Human Pathology (2018) **75**, 167–178

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Cell of origin markers identify different prognostic subgroups of lung adenocarcinoma ☆

Fabrizio Tabbò MD, PhD[a,b,*,1], Alessia Nottegar MD, PhD[c,1], Francesco Guerrera MD[d,1], Enrica Migliore PhD[e], Claudio Luchini MD[c,f,g], Francesca Maletta MD[h], Nicola Veronese MD[i,j], Licia Montagna MSc[c], Marcello Gaudiano MSc[b], Filomena Di Giacomo PhD[a,b], Pier Luigi Filosso MD[d], Luisa Delsedime MD[h], Giovannino Ciccone MD[e], Aldo Scarpa MD, PhD[c], Anna Sapino MD[h,k], Alberto Oliaro MD[d], Enrico Ruffini MD[d], Giorgio Inghirami MD[a,b,l], Marco Chilosi MD[c,m]

[a]*Department of Molecular Biotechnology and Health Science and Center for Experimental Research and Medical Studies, University of Torino, 10126 Torino, Italy*
[b]*Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY 10021, USA*
[c]*Department of Diagnostics and Public Health, University and Hospital Trust of Verona, 37134 Verona, Italy*
[d]*Department of Thoracic Surgery, AOU Città della Salute e della Scienza di Torino, 10126 Torino, Italy*
[e]*Unit of Cancer Epidemiology, AOU Città della Salute e della Scienza di Torino and CPO Piemonte, 10126 Torino, Italy*
[f]*ARC-Net Research Center, University and Hospital Trust of Verona, 37134 Verona, Italy*
[g]*Department of Pathology, Santa Chiara Hospital, 38100 Trento, Italy*
[h]*Department of Medical Sciences, University of Torino, 10126 Torino, Italy*
[i]*National Research Council, CNR, Padua, 38121, Italy*
[j]*Institute of Clinical Research and Education in Medicine, 38121 Padua, Italy*
[k]*Candiolo Cancer Institute - FPO, IRCCS, I-10060, Candiolo (To), Italy*
[l]*Department of Pathology and NYU Cancer Center, New York University School of Medicine, New York, NY 10016, USA*
[m]*Department of Pathology, Pederzoli Hospital, 37134 Verona, Italy*

Received 6 October 2017; revised 6 January 2018; accepted 15 January 2018

Keywords:
Lung adenocarcinoma;
Biomarkers;
Immunohistochemistry;
Morphology;
Genetic mutations;
Survival analysis

Summary Strong prognostic markers able to stratify lung adenocarcinoma (ADC) patients are lacking. We evaluated whether a six-immunohistochemical markers panel (TTF1, SP-A, Napsin A, MUC5AC, CDX2 and CK5), defining the putative neoplastic "cell of origin," allows to identify prognostic subgroups among lung ADC. We screened a large cohort of ADC specimens (2003–2013) from Torino Institutional Repository identifying: (i) marker positivity by immunohistochemistry, (ii) main morphological appearance by light microscopy, (iii) presence of "hotspot" mutations of candidate genes by Sequenom technology. To evaluate possible predictors of survival and time to recurrence, uni- and multivariable-adjusted comparisons were performed. We identified 4 different subgroups: "alveolar," "bronchiolar," "mixed" and "null type." Alveolar-differentiated ADC were more common in young (P = .065), female (P = .083) patients,

☆ No disclaimers in the paper.

* Corresponding author: University of Torino, Department of Oncology, Regione Gonzole, 10 - 10043, Orbassano, TO, Italy.
E-mail address: fabrizio.tabbo@unito.it (F. Tabbò)

[1] These authors contributed equally.

https://doi.org/10.1016/j.humpath.2018.01.017
0046-8177/© 2018 Elsevier Inc. All rights reserved.

frequently harboring *EGFR*-mutated ($P = .003$) tumors with acinar pattern ($P < .001$). Bronchiolar-differentiated ADC were more associated with mucinous and solid pattern ($P < .001$), higher degree of vascular invasion ($P = .01$) and *KRAS* gene mutations ($P = .07$). Bronchiolar, mixed, and null types were independent negative predictors for overall survival, and the latter two had a shorter time to recurrence. This "Cell of Origin" classifier is more predictable than morphology and genetics and is an independent predictor of survival on a multivariate analysis.
© 2018 Elsevier Inc. All rights reserved.

