RESEARCH ARTICLE

Comparison of Metabolic and Anatomic Response to Chemotherapy Based on PERCIST and RECIST in Patients with Advanced Stage Non-small Cell Lung Cancer

Cetin Ordu[1]*, Nalan A Selcuk[2], Cengiz Akosman[3], Orhan Onder Eren[3], Elif C Altunok[4], Turkay Toklu[2], Basak Oyan[3]

Abstract

Background: The aim of this study was to explore the prognostic role of metabolic response to chemotherapy, determined by FDG-PET, in patients with metastatic non-small-cell lung cancer (NSCLC). Materials and Methods: Thirty patients with metastatic NSCLC were analyzed for prognostic factors related to overall survival (OS) and progression free survival (PFS). Disease evaluation was conducted with FDG-PET/CT and contrast-enhanced CT prior to and at the end of first-line chemotherapy. Response evaluation of 19 of 30 patients was also performed after 2-3 cycles of chemotherapy. Morphological and metabolic responses were assessed according to RECIST and PERCIST, respectively. Results: The median OS and PFS were 11 months and 6.2 months, respectively. At the end of first-line chemotherapy, 10 patients achieved metabolic and anatomic responses. Of the 19 patients who had an interim response analysis after 2-3 cycles of chemotherapy, 3 achieved an anatomic response, while 9 achieved a metabolic response. In univariate analyses, favorable prognostic factors for OS were number of cycles of first-line chemotherapy, and achieving a response to chemotherapy at completion of therapy according to the PERCIST and RECIST. The OS of patients with a metabolic response after 2-3 cycles of chemotherapy was also significantly extended. Anatomic response at interim analysis did not predict OS, probably due to few patients with anatomic response. In multivariate analyses, metabolic response after completion of therapy was an independent prognostic factor for OS. Conclusions: Metabolic response is at least as effective as anatomic response in predicting survival. Metabolic response may be an earlier predictive factor for treatment response and OS in NSCLC patients.

Keywords: Advanced stage - non-small cell lung cancer - PERCIST - RECIST - FDG-PET - survival

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Introduction

Lung cancer is the leading cause of cancer death worldwide (Jemal et al., 2011). Approximately 80% of primary lung cancers are classified as non-small cell lung cancer (NSCLC) and two thirds of NSCLC patients present with locally advanced or advanced disease that is not amenable to curative surgery (Martin et al.,2002). Patients with stage IV disease are generally treated with systemic therapy. Early prediction of tumor response is of particular interest in patients with advanced NSCLC. Tumor progression during first line therapy occurs in 30% of patient (Azzoli et al., 2011). So, a significant number the patients undergo a toxic treatment for weeks without any benefit prior to detection of progression. Non-responders should be identified as early as possible to minimize side effects and to switch a potentially effective second-line therapy earlier.

Computed tomography (CT) remains to be the standard technique for response evaluation to systemic therapy. Response evaluation after chemotherapy or targeted therapies is an evolving issue in Oncology. CT examinations are interpreted in accordance with the Response Evaluation Criteria for Solid Tumor (RECIST) guidelines (Eisenhauer et al., 2009). Since early 1980's, tumor response assessment has been done by comparison of tumor size on CT scans before and after treatment. The WHO criteria to evaluate radiologic response were developed in 1979, followed by RECIST criteria in 2000 and finally RECIST 1.1 in 2009 (Weber and Figlin, 2007; Eisenhauer et al., 2009; Wahl et al., 2009). However, conventional CT is generally insufficient for early response, as changes in tumor size can be insignificant in early follow-up. In addition, CT has limitations in

*[1]Department of Internal Medicine, Faculty of Medicine, Bilim University, [2]Department of Nuclear Medicine, [3]Medical Oncology Section, Department of Internal Medicine, [4]Department of Biostatistics, Yeditepe University Hospital, Istanbul, Turkey *For correspondence: cetinordu@hotmail.com*

distinguishing necrotic tumor or fibrotic scar from residual tumor mass (Suzuki et al., 2008).

