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Mini-Review: A Multimodal Radiomics Model for Preoperative Prediction of Tertiary Lymphoid Structures in Stage I Lung Adenocarcinoma

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Text

As one of the most prevalent forms of malignancies[1], lung cancer has claimed the lives of numerous patients. Lung adenocarcinoma(LUAD), as its main histological subtype, have shown a recurrence rate as high as 20–50% after Stage I completing surgical resection[2]. Advanced-stage tumors are frequently deemed inoperable, with a median survival duration of less than a year. They are characterized by a heightened risk of recurrence and metastasis, leading to a generally unfavorable prognosis. Therefore, it is imperative to promptly recognize high-risk factors and implement timely adjustments to treatment strategies, which are essential for curbing recurrence rates in early-stage LUAD, extending survival for patients in advanced stages, and enhancing the overall prognosis.

Tumors, as a form of chronic inflammation, continuously stimulate the production of cytokines by the host through their inherent tumor antigens and the immunogenic cell death they induce[3]. The coordinated interplay of these factors ultimately leads to the formation of well-organized networks of innate and adaptive immune cells within the tumor microenvironment (TME), structures that are commonly designated as tertiary lymphoid structures (TLSs). Apart from primary and secondary lymphoid organs[4], TLSs, defined as ectopic lymphoid formations with highly ordered T and B lymphocyte colonies found in nonlymphoid tissues, are developed from any non-lymphoid tissue that has been subject to prolonged/chronic inflammation. Drawing on insights from the SLO (Secondary Lymphoid Organ) formation process and preliminary mechanistic studies in mouse models of TLSs, the development of TLSs appears to involve multiple concurrently active signaling pathways that engage in intricate cross-interactions[5]. During its formation, chemokines like CCL19, CCL21, and CXCL13 are expressed, indicting that naive and effector CD4+ and CD8+ and memory CD4+ T cells, B cells, and NK cells to sites of inflammation have been recruited.[6] Study also shows that the primary cell populations are found within TLSs which include dendritic cells (DC), B cells, and naive and memory T cells.[7] These allow tumor-antigen specific immune cells to be activated within the tumor microenvironment. The establishment of these structures serves as a more accessible and strategically positioned outpost within the body, significantly enhancing the efficiency of the anti-tumor immune response.

As TLSs continues to be subjected to sustained antigenic stimulation or influenced by antitumor therapies such as

chemotherapy and immunotherapy, the emergence of FDCs and the proliferation of B-cell components within TLSs occur[5,8]. These changes lead to the classification of TLS into three categories: Early TLSs (E-TLSs), Primary Follicle-like TLSs (PFL-TLSs), and Secondary Follicle-like TLSs (SFL-TLSs) [9–11]. Early TLSs (E-TLSs) are characterized by dense aggregations of lymphocytes devoid of FDCs and lacking segregated T and B cell zones. Primary Follicle-like TLSs (PFL-TLSs) demonstrate the presence of FDCs, yet no germinal centers (GCs) are discernible. In contrast, Secondary Follicle-like TLSs (SFL-TLSs) exhibit an active GC reaction and closely resemble the structure of secondary lymphoid organs (SLOs).

The study of TLSs structure in NSCLC was one of the earliest of its kind[12]. Retrospective studies have linked the prognosis of NSCLC patients to immunohistochemistry on paraffin-embedded tissue specimens, revealing a direct correlation between the presence of TLSs and the patients' overall prognosis. Subsequent studies on TLSs have further elucidated the structural distinctions between TLS at different stages, providing deeper insights into their morphological evolution[13]. Immature TLSs are characterized by a compact and irregular aggregation of various immune cells, while mature TLSs exhibit distinct cellular zone distributions, often with clearly delineated light and dark regions. In studies concerning primary rectal carcinoma in humans, TLSs have been demonstrated to be comprised three main components, consisting of an outer T-cell layer, an inner B-cell layer, and surrounding HEV layers[14].

