment as it can prolong the overall survival of patients while maintaining a safe profile.

Keywords: Iodine-125 particles, iodine refractory, differentiated thyroid carcinoma, efficacy

Introduction

Thyroid cancer is a malignant tumor that affects the endocrine system, accounting for approximately 2% of all malignant tumors [1]. Differentiated thyroid cancer (DTC) is a primary thyroid cancer, accounting for about 90% of thyroid cancers [2]. DTC cells take up iodine from the blood under the regulation of thyroid stimulating hormone (TSH) to generate thyroid hormone. Radioiodine (RAI) uses this characteristic to treat DTC. Radioactive iodine-131 (^{131}I) combined thyroid hormone therapy is a traditional strategy for the treatment of DTC. ^{131}I is used to ablate residual thyroid cells and metastases after surgical resection of the primary tumor to reduce the recurrence rate and prolong the survival. However, studies reported that up to 30% of patients had local recurrence, cervical lymph node metastasis, and distant metastasis [3, 4]. Moreover, up to 2/3 of these patients develop resistance to radioactive ^{131}I treatment, known as radioactive iodine refractory DTC (RAIR-DTC) [5]. At present, targeted drugs such as sorafenib and renvatinib are the first-line treatment for RAIR-DTC, which can significantly extend the progression-free survival of patients, but the impact on overall survival is not significant, with obvious drug resistance and adverse reactions, which makes it difficult to meet clinical needs [6]. Recently, interstitial brachytherapy of radioactive particles has developed rapidly as local treatment for malignant tumors. Iodine-125 (^{125}I) is a hot research spot as its decay produces the gamma rays which continue to kill tumor cells but cause minor damage to surrounding normal tissues [7-9]. There are some preliminary studies on treating RAIR-DTC with ^{125}I seeds [10-12], but more clinical evidence is still needed to prove