In recent years, ^{18}F-fluoro-deoxyglucose (^{18}F-FDG) positron emission tomography (PET) has become an established method for staging of patients with NSCLC (Dwamena et al.,1999; Cerfolio et al., 2004). Beyond the initial staging, increased FDG uptake in most lung cancers and the reduction in uptake with successful treatment have led to increased enthusiasm for the use of PET or PET-CT to assess the therapeutic response (Weber et al., 2003; Hoekstra et al., 2005). Post-treatment ^{18}F-FDG-PET and CT have been compared in a prospective manner in patients treated with definitive radiation or chemo-radiation and ^{18}F-FDG-PET response was found to be more significantly correlated with survival than response as assessed by CT (Mac Manus et al., 2003). When ^{18}F-FDG-PET is compared with structural imaging techniques, one of the major theoretical advantage is a more rapid change in cellular metabolism than a change in the tumor size. So ^{18}F-FDG-PET can provide information about sensitivity to treatment even after first cycle (Novello et al., 2013).

This retrospective study aims to determine whether metabolic response measured by ^{18}F-FDG-PET-CT after completion of first-line chemotherapy predicts outcome of patients with advanced NSCLC and to compare these results with the standard morphological evaluation. The predictive value of early metabolic response after 2-3 cycles of chemotherapy on survival was also evaluated.

Materials and Methods

Patients

In this study, patients diagnosed with advanced stage NSCLC between 2006 and 2010 were evaluated and re-analyzed. This study was approved by scientific ethic committee of Yeditepe University Hospital. All patients provided informed consent for their information to be stored in the hospital database and be used for research. Those patients who were staged with contrast enhanced CT of chest and abdomen, in addition to PET/CT were eligible. In the presence of clinical symptoms of brain or bone metastases, magnetic resonance imaging of brain or bone scintigraphy was also performed. Inclusion criteria included histologically or cytologically proven advanced stage (stage IIIB with effusion or stage IV) NSCLC and at least one measurable lesion. The patients were excluded if PET/CT had not been performed for staging and response evaluation procedure.

PET Imaging

FDG-PET imaging with I.V. range 300-600 MBq of FDG administrations were performed after six hours of fasting so that the patients could have serum glucose level between 70-150 mg/dl. After one hour waiting for distribution of FDG into the body, the patients were imaged using PHILIPS Gemini integrated PET/CT scanner. PET/CT scan was performed from vertex to pelvis. A baseline FDG-PET was carried out for all patients before initiation of chemotherapy. In-terim FDG-PET was performed to three groups of patients.

For quantitative assessment of tumor FDG uptake, regions of interest (ROIs) were placed over all primary tumors and metastatic lesions. Maximum SUL values (standard uptake value normalized to lean body mass) were recorded for each lesion.

Study design and response evaluation

All patients received 4 to 6 cycles of platin-based chemotherapy. All patients were staged by PET/CT and contrast enhanced CT at diagnosis. Response evaluation was done one month after completion all cycles of chemotherapy in all patients. The objective response rate (CR+PR) and no response (SD+PD) rate achieved with the first-line chemotherapy regimen were determined by contrast-enhanced CT and PET/CT. The interim response evaluation was done with contrast-enhanced CT in all patients and with PET/CT in some patients (n=19).

Tumor anatomic responses and metabolic responses were evaluated according to RECIST criteria, version 1.1. and PERCIST criteria, respectively (Eisenhauer et al., 2009; Wahl et al., 2009). For evaluation of morphological response,a maximum of five lesions total (and a maximum of 2 lesions per organ) representative of all involved organs was identified as target lesions. The longest diameter of all lesions were measured. A sum of the diameters for all target lesions was calculated at baseline, after 2-3 cycles of chemotherapy and at the end of the treatment. The objective tumor response for target lesions were defined as follows (Eisenhauer et al., 2009): *(i)* Complete response (CR): Disappearance of all lesions; *(ii)* Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking reference as the baseline sum of diameters and no new lesion(s); *(iii)* Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking reference as the smallest sum of diameters while on treatment; or the appearance of new lesion(s); *(iv)* Stable disease (SD): Neither sufficient shrinkage to qualify PR nor sufficient increase to qualify for PD, taking reference as the smallest sum of diameters during treatment.

The metabolic tumor response for target lesions were defined as follows (Wahl et al., 2009): *(i)* Complete metabolic response (CMR): Complete resolution of ^{18}F-FDG uptake; *(ii)* Partial metabolic response (PMR): A minimum of 30% reduction in the sum of SUV of target lesions and no new lesions; *(iii)* Progressive metabolic disease (PMD): >30% increase in the sum of SUV of the lesion(s); *(iv)* Stable metabolic disease (SMD): Not CMR, PMR or PMD.

