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# Radiofrequency Ablation Before Intratumoral Injection of $^{131}$I-chTNT Improves the Tumor-to-Normal Tissue Ratio in Solid $VX_2$ Tumor

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## Abstract

***Purpose:*** This study was aimed to investigate whether the tumor necrosis induced by radiofrequency ablation (RFA) can improve the ratio of tumor-to-normal tissue (T/NT) after intratumoral injection of $^{131}$I-chTNT.
***Materials and Method:*** Eighteen New Zealand rabbits bearing $VX_2$ tumor on the thigh were randomly divided into two treatment groups (control group: intratumoral injection of $^{131}$I-chTNT alone; RFA group: RFA + intratumoral injection of $^{131}$I-chTNT 3 days after RFA) and each group was further divided into three subgroups I, II, and III (1–2 cm, 2–3 cm, and 3–4 cm in maximum diameter, respectively), by the tumor size. SPECT was performed to evaluate the T/NT on days 1, 8, and 15 after $^{131}$I-chTNT injection.
***Results:*** After treatment, all rabbits underwent the SPECT whole-body scan and the T/NT was analyzed. The results showed that T/NT in the RFA group (55.45 ± 41.83) was significantly higher compared with the control group (7.23 ± 5.61) ($F = 18.89$, $p = 0.001$). Meanwhile, a linear ascending trend was found for T/NT in the RFA group along with the follow-up time ($r = 0.47$, $p = 0.01$). The tumor size or the dose of $^{131}$I-TNT injection had no significant effect on the variation of T/NT in both groups ($p > 0.05$).
***Conclusion:*** RFA before intratumoral injection of $^{131}$I-chTNT can dramatically improve T/NT, demonstrating the potential application of this combination therapy.

**Key words:** radioimmunotherapy, radiofrequency ablation, ratio of tumor to normal tissue, tumor necrosis therapy

## Introduction

Radioimmunotherapy (RIT), using the radiolabeled monoclonal antibody (MAB) targeted against tumor-associated antigens, delivers cytotoxic decay radiation to kill the tumor. RIT has a long history beginning from the end of 19th century, but until recent decades, a remarkable progress of tumor RIT has been made with the development of biologic and immunologic techniques.[1,2] Nowadays, the promising results have been obtained in RIT for the treatment of B-cell non-Hodgkin's lymphoma (NHL) by using two RIT agents: yttrium-90 ($^{90}$Y)-ibritumomabtiuxetan (Zevalin) and iodine-131 ($^{131}$I)-tositumomab (Bexxar) (20%–40% complete response rates, 60%–80% overall response rates, and mild toxicity), which have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of NHL.[1–3] However, for treating solid cancers, the results of both preclinical studies and clinical trials with RIT have still been modest.[4–8]

The unsatisfactory therapeutic response of solid tumor RIT mainly attributes to the limited penetration or poor targeting capability, undesirable tumor radiosensitivity, and inadequate dose for consideration of excessive hematopoietic toxicity.[2,4,8] Several strategies have been explored with an aim to improve the therapeutic efficacy of RIT for solid tumors, for example, application of the pretargeting technique, novel isotope, and combination with chemotherapy, and radiofrequency ablation (RFA).[5,7–13] Fortunately, combination therapies by coupling or sequencing RIT with

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surgical excision, conventional cytotoxic chemotherapy, and RFA are likely to reflect potential clinical perspective for solid tumors.[2,6,14] In a word, no matter which strategy is used, the application of RIT aims to achieve a higher ratio of tumor-to-normal tissue (T/NT) of RIT agents, which might result in an anticipatory therapeutic response.

Conventionally, RIT uses MABs to bind cell-surface tumor-associated antigens. In contrast, the tumor necrosis therapy (TNT) antibody targets intracellular nuclear antigens that exist throughout tumors at sites of degenerating and necrotic cells. Some previous studies have already demonstrated its practical applicability experimentally and clinically.[15–19] RFA has been demonstrated to be an effective method for some small or early-stage solid tumors, the thermal damage of which can result in peripheral degeneration and central necrosis of solid tumors.[20–23] On the basis of these theories, we assumed that an artificial necrosis induced by RFA inside solid tumors might be an ideal targeting site for the TNT antibody, which might improve its T/NT accordingly.

