Research Square

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Ultrasound-guided implantation of radioactive 125 I seed in radioiodine refractory differentiated thyroid carcinoma

Wei Chen
PLA Medical College & General Hospital of Chinese PLA
Yu Kun Luo (lyk301@163.com)
Department of Ultrasound, First Medical Center, General Hospital of Chinese PLA
Ying Zhang
Department of Ultrasound, First Medical Center, General Hospital of Chinese PLA
Qing Song
Department of Ultrasound, Seventh Medical Center, General Hospital of Chinese PLA
Jie Tang
Department of Ultrasound, First Medical Center, General Hospital of Chinese PLA

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Abstract

Background: Treatment for radioiodine refractory differentiated thyroid carcinoma (RR-DTC) is challenging. The purpose of this study was to assess the efficacy and safety of ultrasound-guided implantation of radioactive ^{125}I-seed in radioiodine refractory differentiated thyroid carcinoma.

Methods: 36 cervical metastatic lymph nodes (CMLNs) diagnosed as RR-DTC from 18 patients were enrolled in this retrospective study. US and contrast-enhanced ultrasound (CEUS) examinations were performed before implantation. Follow-up consisted of US, CEUS, thyroglobulin (Tg) level and routine hematology at 1-3, 6, 9 and 12 months and every 6 months thereafter. The volumes of the nodules were compared before implantation and at each follow-up point. The volume reduction rate (VRR) of nodules was also recorded.

Results: The median volume of the nodules was 522.8 mm^3 (147.5, 2009.6mm^3) initially, which decreased significantly to 53.0mm^3 (0, 285.7mm^3) ($P < 0.01$) at the follow-up point of 24 months with a mean VRR as 87.4±18.1% (the range was 32–100%). During the follow-up period (the range was 24–50 months), 25 (69%) nodules had VRR greater than 90%, of which 12 (33%) nodules had VVR≈100% with structures unclear and only ^{125}I seeds images visible. At the last follow-up visit, the serum Tg level decreased from 57.0 (8.6, 114.8) ng/ml to 4.9 (0.7, 50.3) ng/ml, ($P < 0.01$).

Conclusion: US-guided ^{125}I seed implantation is safety and efficacy in treating RR- DTC. It could be an effective supplement for the comprehensive treatment of thyroid cancer.

Background

Worldwide, the incidence of thyroid carcinoma has been continuously increasing over recent decades[1-3]. Differentiated thyroid carcinoma (DTC), arising from thyroid follicular epithelial cells, accounts for 90% of these cases[4]. With treatments of surgery, suppression of thyroid stimulating hormone (TSH) and selective treatment of radioactive iodine-131 (RAI-131), the vast majority of DTC have an excellent prognosis, as reflected by 5-year relative survival rates of about 95% [1, 5]. However, local recurrence and/or distant metastases may occur in up to 15–30% and two-thirds of them will become radioiodine refractory (RR) during long-term follow-up [6-10]. RAI-131 therapy is first-line systemic treatment in postoperative patients with progressive DTC, so the treatment options for radioiodine refractory differentiated thyroid carcinoma (RR-DTC) have been hampered, leading to a poor overall prognosis [11]. Recently, tyrosine kinase inhibitors (TKIs) as an emerging systemic therapy have shown activity in RR-DTC, but due to lack of long-term survival data and relatively indolent nature of DTC, it is difficult to determine when to initiate TKI therapy [12]. So, localized treatment plays an important role in local recurrence and/or metastases from RR-DTC. Surgery has historically been the mainstay treatment for locoregional metastases from DTC, but repetitive neck excision carries high risk of complications [13, 14]. Therefore, it is desirable to develop alternatives less invasive than repeated surgery as part of a multimodality treatment for DTC.

^{125}I-seed implantation has been suggested as an excellent treatment for head and neck unmanageable recurrent carcinoma [15-19]. However, this method for local control of foci from DTC is rarely reported. In this retrospective study, the efficacy and feasibility of ultrasound-guided ^{125}I-seed implantation for cervical metastatic lymph nodes (CMLNs) from RR-DTC were evaluated.

