Acta Oncologica, 2008; 47: 954–961

informa
healthcare

ORIGINAL ARTICLE

Incidental irradiation of mediastinal and hilar lymph node stations during 3D-conformal radiotherapy for non-small cell lung cancer

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Abstract

Purpose. To estimate the doses of incidental irradiation in particular lymph node stations (LNS) in different extents of elective nodal irradiation (ENI) in 3D-conformal radiotherapy (3D-CRT) for non-small cell lung cancer (NSCLC). *Methods.* Doses of radiotherapy were estimated for particular LNS delineated according to the recommendations of the University of Michigan in 220 patients treated using 3D-CRT with different (extended, limited and omitted) extents of ENI. Minimum doses and volumes of LNS receiving 40 Gy or more (V_{40}) were compared for omitted vs. limited+ extended ENI and limited vs. extended ENI. *Results.* For omission of the ENI the minimum doses and V_{40} for particular LNS were significantly lower than for patients treated with ENI. For the limited ENI group, the minimum doses for LNS 5, 6 lower parts of 3A and 3P (not included in the elective area) did not differ significantly from doses given to respective LNS for extended ENI group. When the V_{40} values for extended and limited ENI were compared, no significant differences were seen for any LNS, except for group 1/2R, 1/2L. *Conclusions.* Incidental irradiation of untreated LNS seems play a part in case of limited ENI, but not in cases without ENI. For subclinical disease the delineation of uninvolved LNS 5, 6, and lower parts of 3A, 3P may be not necessary, because these stations receive the substantial part of irradiation incidentally, if LNS 4R, 4L, 7, and ipsilateral hilum are included in the elective area while this is not case for stations 1 and 2.

There is increasing evidence, derived especially from dose escalation studies that the omission of elective nodal irradiation (ENI) in radiotherapy of non-small cell lung cancer (NSCLC) results in a low incidence of isolated nodal failures (INF) [1–10]. The prerequisite for reporting on the incidence of INF after radiotherapy with the omission of ENI is an evaluation of incidental irradiation received by omitted nodal stations. In some cases the incidental irradiation may be enough to eradicate subclinical nodal disease [11]. Thus, although regional nodes are not purposefully included into the clinical target volume, they might actually receive elective irradiation. In the previous analysis of our data [12], the two-year cumulative incidence of INF for 185 patients treated with 3-dimensional conformal radiotherapy (3D-CRT) and different (limited or extended) extents of ENI was 12%.

INF was defined as a regional failure occurring outside gross tumor volume (GTV) without previous or synchronous local progression regardless of the distant metastases status. There was no difference in the cumulative incidence of INF for patients treated with extended and limited mediastinal ENI. One of the possible explanations of this finding is that the incidental irradiation may play a role in the limited ENI.

The low incidence of INF reported in the dose escalation studies may be related to the unintended dose received by lymph node stations (LNS) at risk. Published data on incidental irradiation in radiotherapy for lung cancer are scarce, based on small patient groups and with no deep consideration of either dosimetric/technical aspects of radiotherapy, or the tumor characteristics [8,13,14].

A recent publication by Chapet et al. [15], providing recommendations on the definition of

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(Received 4 March 2007; accepted 27 August 2007)

ISSN 0284-186X print/ISSN 1651-226X online © 2008 Taylor & Francis
DOI: 10.1080/02841860701654317

the borders of mediastinal and hilar LNS in the CT has produced an opportunity for detailed reporting on the intended and non-intended doses received by particular LNS. Information about an amount of incidental irradiation in different clinical and technical settings may help clinicians construct the ENI volumes which would be smaller than ones traditionally utilized in view of the improvement of the therapeutic ratio. To address this need, this study was undertaken with the objective of assessing the role of incidental irradiation in radiotherapy of particular LNS for different extents of the 3-D planned ENI.

Materials and methods

Patients, radiotherapy planning and targets volumes definition

The current analysis is based on a total of 220 patients enrolled in the consecutive prospective clinical trials. According to the extent of the ENI, four groups were distinguished.

