Relationship Between PET/CT Response and Survival in Patients with Non-Small-Cell Lung Cancer Treated with Definitive Chemoradiotherapy

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ABSTRACT

We aimed to evaluate the relationship between PET/CT response and survival in patients with non-small cell lung cancer (NSCLC) treated with curative chemoradiotherapy. Between January and December 2012, 51 patients were treated. The median age was 61 (29-79) and the M/F ratio was 46/5. Eighty two percent of the cases were stage III and 53% were squamous cell carcinoma. Median 6300 cGy (4860-7525) radiotherapy delivered and 92% of patients received chemotherapy. The median follow-up was 27 months (7-96 months) in November 2019. The objective response was 71% with CT at 1 month and 76% with PET/CT at 3 months. There was a significant correlation between response-1 and response-3 ($p< 0.001$). Tumor $SUV_{mean3} < 2.81$, SUV_{max} change ≥ 70% was associated with response-1 ($p< 0.05$). The median and 5-year overall (OS) and progression-free (PFS) survival rates were 54 months, 40% and 35 months, 38%, respectively. In Cox model, for each 1 unit increase, $SUV_{meanbase}$ (HR: 1.18, 95% CI: 1.01-1.38) and SUV_{mean3} (HR: 2.65, 95% CI: 1.24-5.66) were found unfavorable factors for OS, whereas SUV_{mean3} (HR: 2.01, 95% CI: 1.02-3.93) was also found to be a poor prognostic factor for PFS. PET/CT parameters can be used as useful markers for prognosis in patients with NSCLC undergoing curative chemoradiotherapy. It is believed that early assessment during and after treatment can be advantageous in terms of treatment modification.

Keywords: Non-small cell lung cancer, Definitive chemo-RT, PET/CT response, Survival

INTRODUCTION

The current treatment approach for locally advanced non-small-cell lung cancer (NSCLC) is 60-Gy radiotherapy (RT) concomitant with chemotherapy (CHE), and local recurrence rates vary between 15% and 40%.[1,2,3] In the randomised study by Perez et al., local control (LC) was shown to be associated with the dose of RT and survival.[4] However, this study included a response evaluation based on chest radiography and reported that 3-year overall survival (OS) for complete response (CR), partial response (PR) and stable response were 23%, 10% and 5%, respectively.

The use of computed tomography (CT) in response evaluation and restaging has been a major development.[5] Imaging with CT provides anatomical information based on tumour diameter, and it was reported that the response could be seen for up to 11 months.[6] Increased glucose transport in malignant tissues was first described by Warburg, and it was believed that the biochemical/metabolic changes associated with treatment could be used as a marker of response.[7] Imaging with positron emission tomography (PET) using radioisotope-labelled glucose tracer 18F-fluorodeoxyglucose (18F-FDG) was shown to detect lesions larger than 5 mm with high accuracy.[8] In addition to the metabolic visual correlation that it provides, integration of CT with PET (PET/CT) can also evaluate tumour and nodal spread more accurately.[9]

PET/CT was proven to be superior to CT in terms of diagnosis, staging, RT-planning, response evaluation and survival estimation in patients with lung tumours.[10-13] In a systematic review, it was reported that the clinical CR, PR and stable response rate was 35%, 35% and 30% with CT evaluation following induction therapy in stage (s) II patients while pathological (p) CR was 20%, 5% and 3% for these responses, respectively.[14] In this study, although the false negative (FN) and false positive (FP) rates for tumor were 60% and 31% with CT whereas these rates were 0% and 5%, respectively, if the metabolic response in PET was > 80%. In terms of nodal response, FN rates were reported as 33% and 25% for CT and PET, respectively.

