Computed Tomography RECIST Assessment of Histopathologic Response and Prediction of Survival in Patients with Resectable Non–Small-Cell Lung Cancer after Neoadjuvant Chemotherapy

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Introduction: This study’s objectives were to determine whether tumor response measured by computed tomography (CT) and evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) correlated with overall survival (OS) in patients with non–small-cell lung cancer (NSCLC) after neoadjuvant chemotherapy and surgical resection.

Methods: We measured primary tumor size on CT before and after neoadjuvant chemotherapy in 160 NSCLC patients who underwent surgical resection. The relationship between CT-measured response (RECIST) and histopathologic response (≤ 10% viable tumor) and OS were assessed by Kaplan-Meier survival, univariable, and multivariable Cox proportional hazards regression.

Results: There was a statistically significant association between CT-measured response (RECIST) and OS (p = 0.03). However, histopathologic response was a stronger predictor of OS (p = 0.002), with a more pronounced separation of the survival curves when compared with CT-measured response. In multivariable Cox regression analysis, only pathologic stage and histopathologic response were significant predictors of OS. A 41% overall discordance rate was noted between CT RECIST response and histopathologic response. CT RECIST classified as nonresponders a subset of patients with histopathologic response (8 out of 30 points, 27%) who demonstrated prolonged survival after neoadjuvant chemotherapy.

Conclusion: We were unable to show that CT RECIST is a reliable predictor of OS in patients with NSCLC undergoing surgical resection after neoadjuvant chemotherapy. The failure of CT RECIST to predict long-term outcome may be because of the inability of CT imaging to consistently identify patients with histopathologic response. CT RECIST may have only a limited role as an efficacy endpoint after neoadjuvant chemotherapy in patients with resectable NSCLC.

Key Words: Lung cancer, Neoadjuvant chemotherapy, CT response, Histopathologic response, RECIST.

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Neoadjuvant chemotherapy has been evaluated in patients with nonmetastatic non–small-cell lung cancer (NSCLC) in several randomized, phase III trials.1–4 Although controversial because of the small size of these trials, the impact of neoadjuvant chemotherapy on patient survival has generally been favorable. Recently, we described that histopathologic response to neoadjuvant chemotherapy was strongly associated with long-term overall survival (OS) in patients with clinical stage IB to IIA NSCLC5; patients who exhibited less than 10% viable tumor cells after
neoadjuvant chemotherapy had a significant reduction in the risk of recurrence and/or death compared with patients with greater than 10% viable tumor cells in the surgical specimen, indicating that this could serve as an intermediary endpoint in future neoadjuvant clinical trials. The importance of histopathologic response after neoadjuvant chemotherapy was also corroborated recently by a review of two phase III neoadjuvant chemotherapy intergroup studies from France. However, the utility of standard computed tomography (CT) Response Evaluation Criteria in Solid Tumors (RECIST) after neoadjuvant chemotherapy has not been well studied to date in patients with resectable NSCLC. We therefore investigated whether tumor response measured by CT using the RECIST7 predicted OS and histopathologic response in patients with locally advanced NSCLC who received neoadjuvant chemotherapy and surgical resection.

**PATIENTS AND METHODS**

**Patients and Treatment**

We retrospectively reviewed the medical records of patients with NSCLC treated at the University of Texas M. D. Anderson Cancer Center from January 2001 to December 2008 who underwent neoadjuvant chemotherapy. During this period, 160 patients had CT imaging before and after completion of neoadjuvant therapy and underwent surgical resection with histopathologic assessment of tumor response (Table 1). From the patient medical records, we obtained detailed clinical and pathological information for all patients in the study group, including demographic data, pathological and clinical tumor-node-metastasis staging, and OS. This study was approved by the University of Texas M. D. Anderson Institutional Review Board and was performed in compliance with the Health Insurance Portability and Accountability Act.

**CT and Measurements**

The CTs used in this study were performed before and after neoadjuvant chemotherapy. All chest CTs were performed on a General Electric CT scanner (LiteSpeed, LightSpeed, or HiSpeed; GE Medical Systems, Milwaukee, WI). The CT scan was obtained within 2 weeks before starting chemotherapy and within 4 weeks of completion of chemotherapy. In the RECIST assessment method, lesion size was based on the longest dimension (LD) of the primary tumor. Measurements were performed by a single board-certified thoracic radiologist (JJE) who was blinded to long-term outcome to reduce interobserver variability and bias. The percentage change in the size of the target lesion was calculated between the pre-chemotherapy and post-chemotherapy measurements. Patients with disappearance of the lesion were defined as achieving complete response (CR); a greater than 30% decrease in the LD of the target lesion were defined as achieving partial response (PR); a greater than 20% increase in LD or the appearance of new lesions was defined as having progressive disease (PD). All other outcomes were defined as stable disease (SD). Patients who achieved a CR or PR by RECIST were defined as radiologic responders while patient who demonstrated SD or PD were defined as radiologic nonresponders.

