Editorial Commentary

The impact of radiomics in predicting oncologic behavior of thymic epithelial tumors

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Medical images have substantial quantitative data that could play an important role in the precision medicine for patients with cancer. Radiomics is a new emerging field discipline characterized as a noninvasive, quantitative method to extract a large amount of features buried in medical images like computed tomography (CT), and to utilize the data in differential diagnosis, characterization of tumor phenotype, and prediction of therapy response or prognosis (1). Texture analysis is a representative method of radiomics, and Li *et al.* (2) recently reported on clinical utility of texture parameters obtained from diffusion weighted imaging (DWI), a type of magnetic resonance imaging (MRI) sequences, and value of combining apparent diffusion coefficients (ADC) and the texture parameters for the prediction of pathologic subtypes and stages of thymic epithelial tumors (TETs). In addition to the researches that were associated with the image-based predictors of such information, the texture analysis could have an impact on the improvement of management of TETs because this analysis has a potential to investigate more precise and objective evidences about the tumor heterogeneity. They examined 1,044 radiomic features from DWI, and the cluster shade feature was significantly higher in low-risk thymomas than in high-risk thymomas and thymic carcinomas. The higher cluster shade implies less tumor homogeneity, and their results indicate that the low-risk group had lower tumor homogeneity. Malignant tumors usually tend to have tumor heterogeneity because of more necrotic and heterogeneous growth than benign or low-grade tumors. The authors explained that macroscopic appearance of multiple nodules separated by fibrous septa more frequently seen in low-risk thymomas than in high-risk thymomas or thymic carcinomas, might have caused these unexpected results (2). The significant differences between early and advanced Masaoka stages were seen in ADC values and radiomic features like gray level co-occurrence matrix (GLCM) entropy and spherical disproportion. The mean ADC value in early stage was significantly higher than that in advanced stage ($P<0.001$), while the nine selected texture features of DWI were significantly different between the two stages (P value ranged from 0.007 to 0.041). Area under curves (AUC) for diagnosing TET stages and histologic subtypes were 0.746 and 0.755, respectively, at the ADC value, and 0.862–0.875 and 0.720–0.726, respectively, at particular DWI texture features. Furthermore, when the ADC value and the selected DWI texture features were used together, AUC for diagnosing TET stages were 0.933 at the combination of the ADC value and cluster shade, and AUC for diagnosing histologic subtypes between low-risk and high-risk thymomas/thymic carcinomas were 0.772 at the combination of the ADC value and maximum 3D diameter.

TETs are representative tumors in the anterior mediastinum, but they are relatively rare and account for 0.2–1.5% of all malignancies (3). TETs have a wide spectrum in oncologic behavior. The Masaoka and Masaoka-Koga staging systems have been widely used for evaluating the stage of TETs, and tumor-node-metastasis (TNM) staging system created by the International Association for

