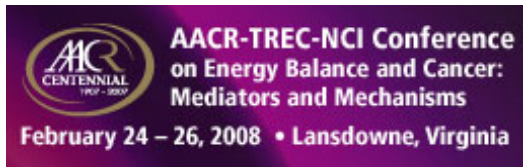


Clinical Cancer Research



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Cancer Therapy: Clinical

Bronchopulmonary Carcinoid: Phenotype and Long-term Outcome in a Single-Institution Series of Italian Patients

Massimo Rugge^{1,4,5}, Matteo Fassan¹, Roberto Clemente⁴, Giovanna Rizzardi², Luciano Giacomelli⁵, Gianmaria Pennelli^{1,4}, Claudia Mescoli¹, Daniela Segat³ and Federico Rea²

Authors' Affiliations: ¹ Department of Medical Diagnostic Sciences and Special Therapies, Pathology Unit; ² Department of Cardio-Thoracic and Vascular Sciences, Thoracic Surgery Unit; and ³ Department of Medical and Surgical Sciences, Surgery Unit, University of Padova; ⁴ Istituto Oncologico Veneto-Istituto di Ricovero e Cura a Carattere Scientifico, Pathology Unit; and ⁵ Azienda Ospedaliera di Padova, Pathology Unit, Padua, Italy

Requests for reprints: Massimo Rugge, Cattedra di Anatomia Patologica, Università degli Studi di Padova, Istituto Oncologico Veneto-IRCCS, Via Aristide Gabelli, 61, 35121 Padua, Italy. Phone: 39-0498-272-252; E-mail: massimo.rugge@unipd.it .

Purpose: The histologic distinction between low-grade typical and intermediate-grade atypical bronchopulmonary carcinoids basically lies on cellular differentiation, mitotic activity, and presence of "neoplastic" necrosis; at single patient level, however, none of these features enables a reliable prediction of the clinicopathologic outcome.

Experimental Design: The long-term postsurgical outcome of a single-institution series of 67 radically treated bronchopulmonary carcinoids was correlated with the tumor phenotype assessed by combining conventional histology with a panel of immunohistochemical markers exploring cell

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differentiation (chromogranin, NSE, TTF1), cell turnover (Mib1), and apoptosis (Bcl2, Bax).

Results: Fifty-eight (86.6%) carcinoids were assessed as low-grade typical and nine (13.4%) were assessed as intermediate-grade atypical. The mean follow-up was of 85.13 months (range, 28-168; median, 82.0). All cases expressed neuroendocrine markers, whereas TTF1 was never expressed. At univariate analysis, tumor recurrence ($n = 6$) correlated significantly with the carcinoid histotype ($P = 0.002$) and with each of the following variables: tumor location ($P = 0.01$), mitotic index ($P = 0.003$), necrosis ($P = 0.002$), tumor vascular invasion ($P = 0.0001$), Mib1 expression ($P = 0.005$), Bcl2 expression ($P = 0.024$), and synchronous node metastasis ($P = 0.028$). The best cutoffs for Mib1 and Bcl2 expression (calculated by receiver operating characteristic curves) discriminating recurrent versus nonrecurrent tumors were 5.4% for Mib1 and 2.0% for Bcl2 (Mib1: sensitivity, 83%; specificity, 97%; area under curve, 0.844 ± 0.14 ; Bcl2: sensitivity, 83%; specificity, 65%; area under curve, 0.769 ± 0.12). By stratifying the patients according to the obtained cutoffs, significant differences emerged in the patients' disease-free survival (log-rank test: Mib1, $P = 0.0001$; Bcl2, $P = 0.01$).

Conclusions: Mib1 and Bcl2 significantly discriminate between recurrent versus nonrecurrent tumors, producing a biologically plausible, diagnostically suitable immunohistochemical pattern.

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