Original Article

Selection of Sublobar Resection for c-Stage IA Non-Small Cell Lung Cancer Based on a Combination of Structural Imaging by CT and Functional Imaging by FDG PET

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Purpose: The purpose of this study was to establish criteria for the indication of sublobar resection or lobectomy in cT1N0M0 non-small cell lung cancer (NSCLC), based on information from both computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG PET).

Materials and Methods: A total of 248 cT1N0M0 NSCLC tumors treated surgically were subjected to high-resolution or thin-slice CT (HR/TSCT) study, and 99 of these tumors were also subjected to FDG PET study. Four types of data were collected: (1) tumor size based on HR/TSCT (0–10 mm, 11–20 mm or 21–30 mm); (2) percentage of ground-glass opacity (GGO) region (GGO type or solid type); (3) pathological type (invasive cancer [INVC] or non-INVC [NINVC]); (4) FDG uptake in the tumor (grades 0, 1, and 2).

Results: One of 42 tumors (2.4%) less than 1 cm in size, 29 of 132 tumors (22.0%) 1–2 cm in size, and 25 of 74 tumors (33.8%) 2–3 cm in size were judged to be INVC ($p = 0.0002$). GGO type tumors (2.3%) were less likely to be INVC than solid type tumors (32.9%) ($p < 0.0001$). None of the 28 GGO tumors less than 1 cm in size was INVC; however, the possibility of INVC remained in solid type tumors less than 1 cm in size. In tumors whose diameter was more than 1 cm, INVC was possible regardless of their size or character (GGO or solid). One of 23 (4.3%), 4 of 33 (12.1%) and 14 of 43 tumors (32.6%) whose FDG uptake showed grades 0, 1, and 2, respectively, microscopically revealed INVC ($p = 0.0028$). All tumors whose FDG uptake was grade 0 and whose size was less than 1 cm were NINVC. On the other hand, tumors whose FDG uptake was grade 1 or 2 or whose size was more than 1 cm retained the possibility of INVC. All 5 tumors (5.0%) which were found to have lymph node metastasis showed grade 2 FDG uptake.

Conclusion: The criteria for operation for cT1N0M0 NSCLC based on HR/TSCT and FDG PET findings are the following: (1) a tumor less than 1 cm in size and either a GGO type or whose PET grade is 0 (wedge resection); (2) a tumor greater than 1 cm in size and whose PET grade is 0 or 1 (segmentectomy with lymph node dissection); or (3) a tumor whose PET grade is 2 (lobectomy with systemic lymph node dissection). (Ann Thorac Cardiovasc Surg 2009; 15: 82–88)

Key words: lung cancer, sublobar resection, fluorodeoxyglucose positron emission tomography, segmentectomy

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Received August 27, 2007; accepted for publication March 17, 2008

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Introduction

The operative mode for lung cancer is usually decided based on clinical tumor-node-metastases (TNM) staging.[1)] The determination of the TNM staging is made based on chest and upper abdominal computed tomography (CT), brain magnetic resonance imaging (MRI), bone scin-

tigraphy, and/or other examination. Clinical tumor (T) status is usually determined by structure-based imaging modalities, such as high-resolution or thin-slice CT (HR/TSCT). CT primarily provides 3 types of information about a tumor (location, shape, and density), and sublobar resection for lung cancer as reported to date has been conducted based on these structural data. Some reports state that the resection was performed based on the size of the tumor, i.e., less than 3 cm in diameter,[2–4] but others based the decision to resect on the area of ground-glass opacity (GGO).[5–7] However, although structural imaging is the current cornerstone, it cannot precisely reflect pathological status because of so-called reactive change, i.e., pneumonia or mucous collection in the tumor, and the most important problem at present is the very low percentage of candidates for sublobar resection identified by this information.[8] There is a strong rationale for the accurate estimation of pathological status to provide more accurate prognostic information and to appropriately select those patients who would benefit from limited surgery.