Methods

Study subjects

Inclusion criteria: (a) patients were required to be aged≥18 years; (b) patients underwent thyroidectomy for DTC; (c) patients had measurable, pathological and/or cytological confirmed CMLN from DTC, evidence of radioiodine refractory according to at least one criteria used in recent clinical trials as follows (i) at least one lesion never concentrate iodine-131, (ii) at least one lesion that has progressed within 12 months after RAI therapy despite iodine-131 avidity, or persistent disease after a cumulative dose of iodine-131 ≥ 600mCi; (iii) partial thyroidectomy leads to thyroid tissue residue, which affects the efficacy of RAI-131 (d) patients who had inoperable CMLN or refused to undergo repeated neck surgical dissection.

Exclusion criteria: (a) cognitive impairment due to neuropathy or psychosis, (b) severe coagulation disorders; (c) patients with severe heart failure/respiratory failure/ liver failure or renal failure, (d) being pregnant or breast feeding.

We performed a retrospective analysis of 18 patients (including 11 males and 7 females) with 36 CMLNs who underwent ultrasound guided ^{125}I seed implantation in our hospital from June 2016 to November 2018. Of all cases, 17 had total thyroidectomy and 1 had partial thyroidectomy. BRAF^{V600E} mutations was found in 17 patients. CMLNs were situated at levels I, II, III, IV, V, and VI respectively, in 0, 6, 12, 10, 1, and 7 cases. The median volume of the initial CMLNs was 522.8 mm^3 (147.5, 2009.6) mm^3. 3 cases showed obvious symptoms of neck compression due to tumor volumes > 10 000 mm^3 and 2 had dysphagia due to esophageal narrowed under tumor compression. 2 case were tracheotomy. 1 case was bilateral vocal cord paralysis. 1 case had skin ulceration on surface of the lesion. The detailed clinical characteristics before implantation of ^{125}I-seeds are listed in Table 1.

Table 1 Clinical characteristics regarding 18 patients of 36 CMLNs treated with implantation of ^{125}I-seeds

Parameter	Characteristics	Result
Sex of patients (n = 18)	M/F	11/7[A]
Age of patients (n = 18)		52.2 ± 20.8 (27−87) [B]
Subtypes of DTC (n=18)	PTC/FTC	17/1(94/6) [C]
No. of neck surgeries performed (n=18)	<3/≥3	16/2(89/11) [C]
Cumulative dose of RAI-131 (n=18)	<600/≥600mci	14/4(78/22) [C]
$BRAF^{V600E}$ mutation (n=18)	P/N	17/1(94/6) [C]
No. of CMLNs (n=18)		
	1	8(44) [C]
	2	4(22) [C]
	≥3	6(34) [C]
Sides of CMLNs (n=36)	L/R	15/21(42/58) [D]
Level of CMLNs (n=36)		
	I	0(0) [D]
	II	6(17) [D]
	III	12(33) [D]
	IV	10(28) [D]
	V	1(3) [D]
	VI	7(19) [D]
Largest diameter of CMLNs (n=36) (mm)		14.0(8.0, 22.5) [E]
Initial volume of nodule (n=36) (mm^3)		522.8(147.5, 2009.6) [E]

M male, F female, PTC papillary thyroid carcinoma, FTC follicular thyroid carcinoma, P positive, N negative, L left, R right

A Number of patients

B Mean ± standard deviation, with range in brackets

C Number of patients, with percentage in brackets

D Number of CMLNs, with percentage in brackets

E Median, with P25 and P75 in brackets

Equipment

Siemens Acuson Sequoia 512 Ultrasound System (Siemens, Mountain View, CA, USA) with a 6L3 linear array transducer was used for guiding core needle biopsy (CNB) and ^{125}I-seed implantation. Siemens Acuson Sequoia 512 Ultrasound System with a 15L8W linear array transducer or a Philips iU22 Ultrasound System (Philips Healthcare, Bothell, WA) with a L12-5 linear array transducer or a Mindray M9 Ultrasound System (Mindray, Shenzhen, China) with a L12-4 linear array transducer was used for image collection before implantation, as well as during follow-up. ^{125}I seeds (radioactivity: 0.4 mCi, the average energy: 27–35 keV, half-life: 60.1 days, antitumor activity: 2.0 cm) in this study were provided by Shanghai Xinke Pharmaceutical Co., LTD.