The aim of the present study was to test the hypothesis whether intratumoral $^{131}$I-chTNT injection after RFA can improve the T/NT. For this purpose, we designed the following study on rabbits bearing $VX_2$ tumors.

## Materials and Methods

### *Animal model*

All experiments had institutional animal care and obtained the approval from the university animal research committee. A total of 18 New Zealand white rabbits, each weighing 2.0–2.7 (2.23 ± 0.42) kg, were purchased from the Laboratory Animal Center and housed in the Laboratory Animal Center of the institution. Food and water were given ad libitum. A $VX_2$ tumor tissue (courtesy of the Laboratory Animal Center of Sun Yat-Sen University) was cut into pieces less than 1 $mm^3$ in size under sterile conditions. The fragments of tumor tissue were kept in 4°C in a Hanks solution. All the recipient rabbits were anesthetized by injection with 3% of the pentobarbital solution (1 mL/kg) through the ear vein, and the right thigh of rabbits were shaved and prepared with povidone–iodine, 0.5 mL $VX_2$ tumor tissue suspension (containing 3–5 fragments) was injected into the right thigh muscle of each rabbit using a 16-gauge trocar.

After the $VX_2$ tumor was implanted successfully, all the rabbits were randomly allocated to two groups on the basis of the random number generation method; those were, the control group (intratumoral injection of $^{131}$I-chTNT alone) and the RFA group (RFA + intratumoral injection of $^{131}$I-chTNT 3 days after RFA). Nine rabbits were allocated in each group. When the tumors developed to the expected size, the rabbits in the two groups were further randomly and equally assigned to three subgroups I, II, and III (1–2 cm, 2–3 cm, and 3–4 cm in maximum diameter, respectively), by the tumor size and underwent treatment thereafter. On days 1, 8, and 15 after $^{131}$I-chTNT injection, all rabbits underwent SPECT scanning for investigating the whole-body distribution of $^{131}$I-chTNT.

### *Treatment*

All rabbits received a solution of potassium iodine orally, beginning 3 days before treatment and continuing until 15 days after $^{131}$I-chTNT injection, to block the uptake of $^{131}$I by the thyroid. The rabbits were fixed on the bed in left lateral decubitus and anesthetized with intravenous injection of 3% pentobarbital sodium (1 mL/kg), then $^{131}$I-chTNT injection or RFA under the guidance of ultrasound (US) was performed.

### *Ultrasound*

The US system was a Sonosite US unit (M-Turbo Ultrasound system; Sonosite, Inc., Bothell, WA). US equipped with a 13-6 MHz transducer was applied in the experiment for monitoring tumor growth, puncture guidance, and measuring the tumor volume according to the following formula: $\pi \cdot xyz/6$ (x, y, z were the three orthogonal greatest dimensions of the $VX_2$ tumors, respectively).

### *Radiofrequency ablation*

RFA procedures were performed using a Cool-tip system (Valleylab, Boulder, CO), which consists of a radiofrequency generator with a maximum power of 200 W, a 20-cm-long 17-gauge internally cooled electrode with a 3-cm active tip, and two dispersive grounding pads. The electrode contains two lumina, which enables the circulation of cooled saline solution in the tip of the shaft. A steady flow pump (Valleylab) is used to push the chilled saline solution circulating within the lumina of the electrode shaft at 30 mL/min, and the radiofrequency electrode temperature is maintained at less than 21°C.

A radiofrequency electrode was inserted into the tumor percutaneously under US guidance. Grounding pads were attached on the depilated back of each rabbit for RFA. Single application of energy was manually adjusted at 50 W for 3 minutes.

