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Beta-catenin expression is prognostic of improved non–small cell lung cancer survival

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Molecular prognosticator

Abstract

INTRODUCTION: The objectives of this study were to determine the frequency and prognostic significance of beta-catenin expression in a cohort of non-small cell lung cancer (NSCLC) patients.

METHODS: Tissue microarrays were constructed using clinically annotated formalin-fixed paraffin-embedded tumor samples from individuals diagnosed with NSCLC who underwent surgical resection with curative intent and had beta-catenin expression status determined by immunohistochemistry.

RESULTS: Negative beta-catenin expression was seen in 28% (103/370) of NSCLC cases and was prognostic of a reduced overall patient survival ($P = .008$) and also was significantly correlated with the presence of lymphatic invasion ($P = .015$). In multivariate analysis, the loss of beta-catenin expression retained independent prognostic significance and showed an adjusted hazard ratio of 3.18 (confidence interval, 1.46-6.91, $P = .004$) for reduced patient survival when adjusting for the presence of lymphatic invasion, tumor grade, nodal status, and tumor stage.

CONCLUSIONS: Beta-catenin represents an important prognostic marker in individuals diagnosed with surgically resectable NSCLC.

Lung cancer remains the leading cause of cancer-related deaths in North America. Despite considerable research, the mortality rate for lung cancer patients is high, and adjuvant chemotherapeutic agents have shown only a modest survival benefit.[1] Many studies have focused on the identification of clinicopathologic characteristics that aid in disease prognostication and treatment. A large number of potential patient-related and tumor-related prognostic factors have been reported although there are many conflicting studies in

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the literature.[2] Currently, the most recognized and reliable clinical variables used in the management of non–small cell lung cancer (NSCLC) patients are disease stage, weight loss, and performance status.

A few prognostic molecular markers that show promise in the management of NSCLC have been reported in the current literature. These include markers involved in oncogenesis and tumor growth, cell cycle regulation, cancer invasion and metastasis, and angiogenesis.[2–4] Cancer cells gain the ability to dissociate from neighboring cells, migrate, and invade local and distant tissues.[5] Thus, invasiveness and metastasis are characteristics that are essential for tumors to evolve and progress and often lead to an aggressive cancer phenotype and advanced tumor stage.

Tumor invasion and metastasis occur when tumor cells gain the ability to detach from the primary tumor and enter into surrounding tissue or lymphovascular channels, a process that is critically dependent on the disruption of adhesion junctions between tumor cells.[6,7] Cadherins are transmembrane glycoprotein domains that form physical interactions between neighboring cells in a dimeric zipper-like configuration,[8] and they are coupled to the cytoskeleton by catenins.[9] The disruption of any component of the adhesion junction, through reduced or altered protein expression, results in disassembly of the adhesion complex and subsequent escape of tumor cells.[10] Clinically, such cancer behavior translates into tumor aggressiveness and advanced tumor stage. The objective of this study was to determine the frequency and potential prognostic significance of beta-catenin expression in patients with NSCLC.

Materials and Methods

Study patients

The study population consisted of 609 patients diagnosed with early-stage NSCLC who underwent surgical resection with curative intent between 1978 and 2002 at a tertiary care referral center in Vancouver, British Columbia, Canada (St. Paul's Hospital). The study patient population has been well characterized and reported in the literature.[11] Patients in the study were evaluated and treated according to provincial guidelines. Individuals diagnosed with non-primary NSCLC, tumors with neuroendocrine differentiation, or mesotheliomas were excluded from the analysis. This study was approved by the Research Ethics Boards of the University of British Columbia.

Abstracted clinical data included patient age, tumor histology, lymph node status, tumor grade, tumor stage, presence of lymphatic invasion, type of local therapy, type of systemic therapy (when applicable), and patient survival at follow-up. Survival census was carried out in February 2009 using the patient registry of the British Columbia Cancer Agency (BCCA). The BCCA is a population-based referral center that provides radiation and systemic therapy consultation, treatment, and follow-up for cancer patients in British Columbia, Canada.

Tissue microarray construction, staining, and evaluation

A tissue microarray (TMA) was constructed using paraffin-embedded archival blocks from each patient's tumor with a methodology that has been previously described.[12] Duplicate 0.6-mm tissue cores were used from each patient's tumor. Beta-catenin expression was evaluated by immunohistochemistry (beta-catenin mouse monocolonal antibody clone 14; Cell Marque Corporation, Rockland, CA) according to the manufacturer's instructions. Heat-induced antigen retrieval was used, and the final antibody concentration was 1:100. Marker expression was evaluated by a pathologist who was blinded to all clinical data. The marker expression was assigned a numeric score based on cytoplasmic and/or membranous tumor cell staining as follows: 0 (<5% of cells stained), 1 (5%–25% of cells stained), 2 (25%–75% of cells stained), and 3 (>75% of cells stained). The marker scores were then

Table 1 Patient clinicopathologic characteristics and survival outcome of the study patients

Clinicopathologic characteristic	Number (%) of tumors
Age (y)	
<50	56 (10.7)
50–59	114 (21.8)
60–69	211 (40.4)
>70	137 (26.2)
Unknown	4 (.8)
Sex	
Female	179 (34.3)
Male	341 (65.3)
Unknown	2 (.4)
Smoking (pack years)	
<50	220 (42.1)
50 or greater	180 (34.5)
Unknown	122 (23.4)
Histological classification	
Adenocarcinoma	219 (42.0)
Squamous-cell carcinoma	242 (46.4)
Large-cell carcinoma	30 (5.7)
Non–small-cell carcinoma NOS	31 (5.9)
Outcome (review February 2009)	**Number (%) of tumors**
Overall survival	
Alive	69 (13.2)
Died	453 (86.8)
Disease-specific survival	
Died of NSCLC	297 (56.9)
Died of non-NSCLC causes	114 (21.8)
Cause of death unavailable	42 (8.0)

NOS = not otherwise specified.