Mini-Review

Tumor-associated prognostic factors extractable from chest CT scans in patients with lung cancer

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Abstract: Accurately predicting the prognosis of patients with lung cancer before or at the time of treatment would offer clinicians an opportunity to tailor management plans more precisely to individual patients. Considering that chest computed tomography (CT) scans are universally acquired in patients with lung cancer for clinical staging or response evaluation, fully extracting and utilizing the prognostic information embedded in this modality would be a reasonable approach. Herein, we review tumor-related prognostic factors that are extractable from CT scans, including the tumor dimensions, presence of ground-glass opacity (GGO), margin characteristics, tumor location, and deep learning-based features. Tumor dimensions include diameter and volume, which are among the most potent prognostic factors in lung cancer. In lung adenocarcinomas, the solid component size on CT scans as well as the total tumor size is associated with the prognosis. The areas of GGO indicate the lepidic component and are associated with better postoperative survival in early-stage lung adenocarcinomas. As for the margin characteristics, which represent the CT manifestation of fibrotic stroma or desmoplasia, tumor spiculation should be evaluated. The tumor location in the central lung is associated with occult nodal metastasis and is a worse prognostic factor *per se*. Last but not least, deep learning analysis enables prognostic feature extraction beyond the human eyes.

Keywords: Prognostication; lung cancer; survival; computed tomography (CT); deep learning

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Introduction

Chest computed tomography (CT) scans are an essential tool for preoperative evaluations, clinical staging, and response monitoring in patients with lung cancer. The prognostic importance of CT features, including the tumor dimension (1,2), density (2), and radiomics features (3), has been summarized previously. Deep learning-based survival probability estimation and feature extraction are also feasible. This mini-review briefly introduces both qualitative and quantitative tumor-associated prognostic

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factors that are extractable from chest CT scans.

Tumor dimensions

The tumor dimensions, which can be measured as diameter or volume, are among the most potent and reliable prognostic factors in lung cancer. These measurements can be easily obtained from CT scans. For clinical staging, the single largest dimension is measured on thin-section CT scans, and the tumor is then classified according to the clinical T categorization system (4). For part-solid nodules, the long axis dimension of the largest solid component is used (4). The solid component on CT scans is a surrogate for the invasive component on microscopy, although the CT measurements often overestimate the pathological measurements (5).

Since the publication of the eighth-edition staging system for lung cancer (6), multiple validation studies have been published (7,8). Those studies have shown that the solid component size is a strong prognostic factor in adenocarcinomas manifesting as part-solid nodules. Nevertheless, the total tumor size, defined as the maximum measurement of the ground-glass component, still matters. The prognoses of part-solid nodules with the same solid component size may vary depending on the total tumor size (9). For cases of clinical T1b disease, Kim *et al.* (9) suggested upstaging part-solid nodules with a total tumor size larger than 3.0 cm to clinical T1c, considering their worse postoperative survival than clinical T1b nodules with a total tumor size ≤3.0 cm [hazard ratio (HR) =3.796; 95% confidence interval (CI): 1.006, 14.317; P=0.049].

In addition, multiple solid components are often observed in part-solid nodules. The staging manual suggests measuring the single largest solid component, but there is little clinical evidence on how many solid portions should be measured and how to summarize those components into a single value. A recent study reported that measuring multiple solid components did not improve predictions of the prognosis of stage IA lung adenocarcinomas (10). Survival discrimination using the single largest solid portion was comparable to that based on measuring up to three solid portions (C-index, 0.82 *vs.* 0.79; P=0.25). Furthermore, multiplicity of the solid component was not a prognostic factor for recurrence-free survival (P=0.83) (10).

Tumor volume has been proposed to be more accurate than tumor diameter in patients with early and advanced-stage lung cancer (11,12). Volume is more sensitive for detecting dimensional changes than size, and it is more accurate for nodules with irregular shapes. Gross tumor volume, encompassing both the volume of the primary tumor and metastases, is also an important prognostic factor (1). A recent meta-analysis on the prognostic factors for overall survival in patients with stage III non-small cell lung cancer found that gross tumor volume was significant in 7 out of 9 multivariable analyses (1).

However, there are obstacles to employing tumor volume measurements in practice, including measurement variability and the limited accessibility of easy-to-use, well-validated software. It is also crucial to obtain measurements promptly to avoid delaying the clinical workflow. Deep learning algorithms are expected to show superior segmentation performance for lung cancer than rule-based models and may help solve those obstacles (13). Studies on volume-based cutoffs for clinical staging or response evaluation are warranted.

