ORIGINAL SCIENTIFIC REPORT

Is Calcification in the Regional Lymph Nodes a Benign Feature in Patients with Lung Cancer?

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Abstract

Background Calcified lymph nodes (LNs) on computed tomography (CT) in patients with lung cancer are generally considered to be a benign feature. However, few studies have evaluated the pathological status of such calcified LNs. We investigated the clinicopathological findings of patients with calcified LNs on preoperative CT who underwent operation for lung cancer and assessed the frequency of metastasis to calcified LNs as well as the risk factors associated with such metastases.

Methods This was a retrospective study of 72 consecutive patients with calcified LNs detected on preoperative CT who underwent pulmonary resection for primary lung cancer between 2011 and 2013. A total of 354 LN stations including 101 LN stations with calcified LNs were evaluated.

Results The frequency of metastasis to calcified LNs was 19.4% (14 of 72 patients) on a per-person basis and 18.8% (19 of 101 stations) on a per-nodal station basis. When the size of calcification was major (>5 mm), the frequency of metastasis to such calcified LNs was significantly lower than when it was minor ($\leqq 5$ mm) on a per-nodal station basis (11.1% vs 27.7%, $P = 0.043$). Furthermore, when the size of calcification was major and the status of LN stations with calcified LNs was single, there was no metastasis to such LN stations (0 of 26 stations).

Conclusions The frequency of metastasis to calcified LNs was about 20% on both a per-person and a per-nodal station basis. Although calcified LNs as well as non-calcified LNs should be dissected during operation, dissection of a single LN station with calcification, particularly major calcification, can be omitted.

Introduction

Preoperative evaluation of regional lymph nodes (LNs) in patients with lung cancer is essential for determining optimal treatment strategies in the management of primary lung cancer. Computed tomography (CT) and fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) are commonly used for this evaluation. However, the diagnostic accuracy of such radiological examinations is sometimes insufficient, particularly in areas where granulomatous disease is endemic because FDG-PET/CT frequently gives false-positive findings due to the uptake of FDG in calcified LNs despite the absence of metastasis from the primary cancer [1–6].

Calcification in LNs is generally thought to be a sequel of old granulomatous disease such as tuberculosis. Accordingly, calcified LNs on preoperative CT or FDG-PET in patients with lung cancer are commonly considered to be benign [4, 5, 7, 8]. However, several reports have demonstrated that metastatic foci from primary lung cancer are sometimes observed in such calcified LNs [9–12].

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Furthermore, recently, the presence of calcified LNs on preoperative CT has been an important consideration in selecting the appropriate surgical approach for lobectomy in lung cancer patients. Several reports have mentioned that calcified LNs on preoperative CT should be assessed to predict intraoperative or perioperative outcomes such as conversion from a video-assisted thoracoscopic surgery (VATS) approach to an open approach, which was associated with adhesion between calcified LNs and hilar structures and subsequent difficulty in their dissection [7, 13–17]. Accordingly, it is important to assess calcified LNs not only with regard to the diagnosis but also from the perspective of surgical treatment. If calcified LNs in patients with lung cancer are probably benign, it might be justified to not dissect those calcified LNs to reduce the possibility of complication. However, the clinicopathological findings for calcified LNs on preoperative CT in patients with lung cancer have not been fully evaluated.

Therefore, we herein investigated the frequency of metastasis to calcified LNs on preoperative thin-slice CT in patients with surgically resected lung cancer. Furthermore, we compared the clinicopathological features and findings on preoperative thin-slice CT in patients with metastasis to calcified LNs and those in patients without metastasis to calcified LNs to assess the risk factors associated with metastasis to calcified LNs from primary cancer.

Materials and methods

Patients

This study was approved by the Institutional Review Board of the National Cancer Center Hospital (Approval No. 2018-045). A total of 1278 patients underwent pulmonary resection for primary lung cancer in our department between January 2011 and December 2013. Among them, 174 patients (13.6%) had calcified LNs on preoperative high-resolution CT scans. Of these 174 patients, those who had LN stations with calcified LNs as detected by preoperative CT that were in the recommended range of LN dissection for the primary lung cancer and that were resected and evaluated by a pathological examination were included in this study (Fig. 1). Ultimately, 72 patients (5.6%) with 354 LN stations (including 253 LN stations without calcified LNs and 101 LN stations with calcified LNs) were enrolled in this study.