Group 1: extended ENI – 124 patients (10 [8%] – stage I, 19 [15%] – stage II, 95 [77%] stage III);
Group 2: limited ENI – 61 patients (all but one with stage III);
Group 3: ENI limited to the ipsilateral hilum – 10 patients (6 – stage I, 3 – stage II, 1 – stage III; seven of these patients had central and three peripheral tumors);
Group 4: omission of ENI – 25 patients (18 [72%] – stage I, 7 [28%] – stage II; four [16%] of these patients had central and 21 [84%] peripheral tumors).

The patients receiving extended ENI were treated according to the following schedules: 66–74 Gy delivered in 2 Gy per fraction over 6.5–7.5 weeks (N = 64), 57 Gy delivered in 1.2–1.8 Gy per fraction BID over 4 weeks (n = 39), 60 Gy in 1.5 Gy per fraction 3 times a day over 2.5 weeks (n = 21). Doses prescribed to the elective Planning Target Volume (PTV_{elect}) varied between 39 and 54 Gy delivered over 2.5–5.5 weeks, mean – 47 Gy.

The patients treated with limited ENI received 56.7–58.8 Gy delivered in 2.7–2.8 Gy per fraction over 4 weeks using simultaneous integrated boost technique. Dose to the PTV_{elect} was 39, 9 Gy delivered in 1, 9 Gy per fraction over 4 weeks.

In group 3, ten patients treated without mediastinal ENI received 66–74 Gy in 2 Gy per fraction over 6.5–7.5 weeks with a planned dose of 50–56 Gy to PTV_{elect} limited to hilum.

In group 4, there were 14 patients receiving 66–74 Gy in 2 Gy per fraction over 6.5–7.5 weeks and 11 patients (all with peripheral tumors) receiving 48–52 Gy in 4 Gy per fraction over 2.5 weeks.

The GTV (Gross Tumor Volume) was defined for each group as the tumor volume visualized in CT and endobronchial extension as described in bronchoscopy. All lymph nodes with the diameter $\geq$1 cm in short axis on CT scans were included in GTV, unless the presence of metastases was excluded by mediastinoscopy. PET was not available for the staging.

The nomenclature of hilar and mediastinal LNS as given by Mountain and Dressler [16] was mandatory for treatment planning and is used in this study (Table I). There were two types of Clinical Target Volume (CTV): CTV_{elect} and CTV_{boost}. The CTV_{boost} included GTV with 0.5 cm margin within pulmonary parenchyma and the entire nodal station with lymph nodes considered as pathologic. An elective CTV (CTV_{elect}) comprised the CTV_{boost} and the elective area. The latter differed in the two analyzed groups. In the group with extended ENI the CTV_{elect} comprised the ipsilateral hilum, 2R, 2L, 3A, 3P, 4R, 4L, 5, 6, 7, and station 8 for tumours located in the lower lobes. In the group with limited ENI only the LNS with the highest probability of microscopic invasion were included in the CTV_{elect}; namely ipsilateral hilum, 4R, 4L, 7, and station 5 for left side. Differences in the definition of the CTV_{elect} for extended and limited ENI are shown in Figure 1. In group 3, the CTV_{elect} encompassed ipsilateral hilum. The CTV_{elect} was not delineated for group 4.

PTV_{boost} and PTV_{elect} were created by adding margins of 1 cm to the respective CTVs. Margins for PTVs were adapted, if necessary, for respiratory motion as visualized under fluoroscopy. The dose was specified to the ICRU point. Treatment was entirely 3D-planned. Dose homogeneity within respective PTVs had to be kept within 95–107% of the prescribed dose.

Table I. Classification of hilar and mediastinal lymph node stations according to the Mountain and Dressler classification [16].

Lymph Nodes Station	
1R, 1L	Highest mediastinal right (R) and left (L)
2R, 2L	Upper paratracheal right (R) and left (L)
3A	Prevascular
3P	Retrotracheal
4R, 4L	Lower paratracheal right (R) and left (L)
Group 5	Subaortic (aortico-pulmonary window)
Group 6	Paraaortic
Group 7	Subcarinal
Group 8	Paraoesophageal
10R, 10L	Hilar right (R) and left (L)