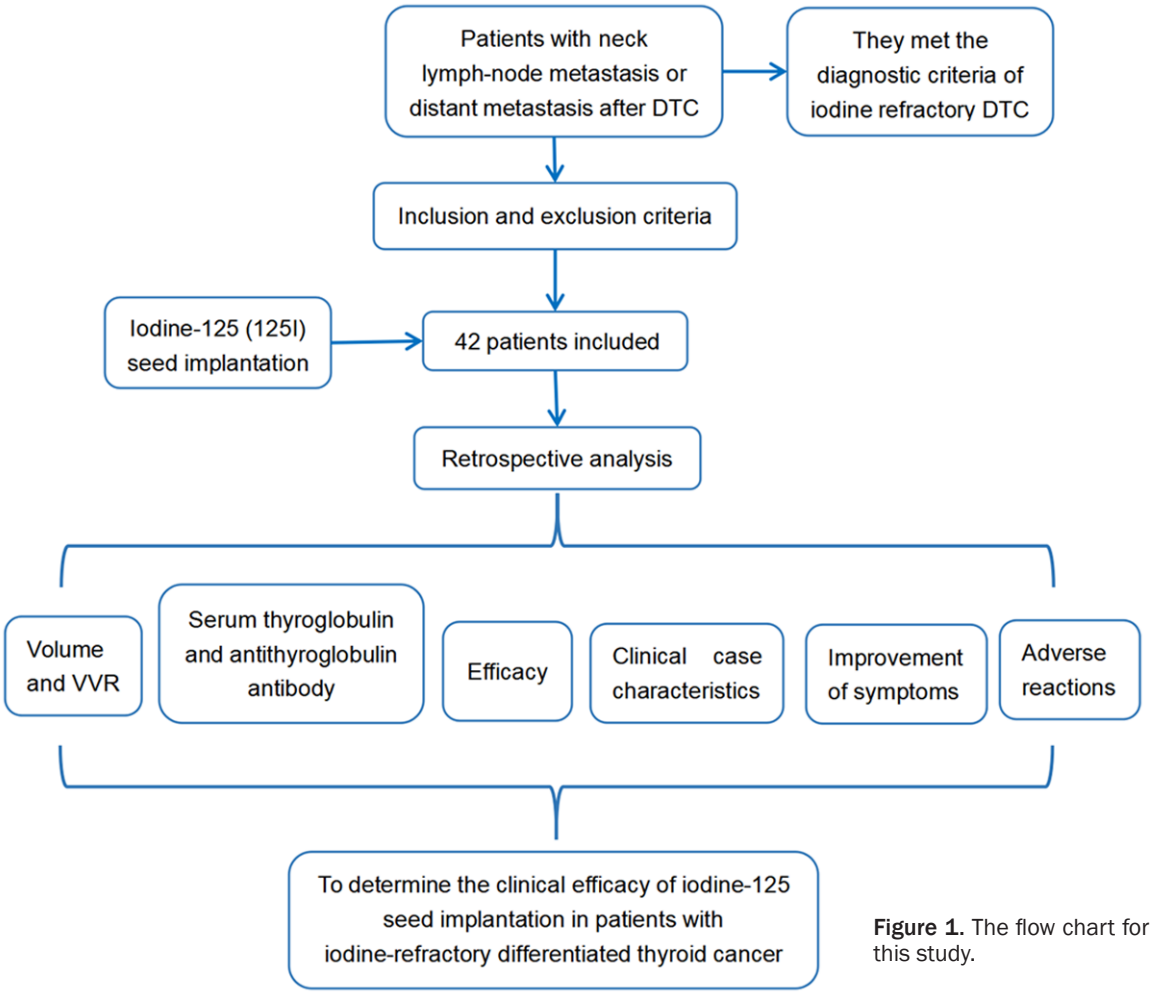

Figure 1. The flow chart for this study.

the effectiveness and safety of ^{125}I. Given this, this study retrospectively analyzed the data of RAIR-DTC patients, with the aim to further systematically explore the efficacy of ^{125}I seed implantation on RAIR-DTC.

Materials and methods

Case selection and ethic approval

This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University. The flow chart of the study is shown in **Figure 1**. Data of 92 patients with DTC and neck lymph-node metastasis or distant metastasis, who were hospitalized in our hospital from February 2016 to January 2020, were retrospectively collected.

Inclusion criteria of the patients: patients were diagnosed as RAIR-DTC with postoperative recurrent lesions according to the diagnosis and treatment guidelines [13]; patients aged over 18 years old; patients had previously received oral ^{131}I treatment at least once; patients were treated with sorafenib or ultrasound guided ^{125}I implantation; patients had complete clinical data. Exclusion criteria of the patients: patients had malignant tumors besides DTC; patients had cardiac insufficiency; women in pregnancy.

Diagnostic criteria of RAIR-DTC

Diagnostic criteria of RAIR-DTC [14]: 1) Target lesions completely lost the ability to take up iodine in radioactive iodine therapy. 2) The interval between every two radioactive iodine treatments was less than 12 months with a dose no less than 3.7 GBq, and at least one stage of disease progression lasting more than 12 months after iodine treatment. 3) Patients

received a single radiation iodine treatment (≥3.7 GBq) within 12 months, but the target lesion indicated disease progressed. 4) The cumulative dose of radioactive iodine treatment was at least 22.2 GBq. 5) All lymph node metastases were confirmed by imaging or pathological examination. Patients who meet one of the above criteria were diagnosed as RAIR-DTC.

Data collection

The clinical characteristics, lesion's volume, volume reduction rate (VRR), serum thyroglobulin (Tg), antithyroglobulin antibody (Tg-Ab), efficacy, adverse reactions and events, and survival of the patients were collected. The efficacy and adverse reactions were evaluated at 6 months after treatment. The survival period was the survival status of patients until January 2023.

The lesion's volume and VRR was measured by conventional ultrasound (Mindray Resona 7 ultrasonic instrument, frequency 5-15 MHz) and contrast-enhanced ultrasound. The maximum diameter of the lesion (a) was measured, then the two lines (b) and (c) perpendicular to the meridian were measured. Tumor volume = πabc/6; VVR (%) = [(original volume - current volume)]/original volume * 100 [15].

The serum Tg and Tg-Ab levels were detected by the E601 automatic electrochemiluminescence immunoassay analyzer (purchased from Roche, Switzerland) and the MAGLUMI 4000 PIUS automatic chemiluminescence instrument (purchased from Shenzhen New Industries Biomedical Engineering Co., LTD) 6 months after the treatment. The decrease rate of Tg and Tg-Ab was calculated: decrease rate = (preoperative level - postoperative level)/preoperative level * 100% [16].

The clinical efficacy was evaluated according to RECIST 1.1 [17] and classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate = (CR + PR + SD)/total number of cases * 100%, objective response rate = (CR + PR)/total number of cases * 100%.

The clinical characteristics including age, gender, pathological type, surgical approach, bilateral tumors, extrathyroidal extension, lymph node metastasis, treatment times of ^{131}I, total dose D/mCi, lymph node region of RAIR-DTC, and the number of metastatic lymph nodes implanted with ^{125}I seeds.

The incidence of adverse reactions were recorded, including hematoma at the puncture site, anabrosis, abnormally high blood pressure, proteinuria, rash, diarrhea, alopecia, hand-foot syndrome, etc. Complications were graded in line with common terminology criteria for adverse events 5.0 (CTCAE 5.0) [18].