the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) is recently adopted in the eighth TNM staging classification (3-7). World Health Organization (WHO) histologic classification, which divides thymomas into type A, AB, B1, B2, and B3 based on the morphological features of the epithelial tumor cells and the proportion of the nontumoral lymphocytic component, also reflects invasive nature of TETs, and is known as an independent prognostic factor. Besides, it has been reported that WHO histologic classification type B2 and B3 TETs have more malignant nature with respect to prognosis and tumor recurrence compared with type A, AB, and B1 tumors (6). Based on the differences in their prognosis mentioned above, more simple classification as low-risk (type A, AB, B1) and high-risk thymomas (type B2 and B3) was also suggested (8). It is also important to differentiate thymic carcinoma with thymomas because the prognosis of thymic carcinomas among TETs is much worse than that of thymomas. Imaging modalities of CT and MRI have played a role in characterization of TETs and evaluation of their invasion to the adjacent organs or distant metastasis (9-14). The CT features that predicted advanced Masaoka Stage III and IV thymomas was large tumor size, lobulated or irregular contour, infiltration to surrounding fat tissue, and presence of calcification or necrosis in the tumor, when compared with early stage I and II thymomas (9,11). Regarding WHO histologic classification, thymic carcinomas tend to have CT findings of irregular contours, necrotic or cystic component, heterogeneous enhancement, lymphadenopathy, and invasion into the great vessels compared with those of low-risk and high-risk thymomas (14). It is also reported that lobular contour was more often seen in high-risk thymomas and thymic carcinomas than in low-risk thymomas. Invasion into the mediastinal fat was more often seen in thymic carcinomas than in low-risk thymomas, and invasion into the great vessels was only seen in thymic carcinomas. Besides, TETs with lobulated or irregular contour, oval shape, mediastinal fat or great vessel invasion, and pleural disseminations could be CT-based predictors of frequent recurrence and metastasis (8). On MRI, the ADC value has been reported to provide useful information in differentiating different subtypes or stages of TETs. The ADC values of low-risk thymomas were significantly higher than those of high-risk thymomas and thymic carcinomas (12), while another data showed ADC values in low-risk and high-risk thymomas were significantly higher than the values in thymic carcinomas (2). The early stage showed higher ADC value compared with the advanced stage (2,12). Low ADC value reflects decreased diffusion status caused by enlarged nuclei, hypercellularity, and reduction of the extracellular matrix and diffusion space of water protons in the extracellular and intracellular dimensions. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) that reflects metabolic activity of glucose could be sometimes used for differential diagnosis between thymomas and thymic carcinomas (10,15) and prediction of the WHO grade of malignancy in TETs by using maximum standardized uptake value (SUV_{max}) (15).

As a trend in the diagnostic radiology of TETs, a new rising field discipline radiomics could improve the quality of imaging biomarker for TET management. Texture features using second- or high-order like GLCM and gray level run length matrix (GLRLM) demonstrate spatial associations of each pixel or voxel in the segmented area (1,16). For example, The GLCM counts voxel pairs with certain gray values at a pre-defined direction and distance from each other, and generates the features homogeneity, contrast, and sum variance. The GLRLM is a texture feature in a specific direction, where fine texture has more short runs whilst coarse texture presents more long runs with different intensity values (1,16-18). On the other hand, first-order histogram features are derived from histogram where x-axis represents pixel or voxel gray level and y-axis represents frequency of occurrence in the region of interest (ROI). Histogram features demonstrate several parameters like mean, standard deviation, kurtosis, entropy, and skewness, but the histogram-based features do not have spatial information about each pixel or voxel (1,16). These various texture features objectively demonstrate quantitative tumor heterogeneity that is caused by the differences in tumor cellular density, proliferation, angiogenesis, hypoxia, and necrosis (2,16,18-20). These tumor statuses are associated with prognosis and tumor response to therapy because the heterogeneity in tumors could be associated with aggressive biological behavior and increased resistance to treatment (16). It is common to evaluate the patients with malignancies by various medical images before treatment, and evaluation of the image-based radiomic features have some advantages in terms of localization, approaching lesions, less invasiveness, and data in vivo, compared with those of specimens obtained from biopsy. There are some steps for texture analysis as follows; image acquisition, lesion segmentation, feature extraction, feature selection, and analysis (2,17,18). Each step has several or many ways for the analyses and these issues should be discussed with

discretion to achieve precision medicine.

