Tumour size measurement on CT and PET-CT in the 7\(^{th}\) edition of the TNM classification of lung cancer

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Purpose

In the new TNM classification, changes were made based on differences in survival in the International Staging Project of the International Association for the Study of Lung Cancer (IASLC). Especially tumor size was found to be more relevant in predicting prognosis[1]. However, no guidelines are proposed how to measure tumor.

- The purpose of this study is first to see whether there is a significant difference in tumor measurement on lung versus mediastinal window and whether this translates to a different T stage and final TNM stage.
- Second, we also compared T stage assessed with the old classification versus T stage according to the new TNM classification, and again we evaluated the impact on final TNM stage.
- Third, in a subpopulation of our study who also underwent dedicated CT, we compared tumor size and T stage on lung and mediastinal window of the dedicated CT with those of PET-CT.
Methods and Materials

Patient Population

- 49 consecutive lung cancer patients from our previous study [2] (43 men, 6 women) with a median age of 65 years for men (range 26-83) and 60 years for women (range 46-72) who underwent an integrated PET-CT were retrospectively included in our study.
- The integrated PET-CT was done for staging a lung lesion that was suggestive of a lung tumor without metastases on previous clinical or radiological examinations. Patients with evidence for metastatic disease were excluded from the study.
- Forty-four lesions were malignant (23 adenocarcinoma, one carcinoid, one metastasis, two squamous cell carcinoma, 13 spinocellular carcinoma, three spinocellular epithelioma, one undifferentiated tumor) and five benign (one granuloma, two chronic infection, one eosinophilic pneumonia, one arteriovenous malformation).
- A subgroup of 23 patients also underwent a dedicated CT.

PET-CT acquisition

All patients were examined on a dual-modality PET-CT tomograph. CT images were acquired with 85 mAs, 130 kV, slice thickness of 5 mm, and table feed of 12 mm per rotation. Single-section whole-body spiral CT was performed starting with the head and subsequently covering the neck, thorax, abdomen, and pelvis. 120 ml of a contrast agent containing 300 mg iodine per milliliter was administered intravenously using an automated injector (1.6 ml/s, scan delay 100 s). CT was performed during breath-hold at expiration tidal volume. This limited breath-hold technique was used to avoid respiration artifacts on the CT images and is necessary for a good matching between the CT images and the PET images, since the latter are obtained during normal breathing.

Dedicated CT acquisition

CT images were acquired with 85 mAs, 130 kV, slice thickness of 5 mm, and table feed of 12 mm per rotation. The scanning area for CT and PET was defined on a CT topogram. To ensure diagnostic CT image quality, 120 ml of a contrast agent containing 300 mg iodine per milliliter was administered intravenously using an automated injector (1.6 ml/s, scan delay 100 s). CT was performed during breath-hold at inspiration tidal volume.

Data analysis
Tumor measurement on CT images

- All tumors were measured on axial lung window and on axial mediastinal window settings. Two measurements were made: the longest diameter on lung window settings (DmaxL) and the longest diameter on mediastinal settings (DmaxM) was chosen and then the longest diameter perpendicular on this measurement was also made.
- The measurement on lung window settings was taken as reference measurement based on literature information [3,4,5].
- Differences between DmaxL and DmaxM were calculated.
- Based on these measurements new T stages were made: one for lung window settings, a second for mediastinal window settings. New TNM grading was done based on the different new T stages with lung and mediastinal window settings. For N and M stages, the information from the previous study [2] was used.
- We compared the new T stages and the new TNM grading based on lung window settings with those on mediastinal window.
- The new T stage for mediastinal window was also compared with the old T stage defined on mediastinal window of CT images and based on the old classification. The same was done with the new TNM grading.
- For the 23 patient who had also underwent a dedicated CT extra measurements were done: longest diameter on lung and mediastinal settings on dedicated CT images and the longest diameter perpendicular on this measurement. These measurements were compared with those of CT images of PET-CT. Eventually, based on these new measurements new T stages were made: for lung window and for mediastinal window settings. These new T stages were than compared with the new T stages on PET-CT.

Statistical analysis

To examine if there was a difference in tumor measurement using lung window or mediastinal window settings, statistical analysis was done using the boxplot method, together with a paired t-test, and the McNemar test. We did the same for tumor measurements on dedicated CT images.
Results

Differences in tumor size on lung versus mediastinal window of PET-CT

Figure 1 and 2 summarize the measurements on lung window and mediastinal window settings. All tumors were measured larger on lung window settings than on mediastinal window settings with ranges from 0 to 7.7 mm. As one can see on figure 2, the median of DmaxL differs from that of DmaxM. Paired t-test demonstrates that this difference is statistically significant.

