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Involved-Field Radiation Therapy (IF-RT) for Non-Small Cell Lung Cancer (NSCLC)

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1. Introduction

1.1 Patterns of lymphatic spread of Non-Small Cell Lung Cancer (NSCLC)

The pattern and incidence of lymphatic spread of non-small cell lung cancer (NSCLC) is differentiated according to location, size and histologic type of primary tumors. As the primary tumor size increases, the incidence of lymphatic metastasis increases. Ogata et al reported the incidence of mediastinal lymphatic metastasis increased from 24% for tumors under 2 cm in size to more than 40% for tumors larger than 5 cm [1]. Hata et al analyzed 192 lymphoscintigraphies in 179 patients to determine the lymphatic drainage from each segmental bronchus into the mediastinum [2]. For the right lobes, most of the lymph flowed into the right supraclavicular nodes through the subcarina or right paratracheal nodes. There were few drainages to the left supraclavicular nodes through subcarinal nodes. In contrast, the lymphatic drainage from the left lung was more variable, and four routes were determined, as follows.

1. The route through the subaortic nodes.
2. The route runs along the left phrenic nerve through the para-aortic nodes to the left supraclavicular nodes.
3. The route runs along the left main bronchus to the left hilar or the left prevascular nodes. From the left hilar nodes, this route divides into two branches. One extends to the right supraclavicular nodes through the right upper paratracheal nodes. The other runs upwards along the left side paratracheal nodes
4. The route runs under the left main bronchus to the subcarinal nodes. After passing the subcarinal nodes, this route extends to the right supraclavicular nodes along the trachea through the pretracheal nodes and the left upper paratracheal nodes. Some branches extend upwards along the left side of the trachea to the upper paratracheal and supraclavicular nodes.

Fig. 1 shows the standard patterns of lymphatic drainage [2]. These results suggest that most of mediastinal lymph node metastasis were found ipsilaterally in the right primary lung cancer, and the mediastinal or supraclavicular lymph node metastasis were found bilaterally in the left primary lung cancer. Nohl-Oser examined the location of nodal involvement in 749 patients based on data obtained via mediastinoscopy, scalene lymph node biopsy and surgical specimen (Table 1) [3]. The right upper lobe tumors spread to the right upper and

