

Treatment of Central Type Lung Cancer by CT Guided Percutaneous Implants of ^{125}I Radioisotopes

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OBJECTIVE To discuss the method, safety and effectiveness of the treatment for central -type carcinoma of the lungs by CT guided percutaneous implants of ^{125}I radioisotopes in tissues.

METHODS Twenty-two cases of central-type lung cancer located by plain and / or enhanced CT scans were retrospectively analyzed, among which 18 cases were verified pathologically using a CT guided percutaneous puncture and biopsy before treatment. The CT guided treatment was conducted immediately after the pathological results were obtained. The number of the radioisotopes used was seven to 16. The intensities of radioactivity for ^{125}I radioisotopes were 22, 26, 30 and 33 MBq per particle. The total intensity of radioactivity was 181 to 355 MBq. The puncture point was only one. The frequency for adjustment of needling direction was two to five times. The punctures were conducted through the anterior chest wall in eight cases, through the lateral chest wall in eight cases and through the posterior chest wall in six cases. Six of the 22 cases were given intravenous chemotherapy.

RESULTS Of the 22 cases, 20 were followed-up for more than one month, 16 over two months, ten over three months and three cases for six months. In the 20 cases which were followed-up for one month, the diameters of the tumors were reduced by 50% or more in 18 cases, showed no change in two cases with none showing enlargement. In the 16 cases followed-up for more than two months, the diameters of tumors were reduced by 50% or more in 15 cases, one case showed no change and none enlarged. In the ten cases with three months of follow-up, the tumor diameters were diminished by 50% or more in eight cases, showed no change in one case and enlarged in one case. In the three cases followed-up for six months, the diameters of tumors were reduced by 50% or more in all the cases. Of the 22 cases, atelectasis occurred in 12 before therapy. The lungs expanded again in nine cases in the follow-up after treatment. Symptoms after therapy included metastases of the mediastinal lymph nodes in four cases, newly -occurring thoracic osseous metastases in one case and hepatic metastases in one case. Complications included pneumothorax in 11 cases and exfoliation of particles in one case.

CONCLUSION The size of cancer can be markedly reduced after therapy by CT guided percutaneous implant of ^{125}I radioisotopes in tissues. It is an accurate and safe procedure and is effective for local metastasis.

KEYWORDS: lung cancer, brachytherapy, radiology, intervention, iodine radioisotope.

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Central-type lung cancer is a common malignant neoplasm. Based on the pathological typing of the tumors, squamous cancers account for the majority of cases, followed by small-cell lung cancer with adenocarcinoma the least. Squamous cancer and small-cell lung cancer are relatively sensitive to radiotherapy. Although a surgical operation is one of the therapeutic methods, quite a few patients fail to receive operative treatment, either because they might be unsuitable for an operation ^[1] or they are unwilling to be a subject for surgical therapy. Therefore, chemotherapy by arterial perfusion of the bronchus is increasingly becoming a conventional therapy, but there are still limitations in its safety and effectiveness. ^[2] In our report, we have summarized and analyzed the therapeutic process and practice for 22 cases of central type lung cancer. The patients were treated using CT guided percutaneous implants of ¹²⁵I radioisotopes during the period from August 2003 to May 2004. In addition we have discussed the technology and methods of operation adopted in the Qilu and Pingyi Cooperation Hospital of Shandong University, as well as their safety and efficacy.

MATERIALS AND METHODS

Clinical data

The 22 cases in the study were comprised of 14 males and eight females, ages ranging from 44 to 82 years. All patients received a normal chest X-ray and plain and enhanced CT scanning. The scans were conducted as follows: 12 cases in the right lung, including three cases in the superior lobe of the right lung, five in the hilum and four in the inferior lobe of the right lung; ten cases in the left lung, including four in the superior lobe and six in the hilum. There were metastases of the lymph nodes at the anterior superior mediastinum in two cases, metastases of lymph nodes at the aortic window in three cases and metastases of lymph nodes below the carina in two cases. Patients with heavy and chronic bronchitis and severe cardiac diseases were not included in the study.