Statistical analysis

All statistical analysis was performed with SPSS version 17 for Windows. Because of limited number of patients, tumor response was grouped as CR+PR (responsive) vs SD+PD. The Kaplan Meier method was used to estimate OS and PFS. OS was calculated from the diagnosis (biopsy date) to the date of death or last follow-up. PFS was calculated from the time of diagnosis to disease progression or death from any cause. Univariate and multivariate analyses were performed to evaluate the effect of prognostic factors on OS. Univariate comparisons between subgroups were made using log-

rank test. Multivariate analysis was performed using the Cox regression model. P value lower than 0.05 was considered statistically significant.

Results

Between January 2006 and January 2010, 76 metastatic NSCLC patients were referred to our clinic. Among these patients, 30 patients who received first-line chemotherapy regimen and followed with PET/CT were eligible for the trial. The median age of the patients was 60 (range 45-77). Demographic characteristics of patients are shown in Table 1. All patients received platinum-based combination chemotherapy. The median of total cycles of chemotherapy was 4 (2-6). All 30 patients were evaluated morphologically and metabolically at the end of the first-line chemotherapy. Nineteen of them were also evaluated morphologically and metabolically after 2 cycles of chemotherapy.

At the interim response evaluation, metabolic PR was achieved in 9 patients, while only 3 of them fulfilled the criteria of PR morphologically according the CT scan. However, this discordance disappeared at the end of the therapy. The response evaluation after the last cycle of chemotherapy revealed that 10 patients achieved PR according to RECİST criteria. According to PERCIST criteria there was 8 patients with PR and 2 patients with CR.

At 12.2 months follow-up, 7 patients (23%) were alive and 23 patients (77%) died. The causes of death were disease progression in 18 patients, infection in 3 patients, and treatment toxicity in 1 patient. The cause of death was unknown in one patient. The median OS was 11.0 months (range 3.7-51.3) and the median PFS was 6.2 months (range 2.1-18.0).

In univariate analyses, the total cycles of first line chemotherapy (>4 *vs* ≤4 cycles) was found to be a prognostic factor for OS (Table 2). The percentages of OS and PFS depending on response to treatment according to RECIST 1.1 and PERCIST 1.0 criteria are shown in table 3. The prognostic value of metabolic response of the primary tumor and metabolic responses of the lesion with the highest SUVmax were also evaluated (Table3).

The OS achieved in the responsive group (CR+PR) according to the PERCIST was significantly longer compared to non-responsive group (SD+PD) at interim analyses (16.6.mo *vs* 5.5 mo, p=0.010). However, at interim analysis the overall survival was not different between responsive and nonresponsive groups evaluated according to RECIST criteria (16.6 mo *vs* 7 mo, p=0.415) (Figure 1). The prognostic value of the metabolic response of the primary tumor and lesion with the highest SUVmax are also shown in Figure 1.

Response at the end of chemotherapy according to both RECIST and PERCIST was prognostic for OS and PFS. In addition to response evaluation according to RECIST and PERCIST, the metabolic response of the lesion with

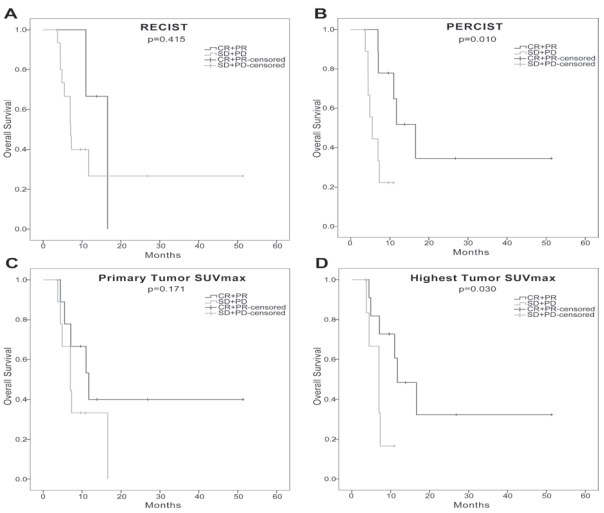

Figure 1. Comparing PERCIST and RECIST in Advanced NSCLC

Table 1. Patient Characteristics

Characteristics	No. of patients	%
Age at diagnosis		
< 60	14	47
³ 60	16	53
Sex Female	8	27
Male	22	73
ECOG performance status		
0-1	27	90
2	3	10
Weight loss prior to diagnosis		
≥ %5	12	40
none	18	60
Histology		
Non-small cell, NOS Adenocarcinoma	24	80
Squamous cell carcinoma	6	20
Only bone metastasis	5	17
Brain metastasis at diagnosis	8	27
Total cycles of chemotherapy		
2 cycles	3	10
3 cycles	5	17
4 cycles	2	7
5 cycles	1	3
6 cycles	19	63