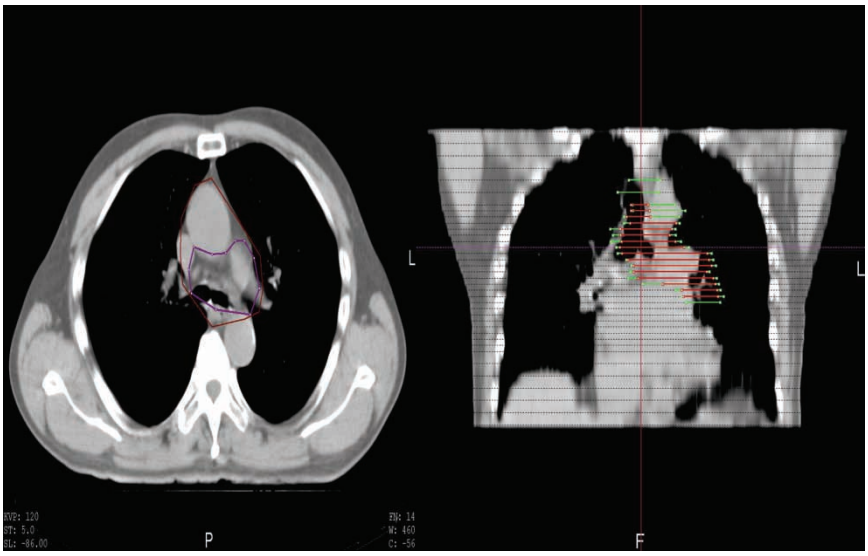

Figure 1. Differences in delineation of the CTV_{elect} for extended (brown and green color on axial and coronal sections, respectively) and limited ENI (violet and red color on axial and coronal sections, respectively).

Treatment was delivered on linear accelerators with 4–15 MV photons. The allowed maximum dose for the spinal cord was 50 Gy for hyperfractionated and conventionally fractionated schedules, whilst for the hypofractionated schedules (as for limited ENI) maximum dose for spinal cord was 45 Gy. In view of keeping dose constraints for lung (the allowed mean lung dose for all schedules was $\leq$20 Gy) a substantial part of treatment (on average 70% of dose) was delivered via the antero-posterior ports with total number of fields by fraction ranging from 3 to 5. Non-coplanar fields' arrangements were not employed.

Evaluation of doses received by particular LNS

On the initial CT scans the particular LNS were delineated by one author (LK) for each patient. The LNS were delineated strictly according to the recommendations of the Atlas from the University of Michigan [15], except superior borders for 3A and 3P, which were placed at the level of superior limits of the aortic arch (as for 4R). This lower placement of the limits for these groups was set, because the dose volume histograms (DVHs) for LNS 1/2R and 1/2L had already given an estimation of the dose in the superior mediastinum**.** For each LNS: namely 1/2R, 1/2L, 3A, 3P, 4R, 4L, 5, 6, 7, 10R and 10L, the separate cumulative DVHs were created from initial dose prescriptions. Initially involved LNS (included in GTV) were not delineated. There was no comparison of doses for station 8, because in a substantial number of patients with extended ENI the entire volume of this station was not included in the elective area in order to reduce pulmonary toxicity. For each LNS the minimum dose and percentage of the volume receiving dose $\geq$40 Gy (V_{40}) were retrieved. The threshold of 40 Gy was chosen, despite the fact that a substantial proportion of patients had the prescribed elective dose in the range of 39.0–39.9 Gy, because the retrieval of doses of 39 Gy from DVHs was imprecise and too complex to be performed. The radiation dose was considered in this study as the physical dose. Otherwise, there was no biological dose equivalent done for accelerated treatment, and/or low doses per fraction of the incidental irradiation.

Statistical analysis

To compare the amount of incidental irradiation between the patient groups, the minimum doses actually received by particular LNS were converted to the percentage of prescribed elective dose by using the following equation: actually received minimum dose divided by prescribed elective dose multiplied by 100%. This conversion was necessary because the different elective doses were prescribed for different groups. In patient group 4 (treated with omission of ENI) the minimum doses for particular LNS were considered as a percentage of 44 Gy (mean elective dose of a total of 195 patients receiving any forms of ENI). This enabled us to make comparisons between the analyzed groups of patients.

The mean values of minimum doses and V_{40} were considered for particular LNS for the four extents of the ENI. Doses received by LNS in the group of patients treated with limited ENI were compared with respective doses in the group of patients with extended ENI. Doses in LNS for patient group 3 and 4 (treated with omission of the mediastinal ENI) were compared with respective doses of patients

receiving any forms of mediastinal ENI, namely group 1 and 2.

