Quantitative Analysis of Tumor Burden in Mouse Lung via MRI

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Lung cancer is the leading cause of cancer death in the United States. Despite recent advances in screening protocols, the majority of patients still present with advanced or disseminated disease. Preclinical rodent models provide a unique opportunity to test novel therapeutic drugs for targeting lung cancer. Respiratory-gated MRI is a key tool for quantitatively measuring lung-tumor burden and monitoring the time-course progression of individual tumors in mouse models of primary and metastatic lung cancer. However, quantitative analysis of lung-tumor burden in mice by MRI presents significant challenges. Herein, a method for measuring tumor burden based upon average lung-image intensity is described and validated. The method requires accurate lung segmentation; its efficiency and throughput would be greatly aided by the ability to automatically segment the lungs. A technique for automated lung segmentation in the presence of varying tumor burden levels is presented. The method includes development of a new, two-dimensional parametric model of the mouse lungs and a multi-faceted cost function to optimally fit the model parameters to each image. Results demonstrate a strong correlation (0.93), comparable with that of fully manual expert segmentation, between the automated method's tumor-burden metric and the tumor burden measured by lung weight. Magn Reson Med 000:000–000, 2011. © 2011 Wiley-Liss, Inc.

Key words: lung tumor quantification; magnetic resonance imaging (MRI); image segmentation; tissue classification

INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States (1). In 2006, the most recent year for which statistics are available, nearly 200,000 men and women were diagnosed with lung cancer, and almost 160,000 people died from the disease (2). Despite recent advances in screening protocols, the majority of patients still present with advanced or disseminated disease (3). While early detection might offer the potential to improve patient survival, the lack of adequate adjuvant therapy after surgical resection hampers long-term survival (4). Preclinical rodent models provide a unique opportunity to test novel therapeutic drugs to target lung cancer.

The ability to noninvasively record patterns of lung-tumor growth and response to therapy in situ, rather than in orthotopically implanted flank tumors, would greatly enhance the utility of small-animal models of lung pathology. This is especially true in light of recent demonstrations that subcutaneous malignancies may undergo progressive growth and regression after the development of an anti-tumor immune response (5). A major limitation in the study of murine thoracic tumors, and a potential reason for the paucity of such studies, is the difficulty in the detection and serial growth analysis of malignant and premalignant lung lesions. Unlike injected flank tumors or primary subcutaneous malignancies, which can be palpated and whose growth can be measured with calipers, the ability to monitor tumor growth or response to therapy in lung is limited (6–13). Serial measurement of lung tumors requires in vivo imaging. While high-resolution microCT is a valuable imaging modality for studying murine lung (14), the scan itself delivers a significant dose of radiation, which can markedly affect tumor growth and tumor immune response. In many studies, small-animal MRI, which employs only non-ionizing radiation, is the imaging modality of choice for characterizing lung-tumor growth and therapeutic response (15). Recently, we have demonstrated the use of respiratory-gated MRI to quantitatively measure lung-tumor burden and to monitor the time-course progression of individual tumors in mouse models of primary and metastatic lung cancer (7,9,13).

Analysis of tumor burden, particularly for heavy or diffuse tumor, by MRI presents significant challenges beyond those associated with data collection. In our previous studies (7,9,13), we visually identified individual tumors or groups of tumors (bright signal against the background of dark lung), encircled these tumors with appropriate regions of interest, and measured the corresponding volumes of the identified regions. While time consuming, this approach works well for well-defined tumor masses (Fig. 1b) and the volumes so-derived correlate well with tumor volumes measured histologically. However, this type of process is impractical for diffuse metastatic disease that results in the replacement of the majority of lung parenchyma with...
FIG. 1. Example MRI slices for (a) control mouse with no visible lung tumor, (b) mouse with several discrete lung tumors, and (c) mouse with diffuse metastatic tumor.

tumor (Fig. 1c). Instead, taking advantage of the large difference in MR image intensity between tumor and healthy lung parenchyma, we propose average lung-image intensity as a quantitative measure of tumor burden. (A related metric, the hyperintense-to-total lung volume ratio, has been used to quantify inflammation in an inflammation-mediated lung injury mouse model (16)). Herein, we describe the implementation and validation of such an approach, in which tumor burden, derived from MR lung-image intensity, is correlated with lung mass, which has recently been used as a quantitative measure of tumor in mice (17).

