Original paper

Effectiveness and safety of a robot-assisted 3D personalized template in ^{125}I seed brachytherapy of thoracoabdominal tumors

Xiaodong Ma, PhD[1], Prof. Zhiyong Yang, MD[1], Prof. Shan Jiang, MD[1], Prof. Bin Huo, MD[2], Qiang Cao, MD[2], Prof. Shude Chai, MD[2], Prof. Haitao Wang, MD[2]

[1]School of Mechanical Engineering, Tianjin University, Tianjin, [2]Department of Oncology, the Second Hospital of Tianjin Medical University, Tianjin, China

Abstract

Purpose: This research aims to evaluate the effectiveness and safety of a robot-assisted 3D personalized template in ^{125}I seed brachytherapy of thoracoabdominal tumors.

Material and methods: Forty-three patients with different tumors were involved in this research between 2013 and 2015. They were all eligible to ^{125}I seed implantation based on robot-assisted 3D personalized template. Meanwhile, 51 patients with similar tumors, which were treated with a conventional coplanar template, were involved for comparison. Follow-up was carried out after the surgery to evaluate the therapeutic efficacy, including overall survival (OS) of the patient and local control (LC) of the tumor. Complications were also summarized to evaluate the safety. Besides, statistical analysis was achieved to investigate possible factors associated with the result.

Results: In the robot-assisted 3D personalized template-guided brachytherapy, the median target volume treated by the prescription dose (V_{100}) was 95.3% (range, 92.4-109.8), and the median dose administered to 90% of the target volume (D_{90}) was 126.1 Gy (range, 114.2-132.0), improved 5% and 8% compared with the conventional template-guided brachytherapy, respectively. The median OS was 30 months (95% CI: 19.4-40.6) and the rates of 2-year OS and LC were 58.1% and 86.0%, respectively. The median OS was prolonged 10 months and the 2-year OS and LC were improved 18.9% and 23.3% compared with the conventional template-guided brachytherapy, respectively.

Conclusions: Through analysis of the selected patients with thoracoabdominal tumors, the robot-assisted 3D personalized template in ^{125}I seed brachytherapy was a more effective and safer method. It can achieve a more favorable OS and LC.

J Contemp Brachytherapy 2018; 10, 4: 368–379
DOI: https://doi.org/10.5114/jcb.2018.77957

Key words: brachytherapy, 3D personalized template, robot-assisted, seed implantation, thoracoabdominal.

Purpose

Malignant tumors are the second leading cause of deaths in the United States, and expected to surpass heart disease as the first factor leading to death [1]. In China, it is becoming one of the leading cause of deaths and an important public health issue. Among the malignant tumors, the incidence and mortality of lung cancer are the highest, followed by liver cancer, gastric cancer, and esophageal cancer [2], and they are all located in thorax and abdomen. Currently, chemotherapy, surgical resection, and radiotherapy are the standard treatment methods for malignant tumors. It is known that different treatment methods have different indications. The same tumor may have different sensibilities to different treatment methods, leading to a different therapeutic effect. Chemotherapy, such as targeted therapy, is an emerging cancer treatment and has great effectiveness for patients with advanced metastases. But the treatment effect will vary due to the unique physique of each person, and chemotherapeutic agents usually have serious side effects on the patient [3,4,5]. Similarly, surgical resection will bring greater trauma to the patients' body and thus cause complications to the patient [6,7]. For a long time, radiotherapy was also one of the treatment methods for cancers because it is suitable for a variety of indications. External beam radiation was the main method of radiotherapy but it causes damage to the normal tissue around the tumor [8]. With the development of medical equipment and technology, three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT) make great achievements in cancer treatment and greatly improve the precision of radiotherapy.

Address for correspondence: Prof. Shan Jiang, MD, School of Mechanical Engineering, 92 Weijin Road, Nankai District, 300350 Tianjin, China, School of Mechanical Engineering, Tianjin University, Tianjin, China, phone: + 86-22-85356612, ✉ e-mail: shanjmri@tju.edu.cn

Received: 13.04.2018
Accepted: 10.08.2018
Published: 31.08.2018

^{125}I seeds implantation as a form of precise radiotherapy for cancer treatment has a history of over 100 years and has been applied to various solid tumors [9,10,11,12,13]. Compared with the conventional treatment, it has three advantages. Firstly, the irradiation affects only a very localized area around the radiation sources. Exposure to radiation of healthy tissues farther away from the sources is therefore reduced. In addition, if the patient moves or if there is any movement of the tumor within the body during treatment, the radiation sources retain their correct position in relation to the tumor. These characteristics of brachytherapy provides advantages over external beam radiotherapy: the tumor can be treated with very high doses of localized radiation while reducing the probability of unnecessary damage to surrounding healthy tissues. Secondly, a permanent implantation. Once the seeds are implanted into the tumor, it can provide continuous irradiation dose. Therefore, the patient does not require multiple hospitalizations for treatment. It has been proved that ^{125}I seed brachytherapy was feasible with minimal radiation-related morbidity [14,15,16].

In the ^{125}I seed brachytherapy, the conventional coplanar template (CCT) is usually selected as a guiding tool [17]. With this template, the needles can be punctured along the planned paths. But all the needles are in a fixed direction, perpendicular to CCT. To overcome this drawback, the 3D personalized template (3DPT) was developed. It is a non-coplanar template, reconstructed from the patient computed tomography (CT) images and dose planning results. The direction of each needle can be designed more individually compared with CCT. In recent years, CCT-guided seed implantation was gradually replaced by 3DPT. Zhang *et al*. [18] successfully performed ^{125}I seed implantation surgeries on thirty-one patients, with recurrent and locally advanced malignant tumors of the head and neck under the guidance of 3DPT. The research demonstrated that this approach can facilitate easier and more accurate implantation with 3DPT in clinical practice. Wang *et al*. [19] used 3DPT to perform surgeries on sixteen patients, with paravertebral and retroperitoneal malignant tumors. Similarly, Wang's group and Han's group performed ^{125}I seed implantation successfully under CT guidance assisted by 3DPT for the treatment of rectal cancer, liver cancer, and cervical lymph node recurrence [20,21,22]. All those clinical reports have achieved great success. Therefore, ^{125}I seed implantation based on 3DPT for cancer treatment is possible. However, the research about the 3DPT focuses mainly on performing clinical surgeries. To our best of knowledge, there were no related evaluations of its effectiveness and safety reported. In this research, the effectiveness and safety of ^{125}I seed implantation based on a robot-assisted 3DPT were evaluated compared with that based on CCT. For this purpose, a variety of comparable surgical cases after receiving ^{125}I seed brachytherapy were selected and analyzed.

Material and methods

Patients

From 2013 to 2015, 93 patients with thoracoabdominal tumors were treated, and 52 of them were eligible for robot-assisted 3D personalized template-guided ^{125}I seed brachytherapy (RTDPTB). Among these 52 patients, 43 patients (82.7%) had complete information on the treatment and follow-up. Therefore, the 43 patients were involved in this analysis. For all the patients, their cancers were confirmed through CT-guided biopsy. All 43 participants treated with RTDPTB were considered as the experimental group. Meanwhile, five years before the 3DPT was applied to ^{125}I seed brachytherapy, there were 108 patients who received conventional coplanar template-guided ^{125}I seed brachytherapy (CCTB), among which 86 (79.6%) patients had complete information on the treatment and follow-up. Out of 86 patients, 51 with similar tumors were selected for comparison, and the 51 patients were considered as the control group. The patients' demographic and clinical characteristics are summarized in Table 1. There were 27 men and 16 women, with median age of 56 years (range, 38-75) in RTDPTB. In CCTB, there were 36 men and 15 women, with median age of 58 years (range, 40-69). The Eastern Cooperative Oncology Group (ECOG) evaluation was 0-1 points in all patients.