Maximum standardised uptake value (SUV_{max}) is widely used to predict the response and prognosis with PET/CT. In the meta-analysis, the SUV_{max} measured at diagnosis or a median week 12 (8-24) following RT was reported to be significant in terms of LC and OS with a minimum cut-off value of ≥ 5.[15] It was underlined that the SUV change should at least be ≥ 30% for response.[16] Cerfolio et al. reported that a decrease of ≥ 80% in SUV_{max} in the first month after treatment was found to be superior than the change in size on CT, and the sensitivity, specificity and accuracy for pCR were reported to be 90%, 100% and 96%, respectively.[17] Eschmann et al. used PET/CT three times to evaluate 65 patients prior to treatment, at 2 weeks following the neoadjuvant CHE and at 2 weeks after completion of sequential RT.[18] This study showed that in patients who exhibited a SUV_{max} decrease of > 60% following neoadjuvant CHE, 5-year OS was significantly increased (60% vs 15%). On the other hand, the cut-off value was reported to be 75% for a survival difference following RT. In another study by Eschmann et al. that included 70 sIII patients treated with neoadjuvant chemo-RT, the sensitivity, specificity and accuracy of PET/CT in detecting residual tumours were 94%, 80% and 91% whereas these values were 77%, 68% and 73%, respectively in detecting nodal involvement.[19] This study underlines that a decrease of ≥ 80% in SUV value is the best prognostic factor (PF) in terms of outcomes, and surgery does not change the outcome in patients with metabolic progression. In the ACRIN6668/RTOG 0235 study that included 173 patients with NSCLC who were administered curative chemo-RT, it was shown that the 2-year OS was significantly increased (47% vs 25%) when SUV_{max} was ≤ 5 at 3 months after treatment.[20]

This study aimed to evaluate the relationship between PET/CT response and survival in patients with NSCLC who were administered curative chemo-RT and to review the relevant literature.

PATIENTS and METHODS

We retrospectively analysed the data of 51 patients treated with curative chemo-RT between 1 January and 31 December 2012 in our department (Table 1). Written informed consent obtained from all patients. The current study was approved by the Institutional Ethics Committee.

CT, PET/CT and cranial magnetic resonance imaging were used for staging cancer in all patients. Radiotherapy was applied using LINAC with three-dimensional conformal RT (3DCRT) or intensity-modulated RT (IMRT). Cisplatin-based multiagent CHE (paclitaxel, docetaxel or gemcitabine) was administered using the standard regimen. In patients receiving weekly concomitant CHE, the number of cycles was calculated as the standard CHE equivalent of the cumulative dose. Comorbidity status was assessed according to the pulmonary, cardiovascular, renal, neurological and endocrine functions.

Responses were assessed at month 1 using CT (response-1), at month 3 using PET/CT (response-3) and at month 6 using CT or PET/CT (response-6) after RT. The patients underwent PET/CT following at least 4 hours of fasting. All PET/CT images performed in our institution was evaluated one by one by the relevant author (GBB) in November 2019. The volume of interest (VOI) that represents the highest radioactivity of the lesion in the 18F-FDG PET/CT images was determined semi-automatically. SUV_{mean} (i.e. the mean of the SUV values), and SUV_{max} that represents the highest SUV value within the identified VOI were calculated. The threshold value of metabolic tumour volume (MTV) was determined to be 42% of the lesion SUV_{max} and was automatically calculated. Total lesion glycolysis (TLG) was calculated by multiplying the MTV and SUV_{mean} values. Toxicity was evaluated according to the Common Terminology

Table 1. Demografic features and treatment parameters

Demografic features and treatment parameters (n= 51)	n (range/ %)
Age (median, year)	61 (29-79)
Male/Female	46 (90) / 5 (10)
KPS (median)	90 (70-100)
Smoking history / median pack/year	45 (88) / 45 (7.5-120)
Tumour size (median, cm)	5.5 (1.4-14)
Symptom time (median, month) (n= 30)	3 (1-24)
T stage (AJCC 2010)	
T1	2 (4)
T2	20 (39)
T3	12 (23)
T4	17 (33)
TNM staging	
I	1 (2)
II	5 (10)
IIIA	28 (55)
IIIB	14 (27)
IV	3 (6)
RT dose (median, cGy)	6300 (4860-7525)
RT fraction dose (median, cGy)	180 (180-250)
RT duration (median, day)	52 (41-65)
RT type - IMRT/ Conformal	14 (27)/ 37 (73)
Treatment break (median, day) (n= 18)	4 (1-20)
Neoadjuvant CHE / median cycles	21 (41) / 4 (1-7)
Concurrent CHE / median cycles	36 (70) / 3 (1-4)
Adjuvant CHE / median cycles	29 (57) / 3 (1-6)
Total CHE / median cycles	47 (92) / 6 (1-10)
Family cancer history	17 (33)
Comorbidity	25 (49)
Second primary	6 (12)
GTV median (cc) (n= 44)	181.7 (10.15-993.73)
CTV median (cc) (n= 42)	784.09 (184-1850.63)
MLD median (Gy) (n= 43)	19,75 (8.75-28.21)
PET/CT parameters	
$SUV_{maxbase}$ (median) (n= 47)	15.25 (2.5-31.5)
$SUV_{meanbase}$ (median) (n= 29)	9.37 (2.23-20.32)
MTV_{base} (median) (n= 29)	29.38 (4.04-129)
TLG_{base} (median) (n= 29)	281.94 (12.8-1141.85)
SUV_{max3} (median) (n= 38)	3.6 (0-13.2)
SUV_{mean3} (median) (n= 20)	2.81 (1.38-5.47)
MTV_3 (median) (n= 20)	15.14 (2.3-215)
TLG_3 (median) (n= 20)	41.83 (8.89-1058.25)
SUV_{max}, change % (median) (n= 38)	81% (3-100%)
SUV_{mean}, change % (median) (n= 16)	65% (11-90%)
MTV, change % (median) (n= 12)	63% (3-92%)
TLG, change % (median) (n= 13)	85% (40-96%)