A new examination method, fluorodeoxyglucose positron emission tomography (FDG PET), that can reveal the malignant aggressiveness of a tumor based on preferential FDG accumulation in malignant tissues with increased glucose uptake and metabolism has recently become available. The use of FDG PET in the evaluation of lung cancer is thought to assist in differentiating malignant pulmonary nodules from benign nodules and in detecting regional lymph nodes (N-staging) or distant metastases (M-staging).[9,10] Another use of FDG PET is to monitor the effect of chemotherapy or radiotherapy because PET allows the assessment of the metabolic activity of viable tumor cells. Given that FDG uptake is related primarily to the number of viable tumor cells, a reduction in FDG uptake after effective treatment may reflect tumor cell death and could therefore be an accurate predictor of response.[11] If low accumulation of FDG indicates low malignant aggressiveness, the operative method for lung cancer can be decided according to functional information from FDG PET. Higashi et al. report that PET reflects postoperative prognosis, especially in cases of pStage IA non-small cell lung cancer (NSCLC), intratumoral vessels, lymphatic invasion, and endothelial cell proliferation.[12–14] They suggest that PET may be able to select appropriate candidates for limited surgery.

Nevertheless, structural information from CT and functional information from FDG PET has not yet been used to advantage in lung cancer surgery because these two types of information have yet to be combined. It is necessary to compare the FDG uptake of primary tumors on PET with the GGO area in the primary tumors on CT as a predictor of intratumoral vascular and lymphatic vessel invasion or lymph node metastasis. The purpose of the present study was to determine criteria for sublobar resection or lobectomy in cT1N0M0 NSCLC based on information from both CT and FDG PET.

Materials and Methods

We conducted three kinds of studies. First, we studied whether the information provided by traditional CT examination concerning the size and GGO percentage of tumors could distinguish between invasive cancer (INVC) and non-INVC (NINVC) preoperatively. Second, we examined whether the information provided by FDG PET could make the same distinction. And lastly, we studied whether the combination of these two types of information could make a precise distinction between INVC and NINVC preoperatively.

The study was a retrospective analysis of patients with cT1N0M0 NSCLC who were treated by surgical resection at Saiseikai Kumamoto Hospital and an associated hospital from April 1997 to December 2006. The clinical stages were determined by preoperative enhanced HR/TSCT, brain MRI and bone scintigraphy or FDG PET scanning and were defined by the TNM system of the Union Internationale Contre le Cancer (UICC).[1] FDG PET was added to routine preoperative examination in April 2004.

HR/TSCT and pathological study

Our subjects included 244 patients (248 tumors) who were diagnosed with cT1N0M0 NSCLC following surgical resection and pathological staging. None had received prior treatment. All patients underwent routine thoracic HR/TSCT. The radiological size was obtained by measuring the greatest diameter on HR/TSCT. The cases were classified into the following 3 tumor size categories: 0 to 10 mm; 11 to 20 mm; and 21 to 30 mm. Moreover, each lesion was determined to be either the GGO type (tumors that showed more than 50% of the GGO area on HR/TSCT) or the solid type (tumors that showed less than 50% of GGO area on HR/TSCT). All lesions were examined pathologically and divided into 2 types: tumors with intratumoral vascular or lymphatic vessel invasion or lymph node involvement (INVC) and those without such invasion or involvement (NINVC). In wedge resection patients, they were classified in no lymph node

involvement when they had no clinical lymph node metastasis and no lymph node recurrence postoperatively.

FDG PET study

The last 95 patients examined during the study period underwent FDG PET preoperatively. The time between the PET study and the surgery was at most 4 weeks in all cases. FDG uptake in tumors was classified using the following 3-point grading scale[15]: grade 0, no tumoral activity; grade 1, increased tumoral activity, but less than or equal to the mediastinal background activity; grade 2, tumoral activity higher than the mediastinal background activity. Following previous reports, the findings were defined as positive for malignancy if tumor activity was higher than the mediastinal background activity.[15,16] We calculated sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) to detect histological INVC by only FDG PET.

Combined assessment by HR/TSCT and FDG PET

The two kinds of structural information provided by CT examination (size and GGO or solid type), the functional information provided by FDG PET (grade of FDG uptake), and the obtained pathological information (INVC or NINVC) were combined, and we examined the relationships among these different kinds of data. We investigated the possibility of recommending sublobar resection based on this combined data.