### *$^{131}$I-chTNT injection*

$^{131}$I-chTNT (Vivatuxin, Shanghai Medipharm Biotech Co. Ltd, Shanghai, China) is a radiolabeled recombinant human–mouse chimeric TNT (chTNT) MAB. The purified chTNT antibody with purity of at least 98% is radiolabeled with $Na^{131}I$, which has an average radioactive range of 2 mm in tissue and a half-life of 8 days. The purity of $^{131}$I-chTNT is over 95% with a specific radioactivity of about 10 mCi/mL (370 MBq/mL).[17,24]

$^{131}$I-chTNT was injected into the $VX_2$ tumor by using a 22-gauge fine needle at a dose of 1.4 $mCi/cm^3$ $VX_2$ tumor. This dose was calculated according to the reported formula for dose translation based on the body surface area by Reagan-Shaw et al.[25] The US guidance made sure of the accurate placement of the needle along the periphery of the tumor at multiple sites (0, 3, 6, 9 o'clock direction), monitored the $^{131}$I-chTNT injection, and observed its distribution in the $VX_2$ tumor simultaneously. After injection of $^{131}$I-chTNT, a following 0.5 mL of normal saline was applied to flush the needle path, and the puncture site was gently compressed using alcoholic cotton gauze for 2 minutes to avoid leakage of $^{131}$I-chTNT or bleeding after withdrawal of the needle.

### *SPECT imaging*

On days 1, 8, and 15 after $^{131}$I-chTNT injection, all rabbits were fixed on the examination bed in a prone position and underwent a whole-body scanning on SPECT/CT (Symbia

T2 SPECT/CT system, Siemens Munich, Germany). The acquisition parameters for whole-body scanning were used as follows: high-energy parallel-hole collimators, 20% energy window at 364 keV photon peak, 10 cm/min for whole-body scanning speed. The whole-body distribution of radionuclide imaged on SPECT (anterior and posterior images) was analyzed by an experienced radiologist. Regions of interest (ROIs) of tumor, thyroid, and normal tissue (the homogenous abdominal area) were drawn on the anterior image, then the mean K count of ROIs was used to calculate T/NT and the ratio of thyroid to normal tissue (THY/NT).

After the whole-body scanning on day 1, a supplemental SPECT/CT fusion image acquisition was performed to investigate whether $^{131}$I-chTNT was injected accurately into the tumor and to confirm the anatomic location of the jugular high radioactive spot detected on the SPECT whole-body scanning. The acquisition parameters for SPECT/CT fusion image were used as follows: zoom 1.5, a $128 \times 128$ matrix with a pixel size of 4.8 mm, 6°/step for 180° rotating for 30 second/step acquisition, the fusion CT acquisition used full-circle rotation, 130 kV, 35 mAs, and 5-mm slices. SPECT/CT reconstruction was performed under the integrated multimodality image fusion system.

### *Statistical analysis*

Continuous data are expressed as mean ± standard deviation. Repeated measures analysis of variance (ANOVA) and Pearson's correlation analysis were used to perform the data analysis. Two-tailed $p < 0.05$ was considered to indicate statistical significance. SPSS software (version 16.0; SPSS, Inc., Chicago, IL) was used to perform the statistical analysis.

## Results

Both of the two groups received intratumoral $^{131}$I-chTNT injection at a dose of 1.4 mCi/cm$^3$ tumor. The US guidance guaranteed the accuracy of $^{131}$I-chTNT injection. In the RFA group, $^{131}$I-chTNT injection was given on day 3 after RFA. Unlike the control group, no obvious tumor progression in the RFA group was found until day 6–12 after RFA. Until the end of the follow-up (day 15 after $^{131}$I-chTNT injection), no rabbit death or severe complications were encountered.

After $^{131}$I-chTNT injection, the SPECT whole-body scanning (Fig. 1) and the fusion images were acquired successfully from all rabbits. On day 1, the typical outline of the rabbit with the two high radioactive spots was displayed on