Implanting system and ¹²⁵I radioisotopes

The implanting system was manufactured by the Lieying Company, Zibo, Shandong. It included the therapy planning system (TPS), implanting gun and implanting needle. The ¹²⁵I radioisotopes were produced at the China Atomic Energy Research Institute, and supplied in an airtight titanium alloy package. The length of the particles was 4.5 mm, with diameters of 0.8 mm. The half-life ($T_{1/2}$) was 59.43 d. The radiation dose for various particles was 22, 26, 30 and 33 MBq and the effective range for each particle was 1.7 cm.

Technology of interventional therapy

Preparation before treatment

a) Routine preparation: routine examination of hemagglutination, ECG and the antitussive medication before treatment. b) Enhanced CT scanning: An enhanced CT examination was conducted in cases of biopsy or embedding therapy because this examination was required for diagnosis, and it was important that the enhanced examination distinctly display the lesion and blood vessels; although the boundary between the two structures in the puncturing process is not as clear as it is in the initial stage. The therapist must view a definite puncturing target, so as to reduce the chance of inappropriate puncture and to prevent complications.

Application of TPS

The methods were as follows: a three-dimensional reconstruction was carried out according to the CT data; the size, shape, site of the tumor and its relation with the great vessels of the hilum of the lung were observed to make sufficient preparation for the selection of puncture points and to plan the route and direction of the puncture, etc. First, the required total activity of ¹²⁵I radioisotopes was calculated according to the size of the focus and Hailar formula: Da (Hailar coefficient) = (sum of the length+ width+ height of the tumor)/3. So the required total activity of ¹²⁵I was $Da \times 185$ MBq. Next the kind of radiation particles was selected: the particles with the major activity series (30, 33 MBq) were chosen for the center of the focus, and those with the minor activity series (22, 26 MBq)

were chosen for the margin of the focus and for some vital structures, such as blood vessels and nerves, etc. ; third, the total sum of the particles needed was calculated. The order was considered first then, the number determined and activity series of the minor particles required, then that of the major particles determined and finally the space between the radion particles was established: the space for the major activity series was 1.5 cm, and the space for the minor ones was 1.0 cm, in order to provide maximum effectiveness.

CT guided localization

The proper body posture was selected by putting the locally made grid closely to the desired position for puncture before scanning; after tumor localization, conventional sterilization was applied, aseptic towels positioned and local anesthesia used paying attention to anesthesia of the pleura. The CT guided needling process was divided into two to three steps and the puncturing focused directly at the target.

Quick pathological examination

First the biopsy gun was used to remove the histo-specimen and for a quick pathological assessment. The pathological results showed 19 cases of squamous cancer, two cases of small-cell carcinoma and one case of adenoma. These figures were in accordance with the data from the literature.^[3] The ¹²⁵I radioisotopes were implanted after obtaining the pathological results.

Implantation process

The implanting needle was first placed at the target tissue and one to four grains of the microparticles released by the gun in sequence order (Fig.1), with a 1.0 to 1.5 cm space between the particles. CT scanning was conducted immediately, then the needle was withdrawn to the margin of the tumor; the needling was renewed after adjustment of the angle (Fig.2). The CT guided needle was placed at the target and the particles released in a similar manner. The angle was adjusted two to five times in the same way.

Immediate observation by scanning

The focal point for observation included the status of the pneumothorax and the position of the particles; concurrently the TOP (test orientation procedure) was performed and the window width and window level were adjusted for further observation; if everything was satisfactory and the pneumothorax-free status was confirmed, or only a little amount of the pneumothorax was found (< 30%), the operation was ended and a roentgenogram of the chest at the normal side was taken for reexamination.

Methods for follow-up and analysis of effectiveness

All of the 22 subjects had completed the treatment by CT guided percutaneous embedment of ¹²⁵I radioisotopes, and underwent the CT rechecks of one, two, three and six months after the therapy. An analysis of the effectiveness was carried out, using three possible outcomes, i.e., 1) reduction of the diameter of the tumor was more than or equivalent to 50% of the original lesion; 2) there was no change in the size of the tumor or 3) there was enlargement.