Therapeutic methods

Procedures of ^{125}I particle therapy were as follows. (1) Pre-operation: Siemens Acuson Oxana 2, HI VISION Preirus, or Mindray Resona 7 with 5-15 MHz high-frequency probes were adopted for treatment. ^{125}I particles were provided by Ningbo Jin'an Pharmaceutical Co., LTD, with a radioactivity of 0.4 mCi, an average energy of 27-35 keV, a half-life of 60.1 d, and a tissue penetration of about 20 mm (approval number from State Food and Drug Administration in China: Sinopiate H20041350). The location, size, blood perfusion, and adjacent relationship with surrounding tissues of suspicious recurrent and metastatic lesions were recorded. An experienced chief physician performed the ^{125}I seed implantation under local anesthesia. Briefly, the number and distribution range of seed implantation was designed according to the lesion size. (2) During operation: Operators selected a suitable body position according to the lesion site and CT scan images then determined the puncture point with in vitro positioning grating. The local anesthesia was performed with 2% lidocaine (produced by Shanghai Pujin Linzhou Pharmaceutical Co., LTD., approved by the National Drug Code H41022244), and the needle was applied layer by layer according to the TPS plan. When entering the lesion, the puncture needle should pass through the center of the tumor and implant particles one by one from the periphery to the center, with a particle interval of 1 cm, and step by step backwards after suction without blood. For bone metastases, operators used the coaxial needle method. If the bone cortex at the lesion was relatively intact, they first used a 13G bone needle to puncture the lesion's edge to establish a channel, then sent an 18G needle with scale implantation into the particle to the target. During vertebral body implantation, they

should select the optimal treatment layer in combination with CT fixation and positioning in vitro. The CT digital modelling system was employed to measure the tilt Angle of the pedicle, the pyracantha opening distance of the puncture point, and the depth of the skin from the puncture point to the pedicle, then ^{125}I particles were implanted from the posterior quarter of the vertebral body to the anterior half of the pedicle. Vital signs, such as blood pressure, respiration, heart rate, oxygen saturation, and consciousness, were monitored during the operation. Following Halarism's ^{125}I empirical formula: mCi = Da × 5 (Da is the average value of the length, width, and height of the target tissue (L + W + H)/3; the unit is cm), the total activity of the ^{125}I particles required during the operation and the number of implanted particles were calculated, namely, [(L + W + H)/3 × 5/activity of each particle = the number of injected particles]. Under ultrasound guidance, ^{125}I particles were implanted into the predetermined site by an 18G puncture needle. The distribution of particles were arranged in a straight line and parallel to each other. The particles were 3-5 mm away from the edge of the lesion and at least 1 cm away from the large blood vessels, nerves, trachea, and esophageal wall in the neck [19]. (3) Postoperative: After implantation, the patient was monitored in an observation room for 2 hours with a focus on assessing bleeding and hematoma.

Sorafenib therapy was prescribed as follows. The patients were given a total of 600 mg/d sorafenib toluene sulfanilamide (Manufactured by Bayer Pharma AG, Approval number: H20160201) orally per day, 400 mg in the morning and 200 mg in the evening (12 h intervals).

Grouping

Patients treated with sorafenib were included in a control group (50 cases with 72 lesions), and patients treated with ^{125}I implantation were included in an observation group (42 cases with 68 lesions).

Statistical methods

The data were processed by SPSS 17.0 software. Measurement data conforming to normal distribution were expressed as mean ± SD ($\bar{x}$ ± SD), and t-test was used for comparison between groups. Counting data was described by n (%) and compared between groups using chi-square test or Fisher's exact test. Data among multiple time points were compared using repeated measure ANOVA and post hoc Bonferroni test. Overall survival was analyzed by Kaplan-Meier. $P<0.05$ indicated that the difference was statistically significant.

Results

Comparison of general data between the two groups

The age, gender, pathological type, surgical method, bilateral tumors, extrathyroidal extension, lymph node metastasis, and treatment times were compared between the observation group and control group, and no significant difference was identified ($P>0.05$) (**Table 1**).

Lesion volume and VVR changes

Repeated measurement ANOVA was performed to compare the effects of ^{125}I particles on lesion volume. At 3, 6, and 9 months after the operation, the lesion volumes of the observation group were lower than those of the control group, and the VVR was higher than that of the control group ($P<0.05$). There were statistically significant differences in lesion volume ($F_{(4, 335)} = 726.517$, $P<0.001$) and VVR ($F_{(3, 268)} = 296.847$, $P<0.001$) between at least two time points in the observation group. There were statistically significant differences in lesion volume ($F_{(4, 335)} = 880.552$, $P<0.001$) or VVR ($F_{(3, 284)} = 614.331$, $P<0.001$) between at least two time points in the control group (**Tables 2**-**4**, S1, S2, S3).

Changes in serum Tg and Tg-Ab

The Tg and Tg-Ab levels at 6 months after treatment were lower than those before treatment in both groups, and the post-treatment Tg and Tg-Ab levels of the observation group were lower than those of the control group ($P<0.05$) (**Table 4**).

The efficacy and adverse reactions

The disease control rate and objective remission rate were not significantly different between the observation group and the control group ($P>0.05$) (**Table 5**).

The incidence of total adverse reactions in the observation group was lower than that in the control group ($P<0.05$) (**Table 6**).