Criteria for Adverse Events v4.[21] The patients with local or distant recurrence during follow-up were administered CHE, targeted therapy, palliative RT or supportive care.

Statistical analysis was conducted using SPSS v.21 in November 2019. Overall survival were calculated from diagnosis until death or last follow-up, and progression-free survival (PFS) was calculated from diagnosis until progression, death or last follow-up. The analysis was performed using median and also various cut-off values were reported in the literature (e.g. ≥ 2.5, ≥ 5, ≥ 10, ≥ 15 and 30%–100%) for all PET/CT parameters. The correlations between the variables were assessed using Pearson chi-square and Fisher's exact tests. Survival rates were analysed using the Kaplan–Meier method and univariate analysis log-rank test. Cox regression analysis was used for multivariate analysis. A p value of < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics and treatment parameters of the patients are presented in Table 1. The median age was 61 (29-79) years, and the male/female ratio was 46/5. Overall, 53% patients were diagnosed with squamous cell carcinoma (SCC), 41% with adenocarcinoma and 6% with NSCLC. In total, 82% of the patients had sIII according to the AJCC 2010 staging and 3 patients were diagnosed with solitary bone or adrenal metastasis. A total of 42% of the 12 patients who were assessed using mediastinoscopy, mediastinotomy or EBUS were found to be at stage pN0, which was considered clinical N0. The clinical nodal stages of Nx, N0, N1, N2 and N3 were found in 10%, 16%, 4%, 61% and 10% of the patients, respectively.

The median symptom duration was 3 (1-24) months. The symptoms at diagnosis were presented in Table 1. In total, 45 patients (88%) had a history of smoking. Twenty-five patients (49%) had comorbidities, and 4 of these (8%) had a history of surgery. Six (12%) patients had second primary malignancy prior (prostate, skin, larynx, endometrium and thymic) or subsequent to diagnosis (rectum, at 32 months).

The median 6300 (4860-7525) cGy RT was administered with 180 cGy (180-250) fractions. Treat-