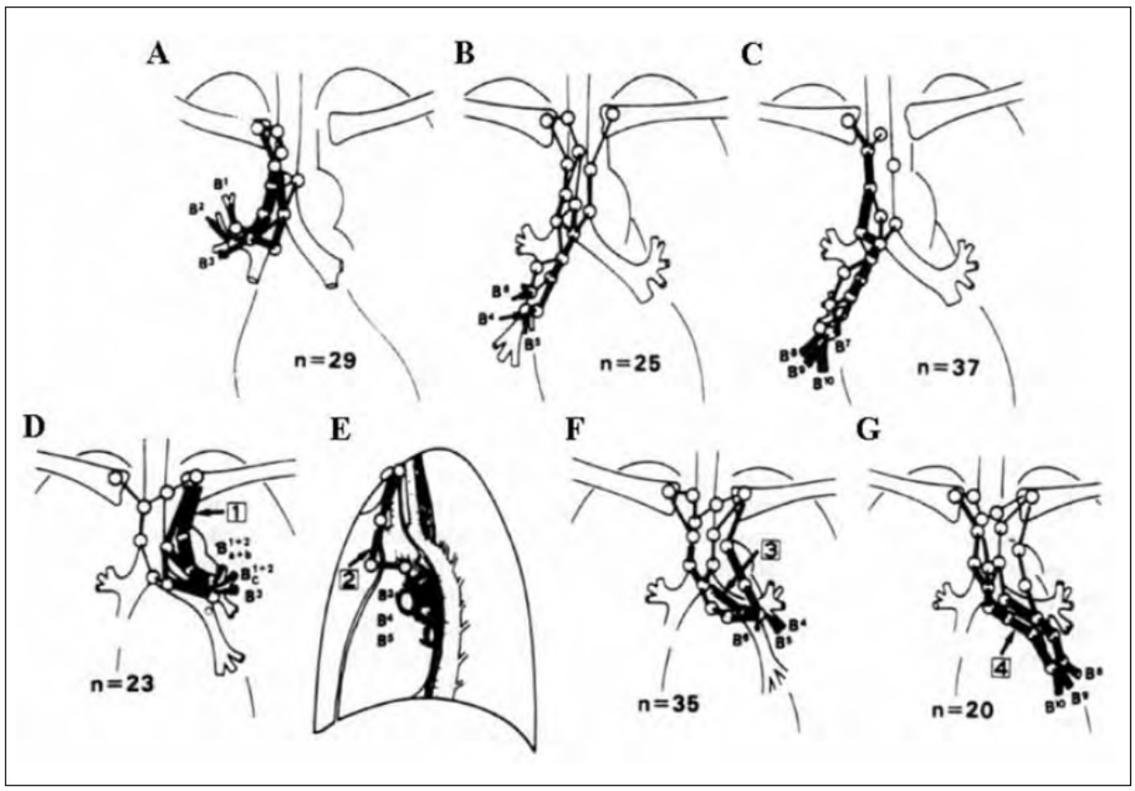


Fig. 1. A-G Standard patterns of lymphatic drainage. Each arrow shows the direction of the pathway of lymphatic drainage. The width of each the drain tubes indicates roughly the frequency of lymphatic drainage along each pathway. (From Hata E et al, References 2)

Lymph node location	Right upper (%)	Right lower (%)	Left upper (%)	Left lower (%)
Ipsilateral				
Scalene	27	10	13	5
Upper and lower tracheal	78	21	4	0
Tracheobronchial	36	9	46	15
Subcarinal	2	13	9	5
Contralateral				
Scalene	6	3	10	6
Upper and lower tracheal	1	1	10	6
Tracheobronchial	0	0	3	5
No. of patients	230	108	202	68

Table 1. Pattern of mediastinal lymph node metastases (From Nohl-Oser HC, References 3)

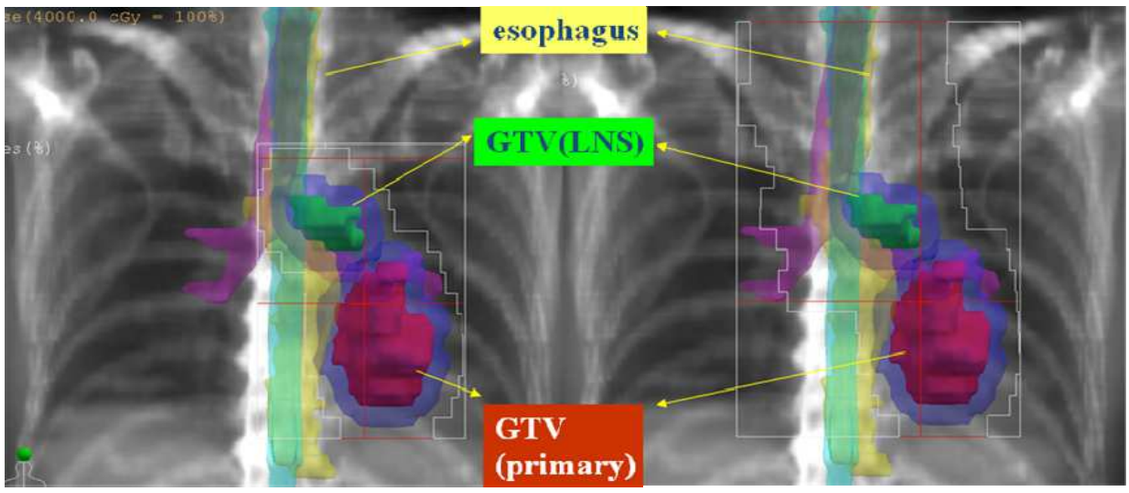
lower paratracheal and supraclavicular nodes and rarely to subcarinal nodes or to the contralateral nodes. In contrast, right lower lobe tumors spread to the right hilar and subcarinal nodes. Left lobe tumors might cross the midline, and the right mediastinal nodes might be invaded.

On the other hand, skip metastasis also occur more frequently in adenocarcinoma than in squamous cell carcinoma[4]. According to several authors, among cases without hilar node dissemination, routine mediastinal dissection revealed 6% unexpected mediastinal lymph node involvement (pN2), and an average of 34% of pN2 cases have mediastinal dissemination without hilar lymph node involvement [5].