NOS: Not other specified

Table 2. Univariate Analysis

	p (Median Overall Survival)
Age	p=0.187
<60 *vs* ³60	(7.3 m *vs* 12.3 m)
Sex	p=0.397
Male *vs* Female	(7.3 m *vs* 11.7 m)
Weight lose (>%5)	p=0.272
None *vs* Yes	(12.5 m *vs* 7.3 m)
Performance status	p=0.218
0 *vs* 1-2	(11.7 m *vs* 10.7 m)
Histopatology	p=0.765
NOS *vs* adenoca. vs squamous cell ca.	(11.0 m *vs* 7.3 m *vs*12.7 m)
No. of chemotherapy	p<0.001
>4 *vs* ≤4	(12.5 m *vs* 4.9 m)
Primary tumor SUVmax	p=0.494
<8 *vs* ≥8	(11.7 m *vs* 8.5 m)
Only bone metastasis	p=0.174
None *vs* Yes	(10.7 m *vs* 15.1 m)
Brain metastasis	p=0.069
None *vs* Yes	(12.5 m *vs* 6.7 m)

Table 3. Overall Survival and Progression Free Survival According to the Response to Chemotherapy (CR+PR *vs* SD+PD)

Criteria	OS		PFS	
	Interim Evaluation	Evaluation at the End of Therapy	Interim Evaluation	Evaluation at the End of Therapy
RECIST	p=0.415 (16.6 m *vs* 7.0 m)	p=0.028 (14.1 m *vs* 7.3 m)	p=0.299 (8.8 m *vs* 4.7 m)	p=0.014 (8.8 m *vs* 5.1 m)
PERCIST	p=0.010 (16.6 m *vs* 5.5 m)	p<0.001 (16.6 m *vs* 7.3 m)	p=0.049 (7.2 m *vs* 3.0 m)	p<0.001 (8.8 m *vs* 5.1 m)
Primary tumor SUVmax	p=0.171 (11.7 m *vs* 7.0 m)	p=0.182 (12.7 m *vs* 8.5 m)	p=0.355 (5.2 m *vs* 6.2 m)	p=0.051 (7.5 m *vs* 5.4 m))
Highest tumor SUVmax	p=0.030 (11.7 m *vs* 7.0 m)	p=0.025 (12.7 m *vs* 8.1 m)	p=0.368 (7.2 m *vs* 3.0 m)	p=0.044 (7.5 m *vs* 5.4 m)

*CR: Complete remission, PR: Partial remission, SD: Stable disease, PD: Progressive disease, OS: Overall survival, PFS: Progression free survival, m: Months

Table 4. Trials Evaluating Metabolic Response in Advanced NSCLC

Author	Stage	n	Design	Timing of PET	Metabolic response criteria	Aim of PET scan	Results
Weber et al.[11]	IIIB-IV	57	Prospective	Basal and after 1 cycle	>20% decline in SUV	Early response evaluation and its effect on prognosis	Metabolic responders *vs* non-responders: Med TTP: 163 days *vs* 54 days, p=0.0003*;* Med OS: 252 days *vs* 151 days p=0.005
Lee et al.[18]	IIIB-IV	31	Prospective	Basal and after 1 cycle	≥20% decline in SUV	Correlation between early metabolic response and best overall response, their effect on prognosis	Early metabolic response and best overall response are correlated*;* Both do not predict OS
Novello et al.[13]	IIIB-IV	22	Prospective	Basal and after 1 cycle	>15%±25% decline in SUV	Early response evaluation and its effect on prognosis	Metabolic responders *vs* non-responders: Med PFS: 45 *vs* 22.2 weeks, p=0.22*;* Med OS: 77 *vs* 47.7 weeks, p=0.15
Nahmias et al.[17]	IIIB-IV	16	Prospective	Basal and weekly	Decrease at SUV	Optimal timing of early response evaluation and prognostic value of PET	Best time for PET evaluation: Week 3 (between day 7 and 21) OS is longer in metabolic responders "Metabolic responders *vs* non-responders: Med PFS: 11 *vs* 3 months, p=0.0009
de Geus-Oei et al.[19]	IB-IV	51	Prospective	Basal and after 2-3 cycle	>35% decline in SUV	Metabolic response evaluation and its effect on prognosis	
Ding et al.[20]	II-IV	44	Retrospective	Basal and after 2-6 cycle	PERCIST(≥30% decline in SUL)	Correlation of metabolic response with response in CT, prognostic value of metabolic response	Med OS: 17 *vs* 9 months, p=0.018; Metabolic responder correlate with anatomic responder. PERCIST was independent significant factor for DFS p<0.001
Present trial	IV	30	Retrospective	Basal, after 2-3 cycle and at the end of therapy	PERCIST (≥30% decline in SUL)	Correlation of metabolic response with response in CT, prognostic value of metabolic response	Metabolic responders *vs* non-responders (at the end of therapy): Med PFS: 8.8 *vs* 5.1 months, p<0.001 Med OS: 16.6 *vs* 7.3 months, p>0.001