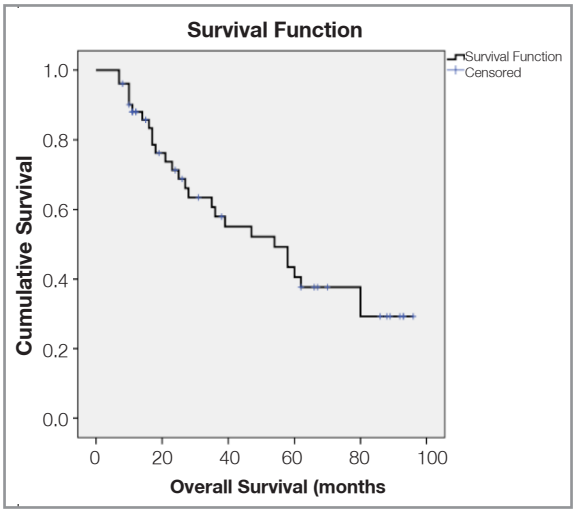

Figure 1. Overall survival

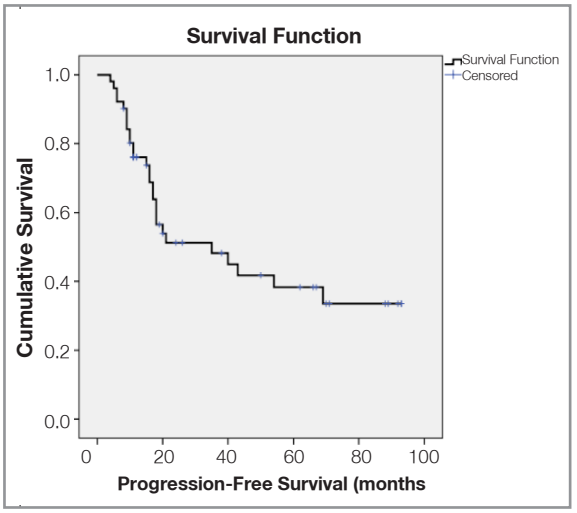

Figure 2. Progression-free survival

ment was interrupted for a median of 4 days (1-20) in 18 cases due to machine breakdown or G1-3 hematologic, lung and esophageal toxicity during RT. Acute grade (G) 1-3 complications occurred in 38 patients (75%). There was no ≥ G4 acute complication. A total of 47 patients (92%) were administered a median of 6 CHE cycles (1-10). Five patients received maintenance erlotinib for a median of 36 (2-60) months.

At 1 month after treatment according to CT evaluation, CR, PR and stable response rates were 6%, 65% and 29%, respectively. In 42 patients who were evaluated using PET/CT on median day of 94 (31-127), CR, PR, stable response and progression rates were found to be 19%, 57%, 21% and 2%, respectively. Excluding patients who had undergone surgery or who were not evaluated, there were 27 patients evaluated by CT or PET/CT at 6 months, and CR, PR, stable response and progression rates were 41%, 37%, 11%, and 11%, respectively. Total of 8 patients underwent surgery at 6 months, and the pCR/near-pCR rate (< 10% residual cells) was 75% (6/8). During the follow-up, pCR was achieved in 1 of 3 patients who underwent surgery at months 13, 36 and 40, and the total pCR/near-pCR rate wAS 64% (7/11). All of the operated patients had clinical N2/3 disease, and the rate of nodal response was 82% (9/11). The median time to operation was 2.5 (1-40) months.

In a median of 3 (3-6) months following the RT, radiation pneumonitis (RP) occurred in 22 (43%) patients: G1 in 2 (4%), G2 in 17 (33%) and G3 in 3 (6%). Pleural effusion was observed in 8 patients (16%) in a median of 3 (3-11) months and pericardial effusion/thickening occurred in 2 patients (4%) in 4 and 7 months.

Locoregional or distant recurrence was observed in 29 patients (57%). Locoregional recurrences were seen in a median of 9 (5-66) months in 8% (n= 4) and distant recurrences were seen in a median of 16 (4-69) months in 29% (n= 15) patients, respectively. In 10 of patients (20%), locoregional and distant recurrences concomitantly developed in a median of 17 (9-35) months. Single-organ or multipl metastases occurred in 17 (33%) and 8 patients (16%), respectively. The most common metastatic sites were bones (n= 15, 29%) and lungs (n= 8, 16%), respectively.

The median follow-up was 27 (7-96) months from diagnosis. Seven patients (14%) were alive, 26 (51%) were deceased and 18 (35%) were lost to follow-up at the time of evaluation. The causes of death were as follows: multiple organ failure with disease progression (88%), lung infection (8%) and toxic hepatitis (4%). The median and 5-year OS and PFS rates were 54 months (28-79), 40% and 35 months (5-64), 38%, respectively (Figure 1, 2).