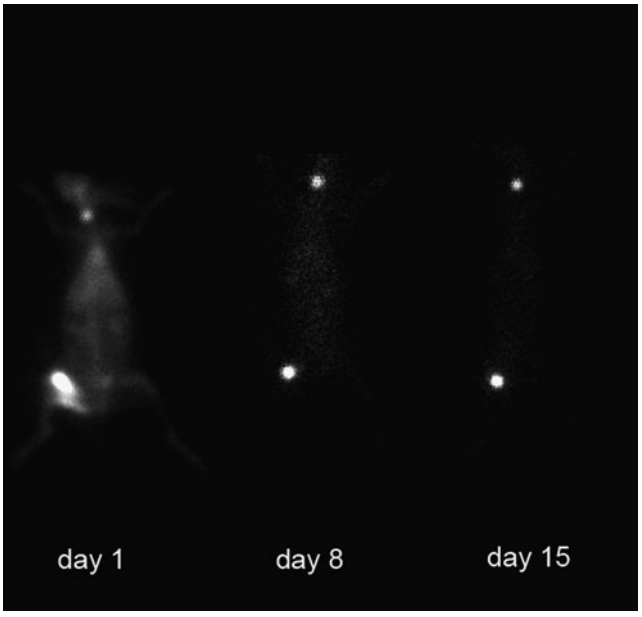


**FIG. 1.** A typical outline of a rabbit in the radiofrequency ablation group with two spots displayed on whole-body SPECT images on days 1, 8, and 15.

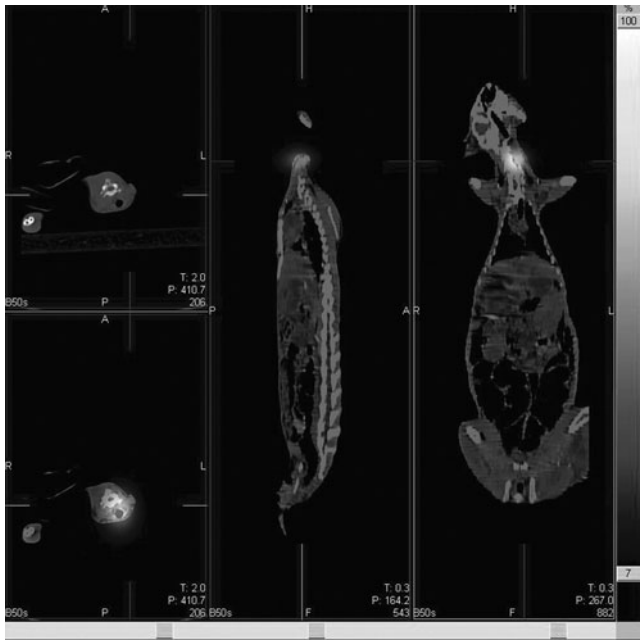

**FIG. 2.** The fusion images illustrate that the jugular high radioactive spot is the high concentration of $^{131}$I-chTNT absorbed by thyroid.

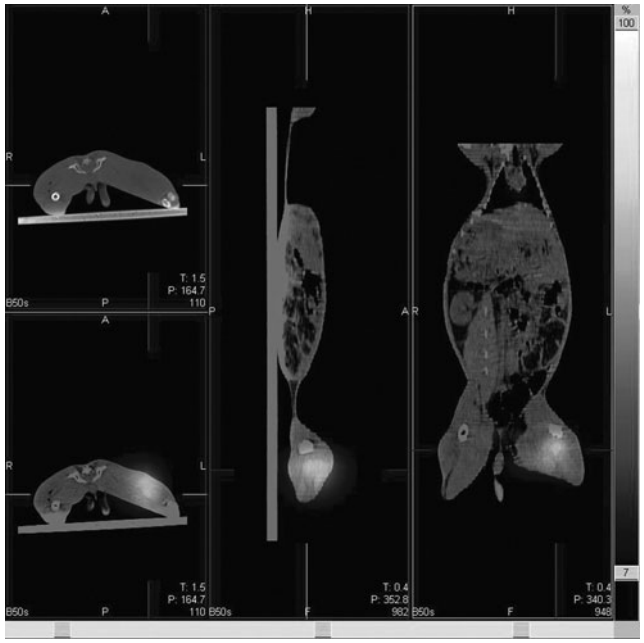

**FIG. 3.** The fusion images show the high radioactive spot on the rabbit's right thigh precisely overlaps with the tumor.