**Histopathologic Response**

Histopathologic response was assessed as previously described by Pataer et al.5 Hematoxylin and eosin (H&E)-stained slides were assessed of sections of the gross residual tumor resected after neoadjuvant chemotherapy (at least 1 section per cm of tumor greatest diameter). The percentage of residual tumor was quantified by comparing the estimated cross-sectional area of the viable tumor foci to estimated cross-sectional areas of necrosis, fibrosis, and inflammation on each slide. The results for all slides were averaged together to determine the mean values of percentage of viable tumor cells for each patient. We previously demonstrated that a cut-off of 10% viable tumor cells could distinguish patients with a high versus low probability of long-term disease-free and OS. As such, patients were considered to be pathologic responders if they had less than 10% viable tumor cells and pathologic nonresponders if they had greater than 10% viable tumor cells.

### TABLE 1. Patient Demographics and Treatment Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range, yrs)</td>
<td>63 (40–85)</td>
</tr>
<tr>
<td>Sex: n (%)</td>
<td>92 (57%)</td>
</tr>
<tr>
<td>Men</td>
<td>68 (43%)</td>
</tr>
<tr>
<td>Histology: n (%)</td>
<td>68 (43%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>51 (32%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>47 (29%)</td>
</tr>
<tr>
<td>Others*</td>
<td>33 (21%)</td>
</tr>
<tr>
<td>Tumor size (cm): n (%)</td>
<td>40 (25%)</td>
</tr>
<tr>
<td>0.0–2.0</td>
<td>40 (25%)</td>
</tr>
<tr>
<td>2.1–3.0</td>
<td>47 (29%)</td>
</tr>
<tr>
<td>3.1–5.0</td>
<td>33 (21%)</td>
</tr>
<tr>
<td>Clinical stage: n (%)</td>
<td>52 (32%)</td>
</tr>
<tr>
<td>IA/B</td>
<td>35 (22%)</td>
</tr>
<tr>
<td>IIA/B</td>
<td>64 (40%)</td>
</tr>
<tr>
<td>IIIA/B</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>IV</td>
<td>143 (89%)</td>
</tr>
<tr>
<td>Type of resection n (%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Wedge or segmentectomy</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Bilobectomy or lobectomy</td>
<td>T+C</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>53 (33%)</td>
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<tr>
<td>Taxol</td>
<td>76 (48%)</td>
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<tr>
<td>Taxotere</td>
<td>68 (42%)</td>
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<tr>
<td>Gemcitabine</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Treatment cycle median (range, cycles)</td>
<td>3 (1–11)</td>
</tr>
</tbody>
</table>

*Others (32 patients with NSCLC-NOS, 4 with adenocarcinoma, 3 with squamous cell tumor, 1 with large cell and 1 with sarcoma). AJCC/UICC 6th edition. T, taxol or taxotere; C, carboplatin or cisplatin.
Statistical Analysis

Correlations were evaluated using Pearson’s linear test or the Spearman rank test. OS was calculated from the time of surgery to the time of death from any cause or to the time of the patient’s last follow-up visit, after which the data were censored. Survival probability as a function of time was computed by the Kaplan-Meier method. The log-rank test was used to compare OS between groups. Univariable Cox proportional hazards regression analysis was used to examine the association between various prognostic factors and OS. Variables found to be significant in univariable analysis (\( p < 0.25 \)) were then evaluated by multivariable analysis using the Cox proportional hazards regression model with backward stepwise Wald elimination. In multivariable analysis, \( p \) less than 0.05 was taken to be significant. Statistical analyses were performed using SPSS version 19.0 software (SPSS, Inc., Chicago, IL).

RESULTS

Patient Demographics and Treatment Characteristics

The study population included 92 men (57%) and 68 women (43%) with a median age of 64 years (range, 40–85 years). Histologic tumor types are shown in Table 1. All patients were treated with a platinum-based doublet, and the majority received a taxane and platinum (143 patients, 89%). The median number of treatment cycles was 3 (range, 1–11 cycles) and 143 patients (89%) received a lobectomy or bilobectomy (Table 1).

Response to Neoadjuvant Chemotherapy
by Radiologic and Pathologic Criteria

CT RECIST demonstrated two (1%) patients with a complete response and 78 (49%) patients with a partial response. Stable disease occurred in 75 (47%) patients and disease progression was rare and seen in only 5 (3%) patients after neoadjuvant chemotherapy. Histopathologic response (≤ 10% viable tumor) was seen in 30 of 160 patients (19%) and occurred more frequently in patients with CR/PR by CT criteria, compared with patients with SD/PD (27% versus 10%, \( p < 0.005 \)) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A385). There was, however, a 41% discordance rate between histopathologic response and CT RECIST response (8 of 80 patients had a histopathologic response despite being classified as SD/PD by CT criteria, and 58 of 80 patients did not achieve pathologic response despite being classified as CR/PR by CT criteria) (Fig. 1). The sensitivity of CT RECIST to identify histopathologic responders was 73% and the specificity was 55%. Representative examples of the dissociation between response by CT and pathologic criteria are shown in Fig. 2.