2. The evidence of IF-RT – Is ENI needed?

In the standard radiation therapy for patients with unresectable advanced non-small-cell lung cancer (NSCLC), elective nodal irradiation (ENI) to the entire mediastinum, ipsilateral hilum and supraclavicular fossa has been deemed necessary due to anatomical lymphatic drainage and pathologic information regarding the high incidence of hilar and mediastinal node metastasis described Section 1. Recently, in order to improve the local control without increasing normal tissue toxicity, involved-field radiation therapy (IF-RT) using three or four dimensional conformal radiation therapy (3 or 4D-CRT) and intensity modulated radiation therapy (IMRT) technique for dose escalation is generally considered (Fig 2).

In IF-RT for advanced NSCLC, whether ENI is necessary or not has been controversial. The argument against the use of ENI may be summarized as follows [6, 7]. 1) Failure is uncommon in nodal regions that are neither clinically involved nor specially targeted from many reports [8-12]. 2) It appears that a dose greater than the conventional 60-70Gy is required to cure a larger fraction of NSCLC patients. 3) The use of ENI causes severe adverse effects, such as radiation pneumonitis and esophagitis. 4) Clear progress has been made in staging by using FDG-PET. On the other hand, the argument against the omission of ENI may be summarized as follows [13-15]. 1) The incidence of pathologically proven nodal metastasis even in stage I NSCLC may be as high as 26% [16], and the incidence of lymphatic invasion or metastasis rises with increasing tumor size [17]. 2) Therefore many patients would die from distant metastasis or local failure, and ENF may not be often observed. 3) None of the studies on IF-RT provided pathologic confirmation of the status of nodal disease, nor data from autopsy findings. Thus, although there is a large discrepancy between IF-RT data and surgical data focused on ENF, actually many authors have reported retrospectively that ENF occurs in fewer than 10% of cases. In a phase I-II dose escalation study using IF-RT (RTOG 9311), the elective nodal failure rate was < 10% at last follow-up of 177 eligible patients [9]. Senan et al reported 50 patients with unresectable stage IIIA or IIIB NSCLC were treated with sequential chemotherapy and IF-RT, and omitting elective mediastinal irradiation did not result in isolated nodal failure [11]. Yu et al treated 80 patients 70 years or more with early stage (I / II) with IF-RT using intensity modulated radiation therapy (IMRT). Although 29 patients (36.7%) with ENF were identified, they concluded IF-RT using IMRT did not cause a significant amount of lymph node regions and improved outcomes in elderly patients [12]. Matsuura et al reported 10 patients with locally advanced NSCLC (9 patients in stage IIIB) were treated with hypofractionated IF-RT (median dose 65 Gy / 26 fr), and no ENF was encountered with good feasibility [18].



ENI (-): IF-RT ENI (+)

Fig. 2.

In the only prospective study comparing ENI with IF-RT, Yuan et al evaluated the effects of IF-RT in their prospective randomized trial in which 193 patients were randomly assigned to IF-RT to 68 to 74Gy or ENI to 60 to 64Gy using 3D-CRT, and reported that ENF was found in only 4% of patients in the ENI arm versus 7% in the IF-RT arm within 5 years [19]. Although the irradiation dose to elective nodal regions was higher in the ENI arm than in IF-RT arm, ENF was not significant in either arm (p=0.351). They also demonstrated an increase in local control with IF-RT of 8%, 8% and 15% at 1, 2 and 5 years, respectively. Fernandes et al reported a comparative analysis of ENI vs IF-RT. They concluded nodal failure rates in clinically uninvolved nodal stations were not increased with IF-RT when compared to ENI, and also resulted in significantly decreased esophageal toxicity, suggesting that IF-RT may allow for integration of concurrent systemic chemotherapy in greater proportion of patients with NSCLC [20]. Although we don't have the conclusions whether ENI is necessary or not, recent clinical trials of NSCLC have adopted IF-RT and IF-RT is going to be mainstream of radiation therapy for NSCLC.