Presence of ground-glass opacity (GGO)

Early-stage lung adenocarcinomas frequently manifest as part-solid nodules on CT scans. As mentioned above, the solid component is a CT surrogate for the invasive component, and the area of GGO indicates the lepidic component (4). In the past decade, researchers have reported that the presence of GGO in lung adenocarcinomas is associated with better postoperative survival. Aokage *et al.* (14) suggested that the overall survival in patients with part-solid nodules was longer than in patients with solid nodules in clinical stages IA2 (log-rank test: P<0.01) and IA3 (log-rank test: P<0.01). Hattori *et al.* (15) observed similar results in clinical stage IA lung adenocarcinomas, using the 5-year overall survival rate as the study outcome (stage IA1: 97.8% versus 86.6%, P=0.026; IA2: 89.3% versus 75.2%, P=0.007; IA3: 88.5% versus 62.3%, P=0.003). Those observations were also supported by parallel pathologic data comparing lepidic versus invasive components (stage IA1: 97.9% versus 85.6%, P=0.031; IA2: 86.1% versus 69.4%, P=0.007; IA3: 77.5% versus 55.8%, P=0.001). In this context, the same authors suggested revising the clinical T categorization system according to the presence or absence of GGO in clinical T1 disease (16). GGO was also associated with long-term survival in a cure model analysis of clinical stage IA lung adenocarcinomas [odds ratio (OR), 0.40, 95% CI: 0.18–0.92, P=0.03] (8).

Nevertheless, debate continues regarding the validity of GGO as a prognostic variable. Some studies have argued that its prognostic value was insignificant after including

other prognostic factors (17,18). In fact, prognostic studies on the GGO component of early-stage lung adenocarcinomas have been heterogeneous in terms of cancer stage (e.g., stage IA *vs.* higher); histology (e.g., the inclusion of non-mucinous adenocarcinomas or non-adenocarcinoma histology); the inclusion of pure ground glass nodules or adenocarcinomas *in situ*, which usually show an extremely good prognosis; study endpoints; survival analytic methods; and covariates. Therefore, a confirmatory study (e.g., a prospective observational cohort study or meta-analysis) would be required to verify the prognostic role of GGO in adenocarcinomas.

Tumor margin characteristics

In cancer development, the stroma becomes a supportive environment for cancer cells. The tumor stroma combines a desmoplastic reaction with a proliferation of fibroblasts and dense deposition of extracellular matrix (19). Cancer-associated fibroblasts (CAFs) promote malignant growth, angiogenesis, invasion, and metastasis through the secretion of growth factors, cytokines, chemokines, and other immune modulators (19). In the setting of tumor growth, CAFs produce transforming growth factor β, platelet-derived growth factor, and fibroblast growth factor 2, which are profibrotic growth factors (19). Of these, fibroblast growth factor 2 plays a fundamental role in tissue fibrosis and desmoplasia and exerts effects on endothelial cells (20). Accordingly, CAFs and fibrotic stroma are associated with worse prognoses in patients with lung cancer (21).

The CT manifestation of fibrotic stroma or desmoplasia is margin spiculation. However, the association of tumor spiculation with survival has not been well established for lung cancer. Park *et al.* (22) reported that the presence of spiculation was associated with brain metastasis in resectable-stage lung cancers (OR, 3.34; P=0.006), but it is unclear whether tumor spiculation is truly a prognostic factor for overall survival or recurrence-free survival.

Pleural retraction or tag

Pleural retraction or a pleural tag on CT is a predictor of visceral pleural invasion, which is an established prognostic factor and a T2 descriptor in lung cancer. Nevertheless, CT definitions of pleural tag or retraction are highly variable among radiologists and often yield false-positive diagnoses for pathological visceral pleural invasion. Kim *et al.* (23) investigated combinations of CT findings, including tumor contact with the pleura, pleural retraction, and tags. None of the combinations were associated with recurrence-free survival in clinical T1N0 lung cancers. Therefore, it is uncertain whether these CT features can be reliably identified and whether these features are genuinely indicative of patients' survival.

Tumor location

Central tumor location is associated with occult nodal metastasis and mediastinal nodal disease in radiologically node-negative, early-stage lung cancers (24). Therefore, staging guidelines recommend invasive diagnostic procedures such as endobronchial ultrasound-guided transbronchial needle aspiration or mediastinoscopy, both for locally advanced disease and for stage I disease involving central lung cancer (25).