Relationship Between CT and Histopathologic Response and OS

We analyzed the relation between response assessed with CT radiologic criteria (RECIST), histopathologic criteria, and OS in NSCLC patients who received neoadjuvant chemotherapy. The Kaplan-Meier survival curves in Fig. 3A show that patients with CR or PR by radiologic criteria have improved OS compared with patients with SD or PD (\( p = 0.03 \)). Patients with a histopathologic response have a statistically significant improvement in OS compared with patients that did not achieve a histopathologic response (\( p = 0.002 \)) (Fig. 3B). The separation of the curves in Fig. 3B is more pronounced when compared with Fig. 3A, suggesting that histopathologic response may more accurately identify patients with a higher chance of long-term survival compared with RECIST.

On univariable analysis, CT response, histopathologic response, and pathologic stage were significantly associated with OS (Table 2). These variables were then included on the multivariable analysis. Wald stepwise elimination excluded CT response from the multivariable model, indicating a stronger association of OS with histopathologic response compared with CT response. Multivariable Cox proportional hazards
regression analysis revealed an association of both pathologic stage ($p < 0.001$) and histopathologic response ($p = 0.05$) with OS (Table 2). We repeated the multivariable analysis using the Cox proportional hazards regression model with backward stepwise Wald elimination, applying more stringent criteria for CT response (i.e., at least 50% or 70% reduction in tumor size). In both cases, CT response was not significantly associated with overall survival ($p = 0.23$ for CT response at the 50% threshold, and $p = 0.98$ for CT response at the 70% threshold). As observed for the 30% threshold, in both cases (50% and 70%), backward stepwise Wald elimination excluded CT response from the multivariable model, while maintaining percentage of viable tumor cells and pathological stage. We conclude, from these findings, that even when using more stringent thresholds to define CT response, pathologic response still outperforms CT response in predicting overall survival.

**Complementary Prognostic Value of Radiological and Histopathologic Criteria**

To determine whether the failure of CT RECIST and histopathologic criteria to predict OS was because of lack of correlation with histopathologic response we combined radiologic CT RECIST and histopathologic criteria into four subgroups: (1) patients who were CT responders and histopathologic responders, (2) patients who were CT responders but histopathologic nonresponders, (3) patients who were CT nonresponders but histopathologic responders, and (4) patients who were CT nonresponders and histopathologic nonresponders. As shown in Fig. 4, Kaplan-Meier survival analysis indicated that the four subgroups had significantly different OS ($p = 0.006$). Patients who were CT responders and histopathologic responders had prolonged OS but CT nonresponders with histopathologic responders also had prolonged survival even greater than CT responders and histopathologic nonresponders. These results suggest that histopathologic response may be the most important predictor of long-term survival and that CT response may not be predictive in all patients because CT response does not identify all patients who have a pathologic response. Furthermore, in patients who were pathologic nonresponders, there was no significant difference in survival between CT responders and CT nonresponder ($p = 0.14$, data not shown), suggesting that CT response does not compensate for a lack of histopathologic response after neoadjuvant chemotherapy with regards to improvement in OS.

**FIGURE 2.** CTs of lung tumors, showing examples of dissociation between radiological assessment of tumors and pathologic response. (A, B) No CT response to treatment by RECIST, despite 5% of viable tumor cells remaining after neoadjuvant therapy. (C, D) PR to treatment by CT criteria, but 86% of viable tumor cells remained in the resected specimen. The percentages shown are the change in the size of the target lesion between pre-chemotherapy and post-chemotherapy measurements. CT, computed tomography; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors.

**FIGURE 3.** Kaplan-Meier estimates of OS for CT (RECIST) and histopathologic response criteria. (A) CT-RECIST grouping into responders and nonresponders demonstrates a difference in OS ($p = 0.03$) (B) With histopathologic response, OS was significantly different between responders ($\leq 10\%$ viable tumor) and nonresponders ($> 10\%$ viable tumor, $p = 0.002$), with a more pronounced separation of the curves when compared to CT-RECIST. CT, computed tomography; RECIST, Response Evaluation Criteria in Solid Tumors; OS, overall survival.
In this study, we demonstrate that in 160 patients with resectable NSCLC who received neoadjuvant chemotherapy, there was an association between CT-measured tumor response (RECIST) and OS ($p = 0.03$). However, histopathologic response was a stronger predictor of OS ($p = \text{<0.001}$).