Influence on T staging

T stage on lung window versus T stage on mediastinal window

T staging based on lung window and mediastinal window was different in 6 patients (12.24%). There was an understaging on mediastinal window in these patients: 2 T1a instead of T1b(Fig. 3), 2 T1b instead of T2a, 1 T2a instead of T2b and 1 T2b instead of T3. These results are summarized in table 1(Fig. 4).

T stage based on old classification versus T stage on mediastinal window of PET-CT based on new classification

In the new classification 37 (75.5%) of the patients had the same T stage as in the old classification. According to the old TNM classification 14 patients were classified as having T1 stage tumors, 13 retained a T1 stage in the new classification (8 as T1a and 5 as T1b). The other T1 tumor became a T2a tumor. Seventeen of twenty-four patients with a T2 tumor were classified again as T2 (12 as T2a and 5 as T2b). 5 patients became a T1b tumor and 2 patients became a T3 tumor. The 5 patients with T3 stage retained their stage. In the old T stage 6 patients were classified as T4 tumor, only 2 of them were T4 tumors in the new classification, 4 patients were T3 (Fig. 5 and 6).

Influence on final TNM stage

TNM stage based on lung window versus TNM stage based on mediastinal window

Final TNM stage based on lung window and mediastinal window was only different in one patient. In this patient there was an understaging on mediastinal window: IIA instead of IIB. The results are summarized in table 3(Fig. 7).
Old cTNM versus new cTNM on mediastinal window

The new cTNM stage was compared with the old one. Based on the new T stages on mediastinal window settings, 34 patients (69%) had the same cTNM stage. There were 12 patients (24%) with a downstaging: 2 patients from IB to IA, one patient from IIIB to IA, 3 patients from IIB to IIA, 2 patients from IIIB to IIB (Fig. 6), one patient from IV to IIB and 3 patients from IIIB to IIIA. 3 patients had an upstaging: 2 patients from IB to IIA, one patient from IB to IIB. These results are summarized in table 4 (Fig. 8).

Tumor size on dedicated CT versus PET-CT

Figure 9 shows the longest diameter on the four different windows. There is a significant difference between DmaxL and DmaxM on dedicated CT ($p=2.32\times10^{-5}$), between DmaxL and DmaxM on PET-CT ($p=3.09\times10^{-7}$), and between DmaxM on PET-CT and DmaxL on dedicated CT ($p=0.0026$). The other differences are not significant and summarized in figure 9.

New T stages on lung window: PET-CT versus dedicated CT

Using dedicated CT images with lung window setting as reference, two patients (8.7%) were underestimated on lung window setting of PET-CT: one patient who was T1b on PET-CT was T2a on dedicated chest CT (Fig. 10), and one T2a patient on PET-CT was T2b on dedicated chest CT. These results are summarized in table 5 (Fig. 11).
Fig. 0: Scatter chart showing difference between longest diameter of tumor (mm) measured on lung window and mediastinal window on CT images of PET-CT in function of longest diameter (mm) on lung window, what we took as standard.

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**Fig. 0:** Longest diameter measured on lung window (L) and mediastinal window (M) on CT images of PET-CT plotted on boxplots. On top of the boxplots the p-value is shown.

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Fig. 0: A 73-year-old man with a tumor in the left lung. The tumor was measured smaller on mediastinal window(A) than on lung window(B). This resulted in a T1b stage for lung window and a T1a stage for mediastinal window. Final TNM stage was IA in both window settings.

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**Fig. 0:** Table 1. T stage on lung window versus T stage on mediastinal window on CT images of PET-CT.

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<table>
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<tr>
<th>Clinical T old</th>
<th>T1a</th>
<th>T1b</th>
<th>T2a</th>
<th>T2b</th>
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<th>T4</th>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>T3(5)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
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<td>0</td>
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<td>4</td>
<td>2</td>
</tr>
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</table>

**Fig. 0:** Table 2. T stage based on old classification (mediastinal window) versus T stage (on mediastinal window) based on new classification on CT images of PET-CT.

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**Fig. 0:** A 56-year-old man with a tumor in the upper lobe of the right lung (A) with satellite nodule in the same lobe (white arrow in B). This is one of the 4 T4 tumors becoming T3 in the new classification. This reclassification is responsible for a migration of IIIB to IIB tumors.

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<table>
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<td>IV(3)</td>
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</table>

**Table 3.** Final cTNM stage based on lung window versus final cTNM stage on mediastinal window on CT images of PET-CT.

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<table>
<thead>
<tr>
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<th>Clinical stage mediastinal new</th>
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**Table 4.** Old cTNM (on mediastinal window) versus new cTNM based on mediastinal window on CT images of PET-CT.

