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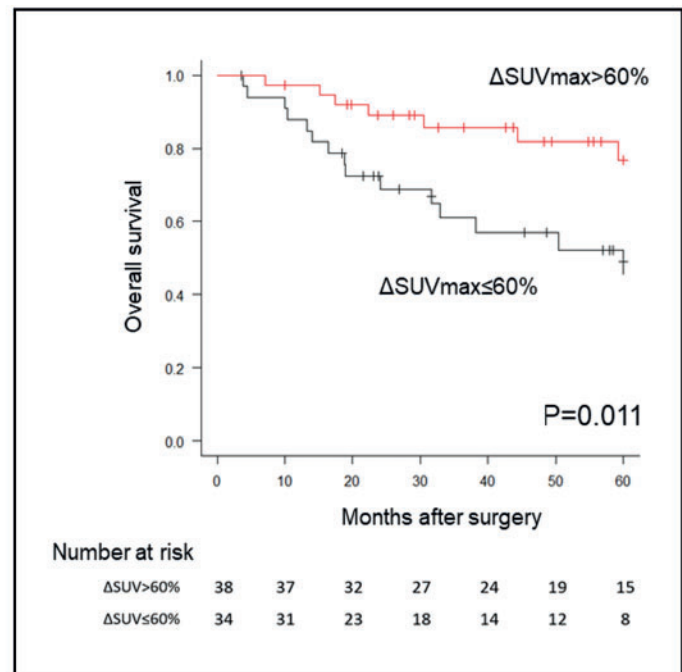
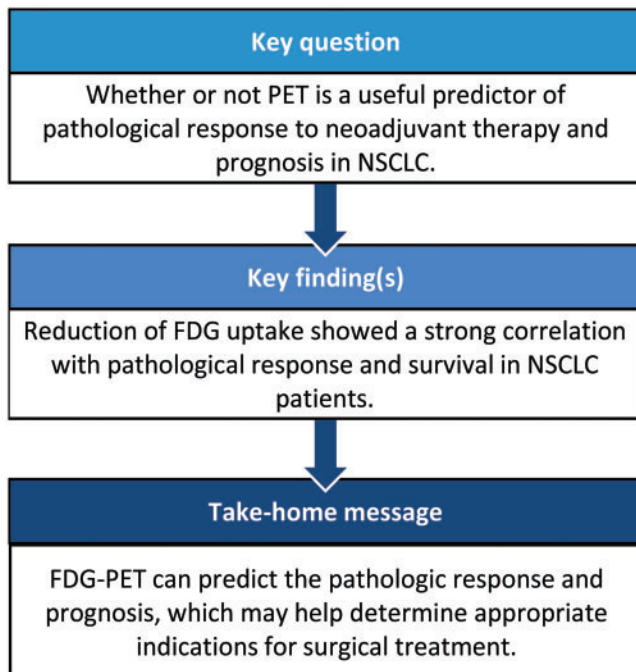
Role of fluorodeoxyglucose-positron emission tomography in predicting the pathological response and prognosis after neoadjuvant chemoradiotherapy for locally advanced non-small-cell lung cancer

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Abstract

OBJECTIVES: The present study compared the utility of fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) for predicting the pathological response and prognosis following neoadjuvant therapy for locally advanced non-small-cell lung cancer (NSCLC).

METHODS: This retrospective analysis included 72 patients in whom adjacent structures showed involvement and/or cN2 NSCLC who received induction chemoradiotherapy (ICRT) and subsequent surgery at our hospital from 2008 to 2019. FDG-PET and CT were performed in all patients before and after ICRT using the same scanner with similar techniques. We calculated the reduction in the maximum standardized uptake value in FDG-PET ($\Delta\text{SUV}_{\text{max}}$) and tumour size on CT ($\Delta\text{CT-size}$) before and after ICRT and investigated the relationship between the pathological response and prognosis.

RESULTS: The disease response was classified as a major pathological response in 43 patients, and a minor response in 29 patients. Δ SUVmax 60% and Δ CT-size 30% were identified as the optimal cut-off values for predicting a major pathological response. Δ SUVmax was superior to Δ CT-size in terms of sensitivity, specificity, positive predictive value and negative predictive value. Furthermore, Δ SUVmax was superior to Δ CT-size for predicting the prognosis.

CONCLUSIONS: Based on the results of the present study, FDG-PET appeared to have greater utility than CT in predicting the pathological response following ICRT and the postoperative prognosis in patients with locally advanced NSCLC.

Keywords: Positron emission tomography • Induction chemoradiotherapy • Pathological response • Lung cancer

ABBREVIATIONS

CT	Computed tomography
FDG-PET	Fluorodeoxyglucose-positron emission tomography
ICRT	Induction chemoradiotherapy
MRI	Magnetic resonance imaging
NSCLC	Non-small-cell lung cancer
SUVmax	The maximum standardized uptake value
OS	Overall survival
DFS	Disease-free survival

INTRODUCTION

Worldwide, non-small-cell lung cancer (NSCLC) is one of the most frequent causes of cancer-related mortality [1]. At the time of their diagnosis, many NSCLC patients (more than a third) present with advanced disease. Patients with locally advanced NSCLC (lung cancer invading adjacent organs and/or N2 lung cancer) who receive surgery alone show poor overall survival (OS), as most of these patients have microscopic distant metastases.