RESULTS

Efficacy

Of the 22 cases, 20 cases had one month or more of follow-up, 16 with more than two months, ten with more than three months and three cases with six months. In the 20 cases with one month of follow-up, there were 18 whose reduction of the diameter of tumor was larger than or just equivalent to 50% (Figs. 3,4), two had no change and none showed enlargement; in the 16 cases with two months of follow-up, there were 15 whose shrinkage of the diameter of tumor was larger than or just equivalent to 50%. One showed no change and no case developed enlargement; in the ten cases with three months of follow-up, there were eight cases whose shrinkage of the diameter of their tumor was larger than or just equivalent to 50% (Fig.5), one had no change and one case showed enlargement; in the three cases with six months of follow-up, the reduction of the diameter of

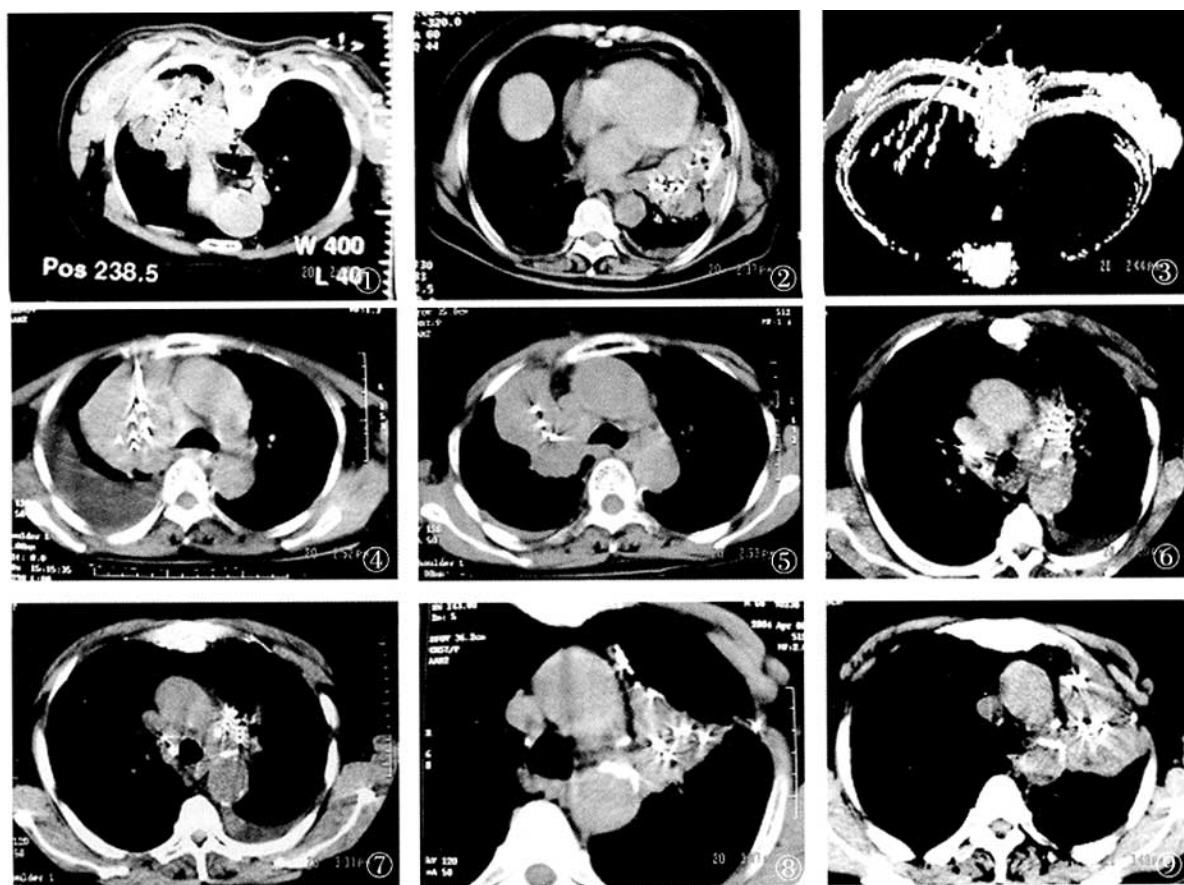


Fig.1. The CT guided implanting needle was first placed on the target, 1 to 4 grains of the microparticles were released by the gun in series, with 1.0 to 1.5 cm space between the particles. CT scanning was conducted immediately.