Differences of minimum doses and V_{40} between different extents of the ENI were tested using the t-test having confirmed the normal distribution of the values with Shapiro-W test. For groups of patients treated with extended (group 1) and limited (group 2) ENI the separate analyses were performed for LNS 5, 10R and 10L with respect to the side of the tumor (left/right). Correlations between the total prescribed dose and the minimum doses in particular LNS were calculated using Spaerman's test. Statistical analysis was performed with SPSS software (version 11.0 for Windows, Chicago, Illinois).

Results

For patients treated with mediastinal ENI, the mean volumes of PTV_{elect} were not significantly different, 591 cc and 583 cc, for extended and limited ENI, respectively, $p = 0.7$. This was related to the fact that patients treated with limited ENI had more advanced stages of the disease.

Mean values of minimum doses received by particular LNS and V_{40} in relation to the extent of ENI are summarized in Tables II and III, respectively.

Doses of incidental irradiation in the groups treated with omission of mediastinal ENI

In the groups treated with omission of mediastinal ENI the doses of incidental irradiation were low and probably clinically insignificant.

Minimum dose to ipsilateral hilum was ≥ 40 Gy in 1 (4%) of 25 patients treated with omission of the mediastinal and hilar ENI. Mean V_{40} for particular mediastinal LNS were $<15\%$ and values of V_{40} for all evaluated LNS were significantly lower than respective values for patients receiving ENI (limited and extended).

For 67% (6 of 9) of patients with inclusion of ipsilateral hilum to the ENI the minimum dose for group 7 was ≥ 40 Gy. As indicated in Table III, a substantial percentage of the volume of station 7 received dose ≥ 40 Gy, as part of incidental irradiation from the treated ipsilateral hilum.

Comparison of doses of incidental irradiation between groups of patients treated with limited and extended ENI.

The minimum doses for stations 1/2R and 1/2L were significantly higher in the extended ENI group, as compared to the limited ENI group. It is striking that a substantial proportion of patients with extended

Table II. Minimum doses received by particular lymph node station (LNS) in relation to the extent of the elective nodal irradiation (ENI). For LNS not included in the elective area values are printed in bold.

	Mean value of minimum dose expressed as actually received minimum dose/prescribed elective dose# $\times 100\%$			
Lymph nodes station*	Group 1-Extended ENI [number of cases] n = 124	Group 2-Limited ENI [number of cases] (p-value)^ n = 61	Group 3. Omission of the mediastinal ENI [number of cases] (p-value)^^ n = 10	Group 4. Omission of the hilar and mediastinal ENI [number of cases] (p-value)^^^ n = 25
1/2 R	74% [112]	**57% [56] (0.04)**	**2% [10] (<0.001)**	**7% [25] (<0.001)**
1/2 L	74% [115]	**57% [60] (0.03)**	**2% [10] (<0.001)**	**5% [25] (<0.001)**
3A	94% [114]	**90% [58] (0.69)**	**13% [10] (<0.001)**	**4% [25] (<0.001)**
3P	100% [121]	**102% [61] (0.75)**	**9% [10] (<0.001)**	**4% [25] (<0.001)**
4R	96% [82]	100% [33]	**16% [10] (<0.001)**	**5% [25] (<0.001)**
4L	109% [109]	111% [55]	**16% [10] (<0.001)**	**4% [25] (<0.001)**
Group 5	92% [101]	**84% [47] (0.40)**	**31% [10] (<0.001)**	**8% [25] (<0.001)**
Group 6	89% [119]	**85% [58] (0.55)**	**7% [10] (<0.001)**	**2% [25] (<0.001)**
Group 7	120% [93]	122% [40]	**90% [9] (0.001)**	**9% [25] (<0.001)**
10R for tumors of right lung	116% [35]	104% [35]	**For contralateral hilum 10% [10] (0.01)**	**For contralateral hilum 2% [25] (<0.001)**
10R for tumors of left lung	**23% [44]**	**27% [21]**		
10L for tumors of left lung	126% [37]	125% [11]	For ipsilateral hilum 120% [10]	**For ipsilateral hilum 22% [25] (<0.001)**
10L for tumors of right lung	**17% [56]**	**12% [30]**		

*LNS included in GTV were not included in the analysis (this explains the reason why the numbers of patients varied for different LNS).
#Prescribed elective dose for groups of patients 1, 2, and 3; for group 4 minimum doses are expressed in percentage of 44 Gy (the mean elective dose for all patients).
^ shows statistical significance of the difference between groups 2 and 1.
^^ shows statistical significance of the difference between groups 3 and 1 + 2.
^^^ shows statistical significance of the difference between groups 4 and 1 + 2.