Table 1. Comparison of general data between the two groups

General data	Observation group (42 cases)	Control group (50 cases)	t/χ^2	*P*
Age (years)	50.17±5.38	50.35±5.12	0.164	0.870
Gender			0.178	0.673
Male	15 (35.71)	20 (40.00)		
Female	27 (64.29)	30 (60.00)		
Pathological type			0.013	0.910
Follicular thyroid cancer	3 (7.14)	5 (10.00)		
Papillary thyroid cancer	39 (92.86)	45 (90.00)		
Surgical methods			4.033	0.258
Near-total thyroidectomy	5 (11.90)	9 (18.00)		
Total thyroidectomy	13 (30.95)	7 (14.00)		
Total thyroidectomy + bilateral central lymph node dissection	4 (9.52)	6 (12.00)		
Total thyroidectomy + bilateral central lymph node dissection + lateral lymph node dissection	20 (47.62)	28 (56.00)		
Bilateral tumors			0.116	0.733
Yes	17 (40.48)	22 (44.00)		
No	25 (59.52)	28 (56.00)		
Extrathyroidal extension			0.207	0.649
Yes	19 (45.24)	25 (50.00)		
No	23 (54.76)	25 (50.00)		
Lymph node metastasis			0.519	0.471
<5	6 (14.29)	10 (20.00)		
≥5	36 (85.71)	40 (80.00)		
Treatment times by using ^{131}I			1.143	0.285
1	10 (23.81)	17 (34.00)		
≥2	32 (76.19)	33 (66.00)		
Total dose *D*/mCi			1.005	0.316
<200	8 (19.05)	14 (28.00)		
≥200	34 (80.95)	36 (72.00)		
Lymph node region of RAIR-DTC			0.070	0.791
I/II/III	19 (45.24)	24 (48.00)		
IV/V/VI	23 (54.76)	26 (52.00)		

Table 2. Focal volume (mm^3) at each time point in the two groups

Time	Observation group (68 lesions)	Control group (72 lesions)	t	*P*
Before operation	416.23±52.82	415.36±48.12	0.102	0.920
After 3 months of operation	283.17±62.11[a]	336.27±52.39[a]	5.479	<0.001
After 6 months of operation	188.32±34.03[a,b]	229.18±36.21[a,b]	6.871	<0.001
After 9 months of operation	95.53±25.02[a,b,c]	116.43±35.62[a,b,c]	3.996	<0.001
After 12 months of operation	86.26±20.21[a,b,c]	87.69±19.73[a,b,c,d]	0.424	0.673
F	726.517	880.552	-	-
P	<0.001	<0.001	-	-

Note: [a]compared with the preoperative data of the same group; [b]compared with the data of the same group after 3 months of treatment; [c]compared with the data of the same group after 6 months of treatment; [d]compared with the data of the same group after 9 months of treatment, *P*<0.05.

Survival

The overall survival of patients in the observation group was longer than that in the control group, χ^2 = 4.430, *P* = 0.035 (**Figure 2**).

Discussion

Patients with DTC usually have a good prognosis and prolonged survival after a comprehensive treatment program of resection, ^{131}I treat-

Table 3. VVR (%) at each time point of the two groups

Time	Observation group (68 lesions)	Control group (72 lesions)	t	*P*
After 3 months of operation	30.94±17.00	18.64±11.22	5.079	0.001
After 6 months of operation	54.24±9.39[e]	44.17±10.51[e]	5.966	<0.001
After 9 months of operation	76.65±6.72[e,f]	71.51±9.31[e,f]	3.727	<0.001
After 12 months of operation	78.92±5.73[e,f]	78.69±5.05[e,f,g]	0.252	0.801
F	296.847	614.331	-	-
P	<0.001	<0.001	-	-

Note: [e]compared with the preoperative data of the same group after 3 months of treatment; [f]compared with the data of the same group after 6 months of treatment; [g]compared with the data of the same group after 9 months of treatment, *P*<0.05.

Table 4. Changes of serum thyroglobulin and Tg-Ab before and after treatment in two groups

Time	Tg (μg/L)		Tg-Ab (U/ml)	
	Before operation	6 months after operation	Before operation	6 months after operation
Observation group (42 cases)	148.56±8.72	41.53±6.59*	1189.56±255.06	637.25±24.96*
Control group (50 cases)	149.02±7.68	68.35±8.24*	1192.36±256.03	726.11±26.58*
t	0.257	17.970	0.050	17.230
P	0.798	<0.001	0.960	<0.001

Note: *indicates intraoperative comparison with preoperative comparison, *P*<0.05.