Induction therapy followed by surgery has recently been applied as a multimodal therapy in the treatment of locally advanced NSCLC [2–4]. The pathological response after induction therapy may be an important prognostic marker for the survival [5, 6]. Indeed, when a good pathological response of induction therapy is achieved, a good prognosis could be expected [7, 8], whereas when a pathological response is only minor, the prognosis tends to be unsatisfactory. Prognostic information for predicting the OS in the induction therapy setting might help establish criteria for selecting good surgical candidates.

Historically, the clinical tumour response has been evaluated by conventional anatomic measurements of changes in tumour size on computed tomography (CT). However, this approach has limitations: for example, viable cancer cells may still exist in an anatomically shrinking tumour, or fibrotic tissue and no viable cells may be contained in a residual mass. Several recent studies have reported the efficacy of fluorodeoxyglucose-positron emission tomography (FDG-PET) for predicting the pathological response [9–11] and prognosis [12, 13]. However, conflicting results regarding the prognostic value of FDG-PET have also been reported [10, 14–16]. For these reasons, the usefulness of FDG-PET in decision-making in relation to surgical options after induction therapy remains controversial.

We investigated whether or not the reduction in the FDG uptake on PET is a useful predictor of the pathological tumour response to induction chemoradiotherapy (ICRT) and prognosis compared with CT in locally advanced NSCLC patients.

PATIENTS AND METHODS

Ethics statement

The retrospective analysis of the present study was approved by the Institutional Review Board of Seirei Mikatahara General Hospital (approval number: 18-30). The informed consent of each patient was not required due to the retrospective nature of the study, which used patient information that was obtained from a database.

Patients

This retrospective study analysed the clinical records of 72 patients with locally advanced NSCLC that involved adjacent structures or major vessels (invasive T3 or T4) and/or cN2. All patients received FDG-PET and CT before and after ICRT at Seirei Mikatahara General Hospital, Hamamatsu, Japan, from July 2008 to May 2019. In order to exclude false-positive cases, we limited enrolment to patients with invasive T3/T4 disease in whom invasion of the surrounding structures invasion was pathologically confirmed after surgery. In the case of cN2, radiological evidence of N2 disease—defined as both mediastinal nodal enlargement (short-axis diameter: >1 cm) on CT and an abnormal FDG uptake on PET—was required, in addition to pathological confirmation of N2 disease.

Induction chemoradiotherapy

ICRT was performed for patients who were ≤ 75 years of age, who had an Eastern Cooperative Oncology Group performance status of 0–1, as well as adequate organ functional reserves. In all cases, the tumour was considered to be potentially resectable after its regression following ICRT. In all cases, the patients were evaluated before treatment by a multidisciplinary team that included a thoracic surgeon, radiation oncologist and medical oncologist. The disease stage was evaluated using chest radiography, enhanced chest and abdominal CT, enhanced brain magnetic resonance imaging (MRI), PET/CT and bronchoscopy. The disease stage and nodal location were defined according to the International Association of the Study of Lung Cancer TNM Staging System for NSCLC (8th edition). In all cases, the chemotherapy regimens consisted of 2 courses of platinum doublet therapy. All patients underwent concurrent radiotherapy with 40 or 50 Gy (2 Gy/day) to the primary tumour and involved lymph nodes. The radiation dose for preoperative treatment was 40 Gy until 2011 and 50 Gy from 2012 in our hospital. The radiation dose for patients requiring bronchoplasty was limited to 40 Gy. Within 4 weeks after ICRT, re-staging was performed using

thoracic CT, PET/CT and brain MRI. Lymph node metastasis after preoperative treatment was evaluated by both CT and PET, and Re-endobronchial ultrasound was not performed. Radical surgery was scheduled for within 6 weeks after the completion of ICRT for patients without progressive disease.

Follow-up surveillance

Follow-up examinations were performed monthly for the first 3 months, every 3 months until 2 years after surgery, then every 6 months. Chest CT and brain MRI were scheduled for every 3 months, while abdominal CT, brain MRI and PET/CT or a radio-nuclide bone scan were scheduled to be performed every 12 months for at least 2 years. Chest CT was repeated every 12 months in the first 3–5 years after the patient finished treatment.

Fluorodeoxyglucose-positron emission tomography and computed tomography data analyses

FDG-PET and CT were performed in all patients before and after ICRT using the same scanner with similar techniques. The FDG uptake was calculated as the maximum standardized uptake value (SUVmax) derived from regions of interest. The rate of reduction in the SUVmax (Δ SUVmax) of the primary tumour was calculated using the following formula:

$$\Delta SUVmax (\%) = \frac{[SUVmax \text{ before ICRT} - SUVmax \text{ after ICRT}] / SUVmax \text{ before ICRT}}{\times 100}$$

The entire thorax was scanned with sections of <1 cm in thickness with maximal inspiration. The primary tumour (longest diameter) was measured before and after ICRT. The rate of reduction in the primary tumour size on CT (Δ CT size) was calculated using the following formula:

$$\Delta CT \text{ size } (\%) = \frac{[(CT \text{ size before ICRT} - CT \text{ size after ICRT}) / CT \text{ size before ICRT}] \times 100}$$

Pathological analyses

The pathological tumour response (Ef) to induction therapy was evaluated using resected specimens according to the Japan Lung Cancer Society's General Rule for Clinical and Pathological Records of Lung Cancer (8th edition), as follows [17]: Ef0, no effect, treatment did not result in any morphological changes (including necrosis or degeneration); Ef1a, minor effect, viable cancer cells were seen in at least two-thirds of the cancer tissue; Ef1b, mild effect, viable cancer cells were observed in at least one-third but less than two-thirds of the cancer tissue; Ef2, moderate effect, viable cancer cells were observed in less than one-third of the cancer tissue; and Ef3, marked effect, no viable cancer cells were observed or any residual cancer cells were judged to be unviable.