Fig.2. The needle was withdrawn to the margin of the tumor; the needling was renewed again after adjustment of the angle, adjusting the angle 2 to 5 times in the same way.

Fig.3. The central type lung cancer at the inferior part on the hilum of the left lung; enhancement before treatment showed a soft connective tissue tumor in the dorsal segment of the hypophyllum in the left lung, and complete blockage of the bronchial debouchment at the sublobe and dorsal segment of inferior lobe in the left lung was seen.

Fig.4. The same case as in Fig. 3: follow up was conducted 1 month after treatment; the diameter of the tumor diminished approximately 50%. The image of metallic density in the focus was the radioisotopes.

Fig.5. The same case as in Fig. 3: follow up started 2 months after treatment and the diameter of the tumor diminished approximately 80%. The tumor was basically absorbed and only a residue of the tumor was found. The image of metallic density in the focus was the radioisotopes. At the same time, the bronchial debouchment at the sublobe and dorsal segment of the inferior lobe at the left lung was basically opened.

Fig.6. The central type lung cancer at the superior lobe of the left lung: the focus was involved in the left and anterior chest wall.

Fig.7. The same case as in Fig. 6: the results of reexamination 6 months after treatment showed that the focus was effectively controlled, the tumor had diminished significantly and there was no adhesions at the left and anterior chest wall.

Fig.8. The central type lung cancer at the superior lobe of the right lung: the soft connective tissue tumor was seen at the superior part on the hilum of the right lung, and before treatment there was apparent atelectasis at the lateral segment on superior lobe of the right lung.

Fig.9. The same case as in Fig. 8: follow up was conducted 1 month after treatment; the soft connective tissue tumor at the superior part of the hilum of the right lung was diminished and atelectasis at the lateral segment in the superior lobe of the right lung basically started reexpansion. At the same time, a secondary pneumothorax occurred because of the reexpansion of atelectasis.

tumor in all the cases was larger than or just equivalent to 50% (Figs.6,7).

Relief of the atelectasis

Of the 22 cases, 12 displayed apparent closure of the pulmonary segment and lobes before therapy and nine showed reexpansion during the follow-up period (Figs. 8,9).

Metastatic status and therapy

In the reexamination after treatment, there were four cases with nascent metastases of the mediastinal lymph nodes, one with metastases of the thoracic bone

and one with liver metastases, all of which treatment by CT guided percutaneous implantation of ^{125}I radioisotopes were performed again. Significant diminution of the foci was found in the reexamination one or two months after the CT guided treatment (Figs. 10-13).

Complications

Eleven cases with pneumothorax were found. Two of these had more than 30 % pneumothorax and needed treatment by air exhaust; exfoliation of particles developed in one case (Fig.14) and three patients developed hemoptysis.