The median values for PET/CT parameters are presented in Table 1. The number of evaluated patients for SUV_{max}, SUV_{mean}, MTV and TLG was different because there were patients who were tested at

Table 2. Corelations between response and other variables (Fisher's exact chi-square test)

Parameters	Response-1 (n: 51)				Response-3 (n= 42)				Response-6 (n= 27)			
	CR	PR	S/P	p	CR	PR	S/P	p	CR	PR	S/P	p
SUVmax3												**0.030**
< 5 (n: 14)									90%	71%	0%	
≥ 5 (n: 6)									10%	29%	100%	
SUVmean3												
< 2.81 (n: 9)	100%	61.5%	0%	**0.014**								
≥ 2.81 (n: 11)	0%	38.5%	100%									
SUVmax, change%												
≥ 70 (n: 25)	100%	77%	%30	**0.019**								
< 70 (n: 13)	0%	23%	70%									
SUVmax, change%												**0.024**
≥ 60 (n: 13)									90%	57%	0%	
< 60 (n: 7)									10%	43%	100%	
SUVmean3	1.90	3.30	5.74	**0.037**					2.60	4.11	7.89	**0.041**
	(0-3.80)	(0-9.73)	(0-13.20)						(0-7.80)	(0-9.52)	(7.72-9.73)	
	(n: 2)	(n: 26)	(n: 10)						(n: 10)	(n: 7)	(n: 3)	
SUVmax3	2.24	2.52	4.00	**0.026**								
		(1.38-5.42)	(2.81-5.47)									
	(n: 1)	(n: 13)	(n: 6)									
Symptom time								**0.013**				
< 3 months (n: 11)					100%	31%	25%					
≥ 3 months (n: 14)					0%	69%	75%					
Radiation pneumonitis								**0.021**				
presence (n: 22)					62.5%	62.5%	55.5%					
absence (n: 20)					37.5%	37.5%	44.5%					

another center, whose lesions could not be localised after treatment and who could not be evaluated owing to RP.

The variables that affected response were analysed (Table 2). A tumour SUV_{mean3} of < 2.81 and SUV_{max} change of ≥ 70% were found to be significantly correlated with response-1 (p= 0.014, p= 0.019). The SUV_{max3} and SUV_{mean3} values for CR, PR and stable response at month 1 were found to be 1.90, 3.30 and 5.74 (p= 0.037) and 2.24, 2.52 and 4.00 (p= 0.026), respectively. A duration of symptoms of < 3 months and presence of RP were significantly correlated with response-3 (p= 0.013, p= 0.021), and a SUV_{max3} of < 5 and SUV_{max} change of ≥ 60% were correlated with response-6 (p= 0.030, p= 0.024). SUV_{max3} values were 2.6, 4.11 and 7.89 for CR, PR and stable response at month 6, respectively and were found statistically significant (p= 0.041).

The correlations between all variables were analysed (Table 3). Response-1 and response-3 and also response-3 and response-6 were significantly correlated each other (p< 0.001, p< 0.001). $SUV_{maxbase}$ was found to be positively correlated with tumour size, clinical tumour volume (CTV), TLG, $SUV_{meanbase}$ and negatively correlated with Karnofsky performance status (KPS) (p< 0.05). There was a positive correlation between SUV_{max3} and SUV_{mean3} (p< 0.001). The rate of RP was higher in patients who were administered a fraction dose of < 200 cGy (55% vs 8%, p= 0.008), who received concomitant CHE for ≥ 3 cycles (65% vs 19%, p= 0.015) and who had an objective response (OR) at month 3 (62.5% vs 11%, p= 0.021). The patients who had RP were found to have significantly larger CTV (865 vs 735 cc, p= 0.039). The patients with a mean lung dose (MLD) ≥ 19.75 had higher adenocarcinoma histology (79% vs 21%, p= 0.016),

Table 3. Correlation coefficients among variables (Spearman's rho test)

Variables	Response-3	Response-6	SUVmaxbase	SUVmean3
Response-1	[+] p< 0.001 r= 0.549			
Response-3		[+] p< 0.001 r= 0.636		
Tumour size			[+] p= 0.010 r= 0.371	
CTV			[+] p= 0.018 r= 0.383	
TLG			[+] p= 0.015 r= 0.446	
SUVmeanbase			[+] p= 0.001 r= 0.992	
KPS			[–] p= 0.037 r= 0.306	
SUVmax3				[+] p< 0.001 r= 0.997

Values = Pearson's r. The positive values [+] indicate a direct correlation and the negative values [-] indicate an inverse correlation.

larger CTV (≥ 784 cc, 68% vs 32%, p= 0.018) and larger MTV (≥ 29, 77% vs 23%, p= 0.043).

