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Analysis of the Long-term Effect of Intraoperative Radiotherapy (IORT) for Non-Small Cell Lung Carcinoma (NSCLC)

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OBJECTIVE To analyze the long-term effects of treatment with an operation + postoperative irradiation (A group) and an operation+intraoperative radiotherapy+postoperative irradiation (B group) in non-small cell lung cancer patients.

METHODS Through a prospective randomized clinical trial, a total of 154 patients with non-small cell lung carcinoma were divided into two groups of 77 cases. Among the 154 cases, there were 134 squamous carcinomas, 17 adenocarcinomas and 3 adeno-squamous carcinomas. TNM staging: there were 17 in Stage Ⅰ, 76 in Stage Ⅱ and 61 in Stage Ⅲ. A dosage of 15~25 Gy IORT, energy 9~16 MeV electrons, was delivered to the tumors. The doses given were 40~60 Gy postoperation.

RESULTS The local control rates in A and B groups were 49.4% and 62.3% respectively (P<0.05). The survivals at 3, 5 and 7 years for group A were 40.3%, 27.3%, and 5.2% and for group B 44.2%, 28.6% and 6.5% (P>0.05). There were 16 deaths from radiotherapy complications, with 2 cases in group A and 14 in group B.

CONCLUSION IORT+postoperative irradiation can enhance the local control rate of non-small cell lung cancer patients and reduce the recurrent rates, but it can not improve long-term survival.

KEYWORDS: lung neoplasms/surgery, lung neoplasms/radiotherapy, radiotherapy intraoperative, prognosis.

INTRODUCTION

The lung cancer occurrence rate ranks first among malignant tumors. Surgical resection is usually the choice of treatment at an early stage while comprehensive therapy is preferred for later stages. Most of the patients need comprehensive therapy with radiotherapy as a priority as patients at an early stage account for a small part of the overall population, and only 20%~30% are suitable for operations. Conventional radiotherapy can not produce a radical cure in most cases, as the peripheral tissues and structures limit an increase in the dosages of irradiation, while the local tumor-control rate increases in direct ratio to dosages of irradiation. Thus the overall 5-year survival with solitary radiotherapy has remained at about 10% for many years, but it may increase to 21%~43% with postoperative radiotherapy.

From October 1992 to December 1994, 154 patients with NSCLC in Stages Ⅰ~Ⅲ were randomized into two groups of 77 cases each for treatment as follows: an operation+postoperative irradiation group (A) and an operation+intraoperative radiotherapy

+postoperative irradiation group (B). The objective was to enhance the local irradiation dose to the tumor and reduce injury to the normal tissue around the tumor and by using IORT decrease the tumor recurrence with the prospect of improving long-term survival.

MATERIALS AND METHODS

Clinical material

There were 154 NSCLC patients with adequate pulmonary functions (KPS >70), at a median age of 57 years (ranging from 32 to 72). The diameters of the tumors ranged from a maximum of 8 cm × 7 cm × 6 cm to a minimum of 2.5 cm × 2.0 cm × 2.0 cm (median 5.0 cm × 4.5 cm × 4.0 cm). Gross characteristics of the two groups were comparable with details shown in Table 1.

Methods of operation

Operations of the A group were carried out in the operation room and of the B group at the treatment bed in the accelerator room. Both the operation room and the treatment bed were disinfected according to requirements before operations. Pulmonary segment resection, lobe resection, removal of all the lung or exploratory operations were conducted based on the connections between the sites of the tumor and the surrounding tissues and organs. Information on those resections is in Table 2.

