Chinese Expert Consensus Workshop Report: Guideline for permanent iodine-125 seed implantation of primary and metastatic lung tumors

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Abstract
Surgery remains the first choice of cure for early stage lung cancer. However, many patients are diagnosed at advanced stage, and thus miss the opportunity to undergo surgery. As such patients derive limited benefits from chemotherapy or radiotherapy, alternatives focusing on local control have emerged, including iodine-125 seed implantation. The Interstitial Brachytherapy Society, Committee of Minimally Invasive Therapy in Oncology, Chinese Anti-Cancer Association organized a group of multidisciplinary experts to develop guidelines for this treatment modality. These guidelines aim to standardize iodine-125 seed implantation procedures, inclusion criteria, and outcome assessment to prevent and manage procedure-related complications.

Introduction
Lung cancer is the leading malignant tumor in the world, with 2,500,000 new cases and 1,600,000 deaths reported per year. The situation in China is even more serious. According to the Chinese Cancer Registry Annual Report, the annual incidence of lung cancer is 57.63/100,000 and the annual mortality is 48.87/100,000, representing the largest rates in the world. Pathogenic factors include smoking, air contamination, and heredity. For early stage lung cancer, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), surgery is the first choice for cure. However, many patients are diagnosed at advanced stage, and thus have missed the opportunity to undergo surgery. Such patients obtain limited benefits from chemotherapy or radiotherapy; therefore, alternatives focusing on local control have emerged, including permanent iodine-125 seed implantation, thermal ablation, and photodynamic therapy. Studies have examined iodine-125 seed implantation for the treatment of lung cancer and
many patients are reported to benefit from this alternative technique.5–8 Iodine-125 seed implantation also has been proven to show good effects on metastatic lung cancer.9–11

In order to integrate international advanced medical technology concepts and provide guidance for clinicians, the Interstitial Brachytherapy Society, Committee of Minimally Invasive Therapy in Oncology, Chinese Anti-Cancer Association organized a group of multidisciplinary experts to develop these guidelines for permanent iodine-125 seed implantation of primary and metastatic lung tumors (Fig 1).

**Concept and principle of iodine-125 brachytherapy**

Radioactive seeds are implanted directly into the lesion as a kind of brachytherapy and kill the tumor cell by consistently releasing rays. Iodine-125 is the most common permanent implanted seed type, measures 4.5 × 0.8 mm, and has an envelope of nickel titanium alloy. The iodine-125 characteristics are listed in Table 1.12,13 γ-rays of < 0.0355 MeV could inhibit cell proliferation and angiogenesis, induce apoptosis, and kill tumor cells.

| Table 1 Characteristics of radioactive iodine-125 seeds |
|---------------------------------------------------------|
| Half-life period | Mean kinetic energy | Peripheral matching dose | Initial dose rate | Half value layer (lead) |
|------------------|---------------------|--------------------------|------------------|------------------------|
| 60.2 days        | 28 KeV              | 12000 cGy/a              | 1 mR/h           | 0.025 mm               |

**Implanting modalities**

**Image guidance**

Percutaneous iodine-125 seed implantation is usually performed under computed tomography (CT) or ultrasound guidance. For lung tumors, CT is the preferred technique.14 Ultrasound can be used for lesions located near or adhering to the chest wall.15 Magnetic resonance imaging (MRI) has shown considerable value in percutaneous biopsy16 and target localization,17 and may be an alternative guidance modality for iodine-125 seed implantation for lung tumors.

**Electronic fibro-bronchoscope**

The electronic fibro-bronchoscope is mainly used: (i) at early stages of central lung cancer18 and (ii) for localized intratracheal tumors that cannot be treated with surgery or other radical therapy.19

**During surgery**

Lung tumors located adjacent to the hilus, large vessels, or heart cannot be treated via radical resection.20

**Other modalities**

Other modalities include iodine-125 seed implantation during robot-assisted surgery.21

**Principles of iodine-125 seed implantation**

**Multidisciplinary team and individualized treatment**

An effective and reasonable treatment plan should be made after consultation with physicians in the Departments of Thoracic Surgery, Respiratory, Oncology, Radiation Oncology, and Interventional Medicine.
### Treatment plan

Delineate the target area according to the lung window, as well as the organs at risk (OARS). Select the appropriate prescription dose and activity of seeds, and develop a treatment plan using a treatment planning system (TPS).

### Seed implantation

Implant seeds into the tumor under CT guidance, and perform intraoperative dose optimization as necessary. Each bilateral lesion should be treated separately.

### Dose

Evaluate the dose to the target tumor via dose volume histogram (DVH) and isodose profile after the procedure.