The variables that positively affect survival according to univariate analysis were age of < 60 years, KPS of ≥ 90, gross tumour volume (GTV) of < 181 cc, response-6, concomitant CHE, and administration of CHE for OS and age of < 60 years, absence of metastases at diagnosis, a GTV of < 181 cc, presence of pathologic response and administration of CHE for PFS (p< 0.05) (Table 4). Absence of metastasis at diagnosis, CTV of < 784 cc and adjuvant CHE cycles of < 3 had borderline significance for survival (p= 0.05). In patients with $SUV_{meanbase}$ and SUV_{mean3} values of less than the median value, there was a trend towards improved survival rates (p> 0.05). According to the Cox regression analysis employing the backward stepwise method, for each 1 unit increase, $SUV_{meanbase}$ (HR 1.18, 95% CI: 1.01-1.38) and SUV_{mean3} (HR: 2.65, 95% CI: 1.24-5.66) were found to be poor PFs for OS, whereas SUV_{mean3} (HR: 2.01, 95% CI: 1.02-3.93) was found to be a poor PF for PFS.

DISCUSSION

The importance of response assessment in prognosis prediction and treatment management has been demonstrated in patients with locally advanced NSCLC.[4-6] Response is known to change based on treatment type and RT dose. In a prospective study, 5-year locoregional PFS (LRPFS) for 67, 80 and 97 Gy was reported to be 12%, 35% and 49%, whereas 5-year OS was reported to be 4%, 22% and 28%, respectively.[22] In the randomised study by Curran et al., significantly higher OR rates (70% vs 61% vs 65%, respectively) and 5-year OS rates (16% vs 10% vs 13%, respectively) were reported for the concomitant 60 Gy chemo-RT regimen in comparison with sequential 63 Gy chemo-RT or concomitant hyperfractionated 69.6 Gy chemo-RT.[2]

Nodal response subsequent to neoadjuvant therapy is known to be important in terms of eligibility for surgery in patients with potentially resectable cancer.[23] Randomised studies have shown a pCR of 10% and an OS benefit of 5% with neoadjuvant CHE (1). In the retrospective study by Higgins et al., the mediastinal pCR in patients received neoadjuvant CHE or chemo-RT was 35% and 65%, respectively, and pCR was found to be associated

Table 4. Survival analysis

Significance in univariate analysis	**Median OS, months (95% CI)**	**p**	**Median PFS, months (95% CI)**	**p**
Age	54 (28.17-79.82), 5-year 40%	**0.037**	35 (5.87-64.12), 5-year 38%	**0.025**
< 60 (n: 30)	Mean 66.10 (49.70-82.51)		Mean 62.47 (45.92-79.02)	
≥ 60 (n: 21)	44.08 (32.65-55.51)		32.80 (19.91-45-69)	
KPS		**0.017**		0.079
≥ 90 (n: 37)	60 (24.42-95.57)		52 (38.46-65.70)	
< 90 (n: 14)	35 (9.28-60.71)		30 (16.38-44.73)	
Metastasis at diagnosis		0.059		**0.028**
Present (n: 3)	23 (11.79-34.20)		15 (6.99-23.00)	
Absent (n: 48)	58 (40.99-75.00)		40 (5.18-74.81)	
GTV, median		**0.020**		**0.021**
< 181 cc (n: 24)	Mean 67.44 (51.99-81.88)		Mean 62 (46.56-77.45)	
≥ 181 cc (n: 20)	40.76 (23.66-57.66)		39 (22.13-57.45)	
CTV, median		0.057		0.093
≥ 784 cc (n: 22)	Mean 44 (28.88-60.62)		Mean 42 (26.28-59.32)	
< 784 cc (n: 20)	66 (39.29-83.04)		59 (40.54-77.99)	
Response-6		**0.020**		0.45
Complete (n: 11)	80 (44.2-115.47)		60 (39.35-81.50)	
Partially (n: 10)	58 (48.00-67.99)		57 (35.96-79.62)	
Stable/progression (n: 6)	27 (1.55-52.44)		39 (0.25-78.74)	
Pathological response		0.083		**0.040**
Present (n: 7)	Mean 69 (42.95-95.04)		Mean 68 (40.40-95.76)	
Absent (n. 4)	37 (13.13-62.36)		20 (7.24-33.75)	
Concurrent CHE		**0.019**		0.091
Present (n: 15)	60 (50.46-69.53)		43 (0.00-88.64)	
Absent (n: 36)	27 (8.60-45.39)		16 (7.37-24.62)	
Total CHE		**0.002**		**0.027**
Present (n: 47)	58 (40.51-75.48)		40 (10.89-69.10)	
Absent (n: 4)	10 (3.14-16.86)		6 (2.08-9.92)	
Adjuvant CHE cycles		0.057		0.058
≥ 3 (n: 23)	Mean 48 (35.24-61.90)		Mean 36 (19.56-53.87)	
< 3 (n: 6)	79 (60.08-98.91)		71 (46.99-96.33)	
$SUV_{meanbase}$, median		**0.30**		**0.28**
≥ 9,37 (n: 15)	28 (11.49-44.50)		16 (5.64-26.35)	
< 9,37 (n: 14)	54 (28.29-79.70)		35 (15.98-64.01)	
SUV_{mean3}, median		**0.97**		**0.95**
≥ 2,81 (n: 11)	39 (0.,00-82.36)		17 (0.00-53.2)	
< 2,81 (n: 9)	58 (0.00-122.13)		18 (0.00-40.93)	
Significance in Cox regression analysis	**OS, HR (95% CI)**		**PFS, HR (95% CI)**	
$SUV_{meanbase}$, numeric	HR: 1.18 (1.01-1.38)	0.033	HR: 1.17 (0.99-1.37)	0.053
SUV_{mean3}, numeric	HR: 2.65 (1.24-5.66)	0.012	HR: 2.01 (1.02-3.93)	**0.041**