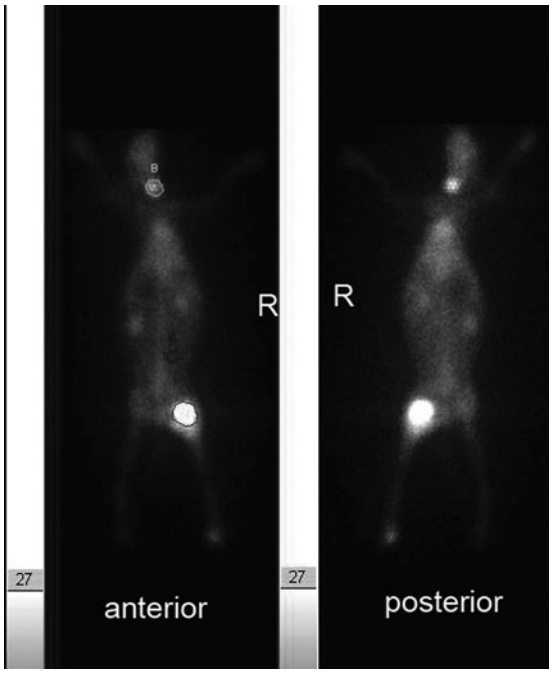


**FIG. 4.** The regions of interest (ROIs) are draw on the anterior image for calculating the ratio of tumor to normal tissue (T/NT) and the ratio of thyroid to normal tissue (THY/NT).

the whole-body SPECT images. The fused SPECT/CT images demonstrated that the jugular high radioactive spot was the thyroid (Fig. 2) and the intratumoral injected $^{131}$I-chTNT was displayed as another high radioactive spot on the right thigh (Fig. 3). There was no macroscopic difference between the two groups on day 1. On day 8, the whole-body SPECT images showed that the two high radioactive spots were still conspicuous, whereas the outline of the rabbit was blurred. On day 15, there were some obvious macroscopic variations on the whole-body SPECT images, and the outline of the rabbit was hardly discernible, especially for the rabbits in subgroup I of the two groups. The radioactivity of tumor in the control group dramatically decayed in comparison with that in the RFA group; even in a rabbit in subgroup I of the control group, the radioactivity of tumors could not be detected (the default T/NT was 1). However, the thyroids of the rabbits in the two groups showed remarkable uptake of radioactive iodine.

On the basis of the mean K count of ROIs on the whole-body images (Fig. 4), T/NT and THY/NT were calculated and listed in Table 1 and Table 2, respectively.

The analysis results with repeated measures ANOVA showed that the T/NT in the RFA group ($55.45 \pm 41.83$) was significantly higher than that in the control group ($7.23 \pm 5.61$) ($F = 18.89$, $p = 0.001$); the variation of T/NT among different subgroups (different size tumors or at different doses of $^{131}$I-TNT injection) was not significantly different ($F = 0.66$, $p = 0.54$); the variation of T/NT at follow-up time points (days 1, 8, and 15) was significantly different ($F = 7.61$, $p = 0.003$); meanwhile, the variation trend of T/NT between the two groups during follow-up was significantly different ($F = 8.37$, $p = 0.002$), T/NT in the RFA group ascended along with the follow-up time ($r = 0.47$, $p = 0.01$), while no linear trend was found for T/NT in the control group along with the follow-up time ($r = -0.03$, $p = 0.87$); the variation trend of T/NT among the subgroups during follow-up was not significant ($F = 0.75$, $p = 0.57$); there was no group (treatment) × subgroup (the dose of $^{131}$I-TNT injection) interaction ($F = 0.37$, $p = 0.70$).

At the same time, the analysis results with repeated measures ANOVA showed that the variations of THY/NT between the groups or among the subgroups were not significantly different ($F = 4.25$, $p = 0.06$; $F = 0.53$, $p = 0.60$, respectively); while the variation of THY/NT at follow-up time points (days 1, 8, and 15) was significantly different ($F = 7.61$, $p = 0.003$); the group × time interaction, the subgroup × time interaction, and the group × subgroup interaction, all were not significantly different ($F = 2.97$, $p = 0.07$; $F = 0.77$, $p = 0.55$; $F = 0.19$, $p = 0.83$, respectively). The same ascending linear trend was found for the THY/NT along with the follow-up time ($r = 0.42$, $p = 0.002$).