Table 5. The efficacy 6 months after the operation in both groups

Group	CR	PR	SD	PD	Death	Disease control rate (%)	Objective remission rate (%)
Observation group (42 cases)	0	35	6	0	1	97.62	83.33
Control group (50 cases)	0	40	8	0	2	96.00	80.00
χ^2	0.259					<0.001	0.168
P	0.879					>0.999	0.682

Table 6. Adverse events and adverse reactions

Group	Hematoma at the puncture site	Anabrosis	Abnormally high blood pressure	Proteinuria	Rash	Diarrhea	Alopecia	Hand-foot syndrome	Total
Observation group (42 cases)	2	4	0	0	0	0	0	0	6 (14.29%)
Control group (50 cases)	0	0	8	10	3	2	3	3	29 (58.00%)
χ^2									18.506
P									<0.001

ment, and TSH suppression. However, some patients gradually lose their differentiation and iodine uptake ability in a natural state or during treatment and eventually develop into RAIR-DTC. Patients with RAIR-DTC has a ten-year survival rate less than 10% [20]. The conventional treatments, such as distant metastasis resection, chemotherapy, and external radiotherapy, are inadequate for RAIR-DTC. Some researchers tried to apply anti-angiogenic drugs to treat RAIR-DTC, but the drugs caused obvious adverse reactions such as hand-foot syndrome and elevated blood pressure [21, 22]. Currently, a few preliminary studies have reported the use of ^{125}I on RAIR-DTC. Therefore, it is still necessary to further systematically analyze its comprehensive effects on efficacy, survival, symptom relief, and quality of life to guide clinical treatment.

By retrospectively analyzing data of patients with RAIR-DTC treated by ^{125}I, we found that

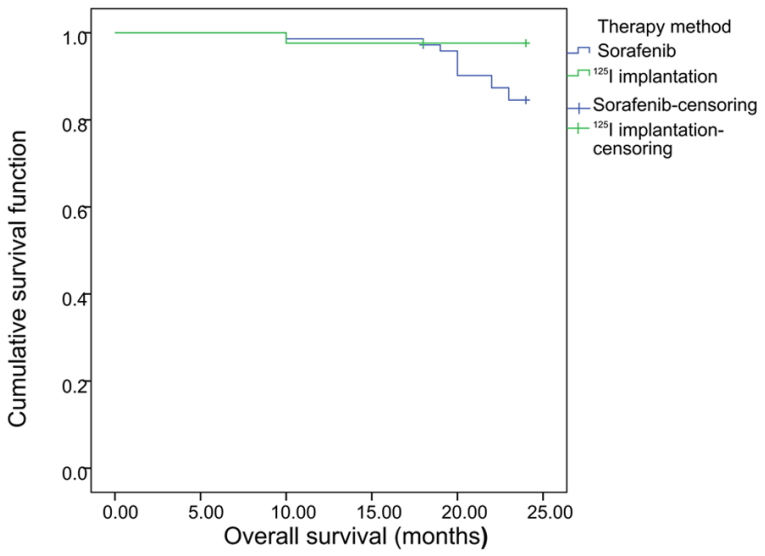

Figure 2. Survival curves of the two groups. Note: Overall survival was analyzed by Kaplan-Meier. Overall survival of patients in the observation group was longer than that in the control group, $\chi^2 = 4.430$, $P = 0.035$.

after 3 months, 6 months, 9 months, and 12 months of treatment, the lesion volume of the patients was significantly reduced, and over time the VVR showed an increasing trend. This suggests that ^{125}I can effectively inhibit tumor growth, and the volume reduction is more significant at 6 months and 12 months of treatment. Long-term medication is expected to have sustainable benefits in inhibiting tumors, but further studies with longer follow-up time are needed to confirm it. We also found that there was no significant difference in disease control rate and objective response rate between patients treated with sorafenib and ^{125}I seed implantation, suggesting that ^{125}I seed implantation can achieve a similar therapeutic effect to sorafenib treatment. In addition, the incidence of adverse reactions was lower in patients treated with ^{125}I implantation than in patients treated with sorafenib, indicating a higher safety of ^{125}I implantation. The significant efficacy of ^{125}I in the treatment of RAIR-DTC may be closely related to the radiobiological and physical characteristics of ^{125}I. The ^{125}I inside the particles decays and releases rays to accumulate to a specific dose, which can kill tumor cells [23, 24]. In addition, radioactive ^{125}I seed implantation technology can make the particles reach the wall of the tumor tissue and extramural lesions to sustainably killing tumor cells [25-28]. Radioactive ^{125}I seed implantation has advantages of minor trauma, low dose, sustainable radiotherapy, and fewer complications. Previously, Zhao et al. reported that ultrasound-guided ^{125}I seed implantation had a significantly effect on lymph node metastasis after thyroid cancer surgery, and no severe complications or adverse reactions occurred [29]. Yuan et al. also proved the efficacy and safety of ^{125}I seed implantation in treating refractory thyroid cancer [30]. Consisting with above studies, our results exhibited that ^{125}I seed implantation could improve the disease control rate and objective remission rate in patients RAIR-DTC, showing that this treatment was effective and safe.