In this study, we defined Ef1a and Ef1b as a minor pathological response, and Ef2 and Ef3 as a major pathological response.

Statistical analyses

Categorical variables were analysed using an χ^2 test. Survival was estimated using the Kaplan–Meier method, with differences in

survival evaluated by a log-rank test. Day 0 was defined as the date of pulmonary resection. The final endpoint of OS was cancer-related death or death from other causes. The final endpoint of disease-free survival (DFS) was the date of recurrence, the date of the last follow-up examination or the date of death in the absence of recurrence. *P*-values of <0.05 were considered statistically significant. The statistical analyses were performed using StatView (SAS Institute Inc., Cary, NC, USA), R (The R Foundation for Statistical Computing, Vienna, Austria) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Patient characteristics

Table 1 shows the characteristics of the 72 patients [male, *n* = 60; female, *n* = 12; median age, 61.0 years (range, 42–71 years)]. The histological subtypes included adenocarcinoma (*n* = 37), squamous cell carcinoma (*n* = 24), non-small-cell carcinoma (*n* = 4), pleomorphic carcinoma (*n* = 4) and adenosquamous cell carcinoma (*n* = 3). The clinical stages were as follows: stage IIB (T3N0, *n* = 20), stage IIIA [*n* = 33: T1N2 (*n* = 12), T2N2 (*n* = 8), T3N1 (*n* = 4), T4N0 (*n* = 5) and T4N1 (*n* = 4)] and stage IIIB [*n* = 19: T3N2 (*n* = 5), T4N2 (*n* = 14)]. In patients with clinical N2 disease, mediastinal

Table 1: Characteristics of the 72 patients who underwent induction chemoradiotherapy followed by surgery

Variable	Number (%)
Age (years), median (range)	61.0 (42–71)
Sex	
Male	60 (83.3%)
Female	12 (16.7%)
Histology	
Adenocarcinoma	37 (51.4%)
Squamous cell carcinoma	24 (33.3%)
Pleomorphic carcinoma	4 (5.6%)
Non-small-cell carcinoma	4 (5.6%)
Adenosquamous cell carcinoma	3 (4.2%)
Clinical stage	
IIB	20 (28.0%)
T3N0	20 (28.0%)
IIIA	33 (45.3%)
T1N2	12 (16.7%)
T2N2	8 (11.1%)
T3N1	4 (5.6%)
T4N0	5 (6.9%)
T4N1	4 (5.6%)
IIIB	19 (26.4%)
T3N2	5 (6.9%)
T4N2	14 (19.4%)
Chemotherapy regimen	
Cisplatin/Docetaxel	31 (43.1%)
Carboplatin/Vinorelbine	31 (43.1%)
Carboplatin/Paclitaxel	10 (13.8%)
Radiation dose	
40 Gy	26 (36.1%)
50 Gy	46 (63.9%)
Tumour response	
Complete response	1 (1.4%)
Partial response	39 (54.2%)
Stable disease	32 (44.4%)

nodal involvement was evaluated using endobronchial ultrasound-guided transbronchial needle aspiration ($n=22$) or CT/PET ($n=17$). No mediastinoscopy was performed. Pathological N2 disease was diagnosed before ICRT in 22 patients who underwent endobronchial ultrasound-guided transbronchial needle aspiration. The ICRT regimens were as follows: cisplatin plus docetaxel ($n=31$), cisplatin plus vinorelbine ($n=31$) and carboplatin plus paclitaxel ($n=10$). In all cases concurrent radiotherapy targeting the primary tumour and involved lymph nodes was performed with 40 Gy ($n=26$) or 50 Gy ($n=46$).

Surgery and adjuvant chemotherapy

Table 2 shows the outcomes of surgery. The following surgical procedures were performed: lobectomy ($n=63$; 87.5%), bilobectomy ($n=4$; 5.6%), pneumonectomy ($n=4$; 5.6%) and segmentectomy ($n=1$; 1.3%). Tracheo-bronchoplasty was performed for 16 patients (22%); in 3 of these patients the procedure included carinal resection. Forty-two patients received combined resection that involved the chest wall ($n=36$), vertebrae ($n=5$), brachiocephalic/subclavian artery ($n=3$), left atrium ($n=2$), superior vena cava ($n=2$) and aorta ($n=1$) (overlapping cases were included). Complete resection (R0) was achieved in 65 (90%) patients. The bronchial stump or anastomotic site was generally covered with an intercostal muscle pedicle flap or pericardial fat tissue. Adjuvant chemotherapy was administered to 43 (51%) patients.

Pathological tumour response

In this study, the therapeutic effect on the pathology was as follows: Ef3 ($n=16$; 22%), Ef2 ($n=27$; 38%), Ef1b ($n=15$; 21%) and Ef1a ($n=14$; 19%) (Table 2). Therefore, a major pathological response was achieved in 43 (60%), and a minor pathological response was observed in 29 (40%) patients.

Table 2: The surgical and pathological outcomes

Variable	Number (%)
Type of surgical resection	
Lobectomy	63 (87.5%)
Bilobectomy	4 (5.6%)
Pneumonectomy	4 (5.6%)
Segmentectomy	1 (1.3%)
Combined resected organs	42
Chest wall	36 (50.0%)
Vertebrae	5 (6.9%)
Brachiocephalic/subclavian artery	3 (4.2%)
Carina	3 (4.2%)
Left atrium	2 (2.8%)
Superior vena cava	2 (2.8%)
Aorta	1 (1.4%)
Complete resection	65 (90.0%)
Pathological response ^a	
Complete response (Ef3)	16 (22.2%)
Major response (Ef2)	27 (37.5%)
Mild response (Ef1b)	15 (20.8%)
Minor response (Ef1a)	14 (19.4%)

^aPathological response: Ef3, no microscopic residual tumour; Ef2, less than one-third of tumour cells viable; Ef1: more than two-thirds tumour cells viable.