Therapeutic method

The robot and 3DPT were developed in our laboratory. In this research, the robot achieved the accurate positioning of 3DPT and the detailed description of the robot is in reference [23]. 3DPT was created in TPS through preoperative planning and saved as "stl" format. Then, the "stl" model was imported into the 3D printing machine (Israel, Stratasys Objet30 pro). The material used for printing 3DPT is a photosensitive resin, with acrylic monomer as the main component. The printing time of a 3DPT is about 15-20 hours, depending on the size of the template. Because whether using CCT or 3DPT in a surgery, there are about two days for preoperative planning and other preparations, and 3DPT can be printed completely during this time. During these two days, no procedure was implemented, whether using CCTB or RTDPTB, so there was no impact on the treatment delivery. The advantage of 3DPT was the ability to match well with the patient's skin, as shown in Figure 1. Using 3DPT, the entry and path of needles were easily determined to avoid damage of vital structures such as large vessels. Before surgery, the low-temperature disinfection method was used to deal with 3DPT. Then, 3DPT was fixed on the end effector of the robot.

Seed implantation

^{125}I seeds used in the surgery were provided by China Institute of Atomic Energy (Beijing, China). The internal dimension of the sliver rod is 3.0 mm x 0.5 mm and the thickness of the titanium capsule is 0.05 mm. The median radioactivity of the seed was 2.59×10^7 Bq or 0.7 mCi (range, $2.22–2.96 \times 10^7$ Bq or 0.6-0.8 mCi) and the energy was 27-35 keV, half-life 59.4 days. Before the surgery, the radioactivity was determined using an activity meter (CRC-15).

Preimplantation preparation

Before the seed implantation surgery, patients received a CT scanning based on a thickness of 2.5 mm. During the

Table 1. Patient characteristics

Characteristics	RTDPTB	CCTB	*p*-value
	Number of patients (%)	Number of patients (%)	
Gender			0.429
Male	27 (63)	36 (70)	
Female	16 (37)	15 (30)	
Median age (range)	56 (38-75)	58 (40-69)	0.649
Tumor size (cm^3)			0.772
≤ 30	19 (44)	21 (41)	
> 30	24 (56)	30 (59)	
Diagnosis			0.723
Lung cancer	8 (19)	12 (24)	
Pancreatic cancer	8 (19)	10 (20)	
Gastric cancer	5 (11)	7 (14)	
Pulmonary atelectasis*	3 (7)	2 (3)	
Hepatocellular carcinoma	8 (19)	7 (14)	
Rectal carcinoma	5 (11)	6 (12)	
Renal carcinoma	6 (14)	7 (13)	
ECOG evaluation			0.669
0	28 (65)	31 (61)	
1	15 (35)	20 (39)	
Therapeutic efficacy			0.016
CR	20 (47)	19 (38)	
PR	17 (39)	16 (32)	
SD	3 (7)	9 (17)	
PD	3 (7)	7 (13)	

*RTDPTB – robot-assisted 3D personalized template-guided ^{125}I seed brachytherapy, CCTB – conventional coplanar template-guided ^{125}I seed brachytherapy, CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease, * – induced by lung cancer*

CT scanning, the patient was wrapped in a negative pressure vacuum pad in order to maintain the patient's posture before surgery and remain unchanged during surgery. It should be noted that some markers were attached on the patient skin. The markers are metal balls, less than 1 mm in diameter, and the location of the marker is aligned with the laser line in the CT room. The negative pressure vacuum pad is used to maintain the patient's posture. The markers and the laser line are used to record the position of the patient on CT table. The repositioning process was completed by the markers, laser line, and the negative pressure vacuum pad. CT data was saved and exported in DICOM format.

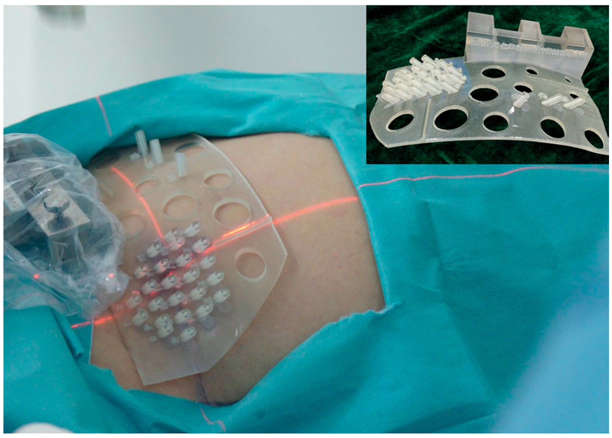

Fig. 1. Printed 3D personalized template matches well with the patient's skin

Implantation plan

The seed implantation plan was achieved using the Body Tumor Brachytherapy Treatment Planning System (BT-BTPS, Tianjin University, Tianjin, China), which was the latest research achievement in our laboratory. The dose calculation in BT-BTPS uses the formalism of "TG43" according to recommendations by the American Association of Physicists in Medicine [24,25]. In this surgery, BT-BTPS will achieve the following steps [13]: 1. Read information from CT images (Figure 2A); 2. Outline gross tumor volume (GTV), clinical target volume (CTV), and planning