In addition, a central tumor location predicts a less favorable prognosis in pathologically node-negative, early-stage lung cancers. Recent studies revealed that central lung cancer on chest CT, defined either qualitatively or quantitatively, was an independent adverse factor for recurrence-free survival in stage IA lung adenocarcinomas (HR, 2.90; 95% CI: 1.06, 7.96; P=0.04) (26,27). This might be attributable to more crowded vessels and lymphatic vessels in the central lung, leading to a higher chance of undetectable micrometastasis at the time of treatment (26). However, there is no consensus on the radiologic definition of central lung cancer. A subjective assessment of the tumor location is vulnerable to reader variability, and in this context, quantitative measurement using anatomic landmarks has been suggested (24,26). Nevertheless, an automated, objective tool is necessary to exploit the tumor location as a meaningful clinical variable for practice and research.

Deep learning-based prognostic CT features

Radiomics and radiogenomics studies have demonstrated that chest CT scans contain both anatomical information for clinical staging and quantitative prognostic data beyond what human eyes can visualize (28). Deep learning models such as convolutional neural networks have recently enabled an end-to-end analysis of chest CT scans without manual feature engineering. For example, a deep learning model can elicit prognostic factors from a CT tumor patch, either three-dimensional or two-dimensional (29-38). One study proposed a three-dimensional convolutional neural network

consisting of dense blocks and transitional layers to estimate the cumulative disease-free survival probability up to 3 years in patients with lung adenocarcinoma undergoing curative resection (29). The model-derived prediction was obtained using a discrete-time survival model and was an independent prognostic factor in an external cohort comprising stage I lung adenocarcinomas (HR, 3.6; 95% CI: 1.6, 8.5; P=0.003) (29). This model was then applied to patients with early-stage lung adenocarcinomas treated with stereotactic ablative radiotherapy and showed good discrimination performance for local recurrence-free survival [area under the curve (AUC), 0.72], disease-free survival (AUC, 0.70), and overall survival (AUC, 0.66) (39). Interestingly, the model showed relatively robust performance regarding the CT acquisition settings considering that the radiotherapy cohort underwent planning CT scans with larger fields of view and lower in-plane resolution than the diagnostic CT scans (39). In addition, multivariable regression analysis showed that the model-derived prognostic factors or CT features were associated with histopathologic risk factors, such as an aggressive adenocarcinoma subtype (cribriform, morular, solid, or micropapillary predominant subtype; OR, 1.03; 95% CI: 1.002, 1.05; P=0.03), venous invasion (OR, 1.03; 95% CI: 1.004, 1.06; P=0.02), and visceral pleural invasion (OR, 1.08; 95% CI: 1.06, 1.10; P<0.001), in patients with resected lung adenocarcinoma (40). Therefore, it can be inferred that the deep learning model could extract CT imaging surrogates for the histopathologic factors of lung adenocarcinomas (40).

Deep learning-based prognostication is also feasible in advanced-stage lung cancers. Deng *et al.* (35) recently proposed a deep learning model using pre-therapy CT scans, which provided a probability score to identify low-risk or high-risk patients receiving tyrosine kinase inhibitors and immune checkpoint inhibitors. The model was able to identify which patients would receive additional survival benefits beyond the median progression-free survival.

Deep learning is not limited to obtaining the cumulative survival probability; this method can be applied to capture the semantic features of lung cancer more broadly. Ahn *et al.* (41) reported that automatic measurements of the solid portions of lung cancer were comparable with manual measurements made by radiologists (intraclass correlation coefficient, 0.82–0.89) and showed good agreement with the invasive component size on microscopic examinations (intraclass correlation coefficient, 0.67). Kawaguchi *et al.* (42) showed that the solid component volume measured using deep learning had higher prognostic discrimination for recurrence or death (AUC, 0.752) than the solid component size (AUC, 0.722) or traditional three-dimensional volumetric analysis (AUC, 0.723). The presence of visceral pleural invasion was also estimated using preoperative CT scans (31). In a study by Choi *et al.* (31), the diagnostic performance of the deep learning model (AUC, 0.75) for visceral pleural invasion was on par with that of board-certified radiologists (AUC, 0.73–0.79).

Conclusions

CT scans include rich prognostic information that could be extracted either by manual human interpretation or machine learning algorithms. In addition to measurements of tumor dimensions and T categorization in the staging system, CT images can be used to assess tumor volume, density, morphology, margin characteristics, and tumor-based survival probability. Future research should focus on the automated extraction and integrative modeling of these tumor-related prognostic factors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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