Tg and Tg-Ab are two widely used and essential biomarkers for evaluating the therapeutic effect and prognosis of thyroid cancer [31, 32]. Tg is synthesized and secreted by thyroid follicular epithelial cells, and its content in circulation is low under normal physiological conditions. When the thyroid gland is damaged, the epithelial cells are stimulated to release a large amount of Tg into the blood circulation [33]. Tg-Ab, as an antibody against Tg, increases with the increase of Tg levels in the blood [34]. Studies have shown that changes in serum Tg levels can be used to determine the recurrence or metastasis after thyroid cancer surgery [35]. Our study showed that serum Tg and Tg-Ab levels were significantly decreased after ^{125}I implantation therapy. However, there are some limitations in this study, such as limited case volume and single center data. Therefore, further multi-center study with large sample size and long-term follow up is need to verify the effect of ^{125}I seed therapy.

In conclusion, ^{125}I seed implantation is effective in treating RAIR-DTC, because it can prolong the overall survival of patients while maintaining a safe profile.

Disclosure of conflict of interest

None.

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References

[1] Hu J, Yuan IJ, Mirshahidi S, Simental A, Lee SC and Yuan X. Thyroid carcinoma: phenotypic features, underlying biology and potential relevance for targeting therapy. Int J Mol Sci 2021; 22: 1950.

[2] Zeng XX, Zhang WW, Ji LQ, Li G, Wang YC, Hao SH and Zhang GX. The efficacy and safety of 125I seeds implantation for the treatment of refractory differentia-ted thyroid carcinoma with regional lymph node or distant metastasis. J Mod Oncol 2020; 28: 4256-4261.

[3] Chen W, Xie F, Zhang MB, Zhang Y, Lin L, Tang J and Luo YK. Ultrasound guided 125I brachytherapy in iodine refractory differentiated thyroid cancer. Chin J Med Imaging 2020; 28: 26-30.

[4] Maniakas A, Dadu R, Busaidy NL, Wang JR, Ferrarotto R, Lu C, Williams MD, Gunn GB, Hofmann MC, Cote G, Sperling J, Gross ND, Sturgis EM, Goepfert RP, Lai SY, Cabanillas ME and Zafereo M. Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000-2019. JAMA Oncol 2020; 6: 1397-1404.

[5] Silaghi H, Lozovanu V, Georgescu CE, Pop C, Nasui BA, Cătoi AF and Silaghi CA. State of the art in the current management and future directions of targeted therapy for differentiated thyroid cancer. Int J Mol Sci 2022; 23: 3470.

[6] Teng LS, Xu ZH and Wang WB. Progress on targeted therapy of radioiodine-refractory differentiated thyroid cancer. Cancer Res Prev Treat 2023; 50: 452-457.

[7] Wang Y, Kang P, He W and Li R. MR-guided 125I seed implantation treatment for maxillofacial malignant tumor. J Appl Clin Med Phys 2021; 22: 92-99.

[8] Xiao L, Tang J, Li W, Xu X and Zhang H. Improved prognosis for recurrent epithelial ovarian cancer by early diagnosis and 125I seeds implantation during suboptimal secondary cytoreductive surgery: a case report and literature review. J Ovarian Res 2020; 13: 141.

[9] Zhang QZ, Li GL, Shang JB, Ren YM and Xie JL. Clinical study of a 125I particle-integrated esophageal covered stent and hyperbaric oxygen in the treatment of advanced esophageal cancer. Rev Esp Enferm Dig 2021; 113: 576-579.

[10] Su L, Huang CG, Yang M, Yang W and Chen MH. Efficacy of SPECT-CT guided 125I seed implantation in the treatment of RAIR-DTC and its effect on tumor blood vessels, serum Ctn, Tg, TGAb. Chin J of CT MRI 2022; 20: 50-54.

[11] Gao LY, Lin YS, Jiang YX, Li JC, Li H, Zhang B, Liu RY, Xi XH, Gao Q, Wang Y and Zhao R. Evaluation of short-term efficacy of apatinib using cervical ultrasound and thyroglobulin in the treatment of progressive radioactive iodine-refractory differentiated thyroid cancer. China Oncol 2019; 29: 418-422.

[12] Chen ZJ, Tan LL, Su Y, Xie JG, Zhou AQ, Zou WW, Wang WJ, Xu B and Xu L. Clinical application of 125I seeds implantation for bone metastasis from iodine-refractory differentiated thyroid cancer. Chin J Nucl Med Mol Imaging 2018; 38: 14-16.

[13] Chinese Society of Clinical Oncology Guidelines Working Committee. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for differentiated thyroid cancer 2021. J Cancer Control Treat 2021; 34: 1164-1200.

[14] Tang XW, Shi L, Wang J, Zhao ZY, Bu T and Wang F. Differential diagnosis of 18F-FDG PET/CT in high risk and radioiodine-refractory differentiated thyroid carcinoma. Chin J Med Imaging 2022; 30: 210-214, 229.

[15] Yang YH, Li WC, Zhong BY, Shen J and Zhu XL. Efficacy and safety of transarterial chemoembolization combined with camrelizumab and apatinib in treatment of advanced hepatocellular carcinoma. J Clin Hepatol 2022; 38: 2755-2760.