Data collection

The medical records of each patient were retrospectively reviewed for age, gender, smoking history, Brinkman Index, preoperative serum levels of tumor marker (carcinoembryonic antigen [CEA]) and calcium, tumor size by preoperative thin-slice CT, clinical nodal status, histology of the primary tumor and pathologic nodal status. Staging was determined based on the seventh edition of the tumor, node and metastasis classification for lung cancer [18]. LN stations were determined based on the International Association for the Study of Lung Cancer (IASLC) lymph node map [19]. In terms of clinical nodal status, we usually considered that LNs with a short-axis diameter of more than 10 mm (size criteria) or for which the maximum standardized uptake value (SUVmax) in PET was more than 2.5 were malignant. Among 72 patients, preoperative PET examination was performed in 46 patients (64%). LNs with calcification were considered to be benign. All resected LN stations were evaluated based on the pathological reports. All 72 patients were divided into two groups: group A, patients with calcified LNs with metastatic foci; group B, patients with calcified LNs without metastatic foci.

Evaluation of preoperative CT images

In all patients, contrast-enhanced or unenhanced CT images were acquired with an Aquilion PRIME CT scanner (Canon Medical Systems). Contiguous 5-mm section and 1-mm thin-slice section images were obtained in all cases. All CT images were retrospectively evaluated by two investigators (K.N. and H.W.). We defined an LN-containing calcification of any size as a calcified LN. Calcification was determined by visual identification on mediastinal window setting images (window width, 350 HU; level, 40–60 HU) of contiguous 5-mm sections and 1-mm thin-slice sections in CT scans (Fig. 2). The presence of calcification in a primary tumor was identified based on the same criteria. We investigated the presence of calcification in the primary tumor and LNs, the size of calcification (major or minor), number of LN stations with calcified LNs (single or multiple) and distribution of LN stations with calcified LNs (unilateral or bilateral). The size of calcification was classified into two groups according to the CT findings: minor (5 mm or less calcification) and major (greater than 5 mm calcification) (Fig. 2) [14].

Statistical analysis

Differences between groups were evaluated using Student's t test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. A multivariate logistic regression analysis that considered all of the significant risk factors from the univariate analysis was performed to analyze the significant risk factors associated with metastasis to LN stations with calcified LNs. For all analyses, P values <0.05 were considered

