A Randomized Study of Involved-Field Irradiation Versus Elective Nodal Irradiation in Combination With Concurrent Chemotherapy for Inoperable Stage III Nonsmall Cell Lung Cancer

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Background: Radiation dose escalation is limited by the high incidence of pulmonary and esophageal toxicity, leading to calls for the omission of elective nodal irradiation (ENI) and the willingness to use involved-field irradiation (IFI) in patients with nonsmall cell lung cancer (NSCLC).

Methods and Materials: A total of 200 eligible patients with inoperable stage III NSCLC were treated with concurrent chemoradiotherapy and randomized into either an IFI or ENI arm. A total of 4 to 6 cycles of cisplatin-based chemotherapy were delivered, and concurrent radiotherapy was started after the second cycle of chemotherapy. Three-dimensional conformal radiotherapy was delivered in once-daily fractions of 1.8 to 2 Gy to 68 to 74 Gy for IFI or 60 to 64 Gy for ENI.

Results: Patients in the IFI arm achieved better overall response rate (90% vs. 79%, $P = 0.032$) and better 5-years local control rate (51% vs.36%, $P = 0.032$) than those in the ENI arm. The radiation pneumonitis rate in patients with IFI was lower than in patients with ENI (17% vs. 29%, $P = 0.044$), and similar trends appeared in the radiation esophagitis, myelosuppression, and radiation pericarditis between 2 study arms, although not significantly. The 1-, 2-, and 5-year survival rates were 60.4%, 25.6%, and 18.3% for the ENI arm and 69.9%, 39.4%, and 25.1% for the IFI arm, respectively. Only the 2-year survival rates were statistically significant ($P = 0.048$).

Conclusion: IFI arm achieved better overall response and local control than ENI arm, and it allowed a dose of 68 to 74 Gy to be safely administered to patients with inoperable stage III NSCLC. Outcome improvement can be expected by conformal IFI combined with chemotherapy for stage III NSCLC.

Key Words: nonsmall cell lung cancer, involved-field radiotherapy, elective nodal irradiation, survival

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Concurrent chemoradiation is the standard of care for unresectable patients with stage III nonsmall cell lung cancer (NSCLC). However, overall survival remains poor because of both local and distant failure. Furthermore, there is a relationship between the lack of local control and subsequent distant metastases.[1] Dose escalation is one way to improve local tumor control and survival, but it is limited by the high incidence of pulmonary and esophageal toxicity.[2,3] These factors are leading to call for the omission of elective nodal irradiation (ENI) and the willingness to use involved-field irradiation (IFI).[4,5] The European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend the use of three-dimensional IFI as a method to reduce the volume of irradiated esophagus and lung.[6] However, concerns about recurrences in the nodal regions, which are not included in the gross target volume (GTV), have limited the willingness to use IFI. A prospective study of chemoradiotherapy was performed to determine the value of IFI administrated by three-dimensional conformal technique for patients with stage III NSCLC.

PATIENTS AND METHODS

In the prospective study, eligible patients were randomized into group either current chemotherapy plus ENI (ENI arm) or current chemotherapy plus IFI (IFI arm) at 1:1 at day 1 of the therapy by a statistical office not involved in the trial.

Patients

This study was conducted according to existing rules for good clinical practice, and the protocol was approved by the local ethics committee. All patients signed informed consents before entry into the study. Those entered into this

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The Institutional Review Board of the hospital approved the study, which complied with the current laws of the state of China, inclusive of ethics approval. Informed consent was obtained from each patient before he or she was enrolled in this study.

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trial were patients with a cytologic or histologic diagnosis of NSCLC; medically or surgically inoperable stage IIIA or IIIB; 18 to 80 years of age; with no prior chemotherapy, immunotherapy, or radiotherapy. Other inclusion criteria were tumor and/or nodal masses ≤6 cm in maximal diameter, a forced expiratory volume in 1 second of ≥30% of the predicted value, normal organ function and fitness for induction chemotherapy, a Karnofsky performance status of ≥80, a weight loss of ≤10% of baseline in the preceding 6 months, an absence of distant metastases on a diagnostic CT scan of the thorax and abdomen, and an isotope bone scan. Patients with prior malignancy were ineligible as were those presenting with supraclavicular nodal metastases, superior vena cava syndrome, pleural effusion, and mixed histologic findings with a component of small cell lung cancer.