[16] Feng X, Yang HT and Wang ZY. 125I radioactive seed implantation combined with microwave ablation for treatment of chest wall giant metastasis. Chin J Interventional Imaging Ther 2021; 18: 438-439.

[17] Wang LN and Mou SM. Clinical effect of Fuzheng Jiedu Xiaoying decoction in treating Hashimoto's thyroiditis. Shaanxi J Tradit Chin Med 2023; 44: 205-208.

[18] Sun YQ, Mu Z, Wei X, Zhang X, Wang X and Lin YS. Serologically biochemical evaluation for patients with locally advanced/metastatic radioactive iodine-refractory differentiated thyroid cancer treated by apatinib. Chin J Nucl Med Mol Imaging 2022; 42: 644-649.

[19] Li M, Wen P, Qian QQ, Qin A, Zeng L and Shi F. Clinical study of iodine-125 seeds implantation in the treatment of lymph node metastasis of radioactive iodine-refractory differentiated thyroid cancer. China Oncol 2020; 30: 122-127.

[20] Du W, Shi X, Fang Q, Zhang X and Liu S. Feasibility of apatinib in radioiodine-refractory differentiated thyroid carcinoma. Front Endocrinol (Lausanne) 2022; 13: 768028.

[21] Lin Y, Qin S, Li Z, Yang H, Fu W, Li S, Chen W, Gao Z, Miao W, Xu H, Zhang Q, Zhao X, Bao J, Li

L, Ren Y, Lin C, Jing S, Ma Q, Liang J, Chen G, Zhang H, Zhang Y, Zhou X, Sang Y and Hou Z. Apatinib vs placebo in patients with locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer: the REALITY randomized clinical trial. JAMA Oncol 2022; 8: 242-250.

[22] Zheng X, Xu Z, Ji Q, Ge M, Shi F, Qin J, Wang F, Chen G, Zhang Y, Huang R, Tan J, Huang T, Li S, Lv Z, Lin Y, Guo Z, Kubota T, Suzuki T, Ikezawa H and Gao M. A randomized, phase III study of lenvatinib in Chinese patients with radioiodine-refractory differentiated thyroid cancer. Clin Cancer Res 2021; 27: 5502-5509.

[23] Wang Y, Zhu L, Lin X, He C, An Z, Tang J, Lv W and Hu J. Therapeutic effect of CT-guided 125I seed implantation on advanced lung cancer and pulmonary metastatic carcinoma. Zhongguo Fei Ai Za Zhi 2020; 23: 424-428.

[24] Qu A, Jiang P, Sun H, Jiang W, Jiang Y, Tian S and Wang J. Efficacy and dosimetry analysis of image-guided radioactive 125I seed implantation as salvage treatment for pelvic recurrent cervical cancer after external beam radiotherapy. J Gynecol Oncol 2019; 30: e9.

[25] Jiang AG, Lu HY and Ding ZQ. Implantation of 125I radioactive seeds via c-TBNA combined with chemotherapy in an advanced non-small-cell lung carcinoma patient. BMC Pulm Med 2019; 19: 205.

[26] Yuan P, LI WH, Yue TH, Yuan L, Chen B and Dai ZY. Efficacy of radioactive 125I seed implantation combined with chemoradiotherapy in the treatment of non-small cell lung cancer and its effect on tumor markers. J Clin ntern Med 2022; 39: 189-191.

[27] Zhang H, Yang A and Zhang J. Efficacy of transcatheter arterial chemoembolization combined with 125I seed implantation and three-dimensional conformal radiotherapy in advanced primary hepatocellular carcinoma. J BUON 2020; 25: 952-958.

[28] Wang H, Peng R, Li X, Wang Y, Jiang Y, Ji Z, Guo F, Tian S, Sun H, Fan J and Wang J. The dosimetry evaluation of 3D printing non-coplanar template-assisted CT-guided 125I seed stereotactic ablation brachytherapy for pelvic recurrent rectal cancer after external beam radiotherapy. J Radiat Res 2021; 62: 473-482.

[29] Zhao W, Liu RG, Yang X and Yu N. Ultrasound-guided 125I seed implantation in the treatment of postoperative lymph node metastasis of thyroid carcinoma. Chin J Ultrasound Med 2019; 35: 205-208.

[30] Yuan DY, Gao Z, Yang ZJ, Du S, Niu SL, Zhang HT and Wang J. The efficacy and safety of 125I seed implantation on the treatment of refractory thyroid carcinoma. Chin J Endocr Surg 2019; 13: 297-300.

[31] Pan M, Li Z, Jia M and Lu X. Combination of stimulated thyroglobulin and antithyroglobulin antibody predicts the efficacy and prognosis of 131I therapy in patients with differentiated thyroid cancer following total thyroidectomy: a retrospective study. Front Endocrinol (Lausanne) 2022; 13: 857057.