Pre-implantation assessment

Before ^{125}I seed implantation, all the CMLNs were evaluated by conventional ultrasound (US) combined with contrast-enhanced ultrasound (CEUS). For each CMLN, three orthogonal diameters (the largest diameter and two perpendicular diameters) were measured by US. Volume was calculated with the equation of $V = \pi abc/6$ (where V represents volume; a is the largest diameter; b and c are the other two perpendicular diameters). CEUS provided visualization of blood supply region and enhancement pattern of the lesion. The ultrasound contrast agent we used was Sulphur hexafluoride (SonoVueR, Bracco. International, Milan, Italy). Bolus injection of SonoVue (2.4 ml) through elbow vein was performed for a single CEUS and each imaging acquisition lasted at least 3 min. Then, situated level, adjacent structures, volume and flow perfusion of each CMLN were recorded in details. Thyroglobulin (Tg) test and routine analysis of blood were also performed before implantation.

Implantation procedure

The procedure was carried out by an experienced US physician with more than 20 years experiences in interventional US. Patients were placed in the supine position with their necks extended. Local infiltration anesthesia with 1% lidocaine was injected at subcutaneous puncture site and periphery of the lesion. Number and distribution of ^{125}I seeds to be implanted were designed according to the volume and location of each CMLN. An interstitial needle (18 Gauge) was gradually inserted into the lesion, and the seeds were implanted using turntable implantation gun guided by US. Every seed was placed at 0.5cm–1.0cm intervals. According to the principles of the Paris system, the distribution of the seeds should be arranged in a straight line and parallel to each other. The seeds should be about 0.3cm-0.5cm away from edge of lesion and at least 1cm away from cervical vital structures such as vessels, esophagus, trachea, recurrent laryngeal nerves, etc. Refer to the Halarism's experienced formula: total activity (A) mCi $=Da\times5$, Da denotes the mean sum value of length (L), width (W) and height (H) of the targeted lesion as $(L+W+H)/3$ (unit is cm). Number of seeds to be implanted were obtained by the equation: total activity (A) ÷ the average activity of a single ^{125}I seed = the number of seeds required [20, 21]. Postoperative observation was conducted for 2 hours. We paid attention to possible complications such as bleeding and hematoma during or immediately after implantation.

Follow-up

Follow-up consisted of US, CEUS, routine hematology, and thyroglobulin (Tg) levels at 1-3, 6, 9 and 12 months and every 6 months thereafter. If Tg levels were significantly elevated, for instance doubled, additional systemic examination was performed to determine whether there was a distant metastasis.

The volume of each CMLN was evaluated by US and we calculated volume reduction rate (VRR) during follow-up as VRR = ([initial volume – final volume] × 100)/initial volume[22]. Blood perfusion of CMLN was evaluated by CEUS. Variation of enhancement pattern of nodule before and after implantation was monitored. Hyper-enhancement before implantation while non-enhancement or hypo-enhancement during follow-up suggested the treatments effective[23, 24]. For those with no changes in CEUS before and after implantation, VRR should be combined with serum Tg values to evaluation. There were the following situations: (a) if VRR ≥ 50%, the treatment was deemed to be effective; (b). if VRR < 50%, but the serum Tg level reduction was more than 50% compared with pre-implantation, “wait and watch” would be recommended; (c). if VRR and the serum Tg level reduction were both less than 50%, further US-guided CNB should be performed to determine whether there was active lesion residue, (d). volume of nodules increased from the original during follow-up, indicating treatment failure. Common symptoms and severity of adverse radiation events were classified by the criteria of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (Version 23.0). Continuous data following normal distribution were represented as `x ± s (the range), and if not, as median (P25, P75). The Wilcoxon signed-rank test was performed to compare the changes of nodules volume before implantation and at each follow-up point as well as the serum Tg levels before implantation and at the last follow-up visit. $P < 0.05$ indicated that the difference was statistically significant.

Results

36 CMLNs in 18 patients were all successfully implanted with ^{125}I seeds as planned. All of them tolerated procedures well. A total of 237 ^{125}I seeds were implanted, with the least 1 and the most 22, median 4 (range 2, 11). All implantations were performed in the outpatient. 6 patients suffered mild pain after implantation and alleviated by themselves without treatment. No serious complications such as massive hemorrhage, soft tissue necrosis, neuropathy or carotid damages were noted. Furthermore, no RTOG/EORTC grade > 2 complications were observed. All patients were followed up for at least 24 months with the longest follow-up period as 50 months. Post-implantation US showed all successfully treated nodules were reduced from their original volumes in the follow-up. Before implantation, the