Intraoperative radiotherapy methods

With regard to unresectable tumors as well as the residual tumor left after an all-tumor or partial resection, specially made electron-beam applicators of different specs and sizes, chosen in accordance with the residual volumes, the sites of the tumor as well as the adjacent lymphatic drainage area, were focused on and inserted into the exposed area, upon which the gantry was circumgyrated and set perpendicular to the treatment bed. Then the irradiation was started, with the normal lung tissues excluded along with the immovable esophagus and heart which were sheltered by a lead sheath. The irradiation area depended upon the type of operation conducted: for an unresected tumor, the primary tumor area was irradiated; for an all-lung resection or lobe resection, the mediastinum, hilum of the lung, and carina lower lymphatic drainage area were exposed to irradiation; and if a wedge resection was conducted or the lymph nodes of the lung hilum showed negative, only the resected nidus area was irradiated. During the 10 min of irradiation, patients were observed with closed-circuit TV. Different dosages of IROT were delivered in terms of the depth of the operation, and the electron energy was 9~20 MeV. A level of 9~12 MeV and 12~20 MeV was delivered to the tumor bed and lung hilum as well as the mediastinum area, respectively, with the irradiation dose of 15~25 Gy. And both of the two parts were irradiated for the two cases (lung hilum, mediastinum lymphatic drainage area and tumor bed). Electron-beam applicators used were made of special organic glass. There were two types of electron-beam applicators applied here, three varieties of round ones (with diameters of 6 cm, 7 cm and 8 cm respectively) and oval ones (spec: 5 cm × 9 cm). Eight cm-diameter round electron-beam applicators and oval ones

Table 1. Clinical data(cases).

Groups	Sex		Position		Pathological type			Clinical stages		
	M	F	Right	Left	Squa	Aden	Squa-Aden	I	II	III
A	65	12	45	32	66	9	2	9	37	31
B	68	9	43	34	68	8	1	8	39	30
χ^2	0.22		0.03		0.42			0.13		
P	0.938		0.639		0.871			0.810		

Table 2. Methods of operation and doses of postoperative irradiation.

Groups	Sex		Methods of operations				Doses of postoperative irradiation (Gy)		
	M	F	PSR	LR	ALR	EXO	40	50	≥60
A	65	12	6	59	7	5	21	36	14
B	68	9	5	64	5	3	49	17	3

PSR=pulmonary segment resection; LR=lobe resection; ALR=all lung resection; EXO=exploratory operation.

were applied for the lung hilum and mediastinum lymphatic drainage area and 6 cm- or 7 cm-diameter round ones for the tumor bed. Electron-beam applicators were connected with the gear end of the accelerator through specially-made adaptors and the Source-Surface Distance was 110 cm. Exposed parts, doses and specs of electron-beam applicators as well as other detailed information are displayed in Table 3.

Table 3. Data for IORT.

IORT	Cases M	F
Diameter of applicator cone (cm)		
6	3	1
7	8	2
8	46	5
5×9	18	2
Energy (MeV)		
9	31	3
12	34	4
16	6	2
20	4	1
Doses (Gy)		
15	13	2
20	54	7
25	8	1
Positions		
Tumor	3	0
Bed of tumor	7	2
Lung hilum and mediastinum	65	8

Postoperative irradiation

X-ray and conventional fractionation were adopted. In Group A, 6 out of 9 cases with Stage I surrounding NSCLC did not go through postoperative radiotherapy (tumor diameter was smaller than 3 cm and there were no metastasis in the lymphatic nodes in the mediastinum). In Group B, 8 cases with a surrounding lung tumor also were not exposed to the radiotherapy. Among the 9 cases receiving 25 Gy of IORT in Group B, 3 were given doses of 70 Gy for postoperative irradiation after an exploratory operation, 4 were administrated 50 Gy and 2, 40Gy. Among the 61 cases given doses of 20 Gy of IORT (2 sites of 5 patients each were under IORT), 2 received a dose of 50 Gy after operations, the rest were given 40 Gy. All the 15 cases given a dose of 15 Gy of IORT (2 sites of 3 patients each were through IORT) received 60 Gy of postoperative irradiation. The details on the postoperative irradiation are showed in Table 2.

Follow-up survey

Until September 2003, 15 cases failed for follow-up and were accounted as having died, among which 9 were from the operation group and 6 from the IORT group. The follow-up rate was 90.3%.

Statistical methods

The survival rate was accounted directly and the significance of difference was determined by the χ^2 test.

