Imaging, Diagnosis, Prognosis
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Tumor Heterogeneity and Permeability as Measured on the CT Component of PET/CT Predict Survival in Patients with Non–Small Cell Lung Cancer

Thida Win1, Kenneth A. Miles2, Sam M. Janes3, Balaji Ganeshan2, Manu Shastry2, Raymondo Endozo2, Marie Meagher2, Robert I. Shortman2, Simon Wan2, Irfan Kayani2, Peter J. Ell2, and Ashley M. Groves2

Abstract

Purpose: We prospectively examined the role of tumor textural heterogeneity on positron emission tomography/computed tomography (PET/CT) in predicting survival compared with other clinical and imaging parameters in patients with non–small cell lung cancer (NSCLC).

Experimental Design: The feasibility study consisted of 56 assessed consecutive patients with NSCLC (32 males, 24 females; mean age 67 ± 9.7 years) who underwent combined fluorodeoxyglucose (FDG) PET/CT. The validation study population consisted of 66 prospectively recruited consecutive consenting patients with NSCLC (37 males, 29 females; mean age, 67.5 ± 7.8 years) who successfully underwent combined FDG PET/CT/dynamic contrast-enhanced (DCE) CT. Images were used to derive tumoral PET/CT textural heterogeneity, DCE CT permeability, and FDG uptake (SUVmax). The mean follow-up periods were 22.6 ± 13.3 months and 28.5 ± 13.2 months for the feasibility and validation studies, respectively. Optimum threshold was determined for clinical stage and each of the above biomarkers (where available) from the feasibility study population. Kaplan–Meier analysis was used to assess the ability of the biomarkers to predict survival in the validation study. Cox regression determined survival factor independence.

Results: Univariate analysis revealed that tumor CT-derived heterogeneity (P < 0.001), PET-derived heterogeneity (P = 0.003), CT-derived permeability (P = 0.002), and stage (P < 0.001) were all significant survival predictors. The thresholds used in this study were derived from a previously conducted feasibility study. Tumor SUVmax did not predict survival. Using multivariable analysis, tumor CT textural heterogeneity (P = 0.021), stage (P = 0.001), and permeability (P < 0.001) were independent survival predictors. These predictors were independent of patient treatment.

Conclusions: Tumor stage and CT-derived textural heterogeneity were the best predictors of survival in NSCLC. The use of CT-derived textural heterogeneity should assist the management of many patients with NSCLC. Clin Cancer Res; 19(13); 3591–9. ©2013 AACR.

Introduction

Non–small cell lung cancer (NSCLC) is a common malignancy with a poor prognosis. Predictive factors are needed to refine the management of these patients, for example, to guide the use of surgical adjuncts and help determine patients who are at risk of early recurrence and require intense monitoring and follow-up (1–4). Current NSCLC guidelines (2–4) reflect survival data based on multiple factors such as performance status (5, 6) and staging (7). Other factors, such as tumor metabolism and vascularity, have been proposed as prognostic indicators (8, 9). Imaging patients with NSCLC with positron emission tomography (PET) and computed tomography (CT) provides important staging information. In addition, these imaging techniques can be used to derive tumor glucose metabolism and vascularity (8, 9). These functional data may in turn be used to predict patient outcome.

Recently, researchers have investigated tumor heterogeneity in the search for oncologic prognostic markers and mechanisms. Indeed, the importance of such an approach has recently been highlighted by the demonstration of genomic tumor heterogeneity with significant implications for treatment and resistance (10). However, such an approach is both time consuming and costly. A potentially easier approach is to evaluate tumor heterogeneity using imaging to assess how grainy or coarse a tumor seems to be. PET and CT have both been used to derive tumor textural information, and the appearance of the tumors has been
shown to relate to patient outcome in esophageal and colorectal cancer (11–13).

In this study, we examined the prognostic potential of tumoral textural analysis using PET/CT in patients with NSCLC compared with tumor staging and other imaging prognostic factors: metabolism and vascularity.

Materials and Methods

Patients

This research study used a feasibility dataset of patients with NSCLC to derive optimal thresholds for the markers (imaging and clinical) that predicted survival and then prospectively applied these thresholds within this validation dataset of patients with NSCLC. Furthermore, the 2 patient cohorts (feasibility and validation) were independent and from different centers.

