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The combination of the blood based tumor biomarkers cytokeratin 19 fragments (CYFRA 21-1) and carcinoembryonic antigen (CEA) as a potential predictor of benefit from adjuvant chemotherapy in early stage squamous cell carcinoma of the lung (SCC)

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ABSTRACT

Objectives: To determine whether the tumor biomarkers cytokeratin 19 fragment (CYFRA 21-1) and carcinoembryonic antigen (CEA), which are prognostic in early-stage non-small cell lung cancer (NSCLC), can predict which patients benefit from adjuvant chemotherapy (CTx).

Materials and methods: Serum samples were collected preoperatively from patients with NSCLC who underwent resection. Samples were retrospectively analyzed for CYFRA 21-1 and CEA via electrochemiluminescence immunoassay. Recurrence-free survival (RFS) was compared for patients who received adjuvant CTx versus surgery alone, stratified based on the following prognostic classifications: (1) tumor stage (pT1-2/N0 [stage I] or pT3/N0 or pT1-2/N1 [stage II]), (2) biomarker-based risk score, (3) clinical characteristics. Absolute 2-year RFS rates were calculated via Kaplan-Meier estimations; statistical significance level: 0.05.

Results: 227 patients were included (stage I: 69%; male: 67%; median age 65 years); 70 received adjuvant CTx. Median duration of sample collection was 58.8 months. All high-risk patients (by all three prognostic classifications) who received adjuvant CTx had a longer RFS versus those who received surgery alone. In patients with squamous cell carcinoma (SCC) classified as high risk by all three prognostic classifications, there was a benefit from adjuvant CTx versus surgery alone (tumor stage hazard ratio [HR] 4.9, $p = 0.004$; biomarker levels HR 9.4, $p = 0.002$; clinical characteristics HR 9.0, $p = 0.003$). None of the prognostic classifications were able to predict a benefit from adjuvant CTx in patients with adenocarcinoma.

Conclusion: Baseline CYFRA 21-1 and CEA levels may provide further information to help clinicians decide which patients with SCC should receive adjuvant CTx. Further evaluation of these biomarkers is warranted.

Abbreviations: ADC, adenocarcinoma; adCTx, adjuvant chemotherapy; CEA, carcinoembryonic antigen; CTx, chemotherapy; CYFRA 21-1, cytokeratin 19 fragments; HR, hazard ratio; NSCLC, non-small cell lung cancer; RFS, recurrence-free survival; SCC, squamous cell carcinoma

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1. Introduction

Lung cancer remains the most commonly diagnosed cancer, with a worldwide incidence of 1.8 million new cases per year; it is also the leading cause of cancer-related mortality, with 1.6 million deaths per year [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [2,3]. The two most frequent histologic subtypes are adenocarcinoma (ADC) and squamous cell carcinoma (SCC), accounting for 50% and 30% of NSCLC cases, respectively [3].

NSCLC is only curable in the early stages of the disease, where treatment of curative intent is primarily surgical resection [4,5]. However, given that the majority of patients present with locally advanced or metastatic disease [2], the 5-year survival rate for all stages of disease is still only 21.6%, though this rises to 59.2% for patients with localized disease [6].

The survival benefit of platinum-based adjuvant chemotherapy (CTx) following surgical resection in patients with early-stage NSCLC has been demonstrated in various large, prospective, phase 3 trials; however, the benefit is more apparent in stages II/IIIA NSCLC than in stage I NSCLC [7–10]. A recent meta-analysis including 8447 patients from 26 published trials confirmed the clear benefit of adjuvant CTx (hazard ratio [HR] 0.86; $p < 0.0001$), with an absolute increase in 5-year survival of 4% (60% to 64%) [8]. However, whether cisplatin-based adjuvant CTx should be used in patients with stage IA disease remains uncertain due to the scarcity of data in this patient subgroup. Consequently, the use of adjuvant CTx is recommended for patients with tumor stage II–IIIA NSCLC and is an option for some patients with high-risk stage IB disease, for example when the tumor is poorly differentiated, > 4 cm in size, or where there is vascular invasion [11–13].

There have been many attempts to identify subgroups of patients with early-stage NSCLC who may potentially benefit from adjuvant CTx. For example, one group showed that a prognostic score based on the combination of cell cycle progression gene expression and tumor stage could identify a subgroup of patients with stage I NSCLC with a higher risk of death after surgical resection [14]. Other groups have shown that multiple somatic mutations are associated with worse outcomes in resected NSCLC [15], and that elevated levels of cytokines, such as transforming growth factor alpha (TGFα) and interleukin-5, may represent independent adverse prognostic biomarkers for patients with NSCLC treated with radiotherapy [16]. Candidate biomarkers evaluated for their potential to predict outcome or sensitivity to platinum-based adjuvant CTx in patients with NSCLC include ERCC1 [17], MSH2 [18], p27 [19], and p53 [20]; however, results are conflicting and there is currently no consensus or recommendation for their use in clinical practice [21].