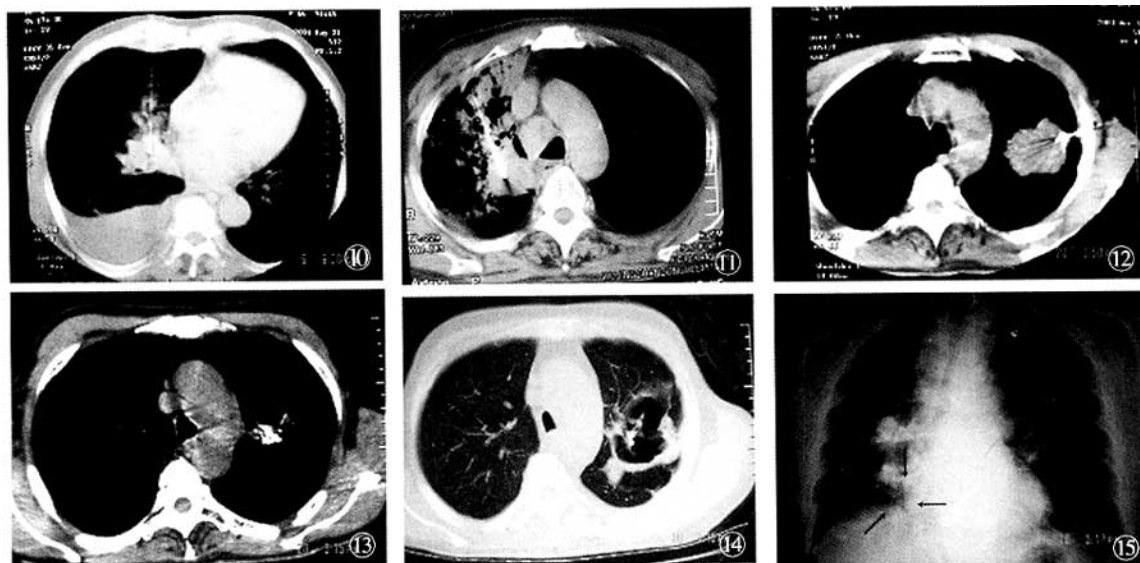


Fig.10. The central type lung cancer at the inferior lobe of the right lung accompanied by metastases at the anterior superior mediastinum, manubrium of the sternum and the right anterior upper breast: the CT guided percutaneous implantation of ^{125}I radioisotopes was conducted again.

Fig.11. The same case as in Fig. 10: follow up conducted 1 month after treatment showed that the metastases at the anterior superior mediastinum were diminished significantly, the ossification occurred at the manubrium of the sternum, and the metastatic soft connective tissue tumor at the right anterior upper breast was reduced significantly.

Fig.12. The central type lung cancer at the right lung accompanied with metastases at the right posterior lobe of the liver: the CT guided percutaneous implantation of ^{125}I radioisotopes was conducted.

Fig.13. The same case as in Fig. 12: follow up started 3 months after treatment and the focus at the right posterior lobe of the liver was overtly diminished. The high density in the center was the radioisotopes.

Fig.14. The exfoliation of the particles was caused by the diminution of the tumor: although the radioisotopes were first placed in the focus, particles were found more than 1.5 cm away from the margin of the focus, the extent of diminution for tumor was unexpected, thus causing exfoliation of the particles and transfer of the radioisotope particles to the far end of the lung by the bronchus or arteries.

Fig.15. The central type lung cancer at the inferior lobe of the right lung accompanied with dorsal atelectasis: the needling through the pulmonary tissue with atelectasis can effectively avoid the occurrence of pneumothorax.

DISCUSSION

Evaluation of treatment of central type lung cancer by percutaneous implants of ^{125}I radioisotopes

The principles and characteristics of treatment

The ^{125}I radioisotopes radiate low dose γ -rays continuously with the γ -rays producing a direct effect on DNA, causing single and double strand cleavage; concurrently it produces an indirect effect, i.e. ionization of the water and the production of free radicals. The free radicals interact with biomacromolecules, thus causing histologic damage. It provides steady irradiation on the tumor cells at all stages of the cell cycle of the cancer, and because the ambient normal tissues are in a non-dividing stage, they are insensitive to radiotherapy and suffer slight damage. At the same time, because the intensity of radioactivity of the particles is minor, the normal tissue outside the cancer receives a low radiation dosage, thus reducing the damage to the ambient normal tissues.^[4]

Compared to external radiotherapy, implants of radioactive ^{125}I have an apparent greater biological effect, i.e., a) duration for local radiotherapy on the cancer is long; b) the dose for radiotherapy is considerably low; c) the damage to the ambient normal tissues is less than that to the tumor and d) the lethality to tumor cells is extensive. Compared to surgical operations, the treatment has various merits, such as extensive indications for treatment, minor trauma, quick recovery, and it can maintain maximum pulmonary function. The treatment is especially adaptive when the patients are unwilling to undergo a radical operation and to prevent local and regional diffusion of the cancer. It is also appropriate for those who have solitary metastases and therefore are unable to undergo an operation, as well as in cases where there is a primary disease preventing an operation because of age, physical status, etc. In cases where the effect of external irradiation therapy was ineffective or failed, it can be used as a supplement to external irradiation.