Feasibility dataset. The feasibility study population consisted of 56 consecutive patients with NSCLC (32 males and 24 females; mean age, 67 ± 9.7 years) who underwent staging fluorodeoxyglucose (FDG) PET/CT as part of their routine clinical care between April 2006 and November 2006 at a hospital different from the one used for the validation dataset (14).

Validation dataset. The study population was of similar size to the feasibility population and consisted of 66 prospectively recruited consecutive consenting patients with NSCLC (37 males, 29 females; mean age, 67.5 ± 7.8 years) who successfully underwent FDG PET dynamic contrast-enhanced (DCE) CT as part of their routine clinical care between April 2006 and November 2006. Sixteen tumors were squamous-cell carcinomas, 32 were adenocarcinomas, and the remaining 18 were mixed/nonspecific NSCLC (see Table 1 for staging). All the patients were followed up in the outpatient setting for at least 3 months. Histologic examination was conducted by needle biopsy/bronchoscopic biopsy or surgery. Histologic diagnosis was made by an expert thoracic histopathologist. All patients gave informed consent, and the Local Ethics Board approved this study.

PET/CT imaging protocol

Feasibility dataset. All images were acquired using a PET/CT system with both CT and PET data acquired in 1 procedure in accordance with a standardized protocol as published (14).

Table 1. Lung cancer staging of the patient cohort by dataset

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients, n (feasibility dataset)</th>
<th>Patients, n (validation dataset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Validation dataset. Following a 6-hour patient fast, images were acquired 1 hour after injection of 370 MBq of \(^{18}\)F-FDG using PET/CT (VCT-XT-Discovery, GE-Healthcare). CT was conducted (for attenuation correction) using 64 × 3.75-mm detectors, a pitch of 1.5, and a 5-mm collimation (140 kVp and 80 mA in 0.8 seconds). Maintaining the patient position, a whole-body \(^{18}\)F-FDG PET emission scan was conducted and covered an area identical to that covered by CT (4 minutes/bed position). Transaxial emission images of 3.27-mm thickness (pixel-size, 3.9 mm) were reconstructed using ordered subsets expectation maximization with 2 iterations and 28 subsets. The axial field of view was 148.75 mm, resulting in 47 slices/bed position. Next, maintaining the patient position, a DCE CT was conducted during shallow respiration. Patients received 50 mL of i.v. contrast medium iohexol (350 mg/mL iodine, GE Healthcare; 25 mL at 5 mL/s), at 4 mL per second, while 12 CT images (1 per 5 seconds with a 5-second delay) were acquired axially at 100 to 150 mAs, 80 KV using 64 × 0.6 mm detectors (4-cm detector coverage).

PET image data analysis

In each of the feasibility and validation datasets, \(^{18}\)FDG analysis was conducted by a nuclear medicine physician with less than 4 years’ experience of region of interest (ROI) with PET/CT. PET/CT images were displayed conventionally on a proprietary workstation. An automated ROI was drawn around the tumor, and FDG uptake was expressed as the maximum standardized uptake ratio (SUVmax).
uptake value (SUV\text{max}). Automation was conducted with a standard ROI analysis tool provided with the scanner, using a threshold method—42% of the max value (Fig. 1; ref. 15, 16).

**DCE image analysis**

In the validation dataset, DCE CT data were analyzed using proprietary CT perfusion software (Winfun, Cambridge Computed-Imaging) under the supervision of an operator with 20 years’ DCE CT experience. On an axial image, a ROI was drawn freehand around the lung tumor within the boundaries of the mass, using PET images for guidance. Vascularity was measured at a single midtumor level, and a manual correction was made for respiratory motion. A further ROI was drawn freehand around the aorta within the boundaries of the vessel. The tumor flow extraction product—a measure of tumor vascular leakiness (permeability)—was calculated using Patlak analysis (17).

**Texture analysis**

**CT texture analysis.** In each of the feasibility and validation datasets, CT texture analysis (CTTA) was conducted from the attenuation correction images acquired for PET/CT, using a proprietary software algorithm (ref. 18; see Supplementary Data for details). The operator who conducted the CTTA in the feasibility study (who had 6 years’ experience in CTTA) was different from the operator who conducted the CTTA in the validation study (chief CT technologist with >10 years of ROI experience under supervision from a researcher with 6 years’ experience in CTTA). All operators were blinded to all other data. A single 2-dimensional lung CT slice with the largest cross-section area of tumor was used for CTTA. A ROI was drawn accurately contouring the tumor (Fig. 2A).
This method followed similar guidelines as for PET image selection/analysis. The tumor heterogeneity was measured selectively at different texture scales—fine, medium, and coarse features (Fig. 2B–D)—using entropy (a measure of irregularity). Texture values were further normalized (12) to the coarsest scale to give a series of relative texture values (i.e., relative contribution to overall texture made by texture components of different scales), as further described in Supplementary Data.