Table III. Percentage of the volume of particular lymph node stations (LNS) receiving dose >40 Gy (V_{40}) in relation to the extent of the elective nodal irradiation (ENI). For LNS not included in the elective area the values are printed in bold.

	Mean of V_{40}			
Lymph nodes station*	Group 1. Extended ENI [number of cases] n = 124	Group 2. Limited ENI [number of cases] (p-value)^ n = 61	Group 3. Omission of the mediastinal ENI [number of cases] (p value)^^ n = 10	Group 4. Omission of the hilar and mediastinal ENI [number of cases]^^^ n = 25
1/2 R	62 [112]	**42 [56] (0.02)**	**0 [10] (<0.001)**	**5 [25]**
1/2 L	62 [115]	**48 [60] (0.04)**	**0 [10] (<0.001)**	**1 [25]**
3A	92 [114]	**90 [58] (0.12)**	**22 [10] (<0.001)**	**11 [25]**
3P	93 [121]	**91 [61] (0.10)**	**32 [10] (<0.001)**	**1 [25]**
4R	92 [82]	90 [33]	**45 [10] (<0.001)**	**8 [25]**
4L	95 [109]	94 [55]	**39 [10] (<0.001)**	**0 [25]**
5	87 [101]	**81 [47] (0.30)**	**18 [10] (<0.001)**	**0 [25]**
6	93 [119]	**88 [58] (0.31)**	**22 [10] (<0.001)**	**1 [25]**
7	97 [93]	94 [40]	**84 [9] (0.03)**	**3 [25]**
10R for tumors of right lung	96 [35]	93 [35]	**For contralateral hilum: 25 [10] (<0.001)**	**For contralateral hilum: 0 [25]**
10R for tumors of left lung	**28 [46]**	**32 [21]**		
10L for tumors of left lung	99 [37]	99 [11]	For ipsilateral hilum: 100 [10]	**For ipsilateral hilum: 24 [25]**
10L for tumors of right lung	**17 [56]**	**11 [30]**		

*LNS included in GTV were not included in the analysis (this explains the reason why the numbers of patients varied for different LNS).
^ shows statistical significance of the difference between groups 2 and 1.
^^ shows statistical significance of the difference between groups 3 and 1+2.
^^^ p-values of statistical significance of the difference between groups 4 and 1+2 are <0.001 for all LNS.

ENI still did not receive the full planned dose in this region. This is because our protocol for extended ENI did not call for inclusion of the highest mediastinal nodes (LNS 1); the fields usually were cranially stopped at the sternal notch.

There were no statistically significant differences in the respective minimum doses for stations 3A, 3P, 4R, 4L, 5, 6, 7, ipsilateral and contralateral hila for both extents of ENI. Noteworthy, there were no differences in minimum doses for LNS not systematically included in CTV_{elect} for limited ENI, as compared to extended ENI, namely stations 3A, 3P, 5 and 6. The results of a separate analysis for left and right sided tumors for group 5 and both hila are summarized in Table IV. There was no significant difference in the received minimum doses for station 5, despite a non-inclusion of this LNS for the right side in the elective area for limited ENI. It may be explained by the finding that a substantial proportion (about ¼) of patients treated with extended ENI did not receive a planned elective dose for group 5 in case of right sided tumors as the result of apprehended pulmonary toxicity. Recapitulating the results of the comparison of minimum doses between limited and extended mediastinal ENI, we can conclude that in case of systematic non-inclusion in the CTV_{elect} of particular LNS, the minimum doses were significantly lower only for LNS located

Table IV. Minimum doses received by particular lymph node station (LNS) in relation to the extent of the elective nodal irradiation (ENI) and side of tumor. Minimum doses are expressed in percentage of the prescribed elective dose. For LNS not included in the elective area values are printed in bold.