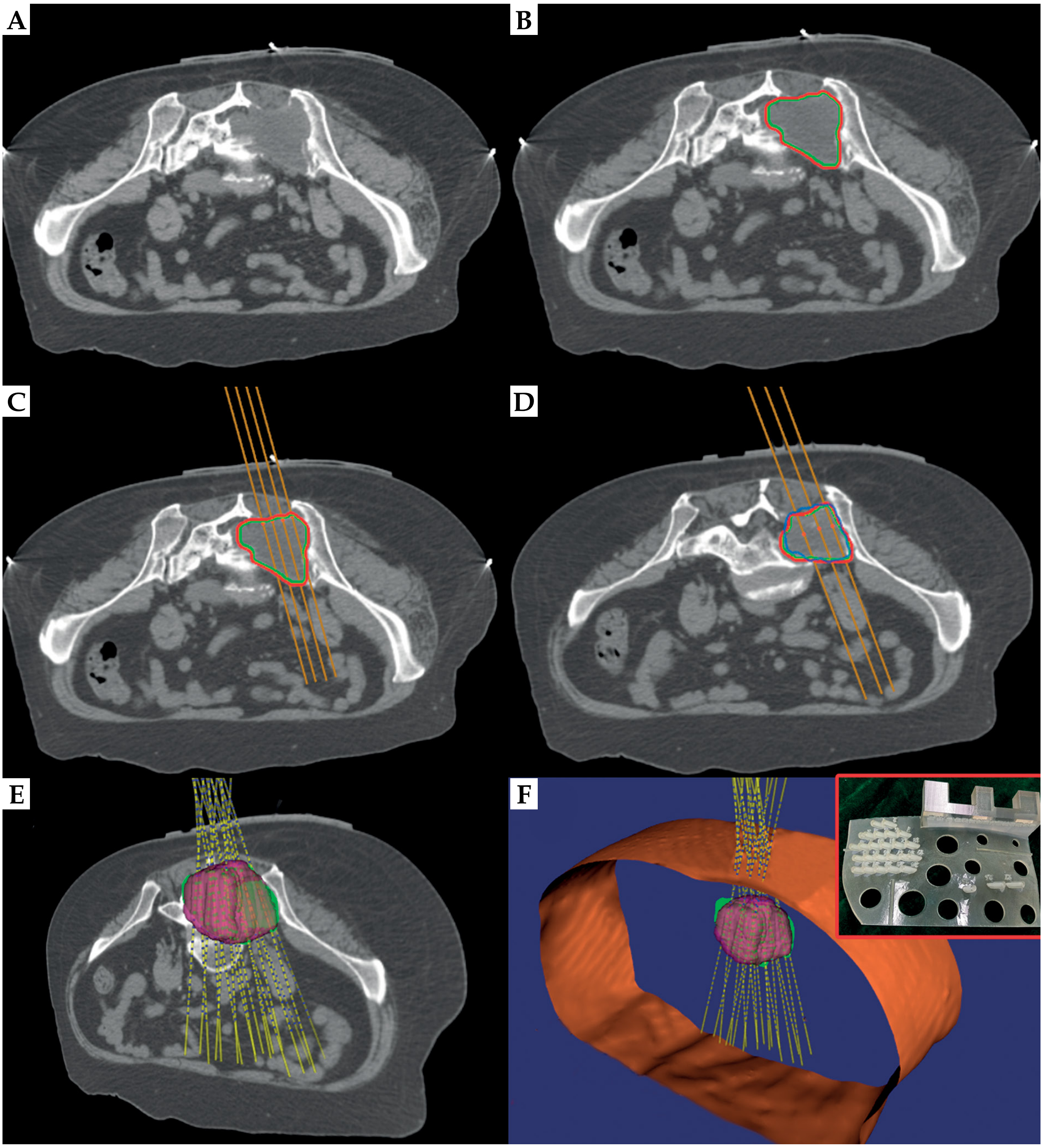

Fig. 2. The steps of BT-BTPS in the ^{125}I seed implantation surgery: **A)** BT-BTPS read and displayed CT images; **B)** The tumor target was segmented and reconstructed in the system; **C)** The needle directions were designed to avoid the bones and vital organs; **D)** ^{125}I seeds were simulated to be implanted in the tumor along the needle paths, and the isodose (blue line) was displayed to evaluate whether the target was covered by the dose; **E)** Three-dimensional view of the implantation plan. Twenty-seven non-parallel needles were designed and 72 ^{125}I seeds were implanted. 100% PTV (the green area) was covered by the prescription dose (the purple area); **F)** After all needles were determined, the patient's skin was extracted from CT images and converted to the 3D printing machine

target volume (PTV); 3. Reconstruct the tumor target and vital organs (Figure 2B); 4. Design the needle direction for seed implantation and avoid vital organs at the same time (Figure 2C); 5. Show a real-time display of the isodose line and isodose surface (Figures 2D and 2E); 6. Extract the patient's skin data to create 3DPT (Figure 2F). In step 4, when designing a needle paths, the bones and vital organs should be avoided, and interference between needles in different slices should also be eluded. Under the above conditions, it is recommendable to choose the needle path where the tumor is closer to the skin. In step 6, 3DPT was created through clipping the patient's skin. Since the positions of the tumor target and the needle were determined before, 3DPT can be guaranteed to cover the tumor target completely by clipping the skin. That is to say, 3DPT showed an advantage that it was customized according to the specific requirement of every patient, while the shape and size of CCT are unalterable. Moreover, TPS can calculate the number of seeds and needles as well as the depth of every needle. To meet the requirements of dose calculation and the dose optimization, prescription dose D_{90} was set to 110-140 Gy. In this research, the dose optimization is achieved manually using the dose–volume histogram (DVH). The DVH should meet the following conditions: $V_{100} > 90\%$, $V_{150} < 50\%$, $V_{200} < 20\%$. In this process, the radio-oncologist needs to adjust the position of needles and seeds repeatedly to meet those requirements.

Therapeutic process

The patient was placed under local anesthesia, and the needles were punctured under the guidance of 3DPT. Before the seed implantation, 3DPT was positioned and attached on the skin with the assistance of a robot. The feasible workflow of the robot in positioning the template was described as follows. In the process of template positioning, there were two positions of the template to be determined: the initial position (IP) and target position (TP), as shown in Figure 3. Firstly, the patient and the robot (3DPT was clamped on the robot) are located on the CT table. A CT scanning (1st CT scanning) is performed for the patient and the template together. Secondly, CT images are transferred to BT-BTPS. The position of the template can be clearly identified in CT images and this is IP of the template. Before that, TP was determined in the preoperative planning. After the preoperative planning, we can get a template in BT-BTPS, and this position is TP. Finally, the relative position of IP and TP can be determined easily. In the template positioning, we sent the relative position of IP and TP to the robot, and the template can be moved from IP to TP.

In the template positioning process above, a new technology was involved. It is easy to find that IP is in the actual space, and TP is in the image space. The problem that needs to be solved is how to unify the positions of these two spaces into the same space. In this research, the relative position of the robot and the patient was kept unchanged, and a CT scanning was performed for the patient and the template (fixed on the end effector of the robot) together. Thus, IP and TP were all in the image space. It is easy to get the relative position of IP and TP in BT-BTPS, and control the robot to move the template from IP to TP.

During the surgery, the doctor inserted needles through the guiding holes on the template. Next, ^{125}I seeds were implanted in the tumor target through the needles. The seed positions in the needle were calculated in the BT-BTPS, and the seeds interval in the same needle was at least 1.0 cm. Standardized treatment was carried out after the seed implantation surgery to prevent bleeding and infection.

Therapeutic evaluation

Post-operative validation

After implanting all seeds, a CT scanning was performed to verify whether the seeds were in the expected position. The CT images after implantation were imported to BT-BTPS. The radio-oncologist outlined the tumor target and identified all the seeds in CT images, so that the seeds could be clearly observed in three dimensions. Through displaying the isodose line, it could be observed, whether the PTV has been covered by the prescription dose. The actual dose distribution in the tumor target was evaluated using DVH. The DVH was compared with the implantation plan.

DVH evaluation

In this research, conformity index (CI) [26,27] and homogeneity index (HI) [28] were analyzed to establish their association with OS and LC. CI and HI were calculated using the DVH in the post-operative validation and the formulas were shown in Eq. (1) and Eq. (2).

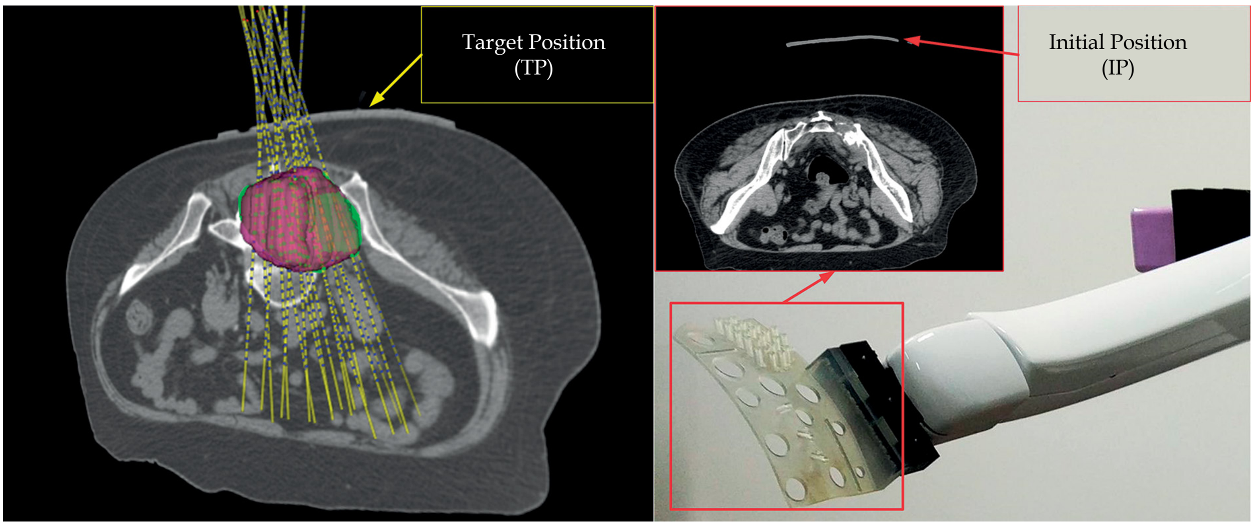

Fig. 3. The process to get the initial position and target position

$$CI = \frac{V_{T,\text{ref}}}{V_T} \times \frac{V_{T,\text{ref}}}{V_{\text{ref}}} \quad (1)$$