Chemotherapy

Patients were treated with 4 to 6 cycles of chemotherapy given every 3 weeks that consisted of a 2-drug combination. Etoposide was administered 75 mg/m^2 per day on days 1 to 5, and cisplatin was administered 25 mg/m^2 per day on days 1 to 3. Dose adjustments or delays were made when hematologic toxicity occurred. Redosing was only permitted when the WBCs were $>3.0 \times 10^9$ L^{-1}, neutrophils $>1.5 \times 10^9$ L^{-1}, platelets $>100 \times 10^9$ L^{-1}, and no clinical signs of infection existed. If these conditions were not fulfilled, the blood counts were repeated after 1 week. Dose reductions were applied for nadirs (platelets $<50 \times 10^9$ L^{-1}; neutrophils $<0.5 \times 10^9$ L^{-1}) with a 25% reduction in the etoposide dose, and a 15% decrease for the cisplatin dose.

For any nonhematologic grade 3 toxicity (except untreated nausea, vomiting and alopecia), the treatment was delayed until recovery.

Antiemetics were given as prophylaxis according to the local practice. The use of growth factors and prophylactic antibiotics was allowed if necessary.

Radiotherapy

The mandatory radiotherapy planning CT scan, with intravenous contrast, was acquired shortly after the end of the first cycle of chemotherapy. The scan area extended from the cricoid cartilage to the second lumbar vertebra using a maximal slice thickness of 5 mm while the patient was immobilized in a supine position on a lung board breathing freely (Picker 2000 CT scanner). The CT data were transferred to the initial computer terminal of the three-dimensional planning system (ADAC-Pinnacle^3, version 5.0). Then target contouring was performed in accordance with a standard protocol.[7] The prechemotherapy gross tumor volume (GTV) was reconstructed for treatment planning. However, the maximal tumor extent on either the prechemotherapy or postchemotherapy CT scan was used to define the GTV when a mixed response or progressive disease was observed on a lung window after chemotherapy. The planning target volume (PTV) for IFI was the primary tumor and all clinically or radiologically involved lymph nodes with a short-axis diameter of ≥1 cm.

The outer wall of the esophagus, lung, and heart along with the spinal canal (which was taken to represent the cord) were contoured on all slices. A software tool was used to derive a three-dimensional margin of 10 to 20 mm around the tumor (depending on the location and/or mobility of the GTV), and a margin of 5 mm around any enlarged mediastinal nodes to derive the PTV of IFI,[8] where a dose of 68 to 74 Gy was delivered over 7 to 9 weeks.

The target volume of ENI included the primary tumor, as described above, and the ipsilateral hilum, mediastinum (from the inferior head of the clavicle through 50–80 mm below the carina), and sometimes the supraclavicular fossa (only for patients with superior mediastinum metastasis), even if there was no evidence of disease in these areas.[9] A dose of 44 Gy was delivered to the PTV prescribed above. Then a CT scan was performed to define the remnant focuses that would accept an escalated dose of 16 to 20 Gy. An overall dose of 60 to 64 Gy was delivered over 6 to 7.5 weeks for patients with ENI.

Megavoltage equipment was used with photon energies of 6 or 8 MV using a multileaf collimator to shape the irradiation portals according to the target volume, and the planned dose of 1.8 to 2 Gy was delivered once daily to the isocenter in 5 fractions weekly using 5 to 6 coplanar fields.

Quality Assurance for Radiotherapy

The optimization for the composite plan was performed to meet the requirements in all patients. 1) The 90% isodose volume covered the entire PTV. 2) The dose variation within the PTV was limited to between 7% and −5% of the prescribed dose. 3) The maximal spinal cord dose did not exceed 45 Gy. 4) The volume of heart receiving a dose ≥45 Gy did not exceed two thirds. 5) The volume of residual lung tissue receiving a dose ≥20 Gy (V20) was kept to a minimum and did not exceed 35% since these parameters predict the risk of radiation pneumonitis.[10] The V20 was derived by subtracting the PTV from the total lung volume. 6) The setup at the treatment unit was determined using an electronic portal imaging device with an off-line correction protocol. A dose-volume histogram was typically produced with a review of the GTV, normal lung, esophagus, heart, and spinal cord. Normal tissue complication probability was calculated at the completion of all treatment planning for data analysis. If the normal tissue complication probability was above 25%, the radiation dose was reduced to a level below the threshold, which leading to a range of radiation dose (ENI, 60–64 Gy; IFI, 68–74 Gy).