Some articles on utility of the texture analysis of TETs have been reported (2,21-25). In the area of ^{18}F-FDG-PET, the high-risk TET and thymic carcinoma group showed higher SUV_{max}, SUV_{mean}, entropy, intensity variability, and size-zone variability than the low-risk TETs. The diagnostic performances of individual SUV_{max} and texture parameters were reported to be relatively low, but combination of these parameters could increase diagnostic performance for differentiating between low-risk and high-risk thymomas or thymic carcinomas. These data were obtained from limited TETs with metabolic tumor volume (MTV) of >10 cm^3 and SUV ≥2.5 because evaluation of quantitative heterogeneity on PET images with texture features could be confounded by tumor volume effects in small volume tumors (23). In the analysis of selected 20 textural features, most of the GLRLM and gray level size zone matrix (GLSZM) derived features showed fair or good results for the differentiation between low-risk and high-risk thymomas/thymic carcinomas, or low-risk/high-risk thymomas and thymic carcinomas. Combination of SUV_{max} and high gray-level short zone emphasis (HGSZE) of GLSZM features might have a complementary value for differentiating the TET subgroups (19). In the field of MRI, histogram analysis based on ADC for assessment of WHO classification and clinical staging of TETs has been reported. Mean ADC values obtained from the three ROIs results, and ADC histogram parameters including mean ADC (ADC_{mean}), median ADC (ADC_{median}), 10 and 90 percentiles of ADC (ADC10 and ADC90), kurtosis, and skewness were evaluated. Significant differences in the first four ADC parameters were seen among low-risk thymomas, high-risk thymoma, and thymic carcinomas, while no significant difference was observed in skewness and kurtosis. The advanced-stage TETs also showed lower ADC parameters and higher kurtosis than early stage TETs, while no significant difference in skewness. Of those parameters, ADC10, that indicated low percentile of ADC and could reflect the areas with hypercellularity, had the best differentiating ability to differentiate low-risk thymoma from high-risk thymoma and thymic carcinoma, and differentiating ability for the differentiation of advanced and early stage TETs (24). In addition, the application of radiomic features to differentiating TETs from other anterior mediastinal tumors has been reported. The histogram analysis of ADC maps could be used for improving the differentiating performance between thymic carcinoma and lymphoma. Several ADC parameters of lymphomas demonstrated lower values than those of thymic carcinomas, and ADC10 was determined as an optimal marker, while kurtosis and skewness did not show significant differences (25). Thymic cysts and bronchogenic cysts in the anterior mediastinum sometimes exist as a high attenuation nodule due to their hemorrhagic or inflammatory, high protein component. So, it is difficult to differentiate those high attenuation cystic lesions from solid TETs on CT, especially without contrast-enhanced CT. Texture analysis was used to solve the problem, and solid anterior mediastinal masses like TETs could be differentiated from those cysts with moderate and high diagnostic performance even on unenhanced CT (21).

It is crucial to select appropriate and effective radiomic features for developing precision medicine because the radiomic features including texture parameters obtained from the medical images are very large and complicated. Furthermore, the combination of various features could improve diagnostic accuracy more precisely compared with application of a particular feature alone as Li *et al.* and other previous researchers reported. However, combination of the features belonging to a similar category seems to have less impact to find clinically effective combination (2). Most of the features also exhibit some correlation with each other, and we have to consider intelligent feature selection strategies (17). Various studies have evaluated various radiomic features with a variety of results, and sample size was small entirely although TET is a relatively rare malignancy. The clinical interpretation of these features still remains one of our main questions. The problem of reproducibility is also important to use radiomic features as an imaging biomarker of cancer management. Robust and well-validated imaging biomarkers should be established by further studies for precision medicine in radiology, especially for the tumors like TETs with a wide spectrum in oncologic behavior.