median volumes of the CMLNs were 522.8 mm^3 (147.5, 2009.6mm^3), which decreased to 287.8mm^3 (76.9, 1638.3mm^3), 155.7mm^3 (50.7, 1057.9mm^3), 91.1mm^3 (37.3, 816.4mm^3), 91.0mm^3 (13.6, 514.2mm^3), 79.1mm^3 (0, 317.4mm^3) and 53.0mm^3 (0, 285.7mm^3) at 1-3, 6, 9, 12, 18 and 24 months after implantation, respectively. There were significant differences in the nodules volume between every 2 follow-up visits (P<0.01). The median volume and mean VRR of the nodules after implantation at each follow-up point are shown in Table 2. Representative findings at ^{125}I-seeds implantation and at follow-up of a CMLN case are shown in Fig 1. The changes of median volume and mean VRR at each follow-up point after implantation were shown in Figs 2 and 3. During the follow-up period (the range was 24–50 months), 25 (69%) nodules had VRR greater than 90%, of which 12(33%) nodules had VVR≈100% with structures unclear and only ^{125}I seeds images visible in US. Pre-implantation, CEUS showed 29 (81%) lesions with hyper-enhancement, 7(19%) lesions with hypo-enhancement, while at the last examination, 34 (94%) lesions with hypo-enhancement or non-enhancement, 2 (6%) lesions still with hyper-enhancement. Among these two cases with persistent hyper-enhancement in CEUS, 1 case had VRR of 72%, so continued observation was recommended, while the other case had VRR of less than 50%, however, the subsequent ultrasound-guided puncture biopsy indicated that there was a little lymphatic tissue in the puncture, but no definite metastatic cancer was found. At the last follow-up visit, the serum Tg level decreased from 57.0 (8.6, 114.8) ng/ml to 4.9 (0.7, 50.3) ng/ml, (P < 0.01).

Throughout the follow-up period, physical examination revealed that three patients developed new CMLNs, one of which with axillary lymph node metastasis and one of which with thoracic vertebral metastasis, but there was no evidence of recurrence at the treatment sites.

Table 2 The median volume and mean reduction rate of the nodules after implantation

Time	Volume (mm^3)		Volume reduction rate (%)	
	Median volume (p25, p75)	p	Mean reduction rate	Range
Before implantation	522.8(147.6, 2009.6)		-	-
1-3month later	287.8(76.9,1638.3)	<0.01	43.7±25.1	(7-84)
6 months later	155.7(50.7,1057.9)	<0.01	61.3±22.6	(12-99)
9 months later	91.1(37.3,816.4)	<0.01	72.4±19.0	(25-100)
12 months later	91.1(13.6,514.2)	<0.01	80.3±19.2	(26-100)
18 months later	79.1(0,317.4)	<0.01	84.5±18.0	(28-100)
24 months later	53.0(0,285.7)	<0.01	87.4±18.1	(32-100)

Discussion

Locoregional recurrence and metastasis may occur in 20-30% of DTC patients within 10 years after initial treatment, which is associated with an increased mortality rate [25] . Most patients diagnosed with recurrent DTC can still achieve not a bad prognosis after undergo salvage treatment which is based on radioactive iodine (RAI) and associated with further surgery and hormone suppression[26, 27]. Nevertheless, a small proportion of patients may develop local metastasis disease which is not only unsuitability to repeated neck surgery but also refractory to RAI ablation. Treatment for these refractory recurrence and metastasis is the major challenge in the management of DTC. Few treatment options exist. Systemic therapy with tyrosine kinase inhibitors, oral antiangiogenic MTKIs, have demonstrated a progression-free survival benefit based on results of phase 3 trials[11, 28]. However, these drugs have significant toxicities which can impair quality of life and some individuals do not tolerate [29, 30]. External beam radiotherapy (EBRT) may be a modality for patients with unresectable tumors, but the role of it in DTC is debated for it achieves optimize locoregional control will cause severe damage to the normal tissues and/or their functions [31]. Recent years, minimally invasive therapy has played an important role in local inoperable metastasis foci in DTC, mainly including ultrasound-guided percutaneous intervention approaches such as ethanol injection, laser ablation, radiofrequency ablation, and microwave ablation [32-34]. Each of them has feasibility and limitation. Ethanol injection is generally recommended for lesions with a maximum diameter of >10 mm and it requires repeated treatment [35, 36]. Laser ablation tends to treat lesions with a maximum diameter of less than 10 mm[37, 38]. Radiofrequency ablation and microwave ablation have certain requirements on lesion site due to the heat conduction and thermal damage during operation[33, 34]. Interstitial permanent ^{125}I seed implantation, as a highly conformal radiotherapy modality, delivering higher radiation doses to target areas while sparing surrounding normal tissue, even to tumors closely surrounded by vital structures, is widely applicable, almost free from the limitation of lesion location and volume, and it has been used in the treatment of unresectable malignant tumors of various organs[39-41]. It is especially suitable for the treatment of head and neck malignant tumors due to its advantages of low energy, sustained accumulated radiation, and homogenous dose distribution in the target area[17, 42]. However, there are few reports about the effects in RR-DTC with this method and its feasibility and safety need clinical data validation.