Statistical analysis

The present study was conducted with the approval of the institutional ethics board. The χ^2-test, the Mann-Whitney U test, and the Spearman rank correlation test were used for statistical analyses. All data were calculated using Stat-View software (version 5.0, SAS Institute Inc., Cary, NC, USA). A p value of less than 0.05 was defined as significant.

Results

Patient characteristics are listed in Table 1. Because 3 patients had multiple tumors, 248 tumors were included in this study of 244 patients. Lobectomy with mediastinal node dissection was conducted in 161 patients, segmentectomy with mediastinal node dissection in 48, and wedge resection without node dissection in 35. A total of 195 patients were histologically diagnosed with adenocarcinoma, 33 with squamous cell carcinoma, and 16 with other cancers. Postoperative pathological examination revealed lymph node metastasis in 8 patients (3.3%).

Table 1. Patient characteristics

	HR/TSCT cases	PET cases
No. of patients (tumors)	244 (248)	95 (99)
Mean age (years) (range)	67.0 (14–87)	69.1 (41–87)
Sex		
Male	121 (49.6%)	53 (55.8%)
Female	123 (50.4%)	42 (44.2%)
Histology		
Adenocarcinoma	195 (79.9%)	74 (77.9%)
Squamous cell carcinoma	33 (13.5%)	12 (12.6%)
Others	16 (6.6%)	9 (9.5%)
Postoperative stage by TNM category		
Stage IA	236 (96.7%)	92 (96.8%)
Stage IIA	4 (1.6%)	1 (1.1%)
Stage IIIA	4 (1.6%)	2 (2.1%)

HR/TSCT, high-resolution or thin-slice computed tomography; PET, positron emission tomography; TNM, tumor-node-metastases.

Table 2 shows the relationship between pathological invasive findings (intratumoral lymphatic or vascular involvement and lymph node metastasis) and tumor character (GGO or solid type) based on CT images and according to the radiological tumor size. One of 42 tumors (2.4%) less than 1 cm in size, 29 of 132 tumors (22.0%) 1–2 cm in size, and 25 of 74 tumors (33.8%) 2–3 cm in size were INVC. The greater the tumor size, the higher the percentage of INVC ($p = 0.0002$). There were 87 GGO-type tumors and 161 solid-type tumors. GGO types showed a lower rate of INVC (2.3%) than solid types (32.9%) ($p < 0.0001$). None of the 28 GGO type tumors less than 1 cm in size showed INVC. In contrast, INVC was present in 1 case of solid-type tumor whose diameter was less than 1 cm. In tumors whose diameters were greater than 1 cm, INVC was possible regardless of the exact tumor size or character.

We investigated the relationship between FDG PET findings and pathological findings. FDG uptake was assigned grade 0 in 23 tumors, grade 1 in 33 tumors, and grade 2 in 43 tumors. Usually, a tumor is expected to be malignant if it has an FDG uptake grade of 2.[15] We examined whether it was plausible to consider grade 2 tumors to be INVC in all cases (Table 3). Fourteen of 43 PET-positive tumors were found to be INVC, and 51 of 56 PET-negative tumors were NINVC. The sensitivity, specificity, accuracy, PPV, and NPV of FDG PET alone in the identification of INVC were 73.7%, 63.7%, 65.6%, 32.5%, and 91.1%, respectively.

Table 2. Relationships among pathological invasive findings, HR/TSCT images and tumor size

CT image and tumor size	Pathological finding		Total
	INVC	NINVC	
GGO type (n = 87)			
< 1 cm	0	28	28
1–2 cm	1	39	40
2–3 cm	1	18	19
Solid type (n = 161)			
< 1 cm	1	13	14
1–2 cm	28	64	92
2–3 cm	24	31	55
Total	55	193	248

CT, computed tomography; INVC, invasive cancer; NINVC, noninvasive cancer; GGO type, tumors with ground-glass opacity areas of more than 50% of the total tumor; solid type, tumors with solid areas showing GGO areas of less than 50% of the total tumor.