The distribution of TLSs structure within an inflammatory peripheral tissue microenvironment does not encompass the entirety of the tumor but is concentrated around the peritumoral area. For example, in Merkel cell carcinoma[15], TLSs were located at the tumor periphery, not in the center of the tumor mass. It has also been observed that the presence of TLSs shows a positive corelating with an increased CD8+-to-CD4+ T cell ratio at the cortex. Such cases can also be observed within breast cancer at early study. In breast cancer models[16], tumor-infiltrating lymphocytes (TILs) are typically found within the tumor stroma rather than embedded directly within the tumor tissue itself. However, this peripheral distribution pattern around the tumor may not be the pivotal factor driving antitumor immune responses. In human oral squamous cell carcinoma and breast cancer,[16,17] biologically active immune lymphocytes (BILs) have been observed to be heterogeneously dispersed throughout the tumor rather than concentrated within aggregates.

In the majority of instances, occurrence of TLSs heralds a more favorable prognosis, along with improved disease-free survival and overall survival outcomes. The emergence of TLSs is associated with improved survival rates and more favorable prognoses in patients, a phenomenon observed across various cancers including non-small cell lung cancer (NSCLC), breast cancer, colorectal adenocarcinoma, hepatocellular carcinoma, and endometrial cancer[9,10,18–20]. Research also indicates that TLSs can also enhance patients' responsiveness to chemotherapy and immunotherapy regimens for malignancies. Studies indicate that the co-presence of tumor-associated CD8+ T cells and CD20+ B cells in melanoma patients who have undergone immunotherapy is linked to enhanced survival rates[18]. Immunofluorescence staining revealed the formation of TLSs within these tumors, which were correlated with improved clinical outcomes. Additionally, tumors enriched with B cells exhibited higher levels of TCF7+ naive and/or memory T cells, which demonstrated a more efficient molecular phenotype.

Immune therapy, by obstructing immune checkpoints, unleashes anti-tumor immune responses, achieving unprecedentedly durable response rates across a wide spectrum of cancers. However, not all patients respond, which makes the identification of precise biomarkers indicative of response is an urgent medical imperative. For melanoma and non-small cell lung cancer (NSCLC) patients undergoing anti-programmed cell death 1 (PD1) therapy, the presence of pre-existing anti-tumor T cells and PD1 ligand 1 (PDL1) expression at the tumor site is a critical factor in achieving a favorable clinical response[21,22]. CD8+ T cells, inhibited by PDL1 expressed by both tumor and myeloid cells, can be reactivated into effector cells under immune checkpoint blockade therapy, enabling the eradication of malignant cells within patients. Another predictive indicator associated with response is the measurement of the number of mutations carried by tumor cells, termed tumor mutation burden[23]. However, these biomarkers alone are insufficient to fully predict responses to immunotherapy, underscoring the critical need for more comprehensive predictive tools. Pan-cancer studies have further substantiated the predictive value of TLSs in the context of immune checkpoint inhibitor therapy. Despite the presence of programmed death ligand 1 (PD-L1) expression, the development of mature TLSs significantly amplifies immune responses and improves survival rates in both PD-L1-positive and PD-L1-negative patient populations. The above-mentioned findings underscore the promising potential of TLSs in oncological diagnostics and therapeutics. However, the limited availability of effective monitoring tools and standardized assessment criteria has constrained its clinical application.

The prevailing techniques for identifying the presence of TLSs encompass H&E staining, multiplex immunohistochemistry (mIHC), multiplex immunofluorescence (mIF), and real-time quantitative polymerase chain reaction (qPCR) analysis of chemokines[24].

H&E and mIHC/mIF are the easiest and the most frequently employed techniques in our clinical practice. Yet statistics shows that in the context of oral squamous cell carcinoma, roughly one-third of tumors exhibiting TLSs might end up unnoticed when pathologists assess only few sections of the tumor[17]. Although qPCR provides a more precise method for detecting TLSs, it lacks the capability to offer an intuitive visual representation of the morphological characteristics of TLSs. Above mentioned methods necessitate surgical sampling, and their accuracy may be compromised due to factors such as the feasibility of the surgical procedure, the quantity of tissue sampled during surgery, and the anatomical location of the sample[10], potentially leading to inadequate or imprecise detection. This necessitates a highly accurate diagnostic tool capable of early detection of TLSs during the initial stages of treatment, enabling timely adjustments to the patient's therapeutic regimen.