In this study, ultrasound-guided ^{125}I seed implantation was performed on 36 CMLNs of 18 DTC patients after thyroidectomy who met the inclusion criteria, and long-term follow-up was conducted to evaluate the efficacy and safety. The somatic BRAF^{V600E} mutation, which was significantly associated with lymph node or disease metastasis and cancer-related mortality [19, 43-45] , was found in 17 (94%) of all subjects. Therefore, a more aggressive attitude than “watch and wait” should be taken in control of neck recurrence and metastasis in these patients. In this study, cases implanted with ^{125}I seeds had a large age span (range 27-87), a large lesions volume span (range10.9 mm^3-25 017.4 mm^3) and variety lesions location, but no procedure failed, indicating that this method is widely applicable and well tolerated. All cases were successfully implanted as planned, no technical failure, suggesting that this method was well operability and could be popularized among experienced ultrasound physicians. In consideration of inert biological characteristic of DTC as well as CMLNs adjacent to trachea, vessels, nerves and other cervical critical tissues, this study adopted low-dose ^{125}I brachytherapy, even so, at the last follow-up, US indicated that all treated lesions had shrunk. Significant differences in volume were found between every two follow-up visits, showing efficacy reliable. No serious complications occurred immediately after implantation or during long-term follow-up suggesting this method is safety. In addition, the overall cost of ^{125}I implantation is low, especially for nodules with small volume, which can reduce the economic burden of patients.

However, some limitations in this study should be taken into account. First, only 18 patients with 36 nodules were recruited here. Second, volume measured by US alone was used as basis for calculating number of seeds to be implanted and evaluating postoperative efficacy, if other image methods could be combined, the radiation dose calculation and efficacy evaluation could be more accurate. Third, during follow-up, 2 nodules underwent secondary implantation, on one hand, it showed that this method was good repeatability, on the other hand, it indicated that there was still radiation cold zone and the tumor had not been completely inactivated in initial treatment. The association between radiation dose and safety needs to be further studied.

There are still some points deserve consideration in this study: the subjects enrolled in were all diagnosed as RR-DTC, the $BRAF^{V600E}$ gene mutation occurred in 17 of 18 patients, however, responses to low-dose ^{125}I radiotherapy were varied. 25 (69%) nodules had VRR greater than 90% after a single treatment while 3 (8%) nodules had VRR less than 50%, even 2 (6%) nodules required secondary implantation. Of 15 (83%) patients, the disease did not progress after CMLNs were controlled, while of remaining 3 (17%) patients, new metastatic lesions had developed. What accounts for these different responses? Further large sample studies need to determine.

In conclusion, ultrasound-guided ^{125}I seed implantation is ease of operation, feasible, efficacy and safe in locoregional control of radioiodine refractory differentiated thyroid carcinoma, which can be an effective supplement for the comprehensive treatment of thyroid cancer.

Abbreviations

RR-DTC: radioiodine refractory differentiated thyroid carcinoma; CMLN: cervical metastatic lymph node; VRR: volume reduction rate; CEUS: contrast-enhanced ultrasound

Declarations

Ethics approval and consent to participate

This research was approved the Ethical Committee of General Hospital of Chinese PLA and was performed in accordance with 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets in this retrospective study are available from corresponding author on reasonable request. The confidential patient data should not be shared.

Competing interests

All authors declare that they have no competing interest.

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Authors' contributions

LYK, TJ and CW designed the study. The first author wrote the manuscript. LYK, CW, ZY, SQ and TJ revised the manuscript. All authors read and approved the final manuscript.