Fig. 1 Flowchart for selection of patients with LN stations with calcified LNs. *LN* lymph node, *CT* computed tomography
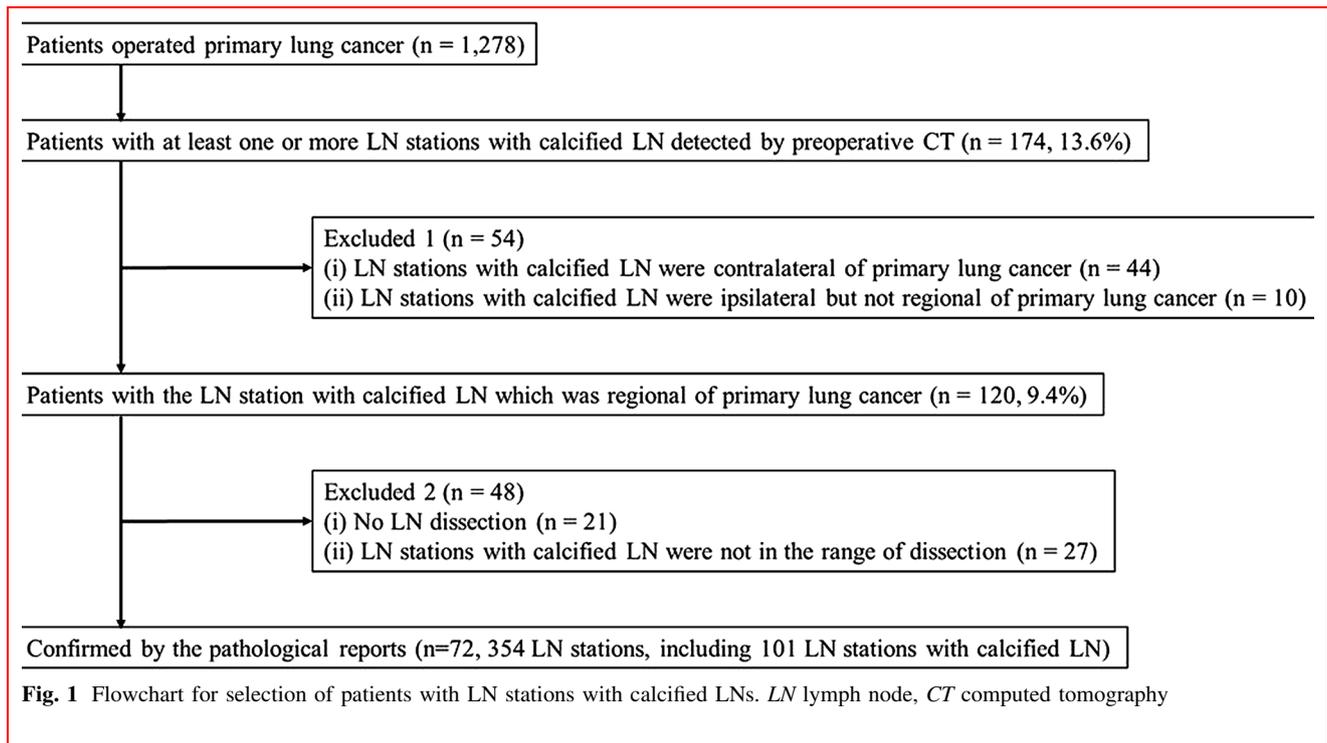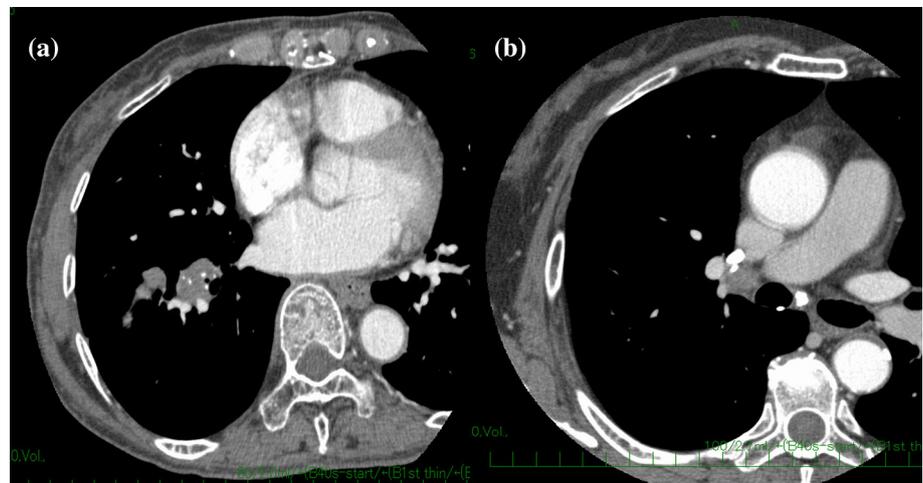

Fig. 2 High-resolution computed tomographic image (mediastinal window setting) showing **a** #11i lymph node station with minor calcification, and **b** #11s lymph node station and #7 lymph node station with major calcification

statistically significant. All statistical analyses were performed using SPSS Statistics 23 (IBM Corporation, Chicago, IL).

Results

Clinicopathological characteristics of the patients

Among 72 patients in the present study, lobectomy with mediastinal lymph node dissection was performed in 53 (74%) patients. No additional procedures such as bronchoplasty and angioplasty were performed. All surgical procedures were performed through mini-thoracotomy. The median operative time was 139 min (range 53–326 min), and median blood loss was 44 mL (range 1–281 mL). No intraoperative complications associated with dissection of calcified LNs were seen. In terms of postoperative complications, prolonged air leakage occurred in six patients and empyema occurred in one patient. Of the 72 patients, 14 (19.4%) were included in group A (patients with calcified LNs with metastatic foci) and 58 (80.6%) were in group B (patients with calcified LNs without metastatic foci). The clinicopathological

characteristics of the two groups are compared in Table 1. Group A included nine men and five women, with an average age of 70 years, while group B included 39 men and 19 women, with an average age of 71 years. There were no significant differences in smoking history, Brinkman Index, serum CEA and calcium levels and a history of tuberculosis between the two groups. There was also no significant difference in tumor size by preoperative thin-slice CT. The percentage of patients with clinical N positive was significantly higher in group A than in group B (36% vs 9%, $P = 0.02$). Calcification in the primary tumor was seen more frequently in group A than in group B (36% vs 5%, $P = 0.006$). Multiple LN stations with calcified LNs were observed more frequently in group A than in group B