Evaluation Criteria

The tumor response was classified according to the World Health Organization criteria,[11] and the final results were recorded when the overall treatments were completed. Acute radiation-induced toxicity was graded according to the RTOG scale.[12] The diagnosis of acute radiation pneumonitis was based on clinical symptoms such as shortness of breath, cough, and fever, after excluding other causes for these symptoms such as infection or tumor progression, as well as correlation with radiologic findings. Overall survival and

time to progression were derived for all eligible patients from the time of registration.

Follow-up of Patients

Patients were assessed 6 to 8 weeks after radiotherapy and then every 3 months for the first 2 years. Both CT scans of the thorax and upper abdomen were performed at 3 and 6 months after treatment completion and, subsequently, when warranted by changes on the chest x-ray or by symptoms. The time between each follow-up visit was usually lengthened to 4 to 6 months if the patient had no evidence of recurrence after 2 years.

Statistical Analysis

This was a single-center prospective study with local control rates as the primary endpoints. Some trials have documented pathologic local failure rates as high as 85% after 65 Gy in unresectable NSCLC.[3] With concurrent chemotherapy and IFI to 70 Gy, a clinical local control rate of more than 50% was expected and a smaller clinical local control rate of 35% for the concurrent chemotherapy and ENI to 60 Gy was assumed. With a power of 0.8 and a P value of 0.05, each treatment group required 100 qualified patients. Overall survival and time to progression were derived for all eligible patients on an intention-to-treat basis using the Kaplan-Meier method. Time to disease progression was calculated from the date of registration to the date of disease progression or death. If disease progression had not occurred by the time of this analysis, progression-free survival was considered censored at the time of the last follow-up. Survival time was measured from the date of initiation of treatment to the date of death. If death had not occurred, survival time was considered censored at the last follow-up time. All eligible patients were included in the analysis of response, chemoradiation-induced toxicity, local control, and failure patterns on an intention-to-treat basis. All comparisons of clinical characteristics, response rates, and toxicity incidences were performed using the ANOVA test.

RESULTS

From October 1997 to November 2001, 200 patients were entered and randomized into either an IFI arm or an ENI arm at 1:1 at day 1 of treatment by a statistical office not involved in the trial. Patient ages ranged from 28 to 76 years, with median ages of 62.5 years in the ENI arm and 63.5 years in the IFI arm. The clinical characteristics of these patients are listed in Table 1. There was no statistical difference in the clinical characteristics of the 2 arms of treatment in terms of sex, age, stage, performance status, histology, and tumor position. Of the patients enrolled, 2 patients in the ENI arm and 2 patients in the IFI arm refused the intended radiotherapy plan, leaving 196 patients (98 in ENI arm and 98 in IFI arm) who agreed to the intended treatment plan. Altogether, 7 patients were lost to follow-up within 3 to 12 months following treatment completion. The median follow-up time was 27 months (range, 3–90 months).

TABLE 1. Clinical Characteristics of NSCLC Patients

Clinical Characteristic	ENI (%)	IFI (%)	P
Sex			0.069
Male	64	67	
Female	36	33	
Median age (year) (range)	62.5 (28–74)	63.5 (30–76)	
Karnofsky performance status			0.611
70–80	42	37	
80–90	50	56	
90–100	8	7	
Weight loss			0.827
None (n)	74	77	
1%–5% (n)	24	20	
5%–10% (n)	2	3	
Stage TNM			0.533
IIIA	63	61	
IIIB	37	39	
Histology			0.741
Adenocarcinoma	54	49	
Squamous cell carcinoma	42	44	
Large cell carcinoma	4	7	
Tumor position			0.086
Left lung	49	39	
Right lung	51	61	

There was no statistical difference in patient clinical characteristics between the 2 treatment groups.