**PET texture analysis.** In the validation dataset, PET texture analysis (PTA) was conducted on the SUV images used to measure the SUV\(_{\text{max}}\). The images (individual pixel values) with initial units of uptake in Bq/mL were converted (scaled) to SUV calibrated by patient weight and actual tracer activity (taking into consideration the initial tracer activity, amount of decay between the tracer measured time and scan time with respect to the half-life period of \(^{18}\)F-FDG = 109.8 minutes) with final units of uptake in g/mL. The tumor heterogeneity was measured only on the SUV image without image filtration using entropy (a measure of irregularity, similar in quantification to CTTA). Image filtration was not appropriate owing to the inherently poor resolution of PET (SUV) data.

**Statistical analysis**
Statistical analyses were conducted using IBM SPSS for Windows version 19.0. The relationships of tumor heterogeneity (CTTA and PTA), stage, SUV\(_{\text{max}}\), permeability, and treatment and their relationship with patient survival were assessed using Kaplan–Meier survival analysis. In the case of CTTA, clinical stage and SUV\(_{\text{max}}\) the optimal thresholds (cutoffs), were determined that best separated the survival plots (poor and good prognostic groups) in the feasibility dataset. These optimal thresholds (cutoffs) were then evaluated in the validation dataset (to test the robustness of the biomarker) using Kaplan–Meier survival analysis. In the case of PTA, permeability, and treatment and their relationship with patient survival were directly assessed using Kaplan–Meier survival analysis in the validation dataset. Differences between Kaplan–Meier survival curves for patients above and below each threshold were evaluated by a nonparametric log rank test (\(P < 0.05\) considered significant; ref. 19). Multivariate Cox regression was used to determine which parameters were independent predictors of survival [along with the hazard ratio (HR) and the confidence interval (CI)], and their interactions with treatment were analyzed in the validation dataset.

**Results**

**Feasibility dataset**
The mean follow-up period was 22.6 ± 13.3 months. The mean survival was 24.1 months, whereas median survival was 28 months. Twenty-seven of 54 patients died within 30 months of their PET/CT. The shortest survival time was 1 month. The mean (range) tumor SUV\(_{\text{max}}\) for all patients was 14.5 (3.4–37.1; ref. 14).

**Validation dataset**
The mean follow-up period was 28.5 ± 13.2 months. The mean survival was 25.8 months, whereas median survival was 20 months. Twenty-nine of 66 patients died within 30 months of their PET/CT. The shortest survival time was 1 month. Mean (range) tumor SUV\(_{\text{max}}\) for all patients was 13.7 (2.1–34.0). A total of 32 of the 66 patients proceeded to radical therapy; 30 underwent surgical resection and 2 had radical radiotherapy.

**Kaplan–Meier analysis—whole-cohort analysis**
The feasibility dataset (described above) identified the optimal threshold for CTTA, clinical stage, and SUV\(_{\text{max}}\) at which these markers were the best predictor of survival by univariate analysis using Kaplan–Meier (Tables 2 and 3, Fig. 3). In the validation dataset, the strongest predictor of survival was tumor textural heterogeneity (\(P < 0.001\)) measured on CT (CTTA at normalized entropy, medium/coarse texture-scale corresponding to 1.5/2.5; Tables 4 and 5; Fig. 4) and staging (\(P < 0.001\); Tables 4 and 5; Fig. 4) based on the optimal threshold derived from the feasibility dataset. Tumor maximum standardized uptake value (at the optimal threshold derived from the feasibility dataset) was not a predictor of survival (Table 5). In addition, the univariate analysis using Kaplan–Meier showed that tumor texture heterogeneity measured on PET, radical therapy (Supplementary Fig. S2; Supplementary

**Table 2. Summary of Kaplan–Meier survival analysis for the prognostic factors in the feasibility dataset (at the optimal-threshold)**