Table 1 Clinicopathological characteristics and CT findings

Characteristics	Total $n = 72$	Group A $n = 14$ (%)	Group B $n = 58$ (%)	P value
Age				0.57
Average, mean ± SD (years)	71 ± 10	70 ± 13	71 ± 9	
Gender				1
Male	48	9 (64)	39 (67)	
Female	24	5 (36)	19 (33)	
Smoking history				1
Former or current smoker	49	10 (71)	39 (67)	
Never smoker	23	4 (29)	19 (33)	
Brinkman Index, mean ± SD	939 ± 748	1165 ± 840	878 ± 722	0.29
CEA, mean ± SD (ng/mL)	4.8 ± 3.9	6.6 ± 5.7	4.4 ± 3.3	0.2
Hypercalcemia				0.35
Yes	2	1 (7)	1 (2)	
No	70	13 (93)	57 (98)	
History of tuberculosis				1
Yes	7	1 (7)	6 (10)	
No	65	13 (93)	52 (90)	
Tumor size				0.68
≦2 cm	10	1 (7)	9 (15)	
>2 cm	62	13 (93)	49 (85)	
Clinical N status				0.02
cN−	62	9 (64)	53 (91)	
cN+	10	5 (36)	5 (9)	
Calcification in the primary tumor				0.006
Yes	8	5 (36)	3 (5)	
No	64	9 (64)	55 (95)	
Number of LN stations with calcified LNs				0.046
Single	27	2 (14)	25 (43)	
Multiple	45	12 (86)	33 (57)	
Distribution of LN stations with calcified LNs				0.44
Unilateral	61	11 (79)	50 (86)	
Bilateral	11	3 (21)	8 (14)	
Metastasis to LN stations without calcified LNs				<0.001
Yes	22	11 (79)	11 (19)	
No	50	3 (21)	47 (81)	
Histology of the primary tumor				0.74
Adenocarcinoma	51	11 (79)	40 (69)	
Others	21	3 (21)	18 (31)	

CT computed tomography, *SD* standard deviation, *CEA* carcinoembryonic antigen, *LN* lymph node

(86% vs 57%, $P = 0.046$). Only two (7.4%) of 27 patients with a single station with calcified LNs had metastatic foci. The percentage of patients with metastasis to LN stations without calcified LNs was significantly higher in group A than in group B (79% vs 19%, $P < 0.001$). In this study, only three (6%) of 50 patients had metastatic foci in LN stations with calcified LNs when there were no metastatic foci in other LN stations without calcified LNs. The results of the multivariate analysis for risk factors associated with metastasis to LN stations with calcified LNs by logistic regression are shown in Table 2. Multiple LN stations with calcified LNs (hazard ratio 9.901, 95% CI 1.698–58.824, $P = 0.011$) and metastasis to LN stations without calcified LNs (hazard ratio 19.089, 95% CI 3.000–121.472, $P = 0.002$) were independent risk factors for metastasis to LN stations with calcified LNs.

Frequency of metastasis to LN stations with calcified LNs on a per-nodal station basis

Of the total 354 LN stations, 101 LN stations included calcified LNs. Among them, metastasis to LN stations with calcified LNs was observed in 19 (18.8%) LN stations. There was no difference in the frequency of metastasis to LN stations between those with calcified LNs and those without calcified LNs. When the size of calcification was major, the frequency of metastasis to LN stations with calcified LNs was significantly lower than that when the calcification was minor (11.1% vs 27.7%, $P = 0.043$). Furthermore, when the size of calcification was major and the status of LN stations with calcified LNs was single, there were no metastases in such 26 LN stations with calcified LNs.

Discussion

The presence of calcification in lymph nodes on preoperative CT or FDG-PET/CT in patients with lung cancer is occasionally observed, particularly in areas where granulomatous diseases, such as tuberculosis, histoplasmosis, are endemic. In our study population between January 2011 and December 2013, calcified LNs among the regional LNs of the primary lesion on preoperative thin-slice CT, which should be dissected during operation, were observed in 120 of 1278 (9.4%) patients who underwent pulmonary resection for primary lung cancer (Fig. 1). Calcified LNs on preoperative CT or FDG-PET in patients with lung cancer are commonly considered to be a benign feature [4, 5, 7, 8]. However, several reports have demonstrated that metastatic foci from primary lung cancer are sometimes observed in such calcified LNs [9–12]. Thus, the clinicopathological findings of such calcified LNs in patients with lung cancer have not been fully evaluated.