Treatment Toxicity

The details of toxicity are summarized in Table 2. No treatment-related mortality was found. More than half of the patients experienced grade 1 or 2 acute radiation esophagitis and were treated with an oral analgesic; it occurred in 56% of patients in the ENI arm and 52% of patients in the IFI arm ($P = 0.570$). Five percent of patients with ENI and 4% of patients with IFI experienced grade 3 acute esophagitis and were given intravenous hydration. Myelosuppression was tolerable for most patients in any group: grade 3 or 4 myelosuppression was seen in only 4% of patients with ENI versus 2% of patients with IFI, while grade 1 or 2 myelosuppression occurred in 27% of patients with ENI versus 18% of patients with IFI. Grade 1 or 2 radiation pericarditis was seen in 14% of patients with ENI versus 11% of patients with IFI. There were no documented cases of transverse myelitis or grade 3 or 4 pericarditis.

The radiation pneumonitis rate of patients in the ENI arm was significantly higher than patients in the IFI arm (29% vs. 17%, $P = 0.044$). Grade 1 or 2 radiation pneumonitis developed in 26 patients with ENI and 16 with IFI. Four patients experienced grade 3 radiation pneumonitis (3 in the ENI arm and 1 in the IFI arm). Dose volume histogram analysis has shown that a strong correlation was seen between V20 and the development of this complication. Only 45% of patients in the ENI arm had a V20 value $<20\%$, which was significantly lower than the 75% in the IFI arm ($P < 0.001$) (Table 3).

TABLE 2. Details of the Treatment Toxicity

	No. Patients (%)		
Toxicity	**ENI**	**IFI**	***P***
Radiation esophagitis	61	56	0.473
Grade 1	37	40	0.663
Grade 2	19	12	0.171
Grade 3	5	4	0.776
Grade 4	0	0	
Myelosuppression	31	20	0.074
Grade 1	5	3	0.470
Grade 2	22	15	0.202
Grade 3	4	2	0.407
Grade 4	0	0	
Radiation pericarditis	14	11	0.521
Grade 1	12	10	0.65
Grade 2	2	1	—
Grade 3	0	0	—
Grade 4	0	0	
Radiation pneumonitis	29	17	0.044
Grade 1	8	6	0.579
Grade 2	18	10	0.103
Grade 3	3	1	—
Grade 4	0	0	

TABLE 3. Lung V_{20} of NSCLC

	No. Patients (%)		
Lung V_{20}	**ENI**	**IFI**	***P***
<20%	45	75	<0.001
20%–25%	35	18	0.007
26%–30%	15	6	0.040
≥30%	6	1	0.056

Response Rate

In the ENI arm, a complete response was seen in 27% of patients, a partial response in 52%, stable disease in 15%, and progressive disease in 6%, while in the IFI arm, a complete response was seen in 35% of patients, a partial response in 55%, stable disease in 8%, and progressive disease in 2%. Patients in the IFI arm achieved a better overall response rate than those in the ENI arm (90% vs. 79%, $P = 0.032$) (Table 4).

Local Control Rate and the Patterns of Failure

Patients who had an initial radiographic response to treatment and a stable mass at each follow-up visit were considered to have local control; patients were considered to have local failure only if clinical, radiographic, or biopsy evidence of progression was observed in the primary tumor or local region. Among them, any first site of failure in involved volume in IFI arm and the corresponding region got full dose irradiation in the ENI arm was considered involved field failure; any first site of failure in region only got prophylactic irradiation in the ENI arm and corresponding region initially

TABLE 4. Overall Response Rate 6 to 8 Weeks After Radiotherapy

	No. Patients (%)		
	ENI	**IFI**	***P***
Overall response	79	90	0.032
Complete response	27	35	—
Partial response	52	55	—
Stable disease	15	8	—
Progressive disease	6	2	—

uninvolved lymph node in the IFI arm was defined as elective nodal failure. The first site of local failure beyond the "prophylactic" was defined as "out of field failure." The outregional lymphatic node metastasis was recorded as distant metastasis.

The patients in ENI arm had 1-year local control rate of 73%, 2-year local control rate of 51%, and 5-year local control rate of 36%, while patients in IFI arm achieved higher local control rate of 81%, 59%, and 51%, respectively ($P = 0.179$, 0.256, and 0.032, respectively). In other words, 64% of patients in the ENI arm and 49% in the IFI arm developed local failure within 5 years. Among them, elective nodal failure was only found in 4% of patients in the ENI arm versus 7% in the IFI arm within 5 years. Similarly, out-of-field failure was found in only 5% of patients in the ENI arm versus 4% in the IFI arm within 5 years. Involved-field failure were the main cause of local failure in both study arms, and this rate of ENI arm was significantly higher than that of IFI arm within 5 years (55% vs. 38%, $P = 0.016$).