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Figures

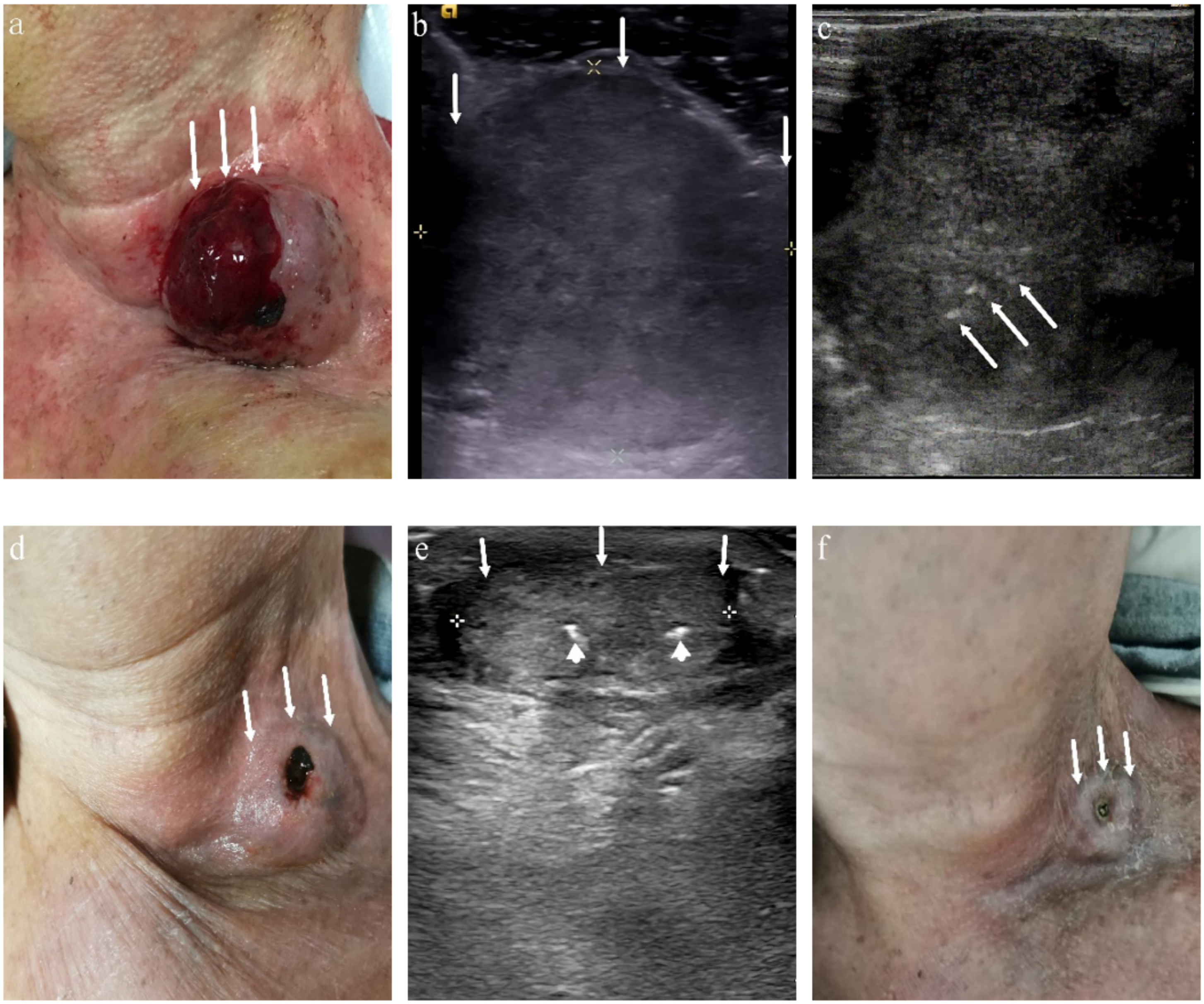

Figure 1

Images of 125I implantation in treatment of a metastatic nodule at left cervical level IV in an 83-year-old man previously underwent left lobe and isthmus excision and left neck dissection due to papillary thyroid carcinoma. a Externally, the CMLN was superficial, broad at the base, with high skin tension and bleeding apical ulcer (white arrows). b Conventional ultrasound image showed the hypoechoic CMLN with no lymphatic hilus was 38 mm × 37 mm × 34 mm in size and 25017.4 mm3 in volume (white arrows). c

During implantation, ultrasound monitoring showed hyperechoic 125I seeds were implanting into lesion (white arrows). d Six month after implantation, the lesion had visibly shrunk (white arrows). e 12 month after implantation, US showed the lesion was 23 mm × 17 mm × 11 mm in size and 2250.9 mm3 in volume with VRR=91 % (white arrows), 125I seeds in the lesion (arrowheads). f The lesion had significantly shrunk and apical ulcer had healed (white arrows).