with disease-free survival (DFS) and LC.[24] In the INT 0159 study that included 402 patients who had pN2 disease, the patients were randomised to surgery or curative RT arms following 45 Gy chemo-RT.[25] The 5-year OS for patients with pN0, persistent N2 disease and those administered curative chemo-RT was 41%, 24% and 20%, respectively; and the importance of nodal response was demonstrated for determining the patients who are eligible for surgery. In this study, pCR was achieved in 46% of the patients with stable response, and it should be noted that anatomical response assessment based on CT is insufficient.

Currently, diameter-based anatomical response assessment (RECIST) has been replaced by metabolic response assessment (PERCIST).[16] In the NEOSCAN study, a change of < 35% in SUV_{peak} of patients treated with 2 cycles of neoadjuvant CHE was found to be predictive and prognostic for CHE regimen change.[26] Lee et al. reported that in 44 patients received neoadjuvant CHE, the time to recurrence was prolonged with a radiological response of ≥ 30% and a SUV_{max} response of ≥ 25% (49 vs 23 months).[27] The accuracy of pathologic response prediction was reported to be 70% with radiological evaluation, 52 to 75% with metabolic evaluation and 73 to 82% with both evaluation.

In a study by Iravani et al. that included 87 patients treated with RT or chemo-RT, it was reported that the PET/CT response at 3rd month after treatment was associated with OS.[28] Conversely, Chen et al. evaluated 25 patients at week 5 during chemo-RT (at a median of 46 Gy) and 3rd month after chemo-RT and reported that TLG (cut-off 65%) and MTV (cut-off 42%) changes during RT resulted in significantly increased OS and PFS but these changes were not significant at 3rd month.[29] It has been shown that evaluation using PET/CT can led to a dose increase or treatment modification during the treatment and it has also been found to provide 3% benefit in terms of salvage therapy for patients who progress 3 months after the treatment.[12,30,31]

Because RT causes inflammatory reactions in lung tissues, there is an ongoing discussion about the best time to evaluate response using PET/CT.[32,33] Choi et al. underlined that the biological lethal damage to tumour cells occurred 8-12 weeks after RT; however, this could not be beneficial in terms of treatment modification and LC.[34] In a study by Massaccesi et al., the median tumour and nodal SUV_{max} values at the baseline, at week 3 during treatment and at 1 month after chemo-RT were 16.1 and 10, 4.7 and 7.7, 4.6 and 2.1, respectively.[35] It was reported that the response started during the treatment (76% OR) and continued in month 1 after treatment (95% OR, 38% CR), it was correlated with the total dose and the DFS significantly increased with metabolic CR at month 1. On the other hand, it was emphasized that response evaluation would be challenging up to 6-24 months due to persistent hypermetabolism in patients with early stage lung cancer treated with stereotactic body RT.[36] Limited resolution, difficulties in determining margins of lymph nodes (conglomerate or adjacent to tumour), high rates of FP and lack of a consensus concerning which stations should be assessed were reported to be the reasons for nodal response accuracy being lower in PET/CT.[9,16,19,34,37] Arnett et al. could not demonstrate any significant correlation between nodal PET parameters and nodal pCR.[38] Contrarily, Okazaki et al. reported that both tumour and nodal TLG were significant in terms of LC and disease-specific survival.[39] In our study, nodal PET/CT parameters were not assessed due to the difficulties in measurement. At month 3, OR was observed to be 76% in PET/CT evaluation and the correlation between metabolic parameters and responses indicated that the response continued for up to 6 months.