A key to the success of our approach for measuring tumor burden is the ability to accurately and reproducibly segment the lungs across the many slices of a 2-D multi-slice image. In our 0.5 mm-thick, coronal-slice images, lungs are often represented in 15–20 total slices. As with drawing regions of interest around individual tumors, the manual segmentation of lungs can be slow and time-consuming. The efficiency and throughput of the analysis would be greatly aided by the ability to automatically segment the lungs.

A variety of algorithms for automated and semiautomated tissue segmentation have previously been developed for and applied to lung MR images (18–23), though none have been applied to the segmentation of lung in the presence of either heavy tumor burden or diffuse tumor. These methods generally rely on the high contrast between healthy lung tissue, which has very low intensity in MR images, and surrounding tissue. Due to the strong intensity gradients at the lung boundary, active contours have been applied successfully in healthy lungs (18,19). Threshold-based methods have also been developed (23). However, these methods are not appropriate for segmentation of lungs with diffuse tumor (Fig. 1c), as the intensity characteristics upon which they rely may not be valid in such images. For example, lung edges may be weak or undetectable, as in the upper-right quadrant of the lung in Fig. 1c. Motion artifacts and partial volume effects can lead to elevated intensity levels in voxels within the lungs, contributing an additional source of potential error for threshold-based methods.

Model-based lung segmentation methods have also been proposed (20,21). However, the method proposed is suitable only for coarse segmentation of a collection of objects, rather than locally accurate segmentation of a single object, as in our study. Finally, atlas-based 3D segmentation methods have been developed (24,25); however, such methods assume that the image area to be segmented is very similar to the atlas, and can be aligned with the atlas through a series of registration steps, which may not be the case for tumor-filled lung. For lungs with diffuse tumor (Fig. 1c), new segmentation methods are required.

To address the challenges of lung segmentation in the presence of varying tumor burden, we developed a new, 2-dimensional parametric model of the mouse lungs. The model preserves the overall shape of the lungs, avoiding the inclusion or exclusion of large sections of lung that might occur with nonparametric, threshold-based approaches or edge-detection methods. The parameters of this model are iteratively fit to each MRI slice by utilizing optimization of a multi-faceted cost function. This cost function is novel in that it is evaluated as a function of the intensity distributions both inside and outside the parametric model. While specifically developed and tested in mouse lung, we expect that this new algorithm will have broad application to a variety of segmentation problems.

The dual goals of this work are to: (1) validate average lung-image intensity as a quantitative measure of lung-tumor burden and (2) develop and validate a new algorithm for automated lung segmentation. MRI measurements of lung-tumor burden are validated by correlating lung-image intensities with corresponding lung weights, while the results of automated segmentation are validated by direct comparison with manual image segmentations performed by a series of four experts. Excellent congruence is observed between lung volumes derived from the automated and manual lung segmentations, and average image intensities derived from these segmentations correlate well with measured lung weights.

MATERIALS AND METHODS

MRI

All studies were performed in accordance with the guidelines of the Washington University Animal Studies Committee and in accordance with protocols approved by the
Washington University Division of Comparative Medicine that met or exceeded American Association for the Accreditation of Laboratory Animal Care standards. Respiratory-gated, spin-echo MR images of mice were collected with a small-animal MR scanner based on an Oxford Instruments (Oxford, UK) 4.7 tesla, 40-cm bore magnet. The magnet is equipped with Agilent/Magnex Scientific (Yarnton, UK) actively shielded, high-performance (21 cm inner diameter, \( \sim 30 \text{G/cm}, \sim 200 \mu \text{s rise-time} \)) gradient coils and International Electric Company (Helsinki, Finland) gradient power amplifiers and is interfaced with an Agilent/Varian NMR Systems (Santa Clara, CA) DirectDriveTM console. All data were collected using a Stark Contrast (Erlangen, Germany) 2.5-cm birdcage-style rf coil. Prior to the imaging experiments, mice were anesthetized with isoflurane and were maintained on isoflurane (1–1.25% v/v) throughout data collection. Animal core-body temperature was maintained at 37°C (Erlangen, Germany) 2.5-cm birdcage-style rf coil. Prior to the imaging experiments, mice were anesthetized with isoflurane (1–1.25% v/v) throughout data collection. Animal core-body temperature was maintained at 37°C by circulation of warm air through the bore of the magnet. During the imaging experiments, the respiration rates for all mice were regular and \( \sim 2 \text{s}^{-1} \). Synchronization of MR data collection with animal respiration was achieved with a home-built respiratory-gating unit (26) and all images were collected during post-expiratory periods. Twenty-four contiguous coronal slices, ventral to dorsal, were collected for each mouse. Imaging parameters were TR \( \sim 3 \text{s} \), TE \( = 20 \text{ms} \), FOV \( 2.5 \text{cm} \times 2.5 \text{cm}^2 \), slice thickness \( = 0.5 \text{mm} \), 128 \times 128 data matrix, 4 averages. These scan parameters were chosen to maximize the contrast between healthy lung tissue and tumor.