A potential advantage of developing neoadjuvant treatment strategies for resectable NSCLC is the opportunity to evaluate response as an intermediary endpoint of efficacy. If a close correlation between response to treatment and OS is demonstrated, then it would be possible to design more efficient clinical trials incorporating novel neoadjuvant therapies that would evaluate response as a surrogate marker for improved long-term outcomes. This strategy would allow for an early readout of efficacy, and could streamline drug development. It would also allow investigation of intensification of adjuvant treatment in patients who did not respond adequately to neoadjuvant therapy, in an attempt to improve long-term outcomes.

In this study, we demonstrate that in 160 patients with resectable NSCLC who received neoadjuvant chemotherapy, there was an association between CT-measured tumor response (RECIST) and OS ($p = 0.03$). However, histopathologic response was a stronger predictor of OS ($p = \text{<0.001}$).
0.002), with a more pronounced separation of the survival curves when compared with CT-measured response (Fig. 3). The lower performance of CT-measured tumor response (RECIST) in predicting OS after neoadjuvant chemotherapy may be owing in part to the inability of standard measurements of CT tumor size changes to predict histopathologic response. As demonstrated in Fig. 4, 58 of 80 patients with a CT response failed to have a histopathologic response while eight of 30 patients with a histopathologic response failed to demonstrate a response on CT RECIST response. Sensitivity was 73% but specificity was only 55%. This inability of CT RECIST-measured tumor size changes to predict histopathologic response may be because of various factors including the fact that NSCLC tumors are pathologically heterogeneous in composition and include cancer cells, stromal tissue, and associated inflammatory cells.18,19 Because of this, CT RECIST response assessment may provide only a macroscopic evaluation of the primary tumor, and it is possible that the CT RECIST-measured tumor size changes are confounded by inflammatory or fibrotic changes. This latter possibility has been reported previously in patients with advanced stage NSCLC.18

These observations have significant implications for ongoing clinical trials that utilize CT imaging response criteria (RECIST) as intermediary endpoints of treatment response in both metastatic and nonmetastatic NSCLC20 as well as other tumor types.19 Several studies have suggested that there may be more accurate CT response criteria than RECIST21,22 such as volumetric response measurements with automatic deformable image registration (ADIR). Similarly in other tumor types, Choi and colleagues demonstrated that GIST tumors treated with imatinib were more accurately assessed with small CT changes in tumor size or density rather than standard RECIST criteria, while Chun and colleagues found that colorectal liver metastases were more accurately assessed with morphologic CT criteria than RECIST.23 Other authors have suggested that monitoring response with apoptosis molecular imaging or contrast-enhanced MRI may be more accurate.24-26

It has also been suggested that response assessed by [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) after chemotherapy may be more accurate than CT-measured responses (RECIST) in patients with NSCLC.27-31 Not all authors are in agreement with this finding, however, as demonstrated by Tanvetyanon et al who evaluated two consecutive phase II neoadjuvant chemotherapy trials and found that CT response (RECIST) was more accurate than PET.32 This is not unreasonable since FDG-PET imaging may be affected by the cellular composition of the primary tumor as well as the therapeutic-induced inflammatory response.33 In this regard, the exact mechanism of FDG uptake and distribution among cells within the primary tumor is unknown and although FDG uptake in lung cancer is thought to be primarily because of the tumor cells, there is a variable contribution from the inflammatory response owing to competitive uptake in macrophages and lymphocytes.33 Animal studies have shown that up to 30% of the FDG uptake in a tumor may be caused by the macrophage/monocyte system and that some tumors retain high FDG uptake at the end of therapy even with complete histopathological response at the time of resection.34,35 It has recently been reported that the prediction of histopathologic response in patients with locally advanced NSCLC who received neoadjuvant chemotherapy followed by curative surgery is more accurate when defined by a combined radiologic-metabolic response using CT and FDG-PET compared to radiologic and metabolic response alone.36,37 Nevertheless, the accuracy for the prediction of histopathologic response was only 73% to 82% in radiologic-metabolic responders (compared with 70% in radiologic responders and 52% to 75% in metabolic responders).37

In conclusion, our study suggests that changes in CT-measured tumor size by standard RECIST are unreliable in predicting OS or histopathologic response after neoadjuvant therapy in resectable NSCLC. Because of the overall poor reliability of CT in predicting therapeutic response and OS, CT RECIST may have only a limited role as an endpoint for efficacy in clinical trials with novel therapeutics in metastatic and nonmetastatic NSCLC. In the future, novel CT, PET, or molecular imaging response criteria may need to be developed beyond standard CT RECIST changes in tumor size to accurately serve as surrogate endpoints for treatment efficacy.

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REFERENCES