Therapeutic effect

The treatment of central type lung cancer by CT guided percutaneous implants of ^{125}I radioisotopes can significantly diminish the tumor within one month with the rate in our group reaching 81.8% (in 18 cases of the 22). The efficacy was higher than in a group receiving simple chemotherapy (68%) or in a group treated with radiotherapy alone (72%) reported in China, and was near to that in the cases of combined treatment reported internationally (93.3%, 90%).^[5-11] In addition, the duration for the curative effect of a single ^{125}I radiation treatment is extensive, because the half-life of ^{125}I is comparatively long. It was apparently effective in the recovery of the tumor-induced obstructive atelectasis, because the atelectasis was mainly caused by pressure of the tumors on the bronchea. The rate for renewed swelling of the atelectasis in the group was 75.0% (in nine cases of 12). It also was effective for the treatment of patients with solitary metastases who could not be related with an operation. Satisfactory results after treatment were obtained in one case of metastases in the anterior mediastinum, chest wall and thoracic bone, and one case of hepatic metastases.

Evaluation of Efficacy

The treatment method is overtly effective both in the focus and metastases, but only for local therapy. The long-term efficacy is subject to the results of follow-up. In our 22 cases, six cases of new metastases de novo occurred during the follow-up. So it is not known whether the therapy has a definite prevention of metastases or not and needs further study. In general, the treatment method has distinctive characteristics compared to a surgical operation, interventional chemotherapy and external radiotherapy. The treatment method provides a new approach for therapy of central type lung cancer and its metastases.

CT guided percutaneous implantation of ^{125}I radioisotopes is a feasible method

Treatment of central type lung cancer by percutaneous implants of ^{125}I radioisotopes has never been published in the literature. Therefore experience regarding

treatment modality is not available.^[12] Based on our experience the following are some important aspects of the operative process.

Localization system of the TPS (treatment planning system)

TPS is a must for treatment, because the dosage of particles (i.e. total intensity of radioactivity), the number of particles, the optimal and feasible distribution must be determined prior to the treatment. Devising a logical treatment plan is a prerequisite and the basis for therapy.

Location, fixation of the angle, step-by-step needling and targeting

a) selection of a proper body position. The supine position, lateral position or prone position is used according to the position of the focus, and concurrently considering the shortest distance and optimal orientation for the CT scan, as well as the major organs (e.g. the lung arteries and veins, diaphragm and the blood vessels between ribs, etc.).^[13] It should be especially noted that there is a positive correlation between the probability of pneumothorax and the number of layers and of times the pleura are perforated. Therefore perforation of the oblique fissure should be avoided as far as possible when the puncture is conducted. At the same time, one must try to reduce the number of punctures. b) when local anesthesia is applied, note that anesthesia of the pleura is adequate to avoid severe pain which may affect the operation. The priorities are that severe cough must be avoided and the possibility of pneumothorax reduced when puncturing.

Quick pathological examination

Before implantation of ¹²⁵I radioisotopes, a biopsy should be taken first and a quick pathological examination conducted to avoid mistreatment on account of misdiagnosis.

Adjustment of the angle

Different from biopsy puncture, the implantation of ¹²⁵I radioisotopes requires releasing the particles with a

definite spatial distribution. Therefore adjustment of the angle of the needle must be made after every puncture. The authors advise that after releasing the first particle, the angle can be carefully changed to puncture into the focus again, even if the needle is only lifted to the margin of the focus. This is because the lung tissue has a certain amount of elasticity which will not significantly increase the risk of scar formation on account of changing the angle. A pneumothorax can be effectively prevented by placing the needle in the lung tissue with atelectasis (Fig.15).