It is still debatable whether SUV_{max} is the best prognostic marker in response evaluation.[15,20,33] Van Loon et al. reported that each 1% decrease in primary tumour and nodal SUV_{max} following 1 cycle of CHE resulted in a 2% increase in OS (40). In the study by Huang et al. the significant cut-off values with 40 Gy chemo-RT were found to be 42% for SUV_{mean} (37.5 vs. 19.5 months) and 30% for MTV (36.5 vs. 16 months) in terms of median OS.[41] In the study by Van Diessen et al. there were no OS differences based on baseline PET parameters, whereas both intensity (SUV_{max}, SUV_{mean}) and volumetric (TLG, MTV) parameters were correlated with OS at month 1 after treatment.[42] In the ACRIN 6668/RTOG 0235 study, it was found that the baseline SUV_{peak} (10.3) and SUV_{max} (13.1) were not significant for OS; however, each 1-point increase in SUV_{peak3} increased the mortality risk

by 9%.[20] In the 2015 analysis of the study, a nodal residue SUV_{max} of > 5 and change of < 25% were found to be unfavourable in terms of locoregional control.[37] In the 2017 analysis of the study, it was also emphasised that MTV and TLG were promising biomarkers for locoregional control and could be used in routine practice for prognostic classification.[33] In the present study, each 1 unit increase in $SUV_{meanbase}$ and SUV_{mean3} values was found a significantly poor PF for survival. The lack of a significant correlation between MTV, TLG, and survival was believed to be associated with the small number of patients evaluated for these parameters.

Age, sex, KPS, stage, total RT dose, fraction dose, administration of CHE, targeted volumes and risky organ doses are known to be PFs in terms of complications and survival in patients with NSCLC.[1] The rates of severe RP are range from 10 to 20%, which is associated with an MLD of > 20 Gy in patients treated with chemo-RT.[43] Liao et al. reported that although GTV was positively correlated with ≥ G3 RP, increased OS was observed owing to decreased lung V20 dose in 496 patients who were administered 63 Gy chemo-RT with IMRT.[44] In our previous study that included 68 patients, it was found that the therapeutic dose range in where MLD could be kept under 20 Gy with significant survival benefit was between > 59.4 Gy and ≤ 63 Gy.[45] In the study by Warner et al. 180-day early mortality rate was shown to be lower with a GTV of < 100 cc.[46] In the current study, age, KPS, absence of metastases at diagnosis, administration of CHE, concomitant CHE, response-6 and pathologic response were found to be significant in terms of survival consistent with the literature. Increased RP rates among patients who were administered a fraction dose of < 200 cGy can be indirectly attributed to increased CTV and MLD. Conversely, patients with RP may have significantly increased OR at month 3, which could have indirectly affected survival positively. A tumour GTV of < 181 cc was found to be a significantly favourable PF for OS and PFS.

The positive aspect of the study was that it had a long follow-up period. The limitations were as follows: the study was retrospective, evaluation of PET/CT parameters was conducted with small number of patients, 41% of the patients were administered neoadjuvant CHE and not all of these patients were assessed using PET/CT prior to RT; moreover, it could not be determined whether the use of targeted agents as part of maintenance therapy had any effect on survival.

Conclusion

PET/CT parameters can be used as beneficial markers in terms of prognosis, treatment modification and survival in patients with NSCLC who are administered curative chemo-RT. Although imaging with PET/CT was found to be significant in terms of survival at 3 months after the treatment, it can also be a disadvantage owing to the RT-induced changes and the inability to differentiate residual tumours. It is believed that early assessment during and after the treatment can be advantageous in terms of treatment modification.

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