In breast cancer research, Li[25] et al integrated radiomics with clinical data to analyze the predictive role of TLSs. By constructing a radiomics-clinical integrated model, their study demonstrated that the combined model outperformed the clinical-only model in predicting TLSs, exhibiting superior accuracy and validation performance (AUC of 0.820 in the training set and 0.749 in the validation set). In hepatocellular carcinoma research, long et al[26] delved into the intricate relationship between the density of peritumoral tertiary lymphoid structures (pTLS) and patient prognosis as well as immunotherapy response in hepatocellular carcinoma (HCC). Employing spatial transcriptomics and immunohistochemical analysis, their research unveiled a crucial correlation. Moreover, they devised a radiomic classifier based on MRI to non-invasively predict pTLS density, which excelled in external validation with an AUC of 0.91, underscoring its robust predictive efficacy.) Although these studies focus on different types of cancers and encompassed various imaging modalities, they collectively highlight the significant potential of radiomics in non-invasive TLSs prediction.

Our research has developed and validated a multimodal predictive model, the Radiomics Integrated Tertiary Lymphoid Structures System (RAITS)[27], designed to identify TLSs in patients with Stage I lung adenocarcinoma (LUAD) using preoperative CT radiomic features. We employed the most recent preoperative chest CT thin-slice scans and postoperative hematoxylin and eosin-stained pathology sections from Stage I LUAD patients. Tumor segmentation was accomplished using an automated virtual adversarial training segmentation algorithm integrated with a three-dimensional U-shape convolutional neural network (3D U-Net). Radiomic features were extracted from the tumor and peritumoral regions, with extensions of 2 mm, 4 mm, 6 mm, and 8 mm, respectively, while deep learning image features were derived through a convolutional neural network.

The performance of RAITS was rigorously evaluated in both the training and external validation cohorts, showcasing superior AUC, sensitivity, and specificity compared to conventional unimodal models. In the validation cohort, RAITS achieved an AUC of 0.78 (95% CI, 0.69–0.88) and demonstrated greater net benefits across the majority of threshold ranges. The model exhibited robust discriminative capabilities in risk stratification, with $p < 0.01$ in the training cohort and $p = 0.02$ in the validation cohort, consistent with the actual predictive performance of TLSs. Notably, TLS-positive patients achieved significantly higher recurrence-free survival (RFS) rates compared to TLS-negative patients ($p = 0.04$ in the training cohort, $p = 0.02$ in the validation cohort). RAITS demonstrated a sensitivity of 0.71 and a specificity of 0.92 in the training set, with corresponding values of 0.66 and 0.83 in the validation set. The Youden index for RAITS was 0.63 in the training set and 0.49 in the validation set. Across all models, RAITS exhibited the best performance both in the training and validation sets. A DeLong test on the validation set models revealed that RAITS significantly outperformed IntraPeri6mm in predictive performance (0.78 vs. 0.61, $P = 0.03$).

Kaplan-Meier (KM) curve analysis indicated that, compared to patients with TLS negativity, those with TLS positivity exhibited significantly higher recurrence-free survival (RFS) in both the training set ($P = 0.04$) and the validation set ($P = 0.02$). Utilizing the optimal cutoff value of 0.806 for the RAITS model, determined based on the training set, patients in both the training and validation sets were stratified into high-risk and low-risk groups. The KM curves for RFS were then compared between these groups. The findings revealed that RAITS effectively stratified risk in both the training set ($P < 0.01$) and the validation set ($P = 0.02$), demonstrating robust discriminative ability for risk classification. Additionally, significant differences in survival curves were observed between the TLS-positive and TLS-negative groups, indicating that RAITS, as a TLS prediction model, aligns closely with actual TLS predictive performance.

In conclusion, RAITS, as a multimodal predictive model leveraging preoperative CT radiomic features, has demonstrated exceptional performance in identifying TLSs in Stage I LUAD patients and holds significant potential for enhancing clinical decision-making. These findings suggest that RAITS could serve as a valuable tool for refining prognostic assessments in Stage I LUAD patients and guiding personalized treatment strategies. Nevertheless, as a retrospective study with a relatively lengthy follow-up period, the performance of RAITS in the validation set underscores the necessity of augmenting the demographic diversity of our sample cohorts. In the future, we are committed to refining and validating RAITS through high-

quality, multi-center, prospective studies. Furthermore, we aim to integrate RAITS with clinical data and molecular biomarkers from the peri-tumoral region to develop a more comprehensive and precise predictive model.

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Conflict of Interest Statement

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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