*TTP:time to tumour progression; OS :overall survival ; PFS: progression free survival, med: median

the highest SUVmax at the diagnosis was a prognostic factor for OS both in interim and final analysis. However, metabolic response in the primary tumor lesion was not a prognostic factor for OS and PFS.

In multivariate analyses, metabolic response after completion of therapy was the independent prognostic factor for OS.

Discussion

As most of the anti-cancer treatments cause significant side effects, intense efforts have been made to understand the mechanisms underlying the responsiveness of an individual tumor and to identify parameters that correlate with tumor response. About 30% of patients with advanced NSCLC have responsive disease, whereas 40% have progressive disease to first line cytotoxic chemotherapy (Sekine et al., 1999). Early and precise response measurement is mandatory to tailor individual therapy appropriately. In addition, it is well known that tumor prognosis is associated with biologic aggressiveness of the tumor rather than residual tumor volume after therapy (Vansteenkiste et al., 2004).

In a study, early volumetric changes in neo-adjuvant

treatment of NSCLC were shown not to correlate with pathologic response in a study where some of the patients were at stage IIIA or IIIB (Birchard et al., 2009). A large residual mass of after chemotherapy may contain only inflammatory or fibrotic tissue, whereas a smaller residue may contain treatment resistant and aggressive clones that may cause early relapse and death. As ^{18}F-FDG preferentially and avidly accumulates in cancerous tissue, PET can separate viable tumor from necrosis or fibrosis. PET can provide quantitative assessment of metabolic activity of the tumor before and after treatment. Several studies suggest that tumor response can be detected earlier by decreased uptake of FDG in PET rather than through changes in tumor size. Increasing number of published studies increased the enthusiasm for utilizing PET (or PET/CT) for response monitoring in advanced NSCLC (Weber et al., 2003; Hoekstra et al., 2005; Mac Manus et al., 2007).

In our study we evaluated the reproducibility of response monitoring (with interim and final results where available) with PET/CT in patients with advanced NSCLC. We aimed to find out association of PET/CT result with prognosis of patients with advanced NSCLC treated with cytotoxic treatment. Both RECIST and PERCIST criteria were implemented in our trial. We found that both interim and final response predicted PFS and OS. Interim response with CT was not able to predict OS or PFS. However, final CT findings were associated with PFS and OS.

Optimal timing of PET/CT in response evaluation of advanced NSCLC is unknown. There are at least six trials evaluating the correlation between early metabolic response and morphologic response and the prognostic value of early metabolic response to first line chemotherapy in advanced NSCLC (Table 4). Current trials have mixed results about reproducibility of PET or PET/CT for response assessment in advanced NSCLC. The criteria for metabolic response were different in each of these trials.

In Novello's trial, none of the 8 patients without metabolic response had morphologic response on CT (Novello et al., 2013). Seven of the 13 early metabolic responders had also morphologic response on CT performed after two cycles of chemotherapy. In another trial it has been revealed that, patients with progressive metabolic disease on PET-CT hardly have objective responses to first line chemotherapy (Lee et al., 2009).