Table 3. Relationship between FDG PET and pathological findings

	INVC	NINVC	Total
PET^+	14	29	43
PET–	5	51	56

PET^+, grade 2; PET–, grade 0 or 1.
P = 0.0068 (χ^2-test).
INVC, invasive cancer; NINVC, noninvasive cancer; PET, positron emission tomography.

Figure 1 shows the relationship between FDG uptake grade and the microscopic invasiveness of tumors (INVC or NINVC). Of 23 grade 0, 33 grade 1, and 43 grade 2 tumors, 1 (4.3%), 4 (12.1%), and 14 (32.6%) tumors were defined as INVC based on microscopic evaluation. The higher the FDG uptake grade, the higher the percentage of INVC (p = 0.0028).

Figure 2 shows the combined interpretation of HR/TSCT and FDG PET findings. There were 19 lesions of INVC (19.2%) identified in 99 tumors. This percentage is not significantly different from that of the INVC cases found in all 248 tumors (22.9%) (Table 2). All 9 tumors whose FDG uptake was grade 0 and whose size was less than 1 cm were NINVC. On the other hand, some grade 1 and grade 2 tumors and some grade 0 tumors whose size was greater than 1 cm showed INVC. All 5 tumors (5.0%) found to have lymph node metastasis showed grade 2 FDG uptake.

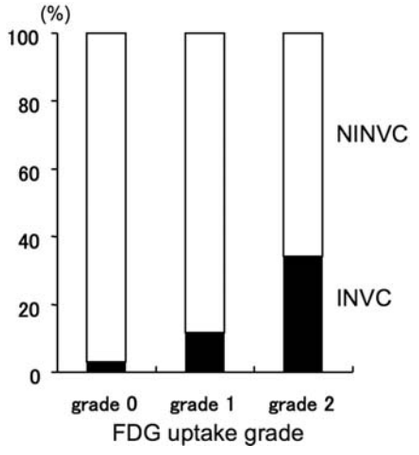

Fig. 1. Percentage of INVC tumors within each FDG uptake grade category.
INVC, invasive cancer (black bar); NINVC, non-INVC (white bar).

Discussion

Almost all thoracic surgeons agree that the standard operation for lung cancer is lobectomy with systematic lymph node dissection. However, thoracic surgeons are now treating more cases of peripheral small lung cancer because of improved early detection and greater use of helical CT or HR/TSCT, and there have been several recent reports on intentional limited resection or sublobar resection.[17,18] There are two methods of sublobar resection, nonanatomical wedge resection and anatomical

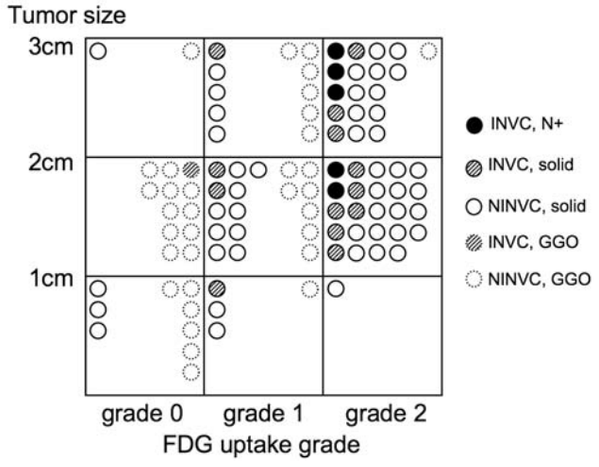

Fig. 2. Relationship between tumor sizes, FDG uptake grade and INVC/NINVC.
FDG, fluorodeoxyglucose; INVC, invasive cancer; N+, pathologically lymph node (metastasis) positive in node dissection patients or clinical lymph node positive cases in no node dissection patients; solid, tumors with solid areas showing GGO areas of less than 50% of the total tumor; NINVC, non-INVC; GGO, tumors with ground-glass opacity areas of more than 50% of the total tumor.