	Mean value of minimum dose expressed as actually received minimum dose/prescribed elective dose ×100%			
	Left Side		Right Side	
Lymph nodes station*	1. Extended ENI [number of cases] n = 57	2. Limited ENI [number of cases] n = 25	1. Extended ENI [number of cases] n = 67	2. Limited ENI [number of cases] (p-value)^ n = 36
LNS 5	118% [39]	125% [12]	73% [62]	**70% [35] (0.71)**
10R	**23% [46]**	**27% [21]**	116% [35]	104% [11]
10L	126% [37]	125% [9]	**17% [56]**	**12% [30]**

*LNS included in GTV were not included in the analysis (this explains the reason why the numbers of patients varied for different LNS).
^ shows statistical significance of the difference between groups 2 and 1.

in the superior mediastinum, but not for LNS located below superior edge of the aortic arch.

When the V_{40} for both types of the ENI (extended and limited) were compared, no statistically significant differences were seen for any LNS, including those not included in CTV_{elect} in limited ENI, except for 1/2R, 1/2L.

Correlations between the prescribed total doses to gross tumor and the doses received by uninvolved LNS

It was noticed that for some nodal regions, the actually received elective dose was larger than the planned elective dose (Table III). To explore this issue the tests were performed in order to look for correlation between prescribed total doses to gross tumor and minimum doses received by uninvolved LNS. These correlations were significantly positive for nodal stations 4R, 4L, 5, 7, and the ipsilateral hilum. Such correlations were not observed for LNS 1/2R, 1/2L, 3A, 3P, 6, and the contralateral hilum (Table V).

Discussion

We did confirm the role of incidental irradiation in the treatment of omitted LNS in advanced stages of NSCLC when limited mediastinal ENI was employed. For LNS located in the plan of the irradiation beams, below the superior edge of the aortic arch, the incidental irradiation was enough to cover the LNS non-included in the elective area, namely 3A, 3P, 5 and 6, in the similar degree as for systematic inclusion of these regions in the ENI. We were not able to show that such a limitation of the elective area may lead to a meaningful reduction of the irradiated volume, because of the retrospective nature of the study. As has been shown in the "Results" section patients treated with limited ENI did not have a significantly reduced volume of PTV as compared with the group receiving extended ENI, because of more advanced stages of the disease in the former group. The difference of doses for LNS in the superior mediastinum was significant in case of systematic non-inclusion of this region in the elective area, despite the fact that a substantial proportion of patients with extended ENI did not receive a full dose in this region. It was basically related to the limitation of the method of the delineation of the LNS. Chapet et al. [15] did not recommend a separate delineation of LNS 1 and 2 in the superior mediastinum, because both stations cover only a very short vertical distance and division by a left innominate vein is not always easy to be found. The fields in the protocol for extended ENI had to be stopped at the sternal notch. This was also recommended by Chapet et al. [15] as the upper limit for LNS of the superior mediastinum. For this reason, it is not surprising, that the full prescribed elective doses were not applied at the border of the field. Despite these limitations we found that the incidental irradiation does not compensate doses in the superior mediastinum whilst we are using coplanar fields limited to the region below the top of aortic arch.

Table V. Correlations between the prescribed total doses to gross tumor and the minimum doses received by uninvolved lymph node stations (LNS) in a total of 220 patients.

LNS	Spearman's Correlation Coefficient R	p-value
1/2 R	−0.04	0.55
1/2 L	−0.02	0.76
3A	−0.01	0.80
3P	0.09	0.20
4R	0.14	0.04
4L	0.16	0.03
5	0.18	0.02
6	0.05	0.46
7	0.35	<0.001
Ipsilateral hilum	0.52	<0.001
Contralateral hilum	0.02	0.82

Other authors have also suggested the meaningful participation of incidental irradiation in the case of radiotherapy of advanced stages of NSCLC. Martel et al. [14] confirmed meaningful doses of incidental irradiation in the treatment of the omitted LNS in ten stage III patients. The doses >50 Gy were given to 100% of the volume of the ipsilateral hilum and to 96% of subcarinal region. Doses of incidental irradiation estimated by Rosenzweig et al. [8] for 171 patients (a majority in stage III) were much lower. Comparisons of those findings with the results from our study are not reliable due to the different definitions of minimum doses and borders of LNS.

