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Predicting the Prognosis and Survival in Early-Stage Lung Cancer after Curative Surgery

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Abstract

Lung cancer remains one of the most important cancer-related mortality. More early-stage lung cancer is expected to be diagnosed, due to the use of low-dose computed tomography in lung cancer screening. Among all cell type, adenocarcinoma was the commonest among Asian population, with EGFR mutation being the commonest driver mutation. Various clinic-pathological factors were reported to be associated with the prognosis of early-stage lung cancer. Prediction rules were also developed based on different prognostic factors, to predict the survival and recurrence of lung cancer after curative surgery. There are also dedicated prediction rules that were developed on specific ethnic subgroup, such as Chinese population. Furthermore, with the advancement of artificial intelligence, deep learning and other advanced technologies, novel prediction rules are being developed that can further enhance the prognostication of early-stage lung cancer. In this mini-review, we present the reported prognostic factors of surgically resected early-stage lung cancer, the prediction rules developed, as well as the future direction of clinical research.

Keywords: Lung cancer; Prognosis; Prediction rule; Survival rate

Introduction

Lung cancer is a major contributor to cancer-related deaths globally because most patients are diagnosed in the advanced stages of the disease. With the advancement in lung cancer screening with Low-Dose Computed Tomography (LDCT), it is anticipated that early stage lung cancer will be detected more frequently [1-3]. A Danish report proposed a shift towards more patients diagnosed with lower stages and with adenocarcinoma. As more lung cancer is being diagnosed at an earlier stage, that incidence will stop increasing, that mortality will decrease further, and that the prevalence will continue to increase substantially [4]. The standard treatment for early-stage lung cancer remains complete surgical resection, with post-operative adjuvant treatment in those stage Infectious Bronchitis (IB) diseases with high-risk features. The reported 5-year survival rate ranges from 77%-92% for Stage 1A and 68% for IB disease [5-7].

Literature Review

Factors affecting the prognosis of early-stage lung cancer

Several factors were reported to affect the prognosis of early-stage lung cancer. Lipford studied 173 Stage I-II primaries Non-Small Cell Lung Carcinomas (NSCLC) that underwent curative-intent segmental resection, lobectomy, or pneumonectomy, and found that large-cell undifferentiated histology, lymph node metastases, tumor size, tumor giant cells in any histologic type and absent or minimal plasma cell infiltration as significant prognostic factors on multivariate analysis [8].

Analyzed the histologic prognostic factors of pulmonary adenocarcinomas less than 2 cm in diameter in 75 surgically treated patients, and found that pathologic stage, lymph node involvement, and pleural involvement were major determinants of prognosis. Other factors such as tumor differentiation, vascular invasion, the degree of collagenization in the fibrotic focus, the nuclear areas and mitotic index were also found to correlate significantly with prognosis. Patients with dense infiltration of "T-zone histiocytes" survived significantly longer than their less infiltrative counterparts. Cox's proportional hazard linear model analysis showed the importance of lymph node or pleural involvement and nuclear area when the pathologic stage was excluded, and of mitotic index when all four factors were excluded [9]. Another reported pathological prognostic factor is the intensity of tumor lymphocytic infiltration [10]. Brambilla reported that intense lymphocytic infiltration, found in a minority of tumors, was validated as a favorable prognostic marker for survival in resected non-small-cell lung cancer. The radiological features also play a role in the prognosis. The presence of a ground-glass opacity component was reported to have favorable prognostic impact compared with solid lesion counterpart in Hattori [11].

As Epidermal-Growth Factor Receptor (EGFR) mutation is common among Asian population, it is worthwhile to investigate whether other prognostic markers can be identified in this population. Yang recruited 252 Chinese patients with completely resected pathological stage I lung adenocarcinoma to retrospectively analyze the associations of recurrence with the following clinicopathological variables: gender, age, cigarette smoking, family cancer history, tumor size, TNM stage, tumor differentiation, visceral pleural invasion, bronchial involvement,

lymphovascular invasion, postoperative adjuvant treatment, pathological subtypes and micropapillary pattern. At a recurrence rate of 48 out of 252 patients, multivariate analysis revealed tumor differentiation, TNM stage, bronchial involvement and micropapillary pattern to be independent risk factors for Disease-Free Survival (DFS), and tumor differentiation, tumor size and lymphovascular invasion to be independent risk factors for OS [12].

Prognostic model development

Integrating prognostic factors into prognostic models facilitate easy clinical implementation and enable for a more objective quantification of the predicted outcome. Liu conducted a retrospective study on 198 patients with stage I lung adenocarcinomas from 2004 to 2013; their aim was to combine conventional clinic-pathological characteristics and pathological architectural grading scores to identify a specific group of patients with stage I lung adenocarcinomas with poor survival following surgery [13]. Three risk factors with weighted scoring, namely T2 staging (score 81), presence of necrosis (score 67) and pathological architectural score of 5-6 (score 58) were identified. The derived prognostic scores stratified patients into low-(score ≤ 103) *vs*. high-(score>103) risk groups, with significant differences in 5-year overall survival (high *vs*. low risk: 49.3% *vs*. 88.0%, respectively; hazard ratio: 4.55; P<0.001). The Area under the Curve (AUC) for the proposed model was 0.717, and the Concordance index (C-index) was 0.693.