$$HI = \frac{D_2 - D_{98}}{D_{\text{ref}}} \times 100\% \quad (2)$$

Where V_T was the total volume of the GTV; V_{ref} was the total volume covered by the prescription dose isodose surface; $V_{T,\text{ref}}$ was the total volume of the GTV covered by the prescription dose isodose surface; D_2 was the dose received by 2 percent of the GTV, regarded as the maximal dose; D_{98} was the dose received by 98 percent of the GTV, regarded as the minimal dose; D_{ref} was the prescription dose in this plan.

Follow-up and statistical analysis

Follow-up was carried out every two months for the first year and every 6 months thereafter, including CT scanning, physical examination, and radiography. The changes in tumor size can be evaluated using the CT images. In this paper, the response evaluation criteria in solid tumors (RECIST) was used to evaluate the target lesions [29]. In this response, criteria were defined as: complete response (CR: disappearance of all target lesions); partial response (PR: at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter); stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started); progressive disease (PD: at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions). The recurrence mostly occurs within 2 years after the surgery and the diagnosis was confirmed by histopathology whenever required. Overall survival (OS) was calculated as the interval between the date of ^{125}I seed brachytherapy and that of death, and if the patient was still alive, OS was censored by the last follow-up data. Local control (LC) was calculated from the date of ^{125}I seed brachytherapy to the recurrence. OS and LC were estimated by the Kaplan-Meier method using the statistical product and service solutions (SPSS) 25.0 for Windows. The Cox regression was used to analyze the association of OS and LC with other factors. Significant association was confirmed when $p < 0.05$.

Ethical approval of the study protocol

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written informed consent to participate in this study.

Results

Outcome of seed implantation

In every surgery, the implantation plan, positioning of 3DPT, seed implantation, and post-operative validation were completely achieved. The median PTV was 35.21 cm^3 (range, 14.36-102.35). Six to eighteen needles (median, 10) and 27-72 seeds (median, 35) were involved in every surgery to achieve the prescription dose of 110-140 Gy (median, 120 Gy). The time spent on each surgery ranged from 35-51 minutes (median, 42 minutes), while it spent 65-96 minutes (median, 78 minutes) using CCT. The steps of a surgery included CT scanning, positioning of a template, implantation of needles and seeds, and post-operative validation, excluding the preoperative planning and printing 3DPT. Therefore, the surgery time recorded in this research included the time spent on CT scanning, positioning of a template, implantation of needles and seeds, and post-operative validation. In the post-operative validation, the median dosimetry information were as follows: V_{100} was 95.3% (range, 92.4-109.8) and D_{90} was 126.1 Gy (range, 114.2-132.0). All the treatment parameters were summarized in Table 2, including information about CCTB.

Treatment effectiveness

The median follow-up time was 23 months (range, 8-42) and 25 months (range, 8-48) in RTDPTB and CCTB, respectively. The overall treatment effectiveness for all patients was collected and evaluated. In RTDPTB, the median OS was 30 months (95% confidence interval: 11.8-40.2), the median LC was 33 months (95% confidence interval: 28.6-37.4), and the 2-year OS and LC rates were 58.1% and 86.0%, respectively. In CCTB, the median follow-up time was 25 months (range, 8-48). The median OS was 20 months (95% confidence interval: 15.5-24.4), the median LC was 33 months (95% confidence interval: 19.1-46.9), and the 2-year OS and LC rates were 39.2% and 62.7%, respectively. Considering that the mixed tumor population can influence the accuracy and scientificity of

Table 2. Treatment parameters

Parameter	RTDPTB	CCTB
	Median (range)	Median (range)
PTV (cm^3)	35.21 (14.36-102.35)	40.34 (12.05-115.46)
PD (Gy)	120 (110-140)	120 (110-140)
D_{90} (Gy)	126.1 (114.2-132.0)	116.4 (105.1-145.7)
V_{100} (% PTV)	95.3 (92.4-109.8)	90.3 (87.6-115.6)
No. of seeds	35 (27-72)	31 (23-68)
No. of needles	10 (6-18)	13 (7-20)
Seed activity (mCi)	0.7 (0.6-0.8)	0.7 (0.6-0.8)
Time per surgery (min)	42 (35-51)	78 (65-96)
CI	0.93 (0.89-0.96)	0.78 (0.69-0.92)
HI	2.97 (2.18-6.51)	5.46 (3.25-10.36)

RTDPTB – robot-assisted 3D personalized template-guided ^{125}I seed brachytherapy, CCTB – conventional coplanar template-guided ^{125}I seed brachytherapy, PTV – planning target volume, PD – prescription dose, D_{90} – the minimum dose covering 90% of the target volume, V_{100} – the target volume treated by the prescription dose, min – minute, CI – conformity index, HI – homogeneity index

Table 3. Treatment effectiveness for each kind of tumor type (RTDPTB/CCTB)

Tumor type	2-year OS rate	2-year LC rate	MOS (month)	MLC (month)
Lung cancer	62.5%/41.7%	75.0%/58.3%	34/22	36/28
Pancreatic cancer	50.0%/30.0%	62.5%/50.0%	28/20	29/26
Gastric cancer	60.0%/28.6%	80.0%/42.8%	30/18	31/20
Pulmonary atelectasis*	66.7%/50.0%	100.0%/50.0%	32/20	38/29
Hepatocellular carcinoma	62.5%/42.8%	75.0%/57.1%	31/22	34/26
Rectal carcinoma	40.0%/33.3%	60.0%/50.0%	23/18	29/24
Renal carcinoma	66.7%/42.8%	83.3%/57.1%	30/18	38/26

*OS – overall survival, LC – local control, MOS – median overall survival, MLC – median local control, RTDPTB – robot-assisted 3D personalized template-guided ^{125}I seed brachytherapy, CCTB – conventional coplanar template-guided ^{125}I seed brachytherapy, * – induced by lung cancer*

the statistics, the treatment effectiveness for each kind of tumor type was summarized separately, including 2-year OS and LC rates, median OS and LC (Table 3).

The therapeutic efficacy of RTDPTB through the follow-up process is summarized in Table 1, and some typical cases are shown in Figure 4. Among the 43 patients, 20 (47%) patients achieved CR, 17 (39%) PR, 3 (7%) SD, and 3 (7%) PD, while there were 19 (38%) CR, 16 (32%) PR, 9 (17%) SD, and 7 (13%) PD in the 51 patients of CCTB.