Algorithm Development

Our algorithm for lung segmentation is based upon a 2D parametric lung-shape model. A 2D model was chosen over 3D modeling because (1) our data are composed of 2D MRI slices, and (2) the number of parameters to jointly optimize is fewer than in a 3D model, without loss of fidelity. Simpler models, i.e., models with fewer parameters, are both more robust and more efficiently optimized.

To fit our proposed parametric model to each torso slice, we propose an objective function, described in detail below, with which we can find locally optimal parameter values using the Nelder-Mead simplex method (27). The Nelder-Mead simplex method is appropriate here because it is an unconstrained, nonlinear optimization method for objective functions in high-dimensional spaces.

This section is organized as follows. First, we introduce our proposed parametric lung model. Next, we describe how our algorithm is initialized. Finally, we introduce our objective function and its components.

**Parametric Model**

We introduce a lung model composed of four curves—parametric segments AC and CB, and mixed parabolic segments AD and DB, shown in Fig. 2a. These curves are defined by their endpoints and by 6 curvature parameters \( a_{AC}, a_{CB}, a_{AD,1}, a_{AD,2}, a_{DB,1}, \) and \( a_{DB,2} \). The equation for any parabolic segment \( JK \) with curvature parameter \( a_{JK} \) and endpoints \( (x_J, y_J) \) and \( (x_K, y_K) \), with \( x_J < x_K \), is

\[
JK = \{(x,y)|y = a_{JK}x^2 + b_{JK}x + c_{JK}, x_J \leq x \leq x_K \}.
\]

where parameters \( b_{JK} \) and \( c_{JK} \) are defined by

\[
b_{JK} = \frac{y_K - y_J - a_{JK}(x_K^2 - x_J^2)}{x_K - x_J} \quad \text{[2]}
\]

\[
c_{JK} = y_J - b_{JK}x_J - a_{JK}x_J^2 \quad \text{[3]}
\]

The mixed parabolic segments are weighted sums of two such parabolic segments. For example, \( AD \) is defined as

\[
AD = \left\{ (x,y)|y = \frac{x - x_A}{x_D - x_A}(a_{AD,1}x^2 + b_{AD,1}x + c_{AD,1}) + \left(1 - \frac{x - x_A}{x_D - x_A}\right)(a_{AD,2}x^2 + b_{AD,2}x + c_{AD,2}), x_A \leq x \leq x_D \right\} \quad \text{[4]}
\]

Because the center line of the lungs is also the approximate symmetry line of the overall lung shape, we reduce the number of parameters by setting \( x_D = x_C \).

To allow for a tighter fit over all images, we also impose a mask (Fig. 2b), with edges defined by two vertical bounds, at \( x_L \) and \( x_R \), and a parabola with curvature parameter \( a_{LR} \), centered at \( (x_C, y_T) \). Only pixels that lie within both the lung model and this mask are classified as lung. In addition, we include a rotation parameter \( \phi \), shown in Fig. 2c, which allows for variation in mouse position within the

![Fig. 2. Illustration of fitted parametric model: (a) threshold-based segmentation of mouse lung slice from 1a; (b) parabolic segments AC, CB, AD, and DB; (c) mask defined by two vertical bounds at \( x_L \) and \( x_R \) and a parabola centered between the two bounds at \( y_T \); and (d) rotation parameter \( \phi \). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]](image-url)
imaging FOV. Thus, the full set of parameters defining the
lung shape, \( \theta \), is defined as

\[
\theta = \{ x_A, y_A, x_B, y_B, x_C, y_C, y_D, a_{AC}, a_{CB}, a_{AD,1}, a_{AD,2}, a_{DB,1}, a_{DB,2}, x_L, x_R, a_{LR}, y_T, \phi \}
\]  

\[ [5] \]

**Initialization**

We manually initialize our algorithm with a rough segmentation of one interior MRI slice. We fit our model parameters to the manual segmentation using the simplex optimization method, maximizing the overlap of the manual segmentation, \( S_{\text{man}} \), and the parametric segmentation, \( S(\theta) \).

\[
\text{Overlap}(S_{\text{man}}, S(\theta)) = \frac{|S_{\text{man}} \cap S(\theta)|}{|S_{\text{man}} \cup S(\theta)|}
\]  

\[ [6] \]

The parameters are propagated forward and backward from the chosen starting slice and used as initializations for the adjacent slices. Using the simplex method, we fit the model parameters to the new slices by minimizing an objective function, which is discussed below. The optimized parameters are then propagated to the next adjacent slices, until the segmentation is complete.