Another prediction model developed by Zhang involved the review of 545 NSCLC patients [14]. A prognostic index for NSCLC (PInscl, 0-6 points) was calculated based on age (≥ 65 years, 1 point), Tumor-Node-Metastasis (TNM) stage (III, 1 point; IV, 2 points), lung lobectomy (no, 1 point), chemotherapy (no, 1 point), and pretreatment hemoglobin level (low, 1 point). The survival time for PInscl=0-6 was 2.71 ± 1.86 years, 2.43 ± 1.53 years, 1.86 ± 1.24 years, 1.45 ± 1.07 years, 1.17 ± 1.06 years, 0.81 ± 0.78 years and 0.65 ± 0.56 years, respectively. Kaplan-Meier survival analysis confirmed that patients with higher PInscl scores had poorer OS than those with lower scores (log-rank test: $\chi 2$=155.82, P<0.0001). The AUC of PInscl for predicting 1-year OS was 0.73 and outperform both Karnofsky performance status and TNM stage alone. In the study by Wu, which included 293 pathological stage I patients (7th American Joint Committee on Cancer, AJCC7), current smoker, the presence of additional primary malignancy, larger tumor size, nonanatomic resections, adenocarcinoma histology, visceral pleural invasion, and angiolymphatic invasion were found to be associated with an increased tumor recurrence risks [15]. A model was subsequently developed based on the factors identified, and it showed a fair discrimination ability (C-statistic=0.68). In this prediction model, patients with intermediate or higher risk group were found to have a higher distal relapse tendency.

Discussion

Kwok also recently published on a prediction model on disease recurrence for low risk resected stage I lung adenocarcinoma [16]. In this large retrospective cohort study with validation, patients with completely resected pathologic stage I adenocarcinoma of lung without any high-risk features (8th Edition of the AJCC TNM Staging System) in a major regional hospital in Hong Kong were included. The derivation cohort consisted of 408 patients. Among the prognostic demographic and clinical factors, there were significant differences in median DFS by gender, smoking status and EGFR status and disease stage. Covariates with P<0.05 (gender, smoking status, EGFR mutation profile and stage of disease) were included in the multivariate model to build the scoring system, and it was confirmed that only 3 of the covariates (namely smoking status, disease stage and gender) were necessary to build the scoring system. Weighted scores were assigned as follow: Stage IB and male-5, Stage IB and female-2, Stage IA and male-1, Stage IA and female-0; ever-smoker-3, non-smoker-0. Three risk groups with distinct DFS can be stratified, and the DFS was 99.4 months, 62.9 months and 33.7 months for low-risk (score 0-2), medium-risk (score 3-4) and high-risk group (score>5) respectively. The AUC by ROC analysis was 0.863, suggesting good predictive power in this model.

Saw conducted a cohort study that included 723 patients with AJCC7 Stage IA to IIIA NSCLC who underwent curative surgical procedures at a specialist cancer center in Singapore. A risk estimation model was developed that incorporated genomic data and an individual patient nomogram using clinicopathologic features for stage I EGFR-positive NSCLC. After controlling for stage, grade, and age at diagnosis, alteration of *RHPN2*, *Catenin Beta 1* (*CTNNB1*), and micropapillary subtype were shown to be associated with increased recurrence risk, whereas copy number loss of RB1 was associated with decreased risk [17].

Future directions

With the advancement of artificial intelligence, deep learning and other advanced technologies, the prognostication can potentially be further enhanced. A population-based cohort involving 17322 consecutive cases of newly diagnosed stages I-IV NSCLC patients in the Surveillance Epidemiology and End Results (SEER) database were used to develop and validate a deep learning-based algorithm on prognosis prediction [18]. The deep learning survival neural network model showed more promise in the prediction of lung cancer-specific survival than TNM staging on the test data set (C statistic=0.739 *vs*. 0.706) and predicted superior survival rates in population who received the recommended treatments than those who did not. Li developed a robust, individualized immune signature that can estimate prognosis in patients with early-stage non-squamous NSCLC [19]. A total of 2414 patients were included and a prognostic immune signature of 25 gene pairs consisting of 40 unique genes was constructed using the meta-training dataset. The immune signature effectively stratified patients with stage I, IA, IB or II disease into high *vs*. low-risk groups with respect to overall survival, both across and within subpopulations, and remained as an independent prognostic factor in multivariate analyses after adjusting for clinical and pathologic factors.

Conclusion

The composite clinical (e.g. age and disease stage) and immune signature showed improved prognostic accuracy in all validation datasets, surpassing the accuracy of molecular signatures alone and another commercialized clinical-molecular signature. Significant progress has been made in the methods to predict the prognosis of early-stage lung cancer, from the identification of individual prognostic factors to prognostic models, followed by the use of machine learning and immune signature. As technology continue to advance, we can anticipate further improvement of both prognostication as well as application of these models to improve the survival by way of more personalized use of novel adjuvant therapies in selected patients.

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