<table>
<thead>
<tr>
<th>Tumor characteristics</th>
<th>Overall—mean survival in months (patients, (n))</th>
<th>Threshold (cutoff)</th>
<th>Above threshold</th>
<th>Below threshold</th>
<th>HR (95% CI)</th>
<th>(P) (Kaplan–Meier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity (CTTA–normalized entropy, medium/coarse scale)</td>
<td></td>
<td></td>
<td>34.5 (8)</td>
<td>22.1 (46)</td>
<td>6.110 (0.828–45.075)</td>
<td>0.038</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td>17.4 (20)</td>
<td>28.2 (34)</td>
<td>2.830 (1.310–6.100)</td>
<td>0.005</td>
</tr>
<tr>
<td>SUV(_{\text{max}})</td>
<td></td>
<td></td>
<td>12.0 (4)</td>
<td>24.7 (50)</td>
<td>3.350 (0.997–11.251)</td>
<td>0.043</td>
</tr>
</tbody>
</table>
Table S1) and permeability (Table 4; Fig. 4) were also significant predictors of NSCLC patient survival (Table 5).

Kaplan–Meier analysis—with radical treatment as stratum
In the curative-intent group, tumoral heterogeneity on CT (CTTA at normalized entropy, medium/coarse texture-scale) was the only factor shown to be associated with survival. In the palliative group, tumoral heterogeneity on CT (normalized entropy, medium/coarse texture-scale), stage, and permeability were associated with survival (see Table 5).

Multivariate analysis—Cox regression
Cox regression analysis indicated that tumoral heterogeneity on CT (CTTA), stage, and permeability were independent predictors (CTTA: HR, 412.241; 95% CI; 1.45–103.05; \( P = 0.021 \); Clinical stage: HR, 5.02; 95% CI: 1.89–13.32; \( P < 0.001 \); Permeability: HR, 6.01; 95% CI: 2.34–15.41; \( P < 0.001 \)), whereas tumor heterogeneity on PET (PTA) and radical therapy were not significant predictors of survival (Table 6). Also, there was no significant interaction between the above significant predictors and treatment on overall patient survival.

Discussion
We show in a prospectively collected population of patients with NSCLC that clinical stage, vascularity, and heterogeneity (on both the CT and PET components of PET/CT) are all significant predictors of patient survival using univariate analysis. Using multivariable analysis, tumor heterogeneity (CTTA), permeability, and stage were all found to be independent predictors of survival. The threshold level for these markers was determined from a previous feasibility study. Given that conducting textural analysis is simple and almost all patients with NSCLC undergo CT, these findings have potential management implications for these patients undergoing either radical or palliative therapy.

Prognostic factors are an essential requirement in the management of NSCLC, and this is reflected in recent changes in Tumor–Node–Metastasis (TNM) staging (7), where each subgroup is indicative of outcome. However, despite such refinements, there remains uncertainty and more predictive data are required. This is particularly true in stage 3A disease, in which outcome remains variable (4). Moreover, the selection and benefit of surgical patients for neoadjuvant/adjuvant treatment is also unclear (20–24). It is important that the possible survival benefits of chemoradiation are balanced by the adverse effects of toxicity to the patient. Moreover, adjunctive regimens are expensive and there may be need for justification by the health care provider.

The role of systemic therapy in palliative regimens is also evolving. The rationale for selection of molecular-targeted therapy and second-line treatment is in need of refining (2, 4, 25, 26). The role of prognostic factors in determining...
selection is yet to be determined. Finally, there is controversy in respect to the need for disease reoccurrence monitoring (4). The use of tumor heterogeneity may also help identify those patients at particular risk for relapse and who would thus benefit from more intensive observation and follow-up.

Why tumoral heterogeneity is related to survival is unclear. It would also be interesting to investigate whether tumor heterogeneity could be related to clonal dominance. It has recently been shown that a genomic heterogeneity exists within tumors, and this observation has significant implications for Darwinist theories of tumor resistance (10). Whether textural heterogeneity on imaging relates to underlying genomics would be important to investigate. However, given the challenges and expense of measuring tumor genomic signatures, imaging may be the more viable option.

Another possible avenue worthy of further exploration is the possible relationship between tumor heterogeneity and hypoxia. It has been recently shown that tumor textural analysis was associated with tumor hypoxia on histologic examinations from patients with NSCLC who were administered i.v. pimonidazole before surgery (27). Hypoxia is a recognized marker of poor outcome, and as such, a positive relationship between tumor hypoxia and tumor heterogeneity would be biologically consistent.