## Discussion

The abilities to kill the tumor cells selectively and avoid damage to normal tissue are the essential characteristics of RIT, which mainly depends on the specificity of MAB.[2,8] At present, a number of MABs have been developed for RIT, and several isotopes have been successfully tested and applied to antitumor therapy.[2,8,12,26,27]

In this study, the radioactive iodine ($^{131}$I) labeled MAB (-chTNT), as RIT agents, was applied to treat the solid tumor ($VX_2$ tumor). $^{131}$I is a mixed $\beta$-$\gamma$ emitter with a half-life of 8 days. The short-range $\beta$ ray is the major cytotoxic radiation and can induce the tumor necrosis; the long-range $\gamma$ ray can be imaged on SPECT for observing the biodistribution of $^{131}$I.[2,26,28] The TNT antibody can bind specifically to the nuclear antigens of the degenerated cells, regardless of the origin of cells. Once binding with the necrotic tissue, $^{131}$I-chTNT will be cytotoxic to adjacent viable tumor cells.[16,17,24]

Table 1. The Ratio of Tumor-to-Normal Tissue in the Control and the Radiofrequency Ablation Groups

| | *Control group* | | | *RFA group* | | |
|---|---|---|---|---|---|---|
| | *Day 1* | *Day 8* | *Day 15* | *Day 1* | *Day 8* | *Day 15* |
| Subgroups | | | | | | |
| I | $3.21 \pm 1.18$ | $10.76 \pm 4.04$ | $7.59 \pm 6.35$ | $34.23 \pm 26.08$ | $62.47 \pm 32.98$ | $59.02 \pm 26.50$ |
| II | $5.68 \pm 3.88$ | $4.89 \pm 3.72$ | $3.99 \pm 3.27$ | $23.57 \pm 10.28$ | $49.76 \pm 34.15$ | $58.22 \pm 23.80$ |
| III | $13.98 \pm 8.98$ | $5.04 \pm 1.97$ | $7.66 \pm 7.10$ | $23.54 \pm 20.74$ | $83.47 \pm 74.73$ | $104.75 \pm 61.00$ |
| Total | $7.23 \pm 5.61$ | | | | $55.45 \pm 41.83$ | |

Control group: $^{131}$I-chTNT alone; RFA group: RFA + $^{131}$I-chTNT combination.

Table 2. The Ratio of Thyroid-to-Normal Tissue in the Control and the Radiofrequency Ablation Groups

| | *Control group* | | | *RFA group* | | |
|---|---|---|---|---|---|---|
| | *Day 1* | *Day 8* | *Day 15* | *Day 1* | *Day 8* | *Day 15* |
| Subgroups | | | | | | |
| I | 1.67 ± 0.34 | 4.73 ± 2.75 | 8.24 ± 9.13 | 1.96 ± 0.58 | 14.78 ± 14.73 | 14.20 ± 14.65 |
| II | 1.20 ± 0.32 | 3.76 ± 0.62 | 2.64 ± 0.97 | 2.39 ± 1.38 | 8.56 ± 6.29 | 11.15 ± 5.79 |
| III | 1.40 ± 0.55 | 4.42 ± 1.70 | 6.97 ± 5.71 | 1.83 ± 0.66 | 14.55 ± 13.39 | 23.95 ± 21.76 |
| Total | | 3.89 ± 3.94 | | | 10.38 ± 11.87 | |

Control group: $^{131}$I-chTNT alone; RFA group: RFA + $^{131}$I-chTNT combination.