3. Incidental irradiation of IF-RT

An interesting question is why the incidence of ENF is so low. It may be that incidental irradiation to clinically uninvolved nodal regions may help to explain the low incidence of ENF. Chen et al reported the results of IF-RT using 3D-CRT technique and examined incidental irradiation and ENF in thirty-five patients with inoperable early-stage NSCLC (T1-3N0M0) [21]. Although the incidental irradiation to regional nodal stations was low (fewer than 10% of all nodal regions received a dose of >40Gy), ENF was observed in only two patients who developed nodal relapse after local progression, and no patients failed initially at nodal sites. They concluded that the incidence of nodal failure was low and did not seem to be due to high-dose incidental irradiation. Rosenzweig et al reported the results of IF-RT in a large number (524) of patients with stage I-III (65% stage III) NSCLC [8]. Only 32 patients (6.2%), 42 nodal regions with ENF were identified, and among the 42 nodal regions,

six regional failures (14%) were in nodal regions that had incidentally received >45Gy, which is a typical dose of ENI. Jeremic analyzing these data of Rosenzweig et al noted that only 14% of nodal failures occurred in regions receiving >45Gy, whereas nodal failures happened in 86% of patients when nodal regions received less than 45Gy ($p<0.01$) [13]. Chapet et al reported the results of IF-RT in 40 patients with stage III NSCLC, and analyzed incidental irradiation to non-involved nodal stations [22]. The doses of incidental irradiation at level 4R, 4L, 7 and 10I were relatively high. They concluded that significant incidental irradiation was observed, with this possibly helping to explain the low rate of regional recurrence observed when ENI is not applied with stage III NSCLC treated with 3D-CRT technique. Kimura et al also evaluated the incidental irradiation dose to elective nodal regions in 50 patients with locally advanced NSCLC who treated IF-RT and the pattern of ENF [23]. ENF was observed in 4 patients (8%) five nodal regions, and no mean dose to the nodal region exceeded 40 Gy. Although these reports were retrospective in nature, as the stage of NSCLC advanced, especially to stage III, we have the impression that high-dose incidental irradiation may contribute to the low incidence of ENF in the patients receiving IF-RT.

4. Treatment planning of IF-RT – Especially, impact of FDG-PET on radiation therapy volume delineation

Although there are some points about the practical treatment planning of IF-RT, the most important point is the judgment of metastatic lymph nodes on CT or FDG-PET. Therefore evidence already exists that PET-based patient selection can improve the apparent survival of patients treated with RT for NSCLC [24], and the routine omission of ENI without considering the accuracy of staging by using FDG-PET may not be advisable. Thus, FDG-PET should be recommended as a useful tool in enhancing staging accuracy and RT planning [25]. The use of FDG-PET also may contribute to the low incidence of ENF in IF-RT.

On the other hand, the SUV (standardized uptake value) cutoff value chosen have been controversial. Using SUV > 2.5 or regions of 40% maximum SUV, a lesion is usually considered malignant unless proved otherwise [24]. However, exclude use of SUV can be misleading [25]. We recommend to diagnose the positive lymph nodes by the following points consulting with the nuclear medicine physician [27]. 1) An increased uptake to a level greater than that in the mediastinal blood pool activity was considered to characterize malignancy. 2) FDG-PET image was performed at 1-hour (early) post-FDG injection and repeated 2-hours (delayed) after injection only in the thoracic area. Using dual-time point FDG-PET (combined early and delayed PET), we calculated the retention index (RI): (SUV delayed – SUV early)×100/ SUV early. RI values of more than 0% were taken to be the PET criterion for malignancy. Fig 3 shows an example.

Although there is no doubt the use of FDG-PET is effective on radiation treatment planning, we should pay attention on some pitfalls. Vanneste et al described one should be cautious to repeat the diagnostic FDG-PET scan for each patient if the time-interval between the staging FDG-PET-CT scan and the start of the irradiation is 4 weeks or more [28]. Additionally, we should reconsider CT diagnosis of metastatic lymph nodes define more than 1cm in the short axis, especially in regions where enlarged lymph nodes are rarely seen (para-aortic, retrocrural or pericardial fat).