In this study, we demonstrated that the frequency of metastasis to LN stations with calcified LNs was 19.4% (14 of 72 patients) on a per-person basis and 18.8% (19 of 101 stations) on a per-nodal station basis. Thus, we consider that metastasis to LN stations with calcified LNs does not seem to be rare; LN stations with calcified LNs should be dissected as well as LN stations without calcified LNs to achieve the radical dissection and appropriate staging of lung cancer. With regard to risk factors for metastasis to calcified LNs, the multivariate analysis in this study showed that multiple LN stations with calcified LNs and metastasis to LN stations without calcified LNs were independent risk factors. Conversely, single LN station with calcified LNs and LN stations with calcified LNs when there are no metastatic foci in LN stations without calcified LNs could be benchmarks for omitting the dissection of calcified LNs.

Calcified fibrotic LNs sometimes make it difficult to accurately differentiate layers around pulmonary vessels or bronchus. In such situations, the dissection of such calcified LNs can be extremely dangerous. In fact, several investigators have reported that it is difficult and time-consuming to dissect calcified LNs [7, 14]. Furthermore, recent studies have revealed that hilar LNs with calcification on CT images could predict intraoperative conversion from VATS to an open approach for lobectomy, which was associated with adhesion between LNs and hilar structures and subsequent difficulty in dissecting the latter [7, 14–17]. Again, although radical LN dissection including calcified LNs is recommended, the dissection of a single LN station with

Table 2 Multivariate analysis for risk factors associated with metastasis to LN stations with calcified LNs by logistic regression

Variables	HR	95% CI	P value
Clinical N stage (cN+)	1.560	0.207–11.768	0.666
Calcification in the primary tumor (yes)	2.363	0.279–19.992	0.430
Number of LN stations with calcified LNs (multiple)	9.901	1.698–58.824	0.011
Metastasis to LN stations without calcified LNs (yes)	19.089	3.000–121.472	0.002

LN lymph node, *CI* confidence interval

calcified LNs or LN stations with calcified LNs when there are no metastatic foci in other LN stations without calcified LNs could be omitted when the operative procedure is difficult due to the presence of calcified LNs.

With regard to the findings for calcified LNs on preoperative CT, the size of calcification was important on a per-nodal station basis. Takamochi et al. demonstrated that morphological features of calcification on CT were important for distinguishing between benign and malignant pulmonary nodules [20]. Another previous report mentioned that punctate or eccentric calcifications could be indicative of possible malignancy, although they were also sometimes observed in benign lesions [21]. However, these studies did not investigate the features of calcification in LNs. To the best of our knowledge, few reports have assessed the morphological features of calcification in LNs. In this study, LN stations with LNs with minor calcifications had metastatic foci more frequently than those with LNs with major calcifications. Moreover, none of the patients having only a single LN station with major-calcified LNs on preoperative CT had metastatic foci in their calcified LNs. There are two possible mechanisms of metastasis to calcified LNs: metastasis to previously existing calcified LNs and metastasis to non-calcified LNs from cancer that secretes calcium. For the latter possible mechanism, previous reports have stated that, in patients with lung adenocarcinoma, CT detected psammomatous calcifications in both the primary lesion and in metastatic foci in mediastinal LNs [11, 12]. Although the precise mechanisms of metastasis to calcified LNs could not be investigated in this study, they should be evaluated in other studies in the near future.

This study has several limitations. First, our study represents a retrospective single-institution experience, with patients drawn from the same ethnic background and geographical region; therefore, the lack of data and external validity are potential problems. Second, PET-CT images were not assessed in this study because of insufficient data. However, as previous studies have reported [4, 5, 8], only 10% or less of LNs that showed high FDG uptake on PET images together with calcification had metastatic foci from primary cancer. FDG-PET might not be useful for the evaluation of calcified LNs in patients with lung cancer. Third, the small sample size might mean that our analysis is underpowered to detect differences in several values.

In conclusion, this study revealed that the frequency of metastasis to LN stations with calcified LNs in patients with lung cancer was about 20% on both a per-person and a per-nodal station basis. Accordingly, calcified LNs as well as non-calcified LNs should be dissected during an operation. The dissection of a single station with calcified LNs, particularly those with major calcification or LN stations with calcified LNs when there are no metastatic foci in other LN stations without calcified LNs, could be omitted when the operative procedure is difficult due to such calcified LNs.

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