The assessment of the primary tumour before and after induction chemoradiotherapy by fluorodeoxyglucose-positron emission tomography and computed tomography

The clinical responses for ICRT determined by CT were complete response in 1, partial response in 39, stable disease in 31 and progressive disease in 1. Among patients with a major pathological response, the mean SUVmax before and after ICRT was 13.7 and 3.9, respectively ($P<0.001$) (Supplementary Material, Fig. S1A). In patients with a minor pathological response, the mean SUVmax before and after ICRT was 11.6 and 6.8, respectively, with a significant difference also noted between these values ($P=0.005$), although it was slightly less significant than that seen with major pathological response (Supplementary Material, Fig. S1B).

A waterfall plot demonstrating the responses of each of the 72 patients is shown in Fig. 1. The larger the Δ SUVmax, the more patients had a major pathological response. The relationship between the reduction in PET scan avidity (Δ SUVmax) or CT size (Δ CT-size) at the primary site and the pathological response to ICRT was examined using a receiver operating characteristics curve, and the cut-off value that gave the best combined sensitivity and specificity was a 60% reduction in the SUVmax or 30% reduction in the CT size (Supplementary Material, Fig. S2). The rate of a major pathological response (Ef2 and Ef3) for Δ SUVmax $>60\%$ and Δ CT-size $>30\%$ was 81.6% and 72.9%, respectively (Supplementary Material, Fig. S3). The predictive value of Δ SUVmax for predicting a major pathological response was as follows: sensitivity, 72%; specificity, 76%; positive predictive value, 82%; and negative predictive value, 65%. In contrast, the predictive value of the Δ CT-size for predicting a major pathological response was as follows: sensitivity, 63%; specificity, 66%; positive predictive value, 73%; and negative predictive value, 54% (Table 3). We found that the Δ SUVmax was superior to Δ CT-size for all variables. Therefore, FDG-PET was deemed more useful for predicting the pathological effect of ICRT than CT.

The prognosis

Based on the response to ICRT, patients with Δ SUVmax $>60\%$ showed better 5-year OS in comparison to patients with Δ SUVmax $\leq 60\%$ (76.8% vs 45.6%, $P=0.011$) (Fig. 2A). In contrast, there was no marked difference in the survival between patients with a Δ CT-size $>30\%$ and those with a Δ CT-size $\leq 30\%$ (66.6% vs 56.9%, $P=0.371$) (Fig. 2B). The Δ SUVmax showed a strong correlation with the survival in patients who underwent ICRT. Therefore, FDG-PET is considered superior to CT for predicting the prognosis. There was no marked difference in the SUV reduction rate, pathological response, or prognosis according to the radiation dose (40 or 50 Gy). In addition, a subgroup analysis of the 72 patients classified into the T3-4N0-1 and N2 groups showed that the patients with Δ SUVmax $>60\%$ had better 5-year OS and DFS than those with Δ SUVmax $\leq 60\%$ in both groups (Figs 3 and 4). In particular, patients in the N2 group with Δ SUVmax $>60\%$ had a significantly better prognosis in comparison to those with Δ SUVmax $\leq 60\%$ [5-year OS; Δ SUVmax $>60\%$ vs Δ SUVmax $\leq 60\%$; T3-4N0-1 group: 83.3% vs 48.8% ($P=0.157$, Fig. 3A), N2 group: 76.8% vs 38.5% ($P=0.004$, Fig. 3B)] [5-year DFS; Δ SUVmax $>60\%$ vs Δ SUVmax $\leq 60\%$; T3-4N0-1 group: 69.6% vs 43.9% ($P=0.218$, Fig. 4A), N2 group: 60.9% vs 15.6% ($P=0.003$, Fig. 4B)].