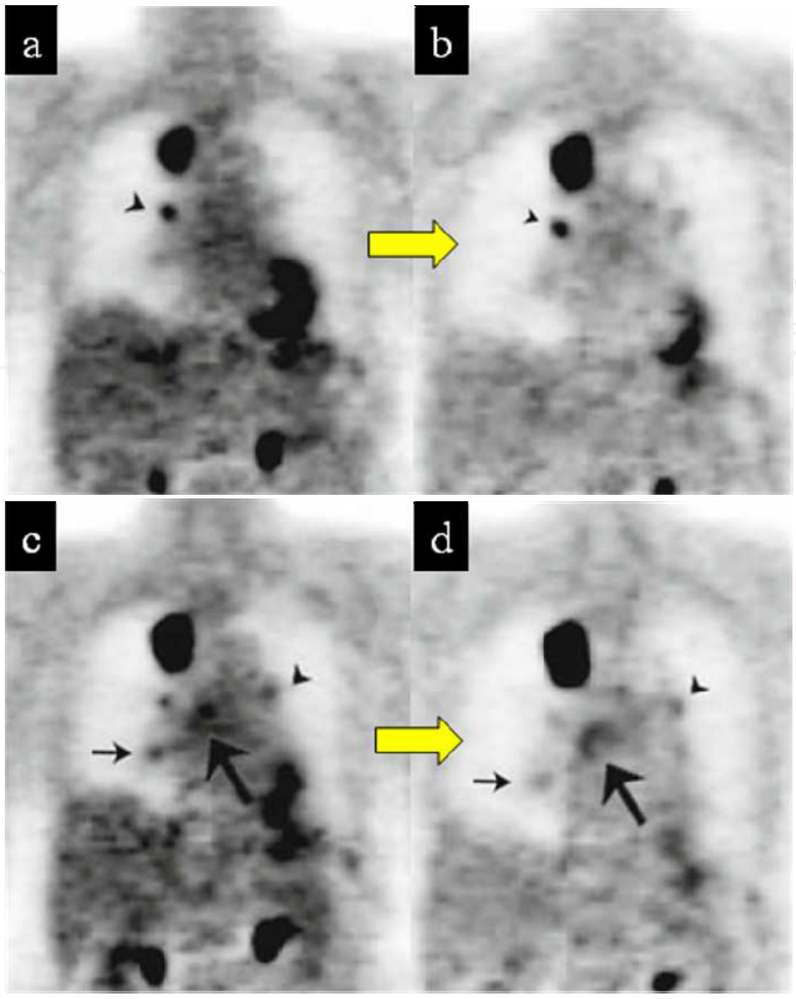


Fig. 3. The right primary lung cancer (squamous cell carcinoma) in a 79-years-old man. a) The early F-18- uorodeoxyglucose positron emission tomography (FDG-PET) image (coronal view) demonstrates focal accumulation in the right upper lobe and right tracheobronchial node (arrowhead). b) The delayed FDG-PET image (coronal view) shows intense FDG uptake at right tracheobronchial node (arrowhead). c) Another early FDG-PET image (coronal view) shows abnormal uptake at right peribronchial node (small arrow), subcarinal node (large arrow), and aortopulmonary node (arrow- head). Standardized uptake value for early images (SUVearly) was 5.86 at right tracheobronchial node, 3.37 at right peribronchial node, 3.92 at subcarinal node, and 3.41 at aortopulmonary node. d) Another delayed FDG-PET image (coronal view) shows slight uptake at right peribronchial node (small arrow) and aortopulmonary node (arrowhead) and mild uptake at subcarinal node (large arrow). Standardized uptake value for delayed images (SUVdelayed) was 7.36 at right tracheobronchial node and retention index (RI) was 25.6. SUVdelayed was 2.71 and RI -19.6 at right peribronchial node, SUVdelayed 3.56 and RI -9.2 at subcarinal node, and SUVdelayed 3.27 and RI -4.1 at aortopulmonary node. Nodal staging based on early and delayed FDG-PET demonstrated N3 stage. However, nodal staging based on combined delayed PET with RI value, demonstrated N2 stage. The surgical result also indicated N2 stage. (From Nishiyama Y et al, References 27)

5. Conclusions

However whether ENI is necessary or not has been still controversial for advanced NSCLC, "If one can't control gross disease, why enlarge the irradiated volumes to include areas that might harbor microscopic disease? [29]" IF-RT is deemed an acceptable method for advanced NSCLC without increasing the risk of ENF or adverse effects, but further clinical trials are needed.

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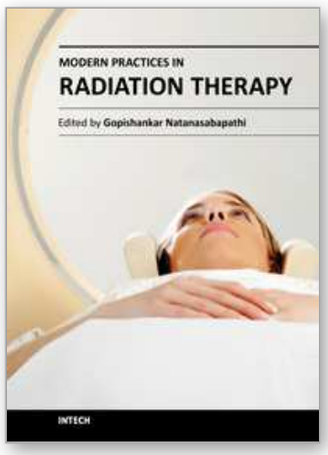
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