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References

1. Lee G, Bak SH, Lee HY. CT radiomics in thoracic oncology: technique and clinical applications. Nucl Med Mol Imaging 2018;52:91-8.
2. Li B, Xin YK, Xiao G, et al. Predicting pathological subtypes and stages of thymic epithelial tumors using DWI: value of combining ADC and texture parameters. Eur Radiol 2019. [Epub ahead of print].
3. Carter BW, Benveniste MF, Madan R, et al. IASLC/ITMIG staging system and lymph node map for thymic epithelial neoplasms. Radiographics 2017;37:758-76.
4. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485-92.
5. Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modi cation of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int 1994;44:359-67.
6. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 2002;94:624-32.
7. Carter BW, Lichtenberger JP 3rd, Benveniste MF. MR imaging of thymic epithelial neoplasms. Top Magn Reson Imaging 2018;27:65-71.
8. Jeong YJ, Lee KS, Kim J, et al. Does CT of thymic epithelial tumors enable us to differentiate histologic subtypes and predict prognosis? AJR Am J Roentgenol 2004;183:283-9.
9. Marom EM, Milito MA, Moran CA, et al. Computed tomography findings predicting invasiveness of thymoma. J Thorac Oncol 2011;6:1274-81.
10. Marom EM. Advances in thymoma imaging. J Thorac Imaging 2013;28:69-80; quiz 81-3.
11. Ozawa Y, Hara M, Shimohira M, et al. Associations between computed tomography features of thymomas and their pathological classification. Acta Radiol 2016;57:1318-25 .
12. Abdel Razek AA, Khairy M, Nada N. Diffusion-weighted MR imaging in thymic epithelial tumors: correlation with World Health Organization classification and clinical staging. Radiology 2014;273:268-75.
13. Tomiyama N, Johkoh T, Mihara N, et al. Using the world health organization classification of thymic epithelial neoplasms to describe CT findings. AJR Am J Roentgenol 2002;179:881-6.
14. Sadohara J, Fujimoto K, Müller NL, et al. Thymic epithelial tumors: comparison of CT and MR imaging findings of low-risk thymomas, high-risk thymomas, and thymic carcinomas. Eur J Radiol 2006;60:70-9.
15. Treglia G, Sadeghi R, Giovanella L, et al. Is (18)F-FDG PET useful in predicting the WHO grade of malignancy in thymic epithelial tumors? A meta-analysis. Lung Cancer 2014;86:5-13.
16. Lubner MG, Smith AD, Sandrasegaran K, et al. CT texture analysis: definitions, applications, biologic correlates, and challenges. Radiographics 2017;37:1483-503.
17. Larue RT, Defraene G, De Ruysscher D, et al. Quantitative radiomics studies for tissue characterization: a review of technology and methodological procedures. Br J Radiol 2017;90:20160665.
18. Scalco E, Rizzo G. Texture analysis of medical images for radiotherapy applications. Br J Radiol 2017;90:20160642.
19. Lee HS, Oh JS, Park YS, et al. Differentiating the grades of thymic epithelial tumor malignancy using textural features of intratumoral heterogeneity via (18)F-FDG PET/CT. Ann Nucl Med 2016;30:309-19.
20. Asselin MC, O'Connor JP, Boellaard R, et al. Quantifying heterogeneity in human tumours using MRI and PET. Eur J Cancer 2012;48:447-55.
21. Yasaka K, Akai H, Abe O, et al. Quantitative computed tomography texture analyses for anterior mediastinal masses: Differentiation between solid masses and cysts. Eur J Radiol 2018;100:85-91.
22. Shiri I, Rahmim A, Ghaffarian P, et al. The impact of image reconstruction settings on 18F-FDG PET radiomic features: multi-scanner phantom and patient studies. Eur

Radiol 2017;27:4498-509.
23. Nakajo M, Jinguji M, Shinaji T, et al. Texture analysis of 18F-FDG PET/CT for grading thymic epithelial tumours: usefulness of combining SUV and texture parameters. Br J Radiol 2018;91:20170546.
24. Kong LY, Zhang W, Zhou Y, et al. Histogram analysis of apparent diffusion coefficient maps for assessing thymic epithelial tumours: correlation with world health organization classification and clinical staging. Br J Radiol 2018;91:20170580.
25. Zhang W, Zhou Y, Xu XQ, et al. A whole-tumor histogram analysis of apparent diffusion coefficient maps for differentiating thymic carcinoma from lymphoma. Korean J Radiol 2018;19:358-65.

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