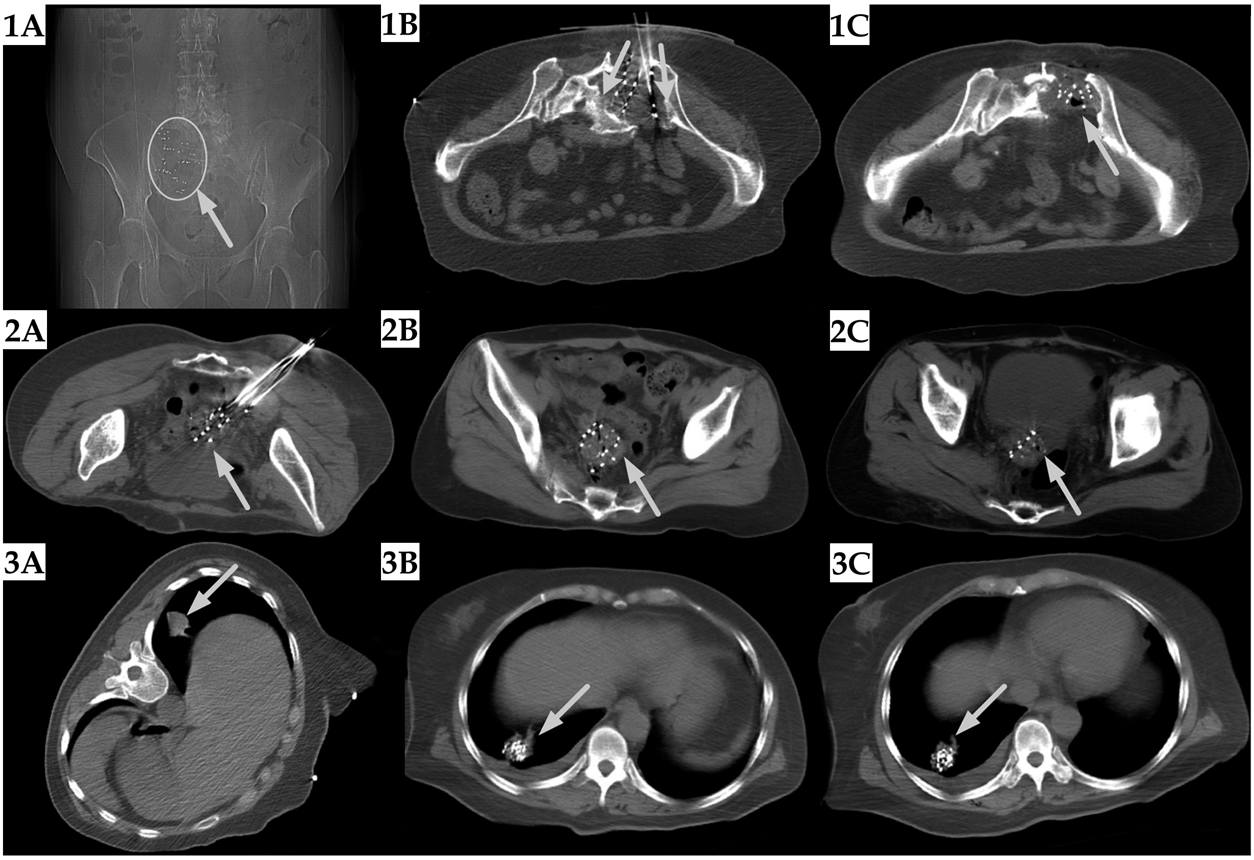

Fig. 4. Computed tomography images of some typical cases. **Case 1: 1A**) the seeds distribution after brachytherapy of a 50-year-old female with renal carcinoma; **1B**) There were bones surrounding the tumor, so 3DPT was used instead of CCT. Along the two arrows, the different directions of needle could be clearly observed; **1C**) Two months after brachytherapy, the tumor was significantly decreased, and the seeds gathered together. **Case 2: 2A**) a 60-year-old patient with pelvic cancer received ^{125}I seed brachytherapy under the guidance of 3DPT. The needle reached the tumor target through the gap of bones; **2B**) The seeds were distributed throughout the tumor volume after brachytherapy; **2C**) Six months after ^{125}I seed brachytherapy, the tumor nearly disappeared. **Case 3: 3A**) A 51-year-old patient was diagnosed with lung cancer and it was surrounded by ribs. Hence, 3DPT was chosen to guide the surgery; **3B**) The seeds distribution was displayed after ^{125}I seed brachytherapy; **3C**) One month after the surgery, the tumor size has significantly decrease

Analysis of factors associated with overall survival and local control

In RTDPTB, median CI and HI were 0.93 (range, 0.89-0.96) and 2.97 (range, 2.18-6.51), respectively. While in the other reference method, they were 0.78 (range, 0.69-0.92) and 5.46 (range, 3.25-10.36), respectively. Besides, we analyzed the following covariates associated with OS and LC: age, gender, and tumor size. The results of the association analysis are summarized in Table 4. The results demonstrated that CI (≤ or > 0.9) and HI (≤ or > 4) were significant factors in OS and LC ($p < 0.05$). And there were no association of OS and LC with other factors (age, gender, and tumor size).

Table 4. Results of association analysis

Factor	*p*-value	
	OS	LC
Age, year (≤ 60 vs. > 60)	0.109	0.095
Gender (male vs. female)	0.153	0.168
Tumor size, cm^3 (≤ 30 vs. > 30)	0.071	0.067
Approach (3DPT vs. CCT)	0.009	0.010
CI (≤ 0.9 vs. > 0.9)	0.009	0.006
HI (≤ 4 vs. > 4)	0.008	0.006

OS – overall survival, LC – local control, CI – conformity index, HI – homogeneity index

Complications

For all patients, surgeries were performed successfully without massive bleeding during or after the surgery. Other complications related to the procedure that occurred during or after the surgery were analyzed. In CCTB, three patients were detected with small local hematomas (one in lung, one in pelvic cavity, and one in kidney) after inserting the needle, probably because of the injured small blood vessels. Two patients presented pneumothorax caused by coplanar puncture damage to lung tissue and recovered after drainage. In RTDPTB, one patient had a small local hematoma in lung, and the symptom disappeared after symptomatic treatment. There were no severe radiation-related complications such as radioactive inflammation. The radiation-related complications as per the Radiation Therapy Oncology Group (RTOG) grading are summarized in Table 5. In CCTB, there were five patients presented fever symptoms, four of grade 1 and one of grade 2, and three patients were detected with leucopenia of grade 1. However, in RTDPTB, there were two patients presented fever symptoms of grade 1, and two patients were detected with grade 1 leucopenia. All those symptoms disappeared in two days after symptomatic treatment.

Discussion

As of now, few articles report on the effectiveness and safety of robot-assisted 3DPT-guided ^{125}I seed implantation. The aim of this work was the attempt to fill this gap. In order to obtain an accurate assessment, we selected as many cases as possible over a long period of time as well as a long follow-up. Finally, in RTDPTB, 43 patients with thoracoabdominal tumors were selected. Meanwhile, in CCTB, 51 patients with similar tumors were selected as reference. The patient characteristics in RTDPTB and CCTB were analyzed using SPSS. The results demonstrated that there were no significant differences in characteristics between the two groups, including gender, age, tumor size, diagnosis, and ECOG evaluation ($p > 0.05$, Table 1). Therefore, the comparison between RTDPTB and CCTB was significative.