RESULTS

Survival rate

Survival in Group A ranged from 4 to 92 months and for group B from 3 to 98 months. The relations between the survival rate and clinical phases/pathological classification/postoperative irradiation dosage are displayed in Tables 4~6. But the difference between the clinical phases and pathological classification in the two groups demonstrated no statistical significance (χ^2=2.36, P>0.05), while the difference between Stages I and III as well as the variable pathological classification was statistically significant (χ^2=4.57, P<0.05). In group A statistical significance was identified in the survival difference of 3 years and 5 years after being given 40, 50 or 60 Gy doses of postoperative irradiation (χ^2=5.08, 3.97, P<0.05). The survival-rate difference in Group B demonstrated no statistical significance (χ^2=2.86, 1.95, P>0.05). No statistical significance was noted in the survival difference of patients receiving 40 or 60 Gy in both groups (χ^2=2.03, 1.84, P>0.05). In Group B, 3, 5 and 7 year survival rates were 53.8%, 23.1% and 0% respectively after being given 15 Gy of IORT ; survival rates were 44.6%, 30.4% and 3.6% at 20 Gy , all 9 cases given 25 Gy ended in 0% survials.

Local tumor control and distant metastasis

Local control rates were 49.4% in group A and 62.3% in group B (χ^2=4.28, P<0.05). Distant metastasis rates of Group A and B were respectively 54.5% and 51.9% (χ^2=1.29, P>0.05).

Irradiation responses and long-term complications

After two weeks of external irradiation, 84.4% of the patients reported mild tracheal and esophageal reactions, such as irritant dry cough, expectorating phlegm and pharyngeal pain which would often lesson or simply disappear without special treatment. Among the patients 27.3% developed serious symptoms and were given temporary remedies, such as taking oral prednisone or a cod-liver oil mixture. The rates of pneumonia development following irradiation were 8.5 % (6/71) in group A and 11.7 % (9/77)

Table 4. Clinical stages and survival rate.

Groups	Cases	Survival rate at 3 y (%)				Survival rate at 5 y (%)				Survival rate at 7 y (%)			
		I	II	III	Total	I	II	III	Total	I	II	III	Total
A	77	77.8	48.6	19.4	40.3	55.6	37.8	6.5	27.3	22.2	5.4	0	5.2
B	77	87.5	53.8	20.0	44.2	75.0	38.5	3.3	28.6	25.0	7.7	0	6.5
χ^2		1.73				1.35				1.09			
P		>0.05				>0.05				>0.05			

Table 5. Pathological type and survival rate.

Groups	Cases	Survival rate at 3 y (%)				Survival rate at 5 y (%)				Survival rate at 7 y (%)			
		Squa	Aden	Squa-Aden	Totle	Squa	Aden	Squa-Aden	Totle	Squa	Aden	Squa-Aden	Totle
A	77	43.9	22.2	0	40.3	30.3	11.1	0	27.3	6.1	0	0	5.2
B	77	48.5	12.5	0	44.2	30.9	12.5	0	28.6	7.4	0	0	6.5

Table 6. Doses of postoperative irradiation and survival rate.

Groups	Cases	Survival rate at 3 y (%)				Survival rate at 5 y (%)				Survival rate at 7 y (%)			
		40 Gy	50 Gy	≥60 Gy	Total	40 Gy	50 Gy	≥60 Gy	Total	40 Gy	50 Gy	≥60 Gy	Total
A	77	14.3	52.8	50.0	40.8	4.8	30.6	35.7	23.9	0	2.8	7.1	2.8
B	77	40.8	58.8	0	43.5	26.5	29.4	0	26.1	2.0	5.9	0	2.9

in group B. In Group B, two patients died of massive hemorrhage of the esophagus after external irradiation, one at 9 months and the other at 12 months. Three were diagnosed with an esophageal fistula, one each at 2, 4, and 7 months after irradiation. Among these patients, one died of cachexia at 62 months after a gastrostomy operation, and the other two died of lung infections.