At present, RIT for solid tumors still has not produced satisfactory responses. One of the main reasons is the relatively low target concentration of RIT agents.[2,8] For consideration of the excessive hematopoietic toxicity and other side effects, the administration dose was strictly limited. The improvement of T/NT indicates a better efficacy of RIT for solid tumor. Conventionally, most of the RIT agents are administrated systemically through oral or intravenous injection, then are diluted by the circulation, and distributed into the whole body, which results in undesirable low T/NT (low target concentration). The locoregional route is preferable for the short-lived radionuclides when targeted by antibodies because using the intravenous route results in significant radionuclide decay before the antibody reaches its target.[12] Therefore, the RIT agents were tentatively administrated locally through the tumor supply blood vessel and some clinical studies using RIT ($^{131}$I-Metuximab administrated through hepatic artery intubation) for hepatocellular carcinoma showed promising efficacy.[29–32] However, the T/NT was observed to be only 0.7–2.7.[30,31] If the T/NT can be improved, the tumor response will be more encouraging. In addition, in the treatment of hepatic metastases with RFA before $^{131}$I-chTNT-1/B infusion, Anderson et al. reported that an average target to the background ratio of 2.9 (ranged from 1.3 to 6.0) was observed at the 3th day after $^{131}$I-chTNT-1/B infusion.[33] It is critical to alleviate or avoid the effect of the circulation dilution and clearance and directly delivering the RIT agents to the target tumor can solve this problem. In a phase II clinical trial in China, 43 patients with advanced lung cancer were treated with administration of $^{131}$I-chTNT through intravenous and intratumoral injection, the intratumoral injection group (T/NT = 14.6, $n$ = 15) showed a higher T/NT and higher efficacy than the intravenous injection group (T/NT = 1.36, $n$ = 19).[24] Although there is no comparability between these previous studies, the contribution of intratumoral injection to the improvement of T/NT is significant.

Similarly, in this study, the mean T/NT in the control group was not high enough (just 7.23), because the $VX_2$ tumor has rich blood supply, the washing of blood still plays a role locally as the effect of the circulation dilution and clearance; furthermore, because of the absence of necrosis, most of the $VX_2$ tumor in the control group has no ideal target site for $^{131}$I-chTNT to dock and lock; thus, on SPECT images, the radioactivity of tumors in the control group faded quickly, especially close to the late period of follow-up. By comparison, T/NT (55.45) in the RFA group improved dramatically and contributed to the effect of RFA significantly. This result not only embodied the expectant characteristics of RIT, but also presented a potential application in clinic. The tumor size and the administration dose of $^{131}$I-chTNT had no significant effect on the improvement of T/NT. Moreover, the T/NT in the RFA group, unlike in the control group, showed an ascending trend during the follow-up. It can be inferred that intratumoral injection after RFA can not only increase the target concentration of $^{131}$I-chTNT, but also prolong its intratumoral retention time. These results were mainly caused by two factors induced by RFA: the first is that RFA induces tumor necrosis, which provides the target site for $^{131}$I-chTNT; and the second is that RFA destroys the tumor blood vessel so that it decreases the effect of the circulation dilution and clearance.

In addition, although previous blockade by using potassium iodine orally in this study, radioactive iodine uptake in the thyroid, unlike that seen in patients, was unavoidable in rabbits. The results showed that the administration dose of $^{131}$I-chTNT and treatment both had no impact on the variation of TYH/NT, which in both groups also showed the same ascending trend during the follow-up. These phenomena like T/NT in the RFA group, we thought, were attributed to the decrease of radioactive iodine in the normal tissue; the macroscopic SPECT images also illustrated these phenomena, which mainly resulted from circulating dehalogenated iodine absorbed by thyroid and circulating $^{131}$I-chTNT reabsorbed by necrotic tumor tissue, except for the physical decay and metabolic clearance.[26] As far as the influence of iodine absorbed by the thyroid is concerned, if it can be avoided, the results will be more compelling. Based on such advantages, we believe that $^{90}$Y might be a better alternative choice for solid tumor RIT in future studies.[26]

Although the results of T/NT were encouraging, several limitations in this study should be mentioned: first, the biodistribution of $^{131}$I-chTNT only expressed by using T/NT, the precise dosimetric investigations of $^{131}$I-chTNT biodistribution in tumor and organs were not available due to the technical limitation; second, the inadequate blockade of thyroid may lead to bias of the results of T/NT; third, the detailed contribution to the improvement of T/NT is not clear; thus, in future studies, the therapeutic effects of $^{131}$I-chTNT and its retention in tumor tissue need to be addressed to evaluate the potential application of this combination therapy, by comparing the tumor's volume and adding the RFA alone group as control. Finally, the detailed mechanism of RFA in improving the T/NT ratio of $^{131}$I-chTNT should be further explored by injecting a nonbinding radiolabeled antibody or free iodine-131.

## Conclusion

RFA before intratumoral injection of $^{131}$I-chTNT can dramatically improve the T/NT, demonstrating the potential application of this combination therapy.

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## Disclosure Statement

No financial conflict of interests exist.

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