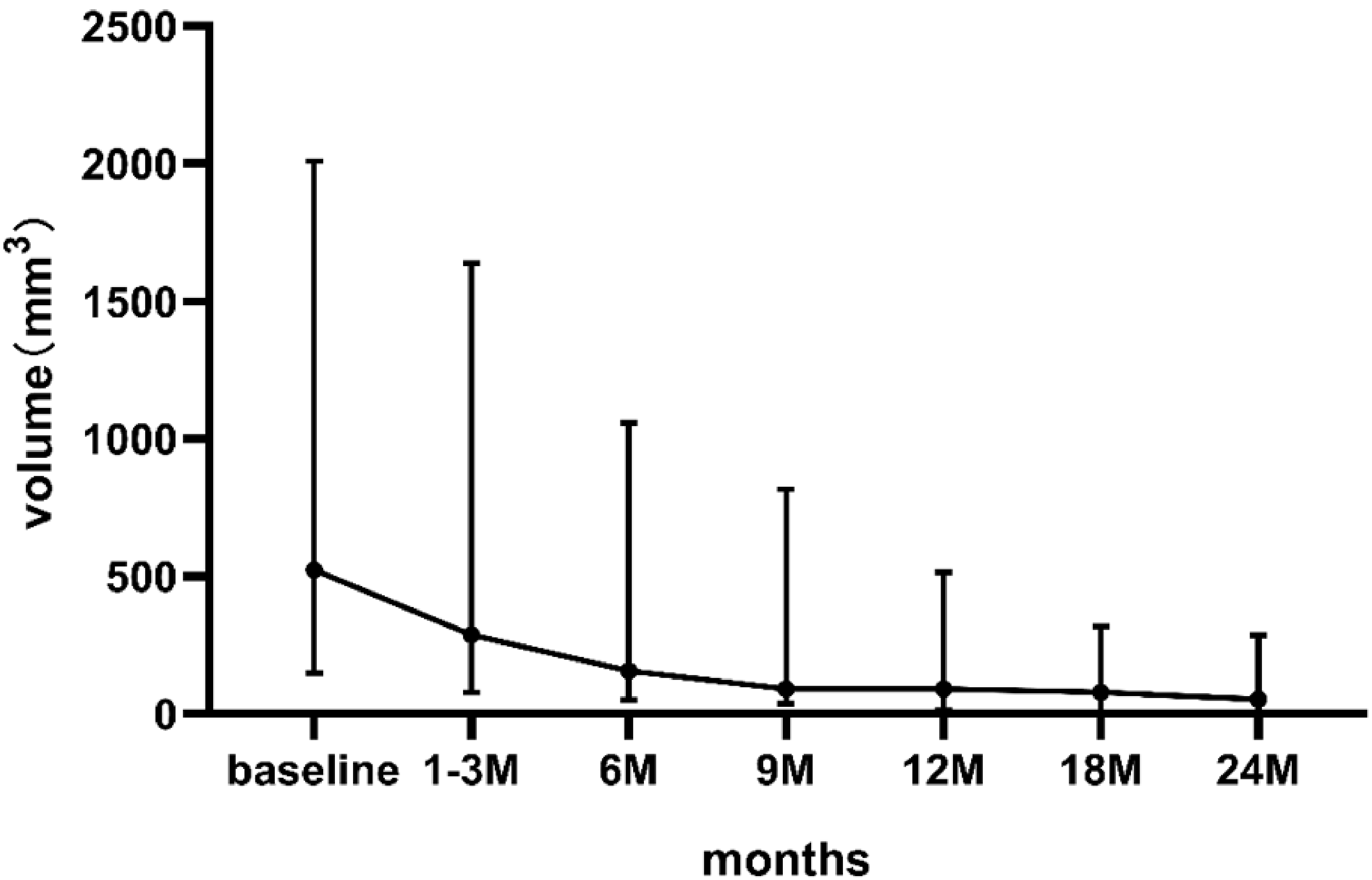

Figure 2

The changes of volume after implantation at each follow-up point