**Objective Function**

To fit our model parameters to the current slice, we minimize an objective function, \( O(\theta) \), that is a sum of several “goodness of fit” metrics: an intensity-weighted overlap metric, \( O_{\text{weight}} \); the Manhattan distance between the interior and exterior voxel distributions, \( O_{\text{distribution}} \); a measure of the magnitude and direction of changes in parameter values from the adjacent slice to the current slice, \( O_{\text{change}} \); and a measure of the symmetry and concavity of the model given the current parameter values, \( O_{\text{shape}} \). We define \( O(\theta) \) as

\[
O(\theta) = O_{\text{weight}}(\theta) + O_{\text{distribution}}(\theta) + \sum_{n} O_{\text{change}}(\theta_n) + \sum_{m} O_{\text{shape}}(\theta_m),
\]  

\[ [7] \]

where \( O_{\text{weight}} \) and \( O_{\text{distribution}} \) take values between zero and one, and \( O_{\text{change}} \) and \( O_{\text{shape}} \) take values greater than or equal to zero.

\( O_{\text{weight}} \)

We want to reward inclusion and exclusion of voxels based on the likelihood that the intensities came from lung or non-lung, given the manual initialization. To this end, we first construct a new image with intensity \( W \).

Let \( I(x, y) \) be the image intensity at voxel \( (x, y) \) of the current slice, as in Fig. 3a. We fit a cubic polynomial \( p \), shown in Fig. 3b, to the difference in histograms of the manually-segmented lung and non-lung.

\[
W(x, y) = \begin{cases} 
 p(I(x, y)) & \text{if } |p(I(x, y))| > 0.2 \\
 0 & \text{else}
\end{cases}
\]  

\[ [8] \]

In this new image \( W \), as in Fig. 3c, most positive areas should be within the lung segmentation, while most negative areas should be outside the segmentation.

Let \( 0 \) be the current set of parameter values, \( M_{\text{in}}(0) \) the set of voxels within the current parametric lung segmentation and \( M_{\text{out}}(0) \) the set outside the segmentation. Note that \( M_{\text{in}}(0) \) does not include “background,” voxels outside the body of the mouse, which are removed as a preprocessing step. We define \( O_{\text{weight}}(\theta) \) as

\[
O_{\text{weight}}(\theta) = 0.75 \left( 1 - \frac{\sum_{(x, y) \in M_{\text{in}}(0)} W_+(x, y)}{\sum_{\text{all } (x, y)} W_+(x, y)} \right) + 0.25 \left( 1 - \frac{\sum_{(x, y) \in M_{\text{out}}(0)} W_-(x, y)}{\sum_{\text{all } (x, y)} W_-(x, y)} \right),
\]  

\[ [9] \]

where we define \( W_+ \) and \( W_- \) as

\[
W_+(x, y) = \begin{cases} 
 W(x, y) & \forall (x, y): W(x, y) > 0 \\
 0 & \text{else}
\end{cases}
\]  

\[ [10] \]

\[
W_-(x, y) = \begin{cases} 
 W(x, y) & \forall (x, y): W(x, y) < 0 \\
 0 & \text{else}
\end{cases}
\]  

\[ [11] \]

Thus, \( O_{\text{weight}}(\theta) \) is zero when all positive voxels in \( W \) lie within the parametric segmentation and all negative voxels lie outside the segmentation. Note that the weightings for
the two components of $O_{\text{weight}}(\theta)$ (Eq. 9) are unequal. The first component rewards inclusion within the lung segmentation of voxels with "lung-like" intensities. The second rewards exclusion from the segmentation of voxels with 'non-lung' intensities. The first component is weighted more heavily because, due to noise and partial-volume effects, it is expected that some voxels within the lungs will have "non-lung" intensities, while extra-lung tissues are, in general, less likely to resemble lung tissue. However, the final segmentation is relatively insensitive to the choice of these weightings—comparison of segmentations found using the 0.75/0.25 weightings and equal 0.5/0.5 weightings had an average overlap of 94%.