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**Fig. 0:** Boxplots of longest diameter measured on lung window and mediastinal window on CT images of PET-CT, respectively L(PET-CT) and M(PET-CT), and longest diameter on lung window and mediastinal window of dedicated CT images, respectively L(CT) and M(CT). P-values are shown on top of the boxplots.

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Fig. 0: A 70-year-old woman with a tumor in the right upper lobe. Staged as T1b on both mediastinal(A) and lung(B) window of PET-CT, becoming a T2a on both mediastinal(C) and lung(D) window of dedicated CT.

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Fig. 0: Table 5. New T stages on lung window of dedicated CT was compared with new T stages on lung window of CT images of PET-CT.

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Conclusion

Discussion

In this study we measured tumor size on mediastinal and lung window settings in 49 patients. For all tumors, measurements on lung window settings was larger than on mediastinal window, differences ranging from 0 to 7.7 mm. The difference of tumor size between both windows has been shown statistically significant. The difference was larger for smaller lesions. There has been little published about how to measure tumor size. Giraud et al. found that measurements on lung window settings (W=1600 and L= -600) were most concordant to actual diameters and volumes [3]. However, in a recent study by Macpherson et al. [6] four different windows were compared with pathological tumor size and no window was shown to be superior in assessing tumor size. Until more and larger studies are conducted, the proposal of Therassse et al. [7] to use the same window (lung or mediastinal) for consecutive CT scans evaluating tumor response to therapy, seems reasonable.

This significant difference in longest diameter translates to a different T stage in 6 patients(12.24%). There was an understaging on mediastinal window in these patients, which can be explained by the fact that lesions are measured smaller on mediastinal window. However, this understaging was hardly translated to final TNM whereas only one patient had a different stage on mediastinal window: IIA instead of IIB. The reason why the other 5 patients didn't had another TNM stage is because tumors with a T1a or a T1b stage have the same TNM stage and because some patients had severe lymph node extension which made the T component less important in final TNM stage. The choice of window settings is probably more important for local tumors(N0M0), where T stage determines final TNM stage.

With the introduction of the seventh edition of the TNM classification for lung cancer we also wanted to examine T stage and final TNM stage changes compared with the old classification.

We found that 12 patients (24.5%) had a new T stage. Two T2 tumors larger than 70mm became T3 concordant with the changes in the new classification. The same can be said of the four T4 tumors that became T3. Surprisingly one T1 became a T2a and also 5 T2 became T1b, this can possibly be the consequence of intraobserver and interobserver variation in measuring. In the literature, percentages of stage migration in the new edition are 10.2% (Chien et al. [8]), 17.7% (Fukui et al. [9]), 21.1% (Kameyama et al. [10]) and 28.1% (Strand et al. [11]). Using the new classification system, there is an increasing number of cases in stages IIA and IIIA together with a decreasing number in stages IB
and IIIB, concordantly to previous studies [9, 10, 11]. Unlike these studies, there was an increasing number in stage IIB in our study. This is again a consequence of a larger group of tumors with satellite nodules in the same lobe: T4 in the old classification and T3 in the new classification.

In our study, we also compared tumor measurements and T stage on dedicated CT with those on CT images from PET-CT. Tumor size was overestimated on both lung and mediastinal window of dedicated CT. This was expected whereas for dedicated CT patients are scanned in inspiration breath hold, while the CT of PET-CT is performed during breath-hold at expiration tidal volume. The overestimation translated to 2 patients (8.7%) having a higher T stage on lung window of dedicated CT. In the literature, we only found studies that compared accuracy of integrated PET-CT with CT images alone [2, 12, 13, 14] or integrated PET-CT with stand-alone or multidetector CT [15, 16]. In both cases integrated PET-CT had better accuracy rates in T and TNM staging.

**Conclusion**

Tumor measurements were significant different on the two windows of CT images of PET-CT. However, final TNM stage was practically the same for both windows. So both window settings are equal in tumor staging, but for evaluating tumor response to therapy the same window should be used as stated in the new RECIST guidelines [7].

Our study also confirmed stage migration in the new edition with increased number of cases in stage IIA and IIIA found in previous studies. Possible therapeutically consequences have yet to be determined.

Third, tumor measurement on dedicated CT was significant different from CT images of PET-CT, with an overstaging of T stage as consequence. Evaluation of the influence on final TNM stage seems an interesting study object. In the future more studies should be performed comparing accuracy of dedicated CT with that of integrated PET-CT. However, nowadays integrated PET-CT has become the golden standard in lung cancer staging and has been shown to be more accurate than CT alone or PET alone.
References


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