Our finding concerning the correlations of doses given to the uninvolved LNS 4R, 4L, 5, 7, and the ipsilateral hilum with doses prescribed to tumor indicate that the nodal regions with the highest probability of harboring micrometastases as shown by surgical and pathological data [17–19] as well as the pattern of regional failure after surgery [20] have also the highest participation of incidental irradiation. This is not surprising, especially when one considers the vicinity of these LNS to the centrally located tumors. It may partially explain the rarity of developing isolated nodal failures in the techniques of radiotherapy which omit ENI, as the LNS most likely containing micrometastases are incidentally treated.

In the group of patients with early stages of NSCLC treated with the omission of ENI, the role

of incidental irradiation in the treatment of hilar and mediastinal LNS was probably meaningless, concurring with other reports [8,13]. We identified two types of the omission of mediastinal ENI, with and without ipsilateral hilar elective irradiation. It was shown that in case of the irradiation of the hilar region, which is done intentionally or not in all centrally located tumors, the subcarinal region may receive a meaningful dose. This may have some clinical value as the likelihood of harboring micrometastases by station 7 is high [17–20].

We should acknowledge the limitations of our study. First of all, the threshold dose of 40 Gy for the evaluation of incidental irradiation may well be questioned. A dose of 50 Gy seems more relevant for sterilization of the microscopic disease, especially accounting for radiobiological data [21]. Our choice of 40 Gy was based on the fact that a substantial number of patients had the dose prescribed to the elective area within the range of 39–40 Gy, which limited our considerations of higher elective doses. It is debatable what range of dose is necessary to eradicate subclinical disease in the omitted LNS. Following the radiobiological concepts of Withers et al. [21] a dose of 50 Gy in 2 Gy per fraction is considered as necessary to achieve an overall 90% reduction in the incidence of metastases and it is a commonly prescribed dose-schedule for subclinical disease. On the other hand, there are also suggestions from the literature that worthwhile benefits can be achieved by doses as low as 14–21 Gy under the condition of being delivered close to the treatment of the primary [22,23]. We did not make any attempt on the biological dose calculation though different dose per fraction and treatment times were used. To the best of our knowledge, there were not any biological dose equivalent (BED) done for incidental irradiation in lung cancer radiotherapy. The linear-quadratic model does not allow for the reliable calculation of BED in the range of very low doses per fraction as is usually observed for incidental irradiation [24].

We should also acknowledge that our findings are only valid for the use of coplanar techniques for lung cancer radiotherapy and any attempts of generalization of our results for more complex beams arrangements and techniques e.g. non-coplanar, IMRT, stereotactics, should be disregarded. However, the techniques which we have used are still largely employed in routine practice.

Another problem of reporting incidental irradiation is the precise definition of regions where evaluation is performed. The recommendations of Chapet et al. [15] for a delineation of the LNS on the cross-sectional imaging were proposed as useful tool for reporting on doses of incidental irradiation. The problem is that those recommendations have not been validated for clinical use. It is not certain whether the delineation according to these guidelines with an addition of margins for movements and set-up errors would lead to the creation of appropriate treatment plans for ENI. In our study, a substantial percentage of patients had too low doses delivered for particular LNS (<40 Gy), because of a discrepancy between initial CTV delineation and a new definition of the borders of LNS according to the recommendations (data not shown). Other reports on incidental irradiation have also failed to solve this problem, reporting on doses for poorly defined regions of the mediastinum [8,14].

In a recently published concept of "electively limited field radiotherapy" Giraud et al. [18] suggest the use of limited elective fields. Our findings may serve as an indication for future delineation of elective areas, depending on the extent at which one is planning to treat subclinical disease. The delineation of uninvolved LNS 5 and 6, as well as the lower parts of 3A, 3P may be not necessary, because these stations receive the substantial part of irradiation incidentally, if LNS 4R, 4L, 7, and ipsilateral hilum are included in the elective area. If one intends to omit superior mediastinal LNS (1/2R, 1/2L, and higher located parts of 3A and 3P), using coplanar fields, one should be aware that incidental irradiation does not compensate for the non-inclusion of this region in the irradiation volume.

Conflicts of interest

There were no financial and/or personal relationships with any other persons and organizations that could inappropriately influence (bias) this work.

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