Imaging-derived survival predictors are recognized in NSCLC, with the most established being staging data. Tumor uptake of FDG (standardized uptake value or SUV) on PET has been suggested as a strong predictor of survival in many studies, including a recent meta-analysis (28). PET is part of the diagnostic pathway for NSCLC in patients being considered for radical therapy, and tumor FDG uptake is relatively easy to measure. As such, PET SUV measurements are a potentially clinically viable option. However, it has been recognized that there are difficulties in assessing whether SUV is an independent survival factor in NSCLC (28). Nonetheless, a recent meta-analysis showed that tumor SUV was not an independent predictor of outcome (8).

In addition to assessing SUV values, PET textural analysis may be useful, and it has been shown to predict survival in esophageal cancer (11). Because survival data are lacking in lung cancer using PET texture, our finding that survival was not an independent survival factor using PET texture was interesting. However, heterogeneity uptake of 18FDG on PET is a clinically important parameter to measure as it can be used to delineate tumor volumes for radiotherapy planning and escalation (boost), for example, in colorectal cancer (29). This approach is likely to be useful in NSCLC as well (30).

DCE CT has been shown to predict treatment response in NSCLC (9), but our data are the first to show a survival association. We also show that it is a significant independent predictor of survival. However, the disadvantage of

![Figure 4. Kaplan–Meier curves (along with the number of patients at risk for each group over time) showing the proportion of patients surviving for (A) heterogeneity–CTTA, (B) clinical stage, and (C) permeability in the validation dataset (using the threshold from the feasibility dataset).](image-url)
Table 5. Summary of Kaplan–Meier survival analysis (overall and subgroup—radical and palliative treatment) for each prognostic factor in the validation dataset (using the threshold from the feasibility dataset)

<table>
<thead>
<tr>
<th>Tumor characteristics</th>
<th>Overall</th>
<th>Below threshold (PTA–entropy)</th>
<th>Below threshold (Heterogeneity)</th>
<th>Above threshold (CTTA–entropy)</th>
<th>Above threshold (Heterogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor characteristics</td>
<td>Threshold</td>
<td>Survival in months</td>
<td>Survival in months</td>
<td>Survival in months</td>
<td>Survival in months</td>
</tr>
<tr>
<td>Heterogeneity (CTTA–entropy)</td>
<td>&lt;1.233</td>
<td>14.0 (26)</td>
<td>0.042</td>
<td>14.2 (23)</td>
<td>0.313</td>
</tr>
<tr>
<td>Heterogeneity (CTTA–entropy)</td>
<td>&gt;3.209</td>
<td>16.3 (33)</td>
<td>0.003</td>
<td>34.5 (23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical stage IIa</td>
<td>11.5 (6)</td>
<td>33.1 (40)</td>
<td>0.001</td>
<td>11.0 (9)</td>
<td>33.0 (29)</td>
</tr>
<tr>
<td>Clinical stage IIIB</td>
<td>11.6 (6)</td>
<td>33.0 (29)</td>
<td>0.001</td>
<td>11.0 (9)</td>
<td>33.0 (29)</td>
</tr>
<tr>
<td>Clinical stage IV</td>
<td>11.2 (20)</td>
<td>25.6 (12)</td>
<td>0.000</td>
<td>11.4 (6)</td>
<td>16.3 (26)</td>
</tr>
<tr>
<td>Clinical stage IV</td>
<td>11.2 (20)</td>
<td>25.6 (12)</td>
<td>0.000</td>
<td>11.4 (6)</td>
<td>16.3 (26)</td>
</tr>
<tr>
<td>Clinical stage IV</td>
<td>11.2 (20)</td>
<td>25.6 (12)</td>
<td>0.000</td>
<td>11.4 (6)</td>
<td>16.3 (26)</td>
</tr>
</tbody>
</table>

In conclusion, we show that CT-derived tumor heterogeneity and permeability are independent predictors of this approach is that the dynamic CT protocol required is yet to be routinely adopted in clinical practice and there are technical challenges that need to be overcome (31, 32). DCE CT also entails an additional radiation dose that may need to be as high as 30 mSv for reliable whole-tumor assessments (32). In contrast, measuring textural heterogeneity has the advantage of being relatively easy to perform and the textural data can be acquired with conventional CT protocols that are routinely conducted as part of the standard of care in patients with NSCLC. Furthermore, the use of relative texture analysis allows the effect of variations in acquisition parameters (between the feasibility and validation datasets) on lung tumor texture to be minimized, thereby making this approach applicable across centers.