Immediate Observation by scanning

The main point for observation is the status of the pneumothorax; if the volume of the pneumothorax is less than 30%, the observation can be continued; if the volume of the pneumothorax is more than 30%, most gas will be eliminated through the T-tube immediately. After the operation, the patients are told to apply pressure at the point of puncture, in order to reduce the pleural movement at the proper position. The local fluid will tend to prevent pneumothorax.

Safety of the therapy

This mainly relates to the radiation damage, which may be produced during the operation, involving the hospital personnel and the patients. The energy of ¹²⁵I radiation is minor (less than 37 MBq per particle), with cellular damage at a radius of 1.7 cm. All of the radioisotopes were enclosed in a nickel-titanium-alloy vessel. The hermetization of the radioactive source will prevent environmental pollution and prevent radioactive exposure to the patients. In the treatment, a combined dose with several particles was used, a minimal dose of radioactivity with limited penetrating power is employed which will not generate a radioactive hazard to people nearby. The annual radiation dose for a radiotherapist who implants the radioisotopes for patients is calculated based on 8-hour days, 260 days a year and distance of 25 cm between the radioactive source and the radiotherapist. The usual total annual radiation dose to which radiotherapist is exposed will be 0.01127 mSv; the radiation dose for accompanying relatives of the patient will be

calculated based on a 20 cm depth for the radioisotopes implanted in the patient's body and 100 cm of distance between the patients and the relatives. The total radiation dose to which a relative will be exposed is 0.0015 mSv (These dosages are all lower than the government standard, i.e. 1 mSv is the annual restrictive value of exposure accepted by the general public and 50 mSv is the annual restrictive value of exposure accepted by radiotherapists; the data were obtained from the Atomic Energy Research Institute of China).

Prevention and management of complications

Complications

The intraoperative and postoperative complications included mainly the pneumothorax (caused by direct puncturation and renewed swelling after atelectasis), hemoptysis, thoracalgia and the exfoliation of particles (caused by diminution of the tumor). Other overt discomfort did not occur to the present time.

Prevention and management

Pneumothorax is the major complication. The main points to avoid a pneumothorax are as follows: minimize the number of punctures, pass through the pleural layer as infrequently as possible, select reasonable needling points, avoid sudden exertion and sufficiently anesthetize the pleura to relieve a cough of the patients. A pneumothorax did not occur when the implant passed through the lung tissue with atelectasis, but the pneumothorax occurred afterward with a renewed relief of the atelectasis (one case occurred in the group). It is difficult to totally prevent this complication (Fig.9). If a pneumothorax occurs intraoperatively, with an excess of pneumothoraces (>30%), a T-tube is used to exhaust the bulk of the gas (two cases occurred in the group). If it happens postoperatively, one must observe it carefully and prepare to release the gas at any time. In any case, if the pneumothorax is less than 30%, and the patient has no apparent symptoms such as being short of breath or having chest distress, etc., one should follow it carefully, until it is later absorbed. Generally the

complete absorption needs four to 14 days. Another possible complication is hemoptysis. Hemostatic and antitussive agents are usually utilized after the operation, and physical activities are reduced. Breakdown of the particles (one case occurred in the group) is caused by the diminution of the tumor. Although the radioisotopes were placed in the focus first, they were found 1.5 cm or more away from the margin of the focus. The extent of the shrinkage of the tumors still was more than expected and caused breakdown of the particles, thus transferring the radioactive particles to the far end of the lung by the bronchus or the arterial blood vessel (Fig.14). So the implant of radioisotopes should be placed as close as possible to the center of the focus.

In summary, CT guided treatment for central type lung cancer and its metastases by implantation of ^{125}I radioisotopes has the merits of significant efficacy, few side effects and minor complications. It does not cause lesions of the peripheral tissue as a result of treatments, such as surgical operations or external radiotherapy, etc. and serves to maintain maximum pulmonary function. However, whether or not the therapy has a definite preventive effect on the metastasis requires further study. The application of a combined CT three-dimensional planning system will produce a precise location and allow a more uniform distribution of the radiation dose. The curative effect by implants of ^{125}I radioisotopes for treatment of central-type lung cancer and its metastases is significant, and deserves wider application.

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