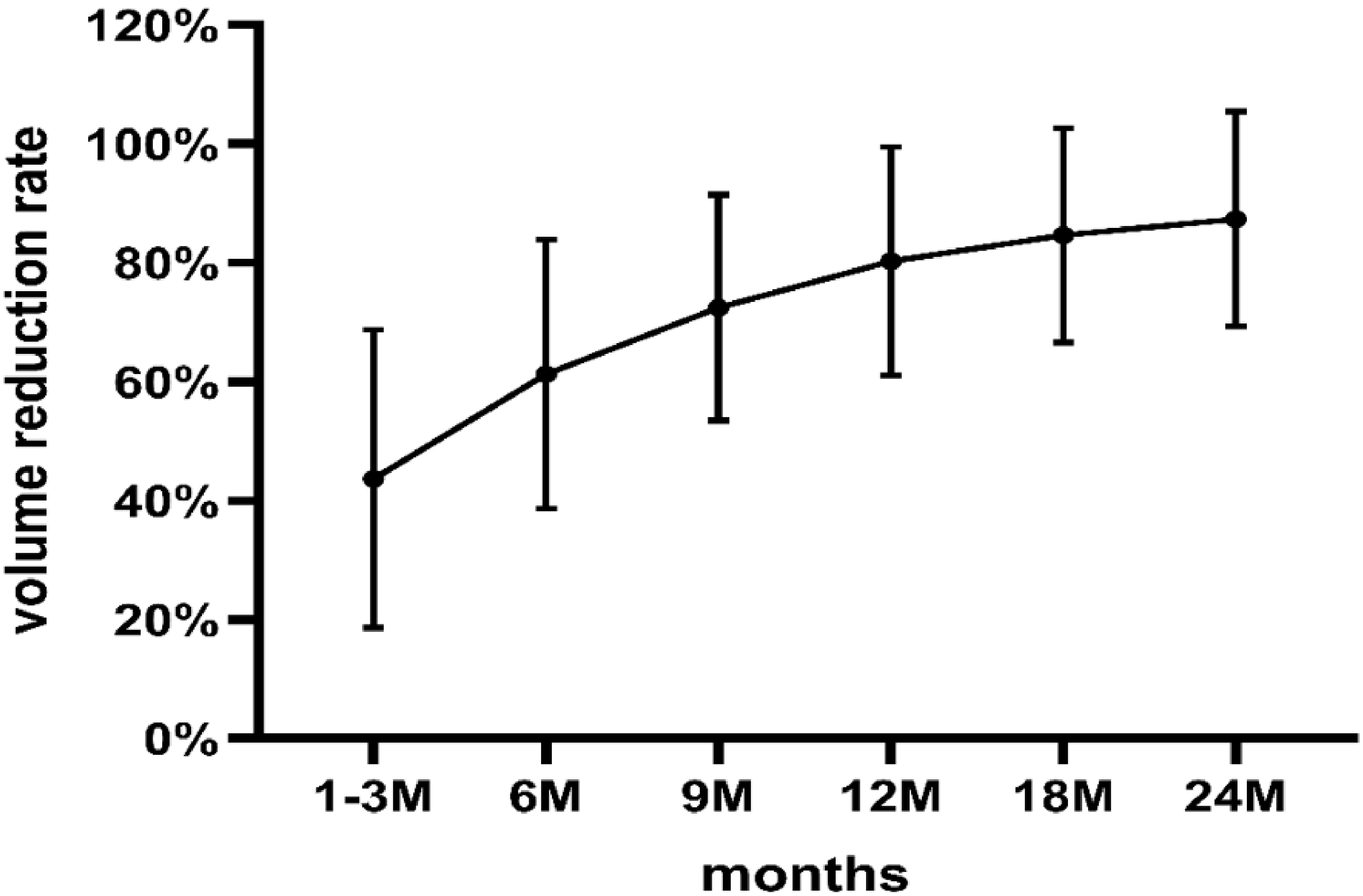

Figure 3

The changes of reduction ratio after implantation at each follow-up point