Study limitations include a limited size population. However, it should be appreciated that all these patients had a substantial array of imaging parameters conducted on each individual: SUVmax from PET, vascularity on DCE CT and textural analysis on conventional CT. Also, 66 patients is a relatively large population for perfusion CT study, even in the absence of PET. The use of a feasibility dataset provided a training population to identify the optimal cutoffs for the markers, which were further evaluated in the validation population and thereby increased the statistical robustness so that we were able to show strong statistical significance. A further possible limitation is the inclusion of patients undergoing both radical and palliative therapy. Yet, by having both sets of patients, it was possible to show that texture heterogeneity was a survival predictor independent of treatment. Density on CT has been observed as a prognostic factor on CT before, for example, using the presence of air in the tumor (33, 34); however, use of the CT component of PET/CT to measure tumor heterogeneity in lung cancer survival as such is novel.

We chose to conduct all image analyses using a single transverse image for each technique. This choice was predicated on the need to match novel image parameters with that most widely proposed as a prognostic marker in NSCLC at the time of study design, i.e., SUVmax which, by quantifying the most FDG-avid pixel, is inherently a single-slice technique. The 4-cm cranio-caudal coverage of the DCE CT was to allow for correction of respiratory motion. DCE CT assessment of whole tumor would have required even greater coverage with a significantly larger radiation dose. However, single-slice measurements of vascular permeability and heterogeneity could potentially miss areas of greater abnormality at other anatomical levels. Hence, comparison of single- and multislice approaches could be included in further validation studies. However, for CTTA, studies to date suggest little difference between these approaches (35). Finally, there should be awareness of the artifacts caused by motion (breathing) and different slice thickness/resolution between the imaging modalities used in this study.

In conclusion, we show that CT-derived tumor heterogeneity and permeability are independent predictors of
survival in addition to clinical stage in NSCLC. This finding has potential to aid the management of patients with NSCLC with both early and late disease.

Disclosure of Potential Conflicts of Interest
K.A. Miles and B. Ganeshan are employed on a consulting basis as directors for TexRAD Ltd. and have an ownership interest (including patents) in TexRAD Ltd.

Authors' Contributions
Conception and design: T. Win, K.A. Miles, A.M. Groves
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Win, S.M. Janes, B. Ganeshan, M. Shastry, S. Wan, I. Kayani, A.M. Groves
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Win, K.A. Miles, B. Ganeshan, M. Shastry, R.I. Shortman, S. Wan, I. Kayani, A.M. Groves
Writing, review, and/or revision of the manuscript: T. Win, K.A. Miles, S.M. Janes, B. Ganeshan, R. Endozo, R.I. Shortman, S. Wan, I. Kayani, P. Ell, A.M. Groves

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Win, M. Meagher, R.I. Shortman
Study supervision: K.A. Miles, B. Ganeshan, A.M. Groves

References

Table 6. Summary of multivariate Cox regression analysis model comprising each prognostic factor in the validation dataset

<table>
<thead>
<tr>
<th>Tumor characteristics</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables included in the Cox equation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity (CTTA-normalized entropy, medium/coarse scale)</td>
<td>12.241</td>
<td>1.454–103.053</td>
<td>0.021</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>5.020</td>
<td>1.892–13.320</td>
<td>0.001</td>
</tr>
<tr>
<td>Permeability</td>
<td>6.009</td>
<td>2.343–15.410</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Variables not included in the Cox equation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity (PTA-entropy without filtration)</td>
<td>0.301</td>
<td></td>
<td>0.583</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.686</td>
<td></td>
<td>0.407</td>
</tr>
<tr>
<td>Heterogeneity (CTTA) treatment</td>
<td>0.825</td>
<td></td>
<td>0.364</td>
</tr>
<tr>
<td>Heterogeneity (PTA) treatment</td>
<td>0.094</td>
<td></td>
<td>0.759</td>
</tr>
<tr>
<td>Clinical stage treatment</td>
<td>1.039</td>
<td></td>
<td>0.308</td>
</tr>
<tr>
<td>Permeability treatment</td>
<td>1.037</td>
<td></td>
<td>0.308</td>
</tr>
</tbody>
</table>

*aIndicates the interaction between the covariates.*
Tumor Heterogeneity

Tumor Heterogeneity and Permeability as Measured on the CT Component of PET/CT Predict Survival in Patients with Non–Small Cell Lung Cancer

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