For treatment of malignant tumors, a good effectiveness is mainly reflected in achieving an effective local control of the tumor and prolonging the survival time after a rationalized treatment. In order to evaluate this, OS and LC of RTDPTB were compared with that of CCTB. For different tumor type, the patients' OS and LC maybe different. In order to improve the comparability, different tumor types were classified and compared between RTDPTB and CCTB (Table 3). However, the results demonstrated that the 2-year OS and LC rates of RTDPTB increased (18.9% and 23.3%, respectively) compared with that of CCTB, respectively, in the mixed tumor population. Statistical analysis showed that there was significant difference in 2-year OS ($p = 0.015 < 0.05$) and LC ($p = 0.007 < 0.05$), respectively. For classified population according to the tumor type, taking the lung cancer for example, the 2-year OS and LC rates (62.5% and 75%, respectively) of RTDPTB increased 20.8% and 16.7% compared with that (41.7% and 58.3%, respectively) of CCTB, respectively.

Table 5. Radiation-related complications and RTOG grade

Grade	Grade 0 (RTDPTB/CCTB)	Grade 1 (RTDPTB/CCTB)	Grade 2 (RTDPTB/CCTB)
Acute complications			
Fever	41 (95.4%)/46 (90.2%)	2 (4.6%)/4 (7.8%)	0 (0%)/1 (2.0%)
Leucopenia	41 (95.4%)/48 (94.1%)	2 (4.6%)/3 (5.9%)	0 (0%)/0 (0%)
Radioactive inflammation	43 (100%)/51 (100%)	0 (0%)/0 (0%)	0 (0%)/0 (0%)
Late complications			
Subcutaneous tissue	43 (100%)/51 (100%)	0 (0%)/0 (0%)	0 (0%)/0 (0%)

RTOG – Radiation Therapy Oncology Group, RTDPTB – robot-assisted 3D personalized template-guided ^{125}I seed brachytherapy, CCTB – conventional coplanar template-guided ^{125}I seed brachytherapy

Statistical analysis showed that there was significant difference in 2-year OS (p = 0.030 < 0.05) and LC (p = 0.025 < 0.05), respectively. The trend is also observed in other tumor types. Furthermore, the OS and LC rates of CCTB declined more quickly in the first two years after surgery (Figure 5), indicating that RTDPTB was more effective in the treatment of thoracoabdominal tumors.

Through the comprehensive association analysis, CI (p-value: 0.009 and 0.006 for OS and LC, respectively), HI (p-value: 0.008 and 0.006), and guidance approach (p-value: 0.009 and 0.010) were significant factors in OS and LC (p < 0.05, Table 4). Moreover, CI and HI in RTDPTB improved (19.2% and 45.6%, respectively) than that of CCTB (CI, 0.93 and 0.78 for RTDPTB and CCTB, respectively; HI, 2.97 and 5.46, respectively) (Table 2). Statistical analysis showed that between RTDPTB and CCTB there was significant difference in CI (p = 0.000 < 0.05) and HI (p = 0.000 < 0.05). No surprisingly, in CCTB, some regions of the tumor target cannot receive adequate radiation dose, leading to a poor local control and effectiveness. This was further conformed through DVH analysis. Under the guidance of 3DPT, the DVH of post-operative validation was almost identical to the implantation plan (Figure 6A). However, there was a large deviation between the two DVHs whenever using CCT (Figure 6B). To make a more comprehensive discussion, CI and HI of pre- and post-operation were also calculated and compared. In RTDPTB, the pre- and post-operation CI were both 0.95, and the pre- and post-operation HI were 1.91 and 2.02, respectively. In CCTB, the pre- and

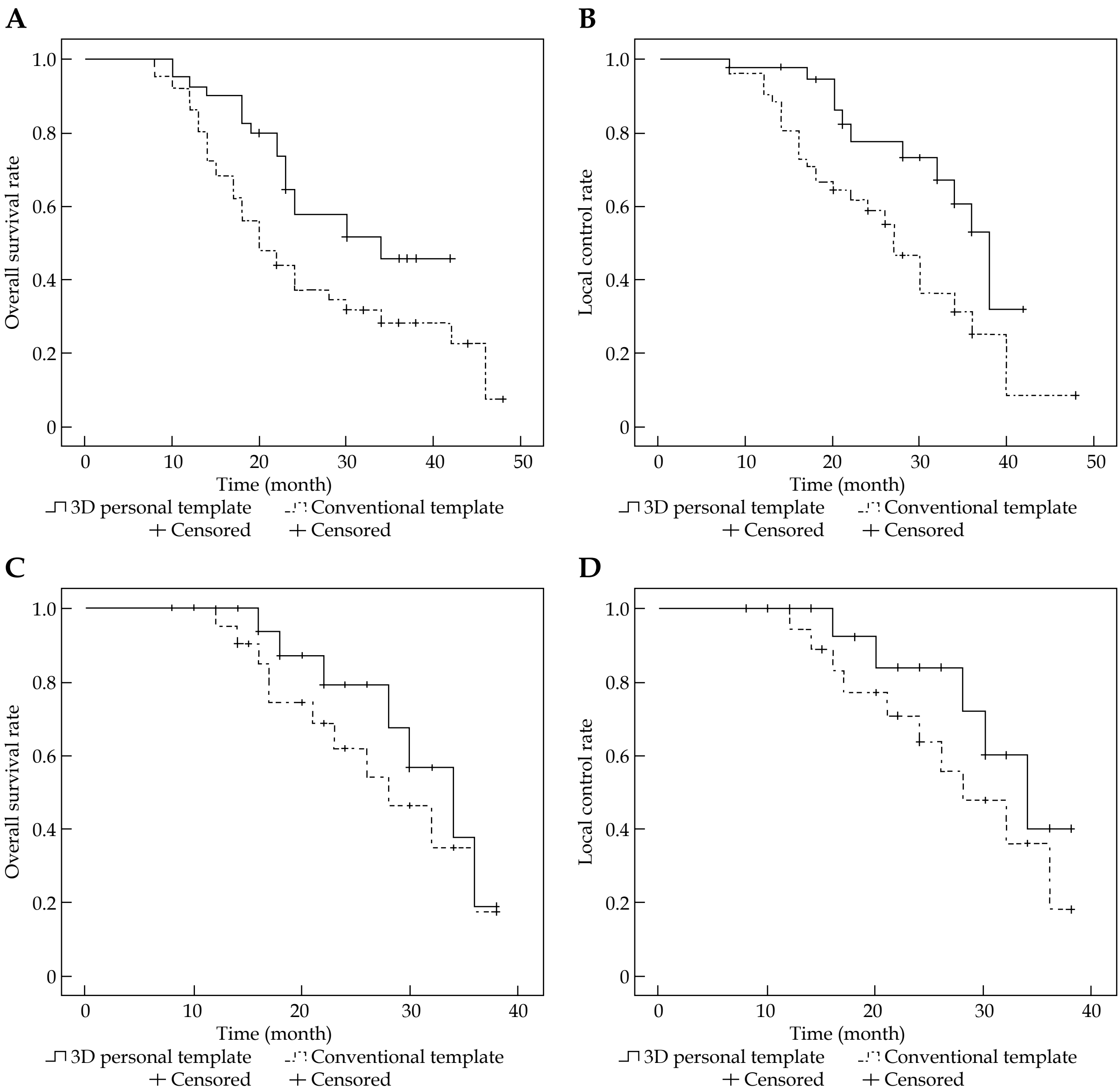

Fig. 5. Kaplan-Meier analysis of overall survival and local control in RTDPTB and CCTB: **A)** Overall survival rate of the two methods; **B)** Local control rate of the two methods; **C)** Overall survival rate of the two methods in the treatment of lung cancer; **D)** Local control rate of the two methods in the treatment of lung cancer