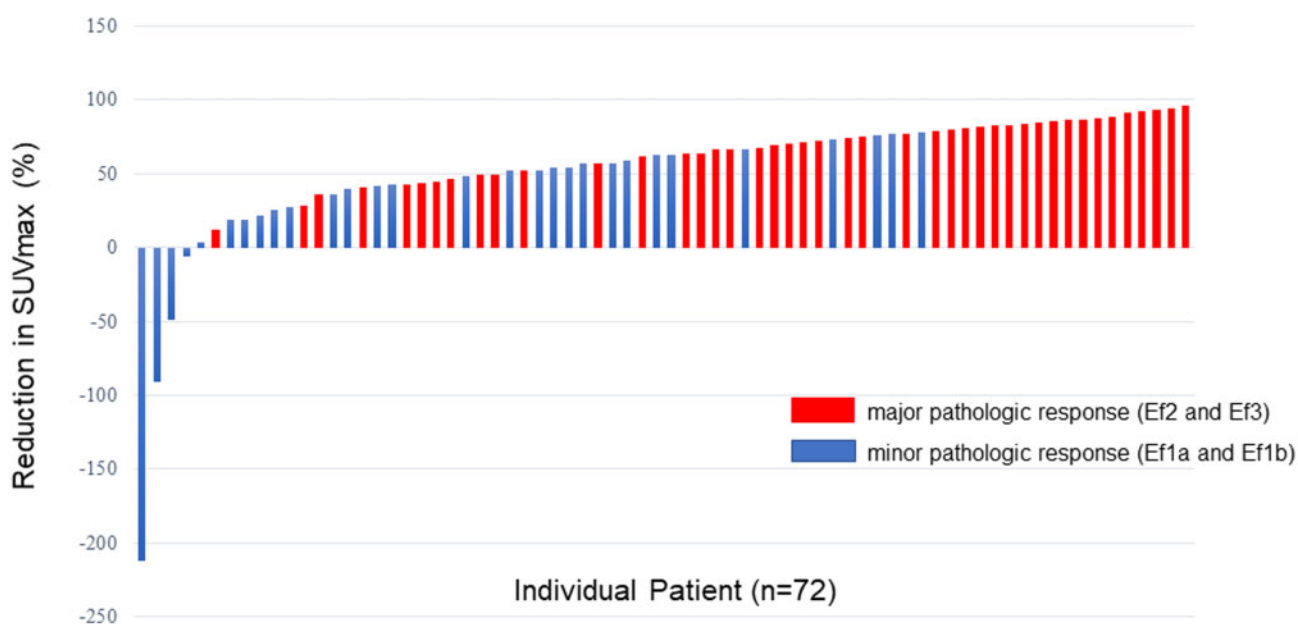


Figure 1: Plot demonstrating responses on positron emission tomography for each patient. The red columns represent patients with a major pathological response (Ef2 and Ef3), and the blue columns represent patients with a minor pathological response (Ef1a and Ef1b). (A color version of this figure appears in the online version of this article)

Table 3: Comparison of PET and CT for predicting major pathological responses

	Sensitivity	Specificity	PPV	NPV
Δ SUVmax	72%	76%	82%	65%
Δ CT-size	63%	66%	73%	54%

CT: computed tomography; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value.

In this study, there were 4 patients in which complete resection was judged to be possible, so surgical treatment was performed despite the elevated SUVmax after preoperative treatment. Complete resection was possible in all cases, but the pathological effect of induction chemoradiotherapy was poor in 2 cases of Ef1a and 2 cases of Ef1b. The outcomes of these 4 patients were also poor, as 2 died of lung cancer, 1 survived after resection of adrenal metastasis and 1 survived without recurrence.

DISCUSSION

The results of the present study suggest the superiority of FDG-PET to CT for predicting the histological response to ICRT and the prognosis after surgery in patients with locally advanced NSCLC.

In patients with locally advanced NSCLC [e.g. lung cancer invading adjacent organs (T3 or T4) and/or N2 lung cancer], surgery alone is associated with poor OS, as most such patients have microscopic distant metastasis before therapy. Accordingly, in the treatment of advanced NSCLC, the physician should aim to control both local and microscopic systemic disease. Multimodal treatment, which can reduce the tumour size, achieve complete resection and eradicate micrometastasis, is considered necessary for improving survival. ICRT followed by surgery was performed

for resectable locally advanced NSCLC invading adjacent organs (classified as invasive T3 or T4) and/or cN2. In our previous study, we found that a favourable prognosis could be expected when a major pathological response (Ef2 or Ef3) was achieved by concurrent chemoradiotherapy followed by surgery in patients with potentially resectable locally advanced NSCLC [18]. If a good pathological response can be predicted preoperatively, we can select patients who can be expected to have a good prognosis with surgical treatment. Thus, the identification of patients likely to be good pathological responders after induction therapy is a critical component for selecting ideal surgical candidates.

In general, the pathological response after induction chemoradiotherapy is assessed by CT. CT provides anatomical information based on morphological tumour changes. However, even after extensive tumour shrinkage, resistant cells may still be present, and the residual masses may be completely necrotic; these tissue types cannot be differentiated by CT. Accordingly, the morphological assessment may be misleading in some patients. On the other hand, FDG-PET is based on the increased glucose metabolism of tumour cells in comparison to normal cells. FDG preferentially accumulates in various types of cancer cells, but not in fibrotic or necrotic tissue. Thus, PET can differentiate viable tumours from scar tissue.

Recently, FDG-PET has been suggested as a better method for determining the pathological response than CT, as it provides additional metabolic information. The usefulness of FDG-PET in the predicting the pathological effects following preoperative treatment for locally advanced lung cancer has been investigated in several studies. Ryu *et al.* [9] reported the usefulness of FDG-PET for monitoring the therapeutic effect of neoadjuvant chemotherapy in NSCLC patients. However, their study only examined the SUV after neoadjuvant treatment and did not determine the SUV ratio before and after neoadjuvant therapy. Cerfolio *et al.* [11] evaluated the association between the SUVmax and viable tumour cells remaining after neoadjuvant therapy. They showed that the ratio of nonviable tumour cells on pathological sections