$O_{\text{distribution}}$

Because our approach is based on differing intensity distributions inside and outside the lung, we also directly compute this difference in distributions, rewarding large differences. We define $O_{\text{distribution}}(\theta)$ as

$$O_{\text{distribution}}(\theta) = 1 - 0.5 \sum_{n=1}^{N} |h_{\text{in}}(\theta) - h_{\text{out}}(\theta)|,$$  \hspace{1cm} [12]

where $h_{\text{in}}(\theta)$ is a normalized histogram of the voxel intensities in $M_{\text{in}}(\theta)$, and $h_{\text{out}}(\theta)$ is a normalized histogram of the voxel intensities in $M_{\text{out}}(\theta)$. Hence, $O_{\text{distribution}}(\theta)$ is equal to one when the histograms inside and outside the parametric segmentation match exactly, and its value decreases to a minimum of zero as the difference between the histograms increases.

$O_{\text{change}}$

Since adjacent lung slices must form a continuous 3D lung surface, we penalize parameters with large changes from one slice to the next. For each parameter $\theta_n$, with value $\theta_{n,0}$ in the adjacent slice, we define $O_{\text{change}}(\theta_n)$ as

$$O_{\text{change}}(\theta_n) = \begin{cases} 0 & \text{if } |\theta_n - \theta_{n,0}| < c \\ |\theta_n - \theta_{n,0}| & \text{else} \end{cases}$$  \hspace{1cm} [13]

where $c$ is a threshold on the magnitude of the parameter change from one slice to the next.

To enforce proper relative size of slices, we include an additional term in $O_{\text{change}}(y_C)$ and $O_{\text{change}}(y_D)$ that penalizes expansion of the lungs as the algorithm progresses toward the back and contraction of the lungs as it progresses toward the chest. For example, we define $O_{\text{change}}(y_C)$ as

$$O_{\text{change}}(y_C) = \begin{cases} 0 & \text{if } |y_C - y_{C,0}| < c \\ |y_C - y_{C,0}| & \text{else} \end{cases}$$  \hspace{1cm} [14]

$O_{\text{shape}}$

In general, the boundary of the lungs is roughly left/right symmetric, so we penalize large asymmetries in the fitted lung shape. For each of the three pairs of curvature parameters $a_i$ and $a_j$, where $a_j$ is the corresponding value for $a_i$ from the opposite side of the lung, we define $O_{\text{shape, sym}}(a_i, a_j)$ as

$$O_{\text{shape, sym}}(a_i, a_j) = \begin{cases} 0 & \text{if } |a_i - a_j| < c \\ |a_i - a_j| & \text{else} \end{cases}$$  \hspace{1cm} [15]

where $c$ is a threshold on the asymmetry of the segmentation. Similarly, each curvature parameter contributes a term $O_{\text{shape, conc}}$ that penalizes convexity of the lung curves.

Pathology

Two tumor cell lines, B16 murine malignant melanoma from the ATCC (Manassas, VA) and WT9614 3-methylchlantherene fibrosarcoma (kindly provided by Robert Schreiber, Washington University in St. Louis), were injected intravenously into age matched C57Bl6 male mice at $2.5 \times 10^5$ cells per animal. These animals were sacrificed, along with age- and sex-matched, saline-injected control mice, at various points after tumor injection ranging from 10 days to three weeks. Upon sacrifice, the lung block was removed through a sternotomy and trimmed free of the mediastinal tissue, leaving only lung parenchyma and airways attached. The tumor bearing lung block was weighed (Series 320 XT Analytical balance, Precisa, Golden, CO).
and the total tumor burden calculated by subtracting the weight of non-tumor bearing control lungs from that of the tumor bearing lungs.

**Evaluation Criteria**

To validate the performance of our segmentation method, we first show that our automatic lung segmentation is comparable with that of expert human segmenters. We then show that the average intensities of the segmented lungs in both the automatic and manual segmenter cases correlate well with the tumor burden measured using lung weight. All validation studies were conducted using only data sets that were not used for algorithm development.

Manual segmentations of the lungs were generated independently by four experts for six of the 27 imaged mice. These mice were selected in an unbiased manner so as to cover, as uniformly as possible, the full spectrum of tumor burdens present in the data.