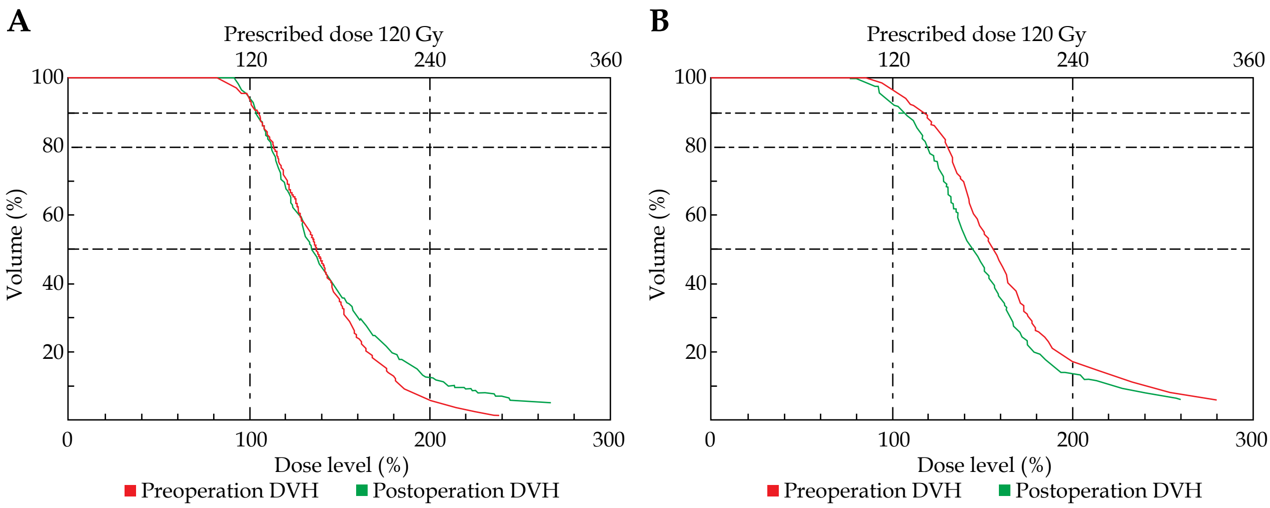

Fig. 6. The comparison of DVHs between implantation plan (red line) and post-operative validation (green line) of one patient. **A)** DVHs in RTDPTB. Pre-operation CI and HI: 0.95 and 1.91; post-operation CI and HI: 0.95 and 2.02. **B)** DVHs in CCTB. Pre-operation CI and HI: 0.95 and 4.58; post-operation CI and HI: 0.91 and 6.45

post-operation CI were 0.95 and 0.91, and the pre- and post-operation HI were 4.58 and 6.45, respectively. Obviously, CI and HI were almost the same in pre- and post-operation in RTDPTB, while there were significant differences in CCTB. The result indicated that the implantation plan could be much more effectively realized by using robot-assisted 3DPT. Based on this outcome, the tumor was effectively controlled, and survival time was lengthened.

To get a more comprehensive and reliable evaluation of effectiveness between RTDPTB and CCTB, several studies based on CCTB reported in the literature were also analyzed [29,30,31,32,33,34,35,36]. The relevant information was summarized in Table 6. Median survival time ranged from 7 to 22 months, and the 2-year OS rates were 10.7-52%. In our research with favorable outcomes, the median OS was 30 months and 2-year OS rate was 58.1%. Through comparative analysis, for every kind of tumor type, the 2-year OS rate of RTDPTB was higher than that reported in the relevant literature. These findings indicated that ^{125}I seed implantation under the guidance of robot-assisted 3DPT was more effective than that of CCT.

The success of ^{125}I seed brachytherapy depends on the accurate placement of radioactive seeds within the tumor target. When using CCTB for the treatment of cancer, there are several unsafe aspects. On one side, irradiation damage to normal tissues around the tumor target may be induced due to the lower CI, which was discussed above. On the other side, all the parallel needle directions were perpendicular to the template. That means, once the CCT was fixed, the needle direction was determined as well. The needle direction cannot be changed to avoid some vital organs. Only when the bones were thinner, they could be drilled to ensure the needles to pass. Otherwise, the implantation plans have to be given up, where there were vital organs or bones blocking the way. Therefore, the application of CCT would lead to a certain risk and limitations. Instead, the application of 3DPT had solved this problem and enhanced the safety. The needle could reach the expected position along a safe path through rotating a certain angle. In addition, 3DPT was produced exactly according to the patient's skin, so it can be completely matched with the skin and reduce the difficulty in positioning.

Table 6. Comparison of present research with other studies

Authors	Tumor type	Number of patients	MST (month)	2-year OS rate/present research
Wang *et al.* [30]	Pancreatic cancer	31	7	25.81%[a]/87.5%[a]
Liu *et al.* [31]	Pancreatic cancer	30	16	40%/50%
Shi *et al.* [32]	Gastric cancer	28	22	52%/60%
Huo *et al.* [33]	Lung cancer	38	21	47.4%/62.5%
Zhang *et al.* [34]	Hepatocellular carcinoma	27	13.5	30.8%/62.5%
Wang *et al.* [35]	Rectal carcinoma	15	10	10.7%/40%
Karam *et al.* [36]	Lung cancer	16	–	78%[a]/100%[a]
Lu *et al.* [37]	Pulmonary atelectasis*	15	16	13.3%/66.7%

*MST – median survival time, OS – overall survival, [a] – one-year OS rate, * – induced by lung cancer*

Hence, using 3DPT can meet the requirements for various tumor locations under safe conditions.

To better evaluate the safety of these two methods, the complications were collected and analyzed (Table 5). The incidence of radiation-related complications in RTDPTB (4.6% fever, 4.6% leucopenia, and 0% radioactive inflammation) was lower than in CCTB (9.8% fever, 5.9% leucopenia, and 0% radioactive inflammation). And there were no late complications observed during follow-up period. The risk of damaging vital blood vessels and organs can be greatly minimized in RTDPTB. Integrating the previous analysis, in can be demonstrated that RTDPTB can achieve a good safety.

In addition, ^{125}I seed implantation surgery with CCT takes usually 78 minutes, while it takes only 42 minutes using robot-assisted 3DPT. It was also an indicator in the evaluation of safety. For ^{125}I seed brachytherapy, long time spent on surgery indicated great damage to the patient. There may be two reasons: 1. CCT positioning is difficult and repeated CT scanning was time consuming and harmful to the patient; 2. Drilling holes on the thin rib would consume a lot of time, and it also causes damage to patient. Consequently, the less time-consuming process in RTDPTB reached a better safety.

In the end, the dose planning and dose optimization of these cases in this research were achieved manually, not by automatic inverse planning. Therefore, it will have a certain impact on the results between RTDPTB and CCTB caused by manual planning and optimizing. In this research, we have tried to reduce this impact. In the final dose optimization, in addition to meeting the basic conditions (V_{100} > 90%, V_{150} < 50%, V_{200} < 20%), we tried to choose the solution that makes the DVH optimal. At present, the automatic inverse optimization has been achieved. In the future work, we will eliminate the interference of manual planning to more accurately evaluate the effectiveness and safety of RTDPTB.

Conclusions

Through our research and comparisons with other studies, robot-assisted 3DPT shows sufficient effectiveness and safety in ^{125}I seed brachytherapy for the treatment of thoracoabdominal tumors. It is proved to be more effective, better tolerated, and less time-consuming. This research was based on a small number of patients and relatively short follow-up time. Hence, a larger patient cohort and longer follow-up periods should be involved to reach a more definite conclusion in the future research.

Acknowledgments

We gratefully acknowledge our research team at the Center for Advanced Mechanisms and Robotics, Tianjin University, for their technical assistance. The Department of Oncology of the Second Hospital of Tianjin Medical University provided great support regarding the clinical experimental environment and equipment.