Median Time to Progression and Overall Survival

The median time to progression from the start of therapy was 11.5 months for patients in the ENI arm and 17.0 months for those in the IFI arm ($P = 0.15$). Overall, patients with a PR had 9.0-month time to progression and patients achieving a CR had 23.0-month time to progression ($P = 0.027$).

Figure 1 shows the overall survival curves, with a median overall survival of 15.0 months (95% CI, 11.4–18.6 months) in the ENI arm and 20.0 months (95% CI, 14.8–25.2 months) in the IFI arm. The 1-, 2-, and 5-year survival rates were 60.4%, 25.6%, and 18.3% for the ENI arm and 69.9%, 39.4%, and 25.1% for the IFI arm, respectively. Statistical significance was noted only in the 2-year overall survival rates ($P = 0.048$).

DISCUSSION

Chemotherapy reduces the incidence of distant metastases but has only a modest effect on survival because of the high incidence of local recurrence for locally advanced NSCLC patients. This argues for more aggressive local treatment that can improve survival.[2,3,8,13] However, dose escalation is limited by the sensitivity of the pulmonary tissue to ionizing radiation. It is well recognized that not only the dose

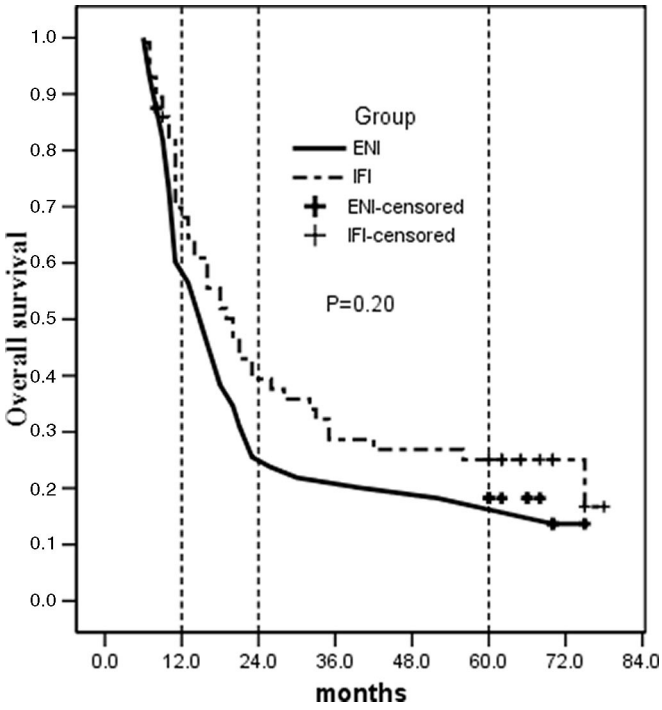

FIGURE 1. Overall survival curve for patients with IFI or ENI.

but also the volume is at play, and irradiation of large volumes increases the risk of radiation complications.

Elective irradiation of mediastinal lymph node has been shown to increase the risk of radiation complications. Furthermore, since combination chemotherapy has become the standard of care for patients with unresectable NSCLC, irradiation of larger volumes allows for more interactions between radiotherapy and chemotherapy, resulting in higher toxicity potential. When ENI was used, fatal radiation pneumonitis was the main dose-limiting factor, especially for patients with severely compromised lung function.[5] As such, efforts to improve local control with IFI may be a more realistic goal than attempting to irradiate the entire mediastinum to higher doses. Indeed, mediastinal nodes located in the proximity of the PTV often receive sufficient radiation doses for the treatment of occult metastases, particularly when doses of $\geq$70 Gy are prescribed.[14,15] On the other hand, chemotherapy reduces the incidence of distant metastases[16] and may also have an effect on occult metastases in unenlarged regional nodes.

This study was performed to evaluate IFI combined with concurrent chemotherapy in toxicity, local control, and overall survival for patients with stage III NSCLC, compared with ENI combined with concurrent chemotherapy.