Causes of death

All patients have died. In Group A, two cases died of respiratory failure caused by lung fibrosis(both cases were given a dose of 70 Gy irradiation at the mediastinum and regional tumor after exploratory operations), 42 of overall recurrent metastasis , 29 of partial tumor recurrence and metastasis [18 cases (85.7%) were given 40 Gy and 11 cases (30.6%) of 50 Gy], and four from non-tumor diseases. In Group B, two cases died of massive hemorrhage of the esophagus, three of esophageal fistula (all received 20 Gy IORT; two of them 50 Gy postoperative irradiation and the other three 40 Gy), two died of pneumonia following irradiation, seven of respiratory failure from lung fibrosis (all were given 25 Gy IORT; three of them 70 Gy postoperative irradiation and the other four 50 Gy), 40 of overall recurrent metastasis, 18 of regional tumor recurrence and metastasis(15 given 40 Gy irradiation and 3, 50 Gy) and five died from non-tumor diseases.

DISCUSSION

IORT involves irradiation on the tumor or tumor bed after the tumor resection is completed, or at the time the tumor is thoroughly exposed. Such therapy has the advantages that the healthy tissues and structures peripheral to the tumor can be exempted from irradiation, and even tissues and organs that are impossible to move can be totally lead-sheathed from irradiation. The aim of IORT is to increase the dosage of regional irradiation on the tumor or tumor bed and to reduce the local recurrence rate. IORT on NSCLC was first introduced in 1959 and has now been in use for 40 years[1]. However, there are very few literaure reports related to IORT as most experts believe that the distant metastasis rate of lung cancer is quite high, so that to simply increase the regional dosage of irradiation makes little sense for long-term survival. By the end of 2003[2-5], there had been no more than 300 cases reported in China and abroad, and no reports on randomized assignment research based on a large number of patients. Among 17 cases reported from France, the 1-, 2-, 3-, 5- year survival rates were 81.2%, 50.0%, 37.5% and 22.5% respectively; from Austria, 31 cases were reported, with a 5 year survival rate of 26%.

According to Zeng et al.[6], 33 cases showed 1-, 3-, 5-year survival rates of 64.2%, 42.8% and 28.5% respectively. In our study, the 3 and 5 year survival rates were 44.2% and 28.6% which were similar to previous reports, demonstrating no difference with the 40.3% and 27.3% from conventional postoperative radiotherapy in terms of long-term survival rates. The absence of postoperative whole-body chemotherapy is the probable chief cause of the rate decrease. Patients who died of distant metastasis accounted for

54.5% and 51.9% in Groups A and B. Considering the next cause of death, local tumor relapse and metastasis were also responsible for deaths with 37.7% and 23.4% in the two groups respectively. Most of these patients had received 40 Gy of postoperative irradiation (85.7% and 30.6% respectively), while those who were given 50 Gy of postoperative irradiation who died of the two causes made up only 30.6% and 17.6% of Group A and B. Statistics demonstrated that the local relapse rate of those who received less than 50 Gy of postoperative irradiation, was apparently higher than those receiving above 50 Gy. Though in Group B, the postoperative dosage was no less than 50 Gy at the hilum of the lung and mediastinum and was included in IORT, it was impossible for the lymphatic drainage to be thoroughly exposed to radiotherapy with the irradiation limited to the tumor area. Local relapse and metastasis is likely to occur when some sites are given only 40 Gy of postoperative irradiation, which is barely enough to prevent a future recurrence.

The dosage of IORT also exerts an influence on the overall survival rate. Research in our group indicated that there were no 3-year survivals exposed to a single dose of 25 Gy. The reason might be that the excessive single dosage gave rise to increasing complications; while the 5-year survival of 20 Gy treated cases demonstrated no statistical difference from that of 15 Gy. According to the meta analysis of the Nebitt reports on mass cases[7], the 5-year survival rate of NSCLC at Stages I and II were 64.6% and 41.2% respectively after solitary operations. Domestic reports related to the results of the operation and postoperative radiotherapy on NSCLC patients at Phase T1~T3N1~N2M0 without naked-eye and under-lens tumor residuals, showed that the 5-year survival rates following the solitary operation and postoperative radiotherapy were 28.1% and 29.3% respectively, and that the local control rates of the two were 55.1% and 68.5% respectively.