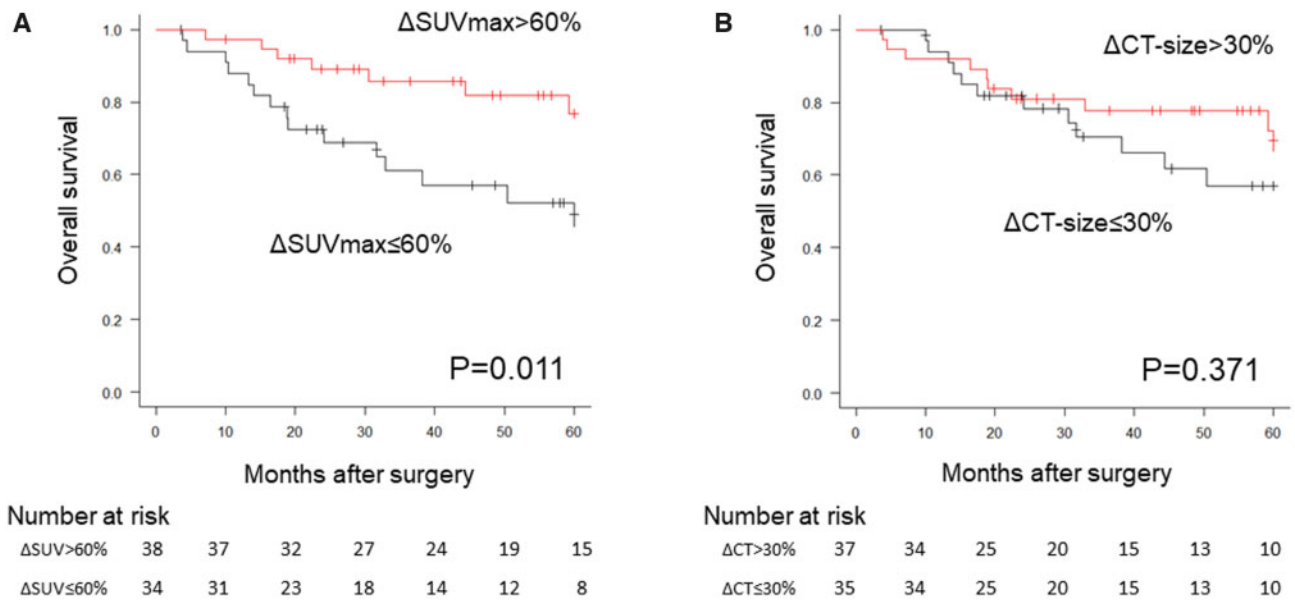


Figure 2: Overall survival according to (A) ΔSUVmax : >60% versus $\leq 60\%$; and (B) $\Delta\text{CT-size}$: >30% versus $\leq 30\%$.

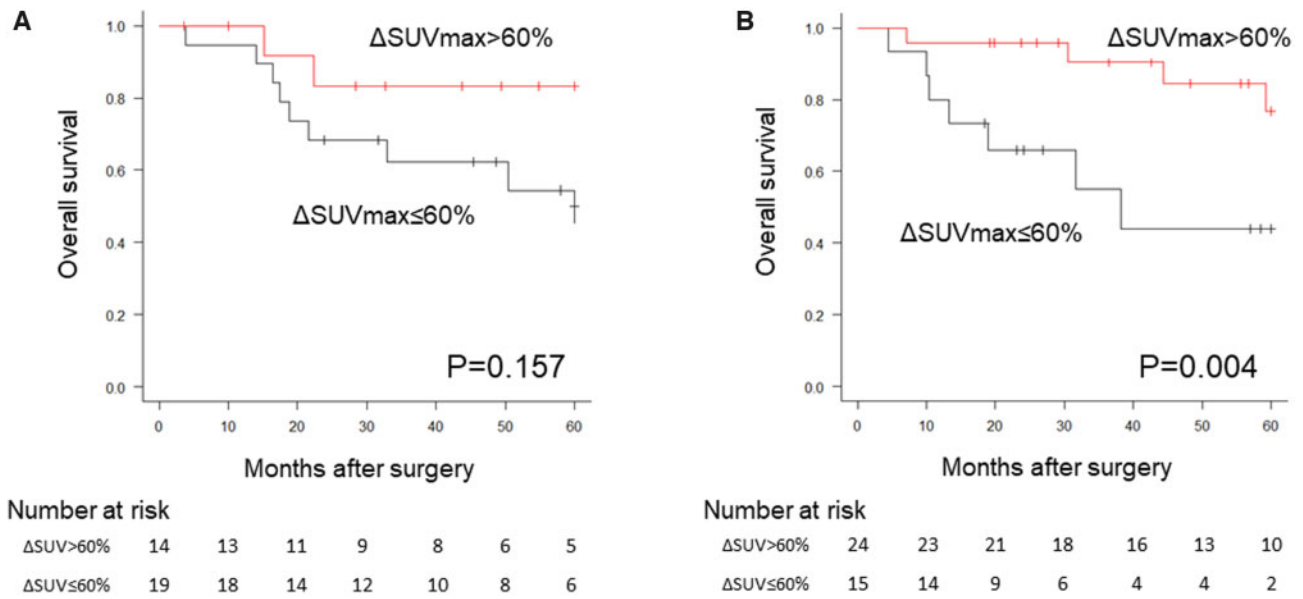


Figure 3: Overall survival according to ΔSUVmax : >60% versus $\leq 60\%$ for (A) patients in the T3-4N0-1 group; and (B) patients in the N2 group.

correlated significantly with FDG-PET but not with CT. Their findings are in line with the results of the present study; however, they did not evaluate the prognostic value of SUVmax.