1. Introduction

Lung cancer represents the first cause of death for cancer in the world, and its global incidence and mortality rates are rising [1]. Despite major discoveries in tumor biology and molecular genomics [2,3], targeted therapies can only be delivered to a small number of individuals (eg, *EGFR*-mutated or *ALK*, *ROS1*-rearranged patients) [4]. The introduction of PD-1/PD-L1 checkpoint inhibitors is revolutionizing the field [5]; nevertheless, therapeutic options remain inaduate, and reliable or reproducible markers are needed to effectively stratify lung cancer patients and improve their clinical outcomes [6].

Lung cancers are classically subdivided in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and this stratification has relevant therapeutic implications. Among NSCLC, the most prevalent tumor entity is represented by Adenocarcinoma (ADC, 38% of all lung cancer) [7]. Although all ADC share common histological features [7], they include a heterogeneous collection of different lesions. The pathological stratification of NSCLC, even if parceled, guides clinical and molecular decisions; for example, *EGFR* mutations are investigated primarily in case of non-squamous lung cancers [8]. As highlighted by the 2011 guidelines of IASLC/ATS/ERS [9] and by the new WHO classification of lung tumors [10], ADC include multiple tumor types, which can be further defined based on the expression of selected markers and the presence of unique molecular lesions.

Since the integration of immunohistochemical and molecular classifiers has been successfully proven to identify specific clinical-biological entities among many human neoplasms (ie, lymphoid tumors), it is reasonable that an analogous method may improve the stratification of lung cancers [11]. Based on the hypothesis that ADC retain features related to their cell origin, we selected a set of markers preferentially expressed by alveolar [Thyroid Transcription Factor 1 (TTF-1), Surfactant Protein A (SP-A) and Napsin A] and bronchiolar [Mucin 5 AC (MUC5AC), Caudal Type Homeobox 2 (CDX-2) and Cytokeratin 5 (CK5)] cells in order to stratify lung ADC. Neoplasms were defined based on the differentiation profiles and then correlated with morphology and canonical *EGFR*, *KRAS*, *PIK3CA* somatic mutations [3].

The objective of our paper was to evaluate whether the proposed 6 immunohistochemical markers panel (TTF1, SP-A, Napsin A, MUC5AC, CDX2 and CK5), defining the putative "cell of origin" of the tumor, allows to identification of prognostic subgroups among lung ADC patients and how these markers correlate with common genetic mutations, classical histology and clinicopathological characteristics.

2. Materials and methods

2.1. Patient selection and ethical regulation

Data of patients from 2003 to 2013 who underwent surgical resection with curative intent for lung adenocarcinoma at Department of Thoracic Surgery - Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino - Italy, were prospectively collected in the database of our Institutional Biobank [12] and retrospectively reviewed. Patients treated with preoperative and postoperative regimens (ie, chemotherapy and/or radiotherapy) were included in our analysis. This study was approved by Institutional Review Board (IRB) of the Azienda Ospedaliera Universitaria, Città della Salute e della Scienza di Torino (protocol number 0081521/2011).

2.2. Tissue microarray and immunophenotypic classification

Three different cores (0.5 mm) with enriched tumor content (>50%) were selected from each tumor sample, and multitissue microarrays were constructed (Beecher Instruments, Inc., Silver Spring, MD, USA). Serial (4-μm-thick) sections were used for immunohistochemical analyses, and staining was performed using a semi-automated instrument [13,14]. Tissue sections were incubated with the following primary antibodies: TTF1 (clone: 8G7G3/1, source: Dako, Carpinteria, CA, USA, dilution: 1:50), Napsin A (clone: TMU-Ad02, source: ARP, Waltham, MA, USA, dilution: 1:500), SP-A (clone: 32E12, source: Novocastra, Burlingame, CA, USA, dilution 1:200), MUC5AC (clone: CLH2, source: Novocastra, dilution: 1:100), CDX2 (clone: CDX2–88, source: Biogenex, Fremont, CA, USA, dilution: 1:40) and CK5 (clone: XM26, source: Novocastra, dilution: 1:100). All samples were processed using a sensitive Bond Polymer Refine detection system in an automated Bond immunohistochemistry instrument (Vision-Biosystem, Leica, Milan, Italy).

Download English Version:

https://daneshyari.com/en/article/8807564

Download Persian Version:

https://daneshyari.com/article/8807564

Daneshyari.com