Comparision of Group A and B showed a statistically significant difference in the local control rate (P=0.036) but no difference was found in the survival rate. Five-year distant metastasis rates of the two Groups were 36% and 44%. We believe that the local control rate rather than the survival rate can be increased with postoperative radiotherapy for patients in Stages I and II NSCLC with lung hilum and mediastinum lymph node metastasis. The overall long-term survival rate for Stages II and III cases of our group showed little difference compared to reports and in the literature, yet the dosage of postoperative irradiation has an influence on the survival rate. Patients with 50 Gy of irradiation of both groups showed an apparently high survival rate compared with those given 40 Gy and 60+Gy. Because 40 Gy of postoperative radiotherapy is barely sufficient to prevent a future tumor, the local control rate declines; while in the B group with a dose of 60 Gy and an increasing local tumor control rate, the distant complications increased since such a dose plus the IORT is too much to bear, and consequently the subsequent survival rate shows no increase. Therefore postoperative radiotherapy of 50 Gy is recommended. Besides, the 5-year survival rate is also influenced by variable pathological types and the range of the resection, for example, the 5-year survivals of bronchioloalveolar carcinoma and adenocarcinoma patients at Stages I were 91% and 63%, respectively, and that of lobectomy and segment resection were 75.2% and 55.0%, respectively.

Experts from the Shanghai Chest Service Hospital pointed out, after analyzing 2,636 cases of lung carcinoma operations, that the overall 5-and 10-year postoperation survivals were 40.6% and 29.8%, respectively. Especially, the 5-year survivals of Stages I, II and III cases were 58.3%, 33.6% and 26.4%, respectively, and the 10-year survival of the three stages were 44.6%, 23.8% and 17.8%. Furthermore, the type of the structure or tissue is also related to the survival rate. For example, the 5-year survival of squama carcinoma patients was 47.9% while that of adenocarcinoma cases only 35.7%. However there was no explanation as to whether adjuvant radiotherapy or chemotherapy was conducted at postoperation. Also, results of our research indicated that the type of pathology had an effect on subsequent survival, as squama carcinoma and adenocarcinoma cases displayed an obvious difference.

Survival rates decrease with the occurrences of distant complications as well. In the B group, 14 cases died of irradiative complications, the cause possibly being the excessive irradiation administered in both the IORT and postoperative radiotherapy. A dosage of 15～25 Gy of IORT and 40～60 Gy was applied postoperatively. If a certain site was given the two irradiation treatments successively, the overall dosage it received added up to no less than 90~110 Gy, with the biological effect of an irradiation in an amount of 2～4 times of that applied in conventional external irradiation. In cases as this, the local control rate was higher than that of the A group, yet causes of death due to distant complications apparently increased, and as a result the subsequent survival dropped. Complications caused by IORT included esophagitis, esophagostenosis, pneumonia, stump fistula, etc. According to the report of Calvo et al.[8], the occurrence rates of bronchial stump fistula, pneumonia and irradiation

esophagitis were 8%, 18% and 35.3%, respectively. In our study, the distant complications that gave rise to death included irradiation pneumonia (2 cases), respiratory failure caused by a pulmonary fistula (9 cases), massive hemorrhage of the esophagus (2 cases), and esophageal fistula (3 cases) with an overall occurrence rate amounting to 10.4%. The massive hemorrhage and fistula were caused because, at first, the esophagus was exposed to IORT rather than being covered by a lead sheath, and with the later postoperative irradiation, the accumulated irradiation was beyond the regional tolerance dose. In the later cases, lead sheaths were installed and such complications did not develop.

In summary, according to our research, IORT can indeed raise the local tumor control of lung carcinoma patients, but the overall subsequent survivals were far from being increased since no effective measures were taken to prevent or reduce distant metastasis. Whole-body chemotherapy before or after the operation might be useful to increase survivals.

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