The correlation between the SUV of FDG-PET and the prognosis after preoperative treatment followed by surgery in patients with locally advanced lung cancer has been evaluated in several studies; however, the findings of the reports were controversial. Tanvetynon *et al.* studied 89 patients with stage IB to IIIB disease and found no significant difference in the survival (cut-off value: a 30% reduction in the SUV after neoadjuvant chemotherapy) [16]. Eschmann *et al.* [12] reported that a reduced FDG uptake was indicative of the prognosis of patients who received induction therapy. They identified 60% over baseline as the threshold value of the SUVmax, and patients with a decrease of more than 60% showed favourable long-term results. However, the relationship between the pathological response and SUV was not

mentioned. Shiraishi *et al.* [10] studied 37 patients with stage IB to IIIB lung cancer who received neoadjuvant chemoradiotherapy and reported that the SUV on FDG-PET was more predictive of the pathological response to preoperative treatment than CT, but neither FDG-PET nor CT were able to predict the prognosis. Romin *et al.* [14] analysed 25 patients with stage IB to IIIB operable NSCLC who had received 3 cycles of cisplatin and pemetrexed neoadjuvant chemotherapy. They defined patients in whom the primary lesion showed a >20% decrease in SUV as metabolic responders. However, that trial did not demonstrate that PET can predict the survival outcomes of patients. In contrast to their results, our present study suggested that FDG-PET was useful for predicting the prognosis after surgery in patients with locally advanced NSCLC who underwent neoadjuvant therapy. The reason their findings differed from our own may be because their study included patients with early-stage (I to II) lung cancer.

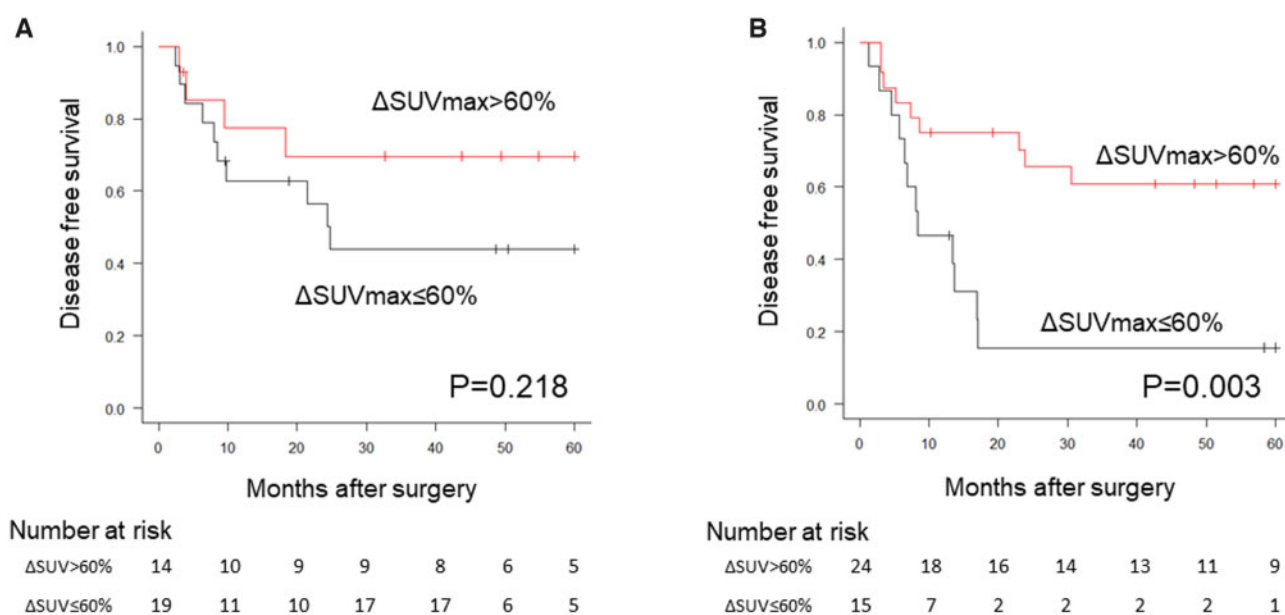


Figure 4: Disease-free survival according to Δ SUVmax: >60% versus \leq 60% for (A) patients in the T3-4N0-1 group; and (B) patients in the N2 group.

Early-stage lung cancer patients can be expected to have a good prognosis, even if the pathological effects of preoperative treatment are poor.

In the PACIFIC trial for unresectable stage III NSCLC, the 5-year OS and progression-free survival rates of patients who received consolidation durvalumab after concurrent chemoradiotherapy (the PACIFIC regimen) were 42.9% and 33.1%, respectively, which was significantly better in comparison to patients treated with placebo [19]. Based on the results of this trial, the PACIFIC regimen is considered the standard treatment for unresectable stage III NSCLC. The prognosis for patients who receive preoperative treatment followed by surgery for resectable stage III NSCLC is expected to be better than that of those who receive the PACIFIC regimen. Based on the subgroup analysis of this study, patients with Δ SUVmax >60% can be expected to show very good long-term survival after surgery. Thus, surgical treatment can be strongly recommended in these patients. Among the patients with Δ SUVmax <60%, T3-4N0-1 patients had better OS and DFS in comparison to the PACIFIC regimen-treated patients; thus, surgery is considered to be a useful treatment option for these patients. In contrast, N2 patients with Δ SUVmax \leq 60% are considered to have a poor prognosis, conversion to radical chemoradiation followed by durvalumab or other chemotherapy regimens rather than surgery may therefore be recommended for these patients.

Limitations

The present study was associated with several limitations that warrant mention. First, this study was retrospective, lacked randomization, and the study population was relatively small and heterogeneous. The single institution design may limit the generalizability of the findings. Finally, the possibility of false-positive caused by radiotherapy cannot be excluded. Radiation is known to produce a substantial inflammatory effect, which could influence the SUVmax via the recruitment of macrophages and other inflammatory response cells to the treatment site. Neoadjuvant chemoradiotherapy can thus cause false-positive results on

restaging PET. The ideal timing of repeat PET to maximize its accuracy for predicting pathological changes is currently unclear. However, Cerfolio *et al.* [20] reported that the ideal interval for performing repeat FDG-PET following neoadjuvant chemoradiotherapy using a high radiation dose of \geq 60 Gy in patients with NSCLC was approximately 1 month. Based on those findings, we performed FDG-PET about 2–4 weeks after the completion of preoperative treatment, which we consider to be a reasonable time frame.