[32] Liu Q, Yin M and Li G. Antithyroglobulin antibody variation during follow-up has a good prognostic value for preoperative antithyroglobulin antibody-positive differentiated thyroid cancer patients: a retrospective study in Southwest China. Front Endocrinol (Lausanne) 2021; 12: 774275.

[33] Gao X, Wang X, Zhong Y, Liu L, Teng W and Shan Z. Serum antithyroglobulin antibody levels are associated with diabetic retinopathy among euthyroid type 2 diabetes patients: a hospital-based, retrospective study. J Diabetes Res 2022; 2022: 2552186.

[34] Ghosh R, Chatterjee S, Dubey S, Pandit A, Ray BK and Benito-León J. Anti-thyroid peroxidase/anti-thyroglobulin antibody-related neurologic disorder responsive to steroids presenting with pure acute onset chorea. Tremor Other Hyperkinet Mov (N Y) 2020; 10: 19.

[35] Wang YB, Deng ZY, Xiao SW and Meng XY. Clinical value of serumnon-stimulated thyroglobulin (nS-TG) in differentiated thyroid cancer (DTC) patients in after thyroidectomy. J Mod Lab Med 2019; 34: 133-134, 138.

Table S1. ANOVA test of lesion volume and VVR at each time point in the two groups

Source of variation	Observation group (68 lesions)					Control group (72 lesions)				
	SS	df	MS	F	*P*-value	SS	df	MS	F	*P*-value
Lesion volume										
Between Groups	5215067.455	4	1303766.864	726.517	<0.001	5656197.009	4	1414049.252	880.552	<0.001
Within Groups	601172.295	335	1794.544			570082.982	355	1605.868	570082.982	
Total	5816239.75	339				6226279.991	359			
VVR										
Between Groups	102851.889	3	34283.963	296.847	<0.001	162811.192	3	54270.397	614.331	<0.001
Within Groups	30952.268	268	115.494			25088.762	284	88.341		
Total	133804.157	271				187899.954	287			

Table S2. Bonferroni test of lesion volume at each time point in two groups

(I) Time	(J) Time	Observation group (68 lesions)				Control group (72 lesions)			
		Mean Difference (I-J)	SE	*P*	95% CI	Mean Difference (I-J)	SE	*P*	95% CI
Before operation	After 3 months of treatment	133.051	7.265	<0.001	112.522-153.581	79.090	6.679	<0.001	60.225-97.956
	After 6 months of treatment	227.909	7.265	<0.001	207.380-248.438	186.189	6.679	<0.001	167.323-205.055
	After 9 months of treatment	320.700	7.265	<0.001	300.171-341.229	298.929	6.679	<0.001	280.063-317.795
	After 12 months of treatment	329.960	7.265	<0.001	309.431-350.490	327.669	6.679	<0.001	308.804-346.535
After 3 months of treatment	After 6 months of treatment	94.857	7.265	<0.001	74.328-115.387	107.099	6.679	<0.001	88.233-125.964
	After 9 months of treatment	187.649	7.265	<0.001	167.119-208.178	219.839	6.679	<0.001	200.973-238.705
	After 12 months of treatment	196.909	7.265	<0.001	176.380-217.438	248.579	6.679	<0.001	229.713-267.445
After 6 months of treatment	After 9 months of treatment	92.791	7.265	<0.001	72.262-113.320	112.740	6.679	<0.001	93.875-131.606
	After 12 months of treatment	102.051	7.265	<0.001	81.522-122.581	141.481	6.679	<0.001	122.615-160.346
After 9 months of treatment	After 12 months of treatment	9.260	7.265	>0.999	-11.269-29.790	28.740	6.679	<0.001	9.875-47.606

Table S3. Bonferroni test of lesion VVR in two groups at each time point

(I) Time	Observation group (68 lesions)					Control group (72 lesions)			
	(J) Time	Mean Difference (I-J)	SE	*P*	95% CI	(J) Time	Mean Difference (I-J)	SE	*P*
After 3 months of treatment	After 6 months of treatment	-23.298	1.843	<0.001	-28.197--18.399	-25.532	1.567	<0.001	-29.694--21.370
	After 9 months of treatment	-45.708	1.843	<0.001	-50.607--40.809	-52.876	1.567	<0.001	-57.038--48.714
	After 12 months of treatment	-47.976	1.843	<0.001	-52.875--43.077	-60.053	1.567	<0.001	-64.215--55.891
After 6 months of treatment	After 9 months of treatment	-22.410	1.843	<0.001	-27.309--17.511	-27.345	1.567	<0.001	-31.507--23.183
	After 12 months of treatment	-24.678	1.843	<0.001	-29.577--19.779	-34.521	1.567	<0.001	-38.683--30.359
After 9 months of treatment	After 12 months of treatment	-2.268	1.843	>0.999	-7.167-2.631	-7.176	1.567	<0.001	-11.338--3.014