No treatment-related mortality was found. For both arms of the study, more than half of the patients experienced grade 1 or 2 acute radiation esophagitis and were treated with an oral analgesic, while less than 5% of the patients experienced grade 3 acute esophagitis requiring intravenous hydration. The low incidence of acute grade 3 or 4 esophagitis observed in the IFI arm is not remarkable from the ENI arm because of different radiation doses and volume. Indeed, the potential high-grade esophagitis limited the dose escalation of ENI and IFI could enable a wider application of concurrent chemoradiation by reducing the risk of high-grade esophagitis.

By administering the drug G-CSF, myelosuppression was tolerable for most patients in either arm; grade 1 or 2 radiation pericarditis was seen in 14% of patients with ENI versus 11% of patients with IFI, while there were no documented cases of transverse myelitis or grade 3 or 4 pericarditis. The similar toxicities resulting from different radiation doses for the 2 study arms further reveals a potential wide application of IFI for stage III NSCLC.

The acute radiation pneumonitis rate in patients with ENI was significantly higher than in patients with IFI (29% vs. 17%, $P = 0.044$). Dose volume histogram analysis has shown that a strong correlation exists between V20 and the development of this complication. Only 45% of patients in the ENI arm had a V20 value $<$20%, which was significantly lower than the 75% in the IFI arm ($P < 0.001$), while the proportion of patients with a V20 value $\geq$26% in the ENI arm was significantly higher than in the IFI arm ($P < 0.001$). Altogether, 4 patients developed grade 3 or 4 acute radiation pneumonitis (3 with ENI and 1 with IFI), and all of them had a V20 value of $\geq$30%. The higher risk of radiation pneumonitis after chemoradiation may indicate the need to limit the use of such schemes on patients with V20 values $<$30%. All of these factors support the application of IFI.

Both arms did not get an ideal local control rate. In other words, the main cause of first site of failure was local progression in both study arms, with 49% of patients in IFI and 64% in ENI developing local recurrence within 5 years. Elective nodal failure was only found in 4% of patients in the ENI arm and 7% of patients with IFI within 5 years ($P = 0.352$). The results of the present study show that omitting ENI in this cohort of patients with stage III disease does not result in an increase in local failure. Conversely, the IFI arm achieved a better local control rate than the ENI arm (51% vs. 36%, $P = 0.032$).

These results indicate that elective nodal treatment does not play much of a role in stage III NSCLC. Indeed, the radiation dose emerged as the most important prognostic factor for overall survival in stage III NSCLC patients.[17] In this study, the IFI cases received a dose of 68 to 74 Gy, which was about 10 Gy higher than the ENI doses (60–64 Gy). A trend soon appeared indicating that IFI may result in a decrease in involved-field failure. The results of the present study show the improvement of the overall response rate in IFI compared with ENI (90% vs. 79%, $P = 0.032$), which may be attributed to the dose escalation. A more important outcome was the discovery of a significant difference in 2-year survival rates between the IFI and ENI study arms (36.1% vs. 25.6%, $P = 0.048$); the same trend appeared in the 5-year survival rates (25.1% in the IFI arm vs. 18.3% in the ENI arm). In the end, the omission of elective nodal irradiation did not sacrifice overall survival.

The results of this study are in accordance with several preceding reports of cases treated with IFI.[15,17] To best of our knowledge, no prior random study compared IFI and ENI in patients with NSCLC. Also, no long-term survival was reported for patients with inoperable NSCLC after IFI was combined with concurrent chemotherapy. The data presented here suggest that IFI in stage III NSCLC patients appears to be both beneficial and feasible. The omission of elective nodal treatment did not result in any increase in isolated nodal failures and may improve the outcome for stage III NSCLC.

While discovering that IFI offered a new perspective for NSCLC treatment, several drawbacks limited our study. First, FDG PET scans or other functional images were not available for this study, which might have impacted the clinical target volume to IFI. Our future studies will limit the clinical target volume to IFI, which should ideally incorporate information from FDG PET scans. Second, this study indicates that the current dose (70–74 Gy) in IFI is still scant; IFI must be combined with other interventions such as breath control, image-guided radiotherapy, or radiosensitizer. Third, the fact that distant metastasis continues to be a major site of failure calls for more effective chemotherapy schemes.

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