Retrospective studies have shown that in patients with NSCLC, particularly those with early-stage disease, elevated levels of the tumor biomarkers, cytokeratin 19 fragment (CYFRA 21-1), and carcinoembryonic antigen (CEA), are associated with a poor prognosis [22–24]. A reduction in serum CYFRA 21-1 and CEA levels has also been correlated with response to treatment among patients receiving chemotherapy, although these studies have largely recruited patients with late-stage disease [25–27]; these findings were also confirmed in a recent meta-analysis [28]. However, the ability of these biomarkers to predict the outcome of adjuvant CTx in patients with early-stage NSCLC has yet to be determined.

As these biomarkers are typically reflective of the level of tumor burden, we hypothesized that preoperative CYFRA 21-1 and CEA levels could potentially predict which patients with clinically early-stage NSCLC would be most likely to derive benefit from adjuvant CTx.

2. Materials and methods

2.1. Sample collection and study design

This was a retrospective analysis of serum samples, which were collected as part of a prospective longitudinal study designed to identify a molecular signature associated with poor prognosis among patients with early-stage NSCLC. In the original study, eligible patients were ≥18 years of age with early-stage ADC, SCC, or mixed histology, defined as pT1-2/N0 (stage I) to pT3/N0 or pT1-2/N1 (stage II) (assigned based on the Union for International Cancer Control [UICC] criteria, 6th edition [29]). Patients were excluded if they had a previous tumor diagnosis, if they had received neoadjuvant chemotherapy or if they had positive tumor margins following resection (≥R1). Blood samples were collected from all enrolled patients before surgery (baseline) and at 3, 6, 12, 18, and 24 months, and then every 6–12 months up to 5 years post-surgery; samples were stored at −80 °C within two hours of venipuncture at Roche Diagnostics GmbH (Penzberg, Germany) and the Lung Biobank (Heidelberg, Germany) – a member of the Biomaterial bank Heidelberg (BMBH) and the Biobank platform of the German Center for Lung Research (DZL). All patients received additional treatment for their disease, including adjuvant chemotherapy where appropriate, according to local best practice. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and approval was granted by the local ethics committee of the University of Heidelberg (no. 270/2001). All patients provided written informed consent for the use of their blood samples for research purposes.

Serum samples for this retrospective analysis were provided by Roche Diagnostics. Samples were only included from patients with information regarding adjuvant CTx treatment received and available survival data. Patients with kidney failure (defined as a glomerular filtration rate of < 15 mL/min) and those who started chemotherapy more than 90 days after surgery were excluded from this analysis. Only presurgical serum samples were included in the current analysis.

2.2. Analysis of samples

All samples were analyzed simultaneously for CYFRA 21-1 and CEA via electrochemiluminescence immunoassay (ECLIA) using Elecsys® assay on the **cobas e** 601 immunoassay analyzer (Roche Diagnostics GmbH, Penzberg, Germany). In these sandwich assays, samples are incubated with two types of antibodies. The ECLIAs for CYFRA 21-1 and CEA include antigen-specific biotinylated monoclonal antibodies and ruthenium complex-labeled monoclonal antibodies. Streptavidin-coated microparticles are added to the resulting sandwich complex in each assay, which becomes bound to the solid phase via the biotin-streptavidin interaction. The reaction mixture from each assay is then aspirated into a measuring cell where the microparticles are magnetically captured onto the surface of an electrode. Application of a voltage to the electrode induces a chemiluminescent emission which is measured using a photomultiplier. Results are determined via a calibration curve.

2.3. Statistical analysis

In this post-hoc analysis, recurrence free survival (RFS) was defined as the time from presurgical serum biomarker sample collection (baseline) to disease recurrence or death from any cause (both defined as events). Events were verified through chart review by the investigator (T.M.). Patients without an event at the time of the analysis were censored at their last known follow-up date.

RFS was evaluated in all patients with NSCLC and in the subgroups of patients with SCC and ADC according to risk of relapse (high versus low) and treatment received (adjuvant CTx versus surgery only). Stratification of patients as high versus low risk was based on three different prognostic classifications: (1) the control prognostic classification based on tumor stage, which defined patients as low risk (pT1-2/N0/M0; stage I) or high risk (pT3/N0/M0 or pT1-2/N1/M0; stage II); (2) the novel biomarker prognostic algorithm, which defined patients as low or high risk for relapse based on presurgical serum values of CYFRA 21-1 and CEA; and (3) a prognostic classification based on the clinical

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