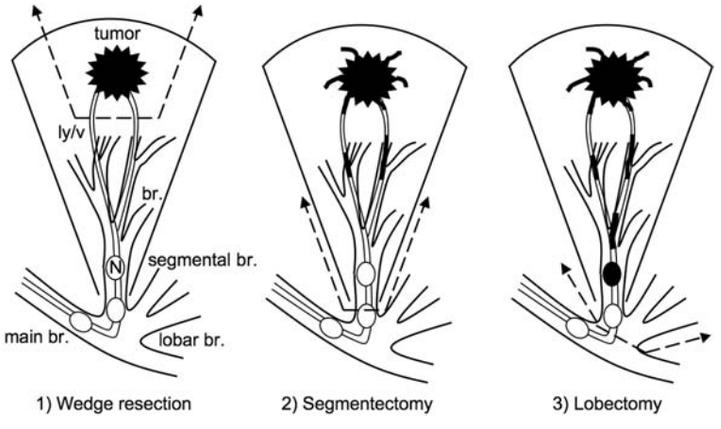

Fig. 3. Selecting operative mode according to pathological invasive findings.
br., bronchus; N, lymph node; ly/v, lymphatic or vascular vessel.
Black areas are those invaded or occupied by cancer cells.

segmentectomy, with a fundamental difference between them. Wedge resection is used to resect only a tumor by nonanatomical techniques. It does not include lymph node sampling or dissection, and its most important purpose is to ensure an adequate surgical margin. Therefore candidates for wedge resection are patients who have only lesions that are strongly expected to be NINVC, for example, Noguchi type A or B bronchioloalveolar cell carcinoma (BAC)[19] (Fig. 3-1). On the other hand, with anatomical segmentectomy it is possible to completely dissect the segmental bronchial lymph nodes and to examine the lobar bronchial lymph nodes to confirm whether the dissected lymph nodes show metastasis based on intraoperative frozen pathological examination. Certainly there may be no remnant cancer microscopically in the surgical margin if the resection was performed based on confirmation of the absence of metastasis in the sampled lymph nodes; the target segment was resected anatomically en bloc based on segmental bronchovascular and lymphatic trees. Therefore candidates for segmentectomy are patients with lesions that are expected to be NINVC or INVC whose sampled lymph nodes show no metastasis on intraoperative frozen pathological examination (Fig. 3-2).

Considerable effort has been made to distinguish preoperatively between INVC and NINVC. The representative NINVC is Noguchi type A or B BAC.[19] Many authors have suggested that GGO on HR/TSCT reflects BAC.[5–8] They suspected BAC based on the quantity of GGO in a tumor and obtained excellent postoperative prognoses after resection. However, BAC accounts for only 10% at most of all resectable lung cancers. It is therefore necessary to take NINVCs other than BAC into account. Other reports have chosen candidates for sublobar resection based on tumor size, specifically, lesions whose diameters are less than 2 or 3

cm.[4,17] Although the results of the present study indicate that the possibility of INVC cannot be ignored even in small lesions, Ichinose et al. mention a potential risk of limited resection for peripheral stage I NSCLC.[20] They report that the incidence of lymphatic vessel invasion was 25% (1/4) for tumors of 1.0 cm or less, 40% (19/48) for tumors of 1.1 to 2.0 cm, and 48% (28/58) for tumors of 2.1 to 3.0 cm, suggesting that even small peripheral tumors with no regional lymph node metastases had a relatively high rate of lymphatic vessel invasion. Because CT gives only the size of the tumor size and of the GGO area, it is of limited use in determining the indication of sublobar resection. On the other hand, FDG PET examination, which has recently become available, is completely different from the structural examination of CT and can estimate metabolic function as well as malignant potential. Some studies have found that FDG PET is useful in estimating the malignant aggressiveness of T1 NSCLC, for example, to distinguish between INVC and NINVC. Higashi et al. report that lesions with more FDG uptake than mediastinal background uptake showed intratumoral lymphatic vessel invasion and nodal involvement more frequently than lesions whose FDG uptake was equal to or less than their mediastinal background uptake; this was especially true in the case of c-Stage IA NSCLC lesions.[13] Although their report was a multicenter study including 132 NSCLC cases whose tumor sizes ranged from 0.8 to 12 cm, the present examination of 99 c-Stage IA tumors gave the same results. Therefore we conclude that FDG PET is capable of showing whether an NSCLC lesion includes intratumoral lymphatic or vascular involvement.