The prognostic value of metabolic response had been shown in several trials (Weber et al., 2003; De Geus-Oei et al., 2007; Nahmias et al., 2007; Ding et al., 2014). Weber et al. showed significant prolongation of time to progression and OS in early metabolic responders when compared with metabolic non-responders (Weber et al., 2003). De Geus-Oei et al. used a timing to perform interim PET (after 2-3 cycles),which was similar to our study (De Geus-Oei et al., 2007). In this trial PFS (median, 11 *vs* 3 months, p=0.0009) and OS (median, 17 *vs* 9 months, p=0.018) were significantly longer in metabolic responders than in non-responders. In our study median OS and PFS of metabolic responders were also significantly longer than non-responders (median OS: 16.6 *vs* 5.5 months, p=0.010 and median PFS: 7.2 *vs* 3 months, p=0.049). Ding et al. (2014) recently published that, both PERCIST and RECIST have good concistency and PERCIST is more sensitive detection in CR and progression of petients with NSCLC. In that study the patients with early stages and advanced stages of NSCLC were subjected to same analysis in contrast to our trial. All these trials conclude that metabolic response in PET is a robust parameter to predict prognosis of patients. Results of some other trials in which PFS and OS were not significantly improved in metabolic responder, but there was a trend for better prognosis (Novello et al., 2013; Lee et al., 2009). However, these results should be interpreted cautiously due to the limited number of patients and lower threshold for partial metabolic response when compared to PERCIST criteria.

Nahmias et al. (2007) used a unique protocol with weekly monitoring of metabolic response by PET-CT for 7 weeks. Change in metabolic response was most prominent in third week of chemotherapy. The authors suggested that best time for response evaluation in advanced NSCLC, is after the completion of first cycle when the metabolic response is most prominent.

Some relevant questions to be answered are: What is the best tool (PET-CT or CT) for response assessment in advanced NSCLC? How will we manage treatment when PET/CT and CT results are unequivocal? What is the optimal timing of response monitoring?

Primary tumor SUVmax change was not predictive for survival in our trial. The findings raise some relevant questions like: Can measurement of metabolic response only in the primary lesion be sufficient for response evaluation? Do the primary lesions and metastases give the same response to a particular chemotherapy? Although these are controversial issues,we believe that response evaluation only in the primary lesion may not provide appropriate response evaluation and prognosis prediction. This is due to several reasons: First, we know that metastatic lesions acquire new genomic changes, which may affect sensitivity to chemotherapeutics or targeted therapies (Miranda et al., 2013). Second, primary tumor SUV value may not reflect total tumor volume. Lastly, the primary lesion may have been irradiated before, may contain a small fraction of viable cancer cells and as a result may have reduced FDG avidity. Besides, in a recently published trial revealed that primary tumor SuvMax was not predictive for both OS and PFS (Hasbek et al., 2013). RECIST recommends assessment of three to five target lesions for response evaluation. PERCIST does not recommend assessment of more than five lesions. For simplicity, PERCIST recommends evaluation of the lesions with most intense SUL in baseline and follow-up scans.

In our trial, the metabolic response of the lesion with the highest SUVmax at the diagnosis was a prognostic factor for OS both in interim and final analysis.To the best of our knowledge, this study was the first to assess the response achievement of the lesion with highest tumor SUVmax. The lesion with the highest SUV was not the primary tumor in 16 patients in our study. This may explain why primary tumor SUV was not correlated with survival in our trial. However, this result should be interpreted with

caution. Metabolically active cells are more vulnerable to effects of cytototoxics. In short term, this vulnerability may increase the chance of response but in long term, these may have a propensity for early progression. We also do not know the cut off point for highest tumor SUVmax that confers highest risk for (early) progression.

In multivariate analysis, response according to PERCIST was found to be the independent prognostic factor associated with OS. This shows that metabolic response to chemotherapy in advanced NSCLC may be a better predictor for overall survival than morphologic response. It is known that tumor shrinkage following chemotherapy may not always be correlated with outcome in advanced NSCLC (Brichard et al., 2009). This finding requires confirmation in larger well-designed trials utilizing standardized methodology.

So, how can we interprete all these results? All of these studies differ in their methodology, timing of PET/CT and criteria for metabolic response. Non-adherence to PERCIST and RECIST criteria are common problems when making comparisons between trials and interpreting the results. It is clear that conventional imaging with CT cannot assess early response to chemotherapy in advanced stage NSCLC, precisely. PET may be more effective for prediction of early response although this has to be confirmed in larger well-designed trials. Not only timing of PET before systemic therapy, but also response evaluation criteria (i.e.PERCIST), timing of early, interim, or final PET should be standardized.

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