CONCLUSION

We demonstrated that the rate of SUV reduction reflects the pathological effect compared to an evaluation by CT. A cut-off of 60% for the SUVmax reduction was the discriminative threshold between long-term survivors and poor survivors. Patients with a Δ SUVmax >60% after preoperative treatment had a higher rate of pathological response, which may have contributed to the favourable prognosis. FDG-PET before and after preoperative chemoradiotherapy can detect not only distant metastasis but also predict the pathological response and prognosis, which may help determine appropriate indications for surgical treatment.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

Data availability statement

All relevant data are within the manuscript and its supporting information files. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Masayuki Tanahashi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Writing—original draft; Writing—review & editing. **Eriko Suzuki:** Data curation. **Naoko Yoshii:** Data curation. **Takuya Watanabe:** Data curation. **Hiroyuki Tsuchida:** Data curation. **Shogo Yobita:** Data curation. **Kensuke Iguchi:** Data curation. **Suiha Uchiyama:** Data curation. **Minori Nakamura:** Data curation.

Reviewer information

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REFERENCES

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.
- [2] Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA *et al.* Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: american College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e314S–40S.
- [3] McElnay PJ, Choong A, Jordan E, Song F, Lim E. Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and metaanalysis of randomised trials. *Thorax* 2015;70:764–8.
- [4] NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for nonsmall-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet* 2014;383:1561–71.
- [5] Pataer A, Kalhor N, Correa AM, Raso MG, Erasmus JJ, Kim ES *et al.* Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. *J Thorac Oncol* 2012;7:825–32.
- [6] Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N *et al.*; University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *Lancet Oncol* 2014;15:e42–50.
- [7] Schreiner W, Gavrychenkova S, Dudek W, Rieker RJ, Lettmaier S, Fietkau R *et al.* Pathologic complete response after induction therapy—the role of surgery in stage IIIA/B locally advanced non-small cell lung cancer. *J Thorac Dis* 2018;10:2795–803.
- [8] Yokomise H, Gotoh M, Okamoto T, Yamamoto Y, Ishikawa S, Nakashima T *et al.* Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2007;133:1179–85.
- [9] Ryu JS, Choi NC, Fischman AJ, Lynch TJ, Mathisen DJ. FDG-PET in staging and restaging non-small cell lung cancer after neoadjuvant chemoradiotherapy: correlation with histopathology. *Lung Cancer* 2002;35:179–87.
- [10] Shiraishi K, Nomori H, Ohba Y, Kaji M, Mori T, Shibata H *et al.* Repeat FDG-PET for predicting pathological tumor response and prognosis after neoadjuvant treatment in nonsmall cell lung cancer: comparison with computed tomography. *Ann Thorac Cardiovasc Surg* 2010;16:394–400.
- [11] Cerfolio RJ, Bryant AS, Winokur TS, Ohja B, Bartolucci AA. Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small cell lung cancer. *Ann Thorac Surg* 2004;78:165–9.
- [12] Eschmann SM, Friedel G, Paulsen F, Reimold M, Hehr T, Budach W *et al.* Repeat 18F-FDG PET for monitoring neoadjuvant chemotherapy in patients with stage III non-small cell lung cancer. *Lung Cancer* 2007;55:165–71.
- [13] Pöttgen C, Gauler T, Bellendorf A, Guberina M, Bockisch A, Schwenzer N *et al.* Standardized uptake decrease on [18F]-fluorodeoxyglucose positron emission tomography after neoadjuvant chemotherapy is a prognostic classifier for long-term outcome after multimodality treatment: secondary analysis of a randomized trial for resectable stage IIIA/B non-small-cell lung cancer. *JCO* 2016;34:2526–33.
- [14] Romine PE, Martins RG, Eaton KD, Wood DE, Behnia F, Goulart BHL *et al.* Long term follow-up of neoadjuvant chemotherapy for non-small cell lung cancer (NSCLC) investigating early positron emission tomography (PET) scan as a predictor of outcome. *BMC Cancer* 2019;19:70.
- [15] Port JL, Kent MS, Korst RJ, Keresztes R, Levin MA, Altorki NK. Positron emission tomography scanning poorly predicts response to preoperative chemotherapy in non-small cell lung cancer. *Ann Thorac Surg* 2004;77:254–9.
- [16] Tanvetyanon T, Eikman EA, Sommers E, Robinson L, Boulware D, Bepler G. Computed tomography response, but not positron emission tomography scan response, predicts survival after neoadjuvant chemotherapy for resectable non-small-cell lung cancer. *JCO* 2008;26:4610–6.
- [17] The Japan Lung Cancer Society. General Rule for Clinical and Pathological Record of Lung Cancer, 8th edn. Tokyo, Japan: Kanehara & Co, 2017.
- [18] Tanahashi M, Niwa H, Yukiue H, Suzuki E, Yoshii N, Watanabe T *et al.* Feasibility and prognostic benefit of induction chemoradiotherapy followed by surgery in patients with locally advanced non-small cell lung cancer. *J Thorac Dis* 2020;12:2644–53.
- [19] Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L *et al.* Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *JCO* 2022;40:1301–11.
- [20] Cerfolio RJ, Bryant AS. When is it best to repeat a 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography scan on patients with non-small cell lung cancer who have received neoadjuvant chemoradiotherapy? *Ann Thorac Surg* 2007;84:1092–7.