### Complications

The patients should be observed for any complications, including hemorrhage or radiation pneumonitis, during follow-up after the procedure.

### Indications and contraindications

#### Indications

**Primary lung cancer:** (i) patient is not a candidate for surgery because of inferior cardiopulmonary function or advanced age; (ii) patient refused surgery; (iii) patient is not a candidate for surgery because of recurrence after surgery; (iv) a residual or progressive tumor is observed after surgery, radiotherapy, or chemotherapy; (v) thermal ablation or surgery failed to distinguish the tumor-free boundary; (vi) Karnofsky Performance Score (KPS) > 60 and predicted life span > 6 months; and (vii) the diameter of largest tumor is < 7 cm.

**Metastatic lung cancer:** (i) the patient has ≤ 3 unilateral lesions ≤ 5 cm in diameter; (ii) if a patient has ≤ 3 bilateral lesions ≤ 5 cm in diameter, these should be treated separately.

#### Contraindications

Contraindications include: (i) cachexia with multi-functional failure; (ii) intractable infection or radiation inflammation around the lesion; (iii) skin infection or ulceration around the puncture site; (iv) severe coagulation disorders or anemia; (v) massive ipsilateral malignant pleural effusion; (vi) KPS score < 60; and (vii) predicted life span ≤ 6 months.

### Preoperative preparation and examination

#### Patient evaluation

Patient eligibility for iodine-125 seed implantation should be determined after multidisciplinary team consultation over the patient's history, and physical and imaging examination results. Enhanced chest CT with slice thickness of 5 mm one week before the procedure is necessary to detect the tumor size, location, and distance to other organs, vessels, and trachea. When use of a three-dimensional printing non-coplanar template (3D-PNCT) is planned, anchor points should be delineated on the skin. Necessary imaging examinations should be performed to detect metastasis and determine tumor node metastasis (TNM) stage, including positron emission tomography (PET)-CT.

#### Pathology

Percutaneous or fiberbronchoscopic biopsy is necessary before iodine-125 seed implantation.

#### Treatment planning system

After importing the enhanced chest CT data into the TPS, delineate the clinical target volume (CTV) according to images on the lung window (width 1000 HU, level –650 HU, and 5 mm slice thickness). The recommended seed activity is 0.6–0.8 mci, and the prescription dose (PD) is 120–160 Gy. The planning target volume (PTV) should cover the CTV and an extra centimeter beyond the margin. OARS around the tumor should also be delineated. Order iodine-125 seeds according to the TPS and plan 3D-PNCT if necessary. An MRI or PET-CT is recommended to delineate the target volume when atelectasis exists. A DVH is applied to evaluate the plan dose.

#### Laboratory examinations

Blood count, urine, stool, blood coagulation, liver and kidney function, blood glucose level, tumor markers, electrocardiogram, echocardiography, and lung function tests should be conducted.

#### Drugs and electrocardiogram monitoring

Anesthesia, analgesia, antitussive, hemostasis, vasodilator, and anti-hypertension drugs and monitoring devices should be prepared before the procedure.
Patient preparation

Signed informed consent is required from the patient or their representative. The patient should fast for four hours before local anesthesia or six hours before intravenous general anesthesia is administered. An oral antitussive is necessary before the procedure.

Operation process

Body position and anesthesia

Select the appropriate body position according to the tumor location and performance status of the patient; vacuum cushions can be applied. Local or intravenous general anesthesia is selected according to hospital practice. Disinfect the surgical field with strict implementation of an aseptic manual. The planar template should be fixed to the frame, while 3D-PNCT should be fixed according to the TPS and anchor points on the skin.33

Iodine-125 seed implantation

*Using CT guidance as an example:* CT with slice thickness of 0.5 cm is performed before the procedure to identify the tumor location and mark the operation field. Select the appropriate intercostal space as a puncture plane, and determine the puncture site, angle, and depth. Auxiliary technologies, such as bone drilling34 or artificial pneumothorax,35 can be applied in cases where bone is a barrier to puncture. Insert the puncture needles into the tumor under CT guidance and implant iodine-125 seeds according to the TPS. The distance between puncture needles is usually 1–1.5 cm. Needle puncture can be accomplished at once or via a fractionation procedure. After all of the needle tips reach the distal edge of the tumor, retrace the needle at an equal distance or according to the TPS, and implant the iodine-125 seeds. Taking a CT scan during the procedure is recommended in order to ensure all of the seeds have been implanted according to the TPS. Revise the implantation plan as necessary. After implantation, re-scan the whole lung and check the distribution and number of iodine-125 seeds in every plane. If there is a cold area, implant more seeds to match the TPS dose requirement. Check for complications, including pneumothorax or hemorrhage,36 and treat it if necessary, such as via percutaneous drainage. Import the CT scan data into the TPS after the procedure and verify if the dose meets the dose requirement in the pre-operative plan.37

Monitoring during the procedure

Heart rate, blood pressure, and blood oxygen saturation should be carefully monitored. Close observation of patient consciousness, breathing, and symptoms, including pain, cough, or hemoptysis is recommended. Treat it if necessary.