To compare segmentations from two different segmenters, we use the following overlap metric:

$$\text{Overlap}(A, B) = \frac{A \cap B}{A \cup B}$$  \hspace{1cm} [16]

where $A$ and $B$ are the two sets of voxels designated as lung by the two segmenters. This metric is useful in this case because we do not have a ground-truth segmentation and, therefore, cannot use a metric like percent error.

**RESULTS**

In this article, we present a method for accurate and reproducible lung segmentation in mice with heavy and/or diffuse tumor (Fig. 4). This method allows nearly fully automatic measurement of tumor burden in the lungs. Table 1 shows the average overlap between each pair of independently drawn manual segmentations. Table 2 shows the total average overlap of our automatic segmentation results with each of the manual segmentations. In all the results, the initializations for the automatic segmentation were generated by an additional segmenter, independently from the expert segmentations. As can be seen from the tables, there is generally good agreement amongst the results for human segmenters, as well as between the human segmenters and the automatic result, in terms of which areas in the MR images are classified as lung.

Because the goal is to quantify tumor via image intensity, a fairer metric of the correspondence between two segmentations may be derived by comparing the average image intensities within the two segmentations. Table 3 shows the average percent difference in intensity between each pair of independently drawn manual segmentations. Table 4 shows the total percent difference in intensity between our automatic segmentation results and each of the manual segmenters. As these tables show, there is good agreement in the average image intensities derived from the expert manual segmenters and the automatic result.

The key validation of our method is the correlation between total tumor burden measured by lung weight and the average intensities of the manual and automatic results. Table 5 shows the correlation of each segmenter’s computed average intensities with the lung weights of the six mice. Outlier intensities were present both in the full set of mice and in the subset of six manually segmented mice. We noted that in these outlier images, the overall intensity of the images for a particular animal was either darker or brighter than the average image in the set. To correct for this variation, lung-image intensities were normalized based upon the image intensity of the liver with the same mouse. The liver intensity was calculated by manual selection of a region of interest containing only liver. Outlier voxels, which may be due to liver tumor or liver vasculature, with intensities beyond one standard deviation from the mean intensity, were automatically discarded prior to computing the average intensity within the region of interest. Table 6 shows corrected correlations, in which the same normalizing liver intensities were used for each segmenter’s average intensities. The results shown in these tables demonstrate an excellent correlation between corrected lung intensities and tumor burden, as measured by lung weight. The correlation between the corrected average intensities found by the automatic method and the lung weights for the complete set of 27 mice was 0.93 (Fig. 5a).
Bland-Altman analysis of the lung weight and the automated corrected average intensities shows that the limits of agreement are 0.3 mg ±168.9 (defined as the bias ±1.96 times the standard deviation of the difference). A plot of this analysis is shown in Fig. 5b.

In summary, Table 2 demonstrates the excellent congruence between our automated lung segmentations and those generated manually by a panel of four experts in a series of six mice. As reported in this table, the percent overlap of lung pixels amongst automated and manual segmentations ranges from 72.0 to 78.7%, compared with a range of 79.3 to 84.7% amongst manual segmentations. The identification of tumor in lung is dependent upon the relatively bright image intensity of tumor compared to healthy lung tissue. As shown in Table 4, differences in average lung-image intensity between automated and manual segmentations in these same mice are relatively small, ranging from 10.7 to 16.3% across the panel of segmenters. Finally, the correlation between average lung-image intensity generated by automated lung segmentation and measured lung weight is greater than 0.93 (Fig. 5a), which corresponds to a coefficient of determination greater than 86%, demonstrating clearly that average lung-image intensity provides a useful measure of tumor burden in lung with diffuse or heavy tumor burden.

CONCLUSION

The use of mouse models to aid in the development and monitoring of new therapies for lung cancer requires the ability to accurately measure lung-tumor burden in vivo. In this article, we have demonstrated that corrected average MR image intensity in mouse lung is an accurate metric of total tumor burden. The tumor measurements were validated by correlating MR image intensities with the weight of the excised lungs. By measuring tumor burden via average MR lung intensity, tumor burden can be measured in vivo, even in cases of diffuse disease where individual tumors cannot be segmented from the MR images. Thus, relative measures of tumor burden for a single animal can be established simply by comparing average lung intensities from images collected at different time points. As described herein, absolute tumor burden measures can also be determined following establishment of a calibration curve between MR image intensities and lung weights. Because this average image intensity approach requires accurate lung segmentation, efficiency and throughput of analysis would be greatly improved through use of an automated segmentation routine.

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