Standard uptake value (SUV) is a common method of expressing the quantity of FDG uptake. However, the FDG uptake grade of a lesion is usually expressed in comparison with the FDG uptake of a neighboring normal organ because the SUV may differ depending on the measuring device or the patient's condition. In the present study, the FDG uptake grade of a lesion was expressed in comparison with the mediastinal background activity. This method is the most commonly used to decide whether a lesion is malignant.[16,21,22] Under this method, a tumor whose FDG uptake is higher than mediastinal background activity is considered to be positive. For example, a pulmonary nodular lesion is identified as lung cancer or a lymph node is occupied by metastatic cancer if the FDG uptake of the lesion is positive. Table 3 shows the identification of the present 99 tumors as INVC or NINVC according to this method, and shows a PPV and NPV of 32.5% and 91.1%, respectively. Thus if we conduct sublobar resection based solely on this method of decision, the percentage of patients with remnant cancer after sublobar resection would not be insignificant. Therefore it is inadequate to use only this FDG PET interpretation method to select candidates for sublobar resection.

For these reasons, we have examined the possibility of identifying tumors as INVC or NINVC, preoperatively using a combination of the morphological information obtained by HR/TSCT and the functional information provided by FDG PET. Figure 2 shows that tumors of any size may be INVC and that tumors whose FDG uptake was grade 2 should not be candidates for sublobar resection because of the possibility of lymph node metastasis. Such tumors that possess the possibility of pathological lymph node metastasis should be candidates for lobectomy with systemic lymph node dissection. Moreover, grade 1 may have a low possibility of lymph node metastasis, but may show intratumoral lymphatic or vascular involvement and therefore should not be candidates for wedge resection, though they could be candidates for anatomical segmentectomy with segmental and lobar bronchial lymph node sampling (Fig. 3). Tumors of less than 1 cm and whose FDG uptake is grade 0 are candidates for wedge resection. Besides HR/TSCT findings that GGO type tumors of less than 1 cm may be NINVC (Table 2), the selection of the operation mode for cT1N0M0 NSCLC should be made as follows: (1) a tumor whose size is less than 1 cm and GGO type or whose PET grade is 0: wedge resection; (2) a tumor whose size is greater than 1 cm and whose PET grade is 0 or 1: segmentectomy with segmental and lobar lymph node sampling or dissection; (3) a tumor whose PET grade is 2: lobectomy with systemic lymph node dissection.

In the case of a small lung cancer, there exists the problem of limited spatial resolution on FDG PET examination. It is generally accepted that lesions less than 1 cm in size are predisposed to false negative results on PET,[9] though there may be few false-positive cancer cases less than 1 cm in size. If tumors less than 1 cm in size show a PET grade of 0, either they are truly NINVC, or they may be cases of false negative results. On the other hand, if tumors less than 1 cm in size show a PET grade of 1 or 2, we can be certain that INVC is a possibility.

Since the present study was based on only 95 cases, the results shown in Fig. 2 might be changed or further clarified when more cases are analyzed in the future. Because anatomical segmentectomy can be used to

confirm the absence of metastasis to regional lymph nodes intraoperatively, we can clarify the adequacy of anatomical segmentectomy more precisely than that based on preoperative HR/TSCT and FDG PET information. In the future, we will include in our analyses more sublobar resection or lobectomy cases based on these criteria and will update the information given in Fig. 2 as necessary. The issue of limited resection for NSCLC will be resolved only with a randomized trial in the modern era with CT and FDG PET. The data that we presented might be better served through a rigorous correlation of clinical versus pathological staging incorporating CT and FDG PET supported by clinical outcome data. We are hopeful that sublobar resection carried out as indicated by the present study might be performed successfully without recurrence.

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