Postoperative treatment

Patients should be escorted back to the ward by doctors, with the surgical field covered by a lead pad with a lead equivalent of 0.025 mm. Electrocardiogram monitoring and oxygen inhalation are required until the patient’s condition is confirmed as stable. X-ray examination or chest CT should be repeated 24 hours after the procedure to determine if there is any pneumothorax, hemothorax, or seed migration.35

Adverse reactions and complications

Adverse reactions and complications after seed implantation should be evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.038 and Radiation Therapy Oncology Group RTOG/EORTC radioactivity response evaluation criteria.

Pneumothorax

No medical treatment is recommended for slight pneumothorax, especially when no symptoms develop. If the compression ratio of the affected lung exceeds 30% and patients suffer from suffocation or dyspnea, thoracic drainage is recommended.

Hemorrhage

*Lung hemorrhage:* For patients with bloody sputum or hemoptysis, medicine (such as pituitrin, reptilase, aminomethylbenzoic acid, or ethamsylate) should be applied. Bronchial artery embolization is recommended if necessary. If > 500 mL of bleeding occurs, blood transfusion and fluid resuscitation are recommended. If these treatments fail, arteriography and embolization are required. Surgery is recommended if necessary, particularly in cases where the blood pressure and heart rate are not stable.
Pleural reaction

Pleural reactions are relatively rare. The main symptoms include a nagging cough, dizziness, sweating, a pale face, palpitation, hypotension, chest constriction, and disturbances to consciousness. The operation should be immediately suspended. Lay the patient on the bed, keep them warm, and monitor their heart rate, blood pressure, and level of consciousness. After rest or psychological counseling, some patients quickly recover. Oxygen inhalation and glucose administration are recommended for patients with unstable vital signs or hypoglycemia. Adrenaline should be administered to avoid shock if necessary.

Infection

Infections are relatively rare. The main symptoms are fever and leukocytosis. The administration of antibiotics is recommended, and strict sterile manipulation can avoid infection.

Puncture tract metastasis

Puncture tract metastasis is relatively rare. Surgery or repeated iodine-125 seed implantation may be effective. Chemotherapeutics, such as 5-fluorouracil or tegafur injection through puncture needles, can reduce incidence.

Seed migration

Iodine-125 seeds may migrate to distal bronchia or the thoracic cavity. The patient should be carefully screened.

Local radiation pneumonitis and radiation pulmonary fibrosis

Local radiation pneumonitis and radiation pulmonary fibrosis is rare but may occur in patients who receive repeat iodine-125 seed implantation.

Other rare complications

Other complications, such as pulmonary embolism, aeroembolism, and nerve damage are rare.

Follow-up and evaluation

Follow-up

Enhanced chest CT is recommended at 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after implantation. After five years, a chest CT scan should be taken once a year. PET-CT or MRI can be applied if necessary.

Evaluation of effect on local lesions

Tumors are evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A complete response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduced at the short axis to < 10 mm. A partial response (PR) is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking the baseline sum diameters as the reference. Progressive disease (PD) refers to at least a 20% increase in the sum of the diameters of target lesions, taking the smallest sum (including the baseline sum if it is the smallest) as the reference. In addition to a relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Stable disease (SD) is considered when there is neither sufficient reduction to qualify for PR nor sufficient increase to qualify for PD, taking the smallest sum diameters as the reference.

Evaluation of clinical effect

Based on an evaluation of the local effect, the state of survival should be recorded at one, two, three, and five years. The patient’s KPS, pain relief rate, and drug administration should be monitored.

Radiation protection after the procedure

The recommended reference is Radiological Protection Standards for Clinical Nuclear Medicine (GBZ120-2006) drafted by the National Health Commission of the People’s Republic of China. Contact within 50 cm is prohibited for at least two months after the procedure, and patients should wear a lead pad for at least four months.

Technology access

The recommended reference is the Radioactive Seed Implantation Technology Management Specification drafted by the National Health Commission of the People’s Republic of China.

Disclosure

No authors report any conflict of interest.

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