This work was supported by the National Natural Science Foundation of China (Grant No. 51775368), the National Natural Science Foundation of China (Grant No. 5171101938), and the Technology Planning Project of Guangdong Province, China (Grant No. 2017B020210004).

Disclosure

The authors report no conflict of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65: 5-29.
2. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115-132.
3. Thorn CF, Oshiro C, Marsh S et al. Doxorubicin pathways: pharmacodynamics and adverse effects. *Pharmacogenet Genomics* 2011; 21: 440-446.
4. Florea AM, Büsselberg D. Cisplatin as an Anti-Tumor Drug: Cellular Mechanisms of Activity, Drug Resistance and Induced Side Effects. *Cancers (Basel)* 2011; 3: 1351-1371.
5. Kawalec P, Łopuch S, Mikrut A. Effectiveness of targeted therapy in patients with previously untreated metastatic breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer* 2015; 15: 90-100.
6. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. *Ann Surg* 2003; 237: 74-85.
7. Van Mierlo KM, Schaap FG, Dejong CH et al. Liver resection for cancer: New developments in prediction, prevention and management of postresectional liver failure. *J Hepatol* 2016; 65: 1217-1231.
8. Jagsi R, Momoh AO, Qi J et al. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. *J Natl Cancer Inst* 2018; https://doi.org/10.1093/jnci/djx148.
9. Yao L, Jiang Y, Jiang P et al. CT-guided permanent 125I seed interstitial brachytherapy for recurrent retroperitoneal lymph node metastases after external beam radiotherapy. *Brachytherapy* 2015; 14: 662-669.
10. Li J, Zhang L, Xu W et al. Computed tomography-guided implantation of ^{125}I seeds brachytherapy for recurrent multiple pulmonary oligometastases: initial experience and results. *J Contemp Brachytherapy* 2017; 9: 132-138.
11. Lu M, Yao W, Zhang T et al. Feasibility and Efficacy of Microwave Ablation Combined with Iodine-125 Seed Implantation in Local Control of Recurrent Retroperitoneal Liposarcomas: Initial Clinical Experience. *Oncologist* 2017; 22: 1500-1505.
12. Sylvester J, Grimm P, Naidoo D et al. First report on the use of a thinner 125 I radioactive seed within 20-gauge needles for permanent radioactive seed prostate brachytherapy: Evaluation of postimplant dosimetry and acute toxicity. *Brachytherapy* 2013; 12: 375-381.
13. Huo X, Huo B, Wang H et al. Implantation of computed tomography-guided Iodine-125 seeds in combination with chemotherapy for the treatment of stage III non-small cell lung cancer. *J Contemp Brachytherapy* 2017, 9: 527-534.
14. Li J, Xie Q, Wang W et al. CT-guided implantation of I-125 seeds (permanent brachytherapy) for metastatic tumors of the hepatic portal system: Effectiveness and safety in 13 patients. *Brachytherapy* 2016; 15: 224-230.
15. Huo X, Huo B, Wang H et al. Percutaneous computed tomography-guided permanent 125I implantation as therapy for pulmonary metastasis. *J Contemp Brachytherapy* 2018; 10: 132-141.
16. Martinez-Monge R, Nag S, Nieroda CA et al. Iodine-125 brachytherapy in the treatment of colorectal adenocarcinoma metastatic to the liver. *Cancer* 2015; 85: 1218-1225.

17. Chai SD, Zheng GJ, Mao YQ et al. CT guided transcutaneous interstitial implantation of (125)I seeds for lung carcinoma. *Chinese J Radiat Oncol* 2004; 13: 291-293.
18. Huang MW, Liu SM, Zheng L et al. A digital model individual template and CT-guided 125I seed implants for malignant tumors of the head and neck. *J Radiat Res* 2012; 53: 973-977.
19. Ji Z, Jiang Y, Su L et al. Dosimetry Verification of (125)I Seeds Implantation With Three-Dimensional Printing Noncoplanar Templates and CT Guidance for Paravertebral/Retroperitoneal Malignant Tumors. *Technol Cancer Res Treat* 2017; 16: 1044-1050.
20. Wang H, Wang JJ, Jiang YL et al. CT guidance 125I seed implantation for pelvic recurrent rectal cancer assisted by 3D printing individual non-coplanar template. *Zhonghua Yi Xue Za Zhi* 2016; 96: 3782-3786 [Article in Chinese].
21. Lin L, Wang J, Jiang Y et al. Interstitial 125I Seed implantation for cervical lymph node recurrence after multimodal treatment of thoracic esophageal squamous cell carcinoma. *Technol Cancer Res Treat* 2015; 14: 201-207.
22. Han T, Yang X, Xu Y et al. Therapeutic value of 3-D printing template-assisted I-125-seed implantation in the treatment of malignant liver tumors. *Oncotargets Ther* 2017; 10: 3277-3283.
23. Dou H, Jiang S, Yang Z et al. Design and validation of a CT-guided robotic system for lung cancer brachytherapy. *Med Phys* 2017; 44: 4828-4837.
24. Nath R, Anderson LL, Luxton G et al. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM-Radiation Therapy Committee Task Group No. 43. *Med Phys* 1999; 26: 2514-2520.
25. Rivard MJ, Coursey BM, DeWerd LA et al. Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations. *Med Phys* 2004; 31: 633-674.
26. Yang B, Sun X, Pang H et al. Dosimetric analysis of rib interference of the CTV during interstitial brachytherapy of lung tumors. *J Contemp Brachytherapy* 2017; 9: 566-571.
27. Feuvret L, Noël G, Mazeron JJ et al. Conformity index: A review. *Int J Radiat Oncol Biol Phys* 2006; 64: 333-342.
28. Kataria T, Sharma K, Subramani V et al. Homogeneity Index: An objective tool for assessment of conformal radiation treatments. *J Med Phys* 2012; 37: 207-213.
29. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; 30: 52-60.
30. Wang Z, Liu Y, Liu F et al. Clinical efficacy of CT-guided iodine-125 seed implantation therapy in patients with advanced pancreatic cancer. *Eur Radiol* 2010; 20: 1786-1791.
31. Liu K, Ji B, Zhang W et al. Comparison of Iodine-125 Seed Implantation and Pancreaticoduodenectomy in the Treatment of Pancreatic Cancer. *Int J Med Sci* 2014; 11: 893-896.
32. Shi L, Wu C, Wu J et al. Computed tomography-guided permanent brachytherapy for locoregional recurrent gastric cancer. *Radiat Oncol* 2012; 7: 114-123.
33. Huo XD, Wang HX, Yang JK et al. Effectiveness and safety of CT-guided ^{125}I seed brachytherapy for postoperative locoregional recurrence in patients with nonesmall cell lung cancer. *Brachytherapy* 2016; 15: 370-380.
34. Zhang L, Chen L, Wang J et al. CT-guided radioactive I-125 seed implantation treatment of multiple pulmonary metastases of hepatocellular carcinoma. *Clin Radiol* 2014; 69: 624-629.
35. Wang JJ, Yuan HS, Li JN et al. CT-guided radioactive seed implantation for recurrent rectal carcinoma after multiple therapy. *Med Oncol* 2010; 27: 421-429.
36. Karam SD, Horne ZD, Hong RL et al. Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer. *Radiat Oncol* 2013; 8: 179.
37. Lu M, Pu D, Zhang W et al. Trans-bronchoscopy with implantation of I-125 radioactive seeds in patients with pulmonary atelectasis induced by lung cancer. *Oncol Lett* 2015; 10: 216-222.