Journal on Oncology

www.journalononcology.org

Research Article

Open Access, Volume 3

Typical Pulmonary Carcinoid Tumours and the Relevance of Ki-67 Index: A Tertiary Centre Experience in South Australia

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Introduction

Pulmonary carcinoid tumours are a rare type of neuroendocrine primary lung malignancy. The WHO classifies carcinoids as typical (TC) and Atypical Carcinoid (AC) based on mitotic rate and necrosis on histology [1,2]. It is widely accepted that TC has a better overall prognosis than AC. A higher stage (the presence of nodal or metastatic disease) at presentation is correlated with poorer outcomes [3]. Ki-67 is an immunohistochemical marker used to determine proliferative activity that is well established as a diagnostic and prognostic tool in gastrointestinal neuroendocrine tumours. However, its use has not been validated in pulmonary carcinoid and there is conflicting evidence of its clinical utility [4]. We performed this retrospective study to determine the relationship between histological subtype, extent of disease at presentation and Ki-67 index in pulmonary carcinoid tumours.

Methods

Patients with biopsy-proven pulmonary carcinoid were retrospectively identified between 1992-2019. 70 patients were identified from the pathology database of Flinders Medical Centre and Royal Adelaide Hospital (tertiary teaching hospitals in South Australia). Demographic data, stage of disease (on imaging), histological subtype and Ki-67 proliferative index data were collected. Specimens included resections (pneumonectomy, lobectomy or wedge resection) and small biopsies (bronchoscopic or percutaneous-guided biopsy) as indicated in routine care of the patient. If both types of samples (biopsy and subsequent resection) were collected from a single individual, only the resected sample was included in the data analysis. Staging was established based on imaging results at diagnosis as per the finalised radiologist report. The imaging modality was noted [Gallium-68 Dotatate positron emission tomography (Ga-PET), Fluorodeoxyglucose positron emission tomography (FDG-PET) or computerized tomography (CT)]. Pathological staging was recorded in resected samples. Non-local disease was defined by nodal or metastatic involvement. For samples with missing Ki-67 index during initial review, blocks were retrieved and IHC for Ki-67 was performed in a NATA accredited pathology laboratory using QAP-validated protocols. All Ki-67 indices were reported by a single experienced pathologist. The Ki67 index was expressed as <5% or > 5%, based on existing studies suggesting this cut-off value as providing the best fit for predicting overall survival [5]. This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (approval number 40.20).

Manuscript Information: *Received: Mar 10, 2023; Accepted: Apr 14, 2023; Published: Apr 21, 2023*

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Citation: *Li A, Dougherty B, Klebe S, Mukherjee S, Rose A. Typical Pulmonary Carcinoid Tumours and the Relevance ofKi-67 Index: A Tertiary Centre Experience in South Australia. J Oncology. 2023; 3(1): 1085.*

Results

In this cohort of 70 patients, 58 (83%) were diagnosed with TC and 12(17%) with AC. Majority of the patients were female. Most patients had a surgical resection 42/70 (79%). Small biopsies (diagnostic sampling) were performed in 28/70 (21%).

Table 1: Patient demographics.

	Females	Males
Typical n (%)	34 (59%)	24 (41%)
Atypical n (%)	7 (58%)	5 (42%)
Age (years) ± SD	51 ± 11.3	58 ± 17.7

Table 2: Proportion of patients with TC and AC with local and non-local disease.

		Typical n (%)	Atypical n (%)
Local		44 (76%)	6 (50%)
Non-local	Locoregional	10 (17%)	2 (17%)
	Metastatic	4 (7%)	4 (33%)
		N = 58	N = 12

A subgroup of patients with typical carcinoid [14/58 (24%)] presented with locoregional or metastatic disease on imaging (8 Ga-PET, 2 FDG-PET, 4 CT) at presentation. A low proliferation index (Ki-67 <5%) was observed in 12/14 (86%). 1 patient with local disease on initial imaging (CT scan) was up-staged with nodal involvement on resection with a normal Ki-67 (<5%).

In patients with atypical carcinoid, 6/12 (50%) presented with non-local disease and 4/6 (67%) had a Ki-67>5%. However, numbers were too small to suggest a trend with Ki-67 in this group.

Discussion

Ki-67 is a proliferation marker that was first investigated as a marker of prognosis in the pancreas. It is established as a diagnostic tool for gastrointestinal neuroendocrine tumours [6-9]. Its utility for risk stratification in pulmonary neuroendocrine tumours is less clear, and the current WHO classification does not suggest its use as a routine investigation for that purpose [10]. The International Association for the Study of Lung Cancer has recommended use of Ki-67 in distinguishing typical carcinoid tumours from higher grade neuroendocrine tumours (large cell neuroendocrine tumour and small cell carcinomas), especially in crushed samples. However, its role in diagnosis and prognosis in pulmonary carcinoid tumours is not established [11].

Despite lack of high-level evidence and consensus in its role, Ki-67 is commonly used in clinical practice. A survey among 33 oncologists at a North American Society for Neuroendocrine tumour society meeting showed a consensus in opinion of the use of Ki-67 proliferation index in treatment related decisions [5]. There has been some evidence suggesting that a cut-off value of 5% may have prognostic value on survival and recurrence rates. The largest retrospective study to date (n=256) analysed patient outcomes with surgically resected pulmonary carcinoid tumours based on histology and Ki-67-index. Patients with TC and Ki-67%<5% had a significantly higher survival probability than those with Ki-67>5% [5]. Other studies have shown Ki-67 did not have a role in survival [12-14].

Results from a review article summarising 12 retrospective studies assessing Ki-67% cut-off values that provide significant prognostic information were inconclusive. A range of cut-off values used in the various studies ranging from 1% to 7% was observed. The heterogeneity in cut-off values limited the ability to interpret and draw meaningful conclusions from these investigations [5]. Another major confounder in interpreting published literature is the different, non-standardised quantitation method for measuring Ki-67%. This includes: 1. eyeballing the entire specimen to identify 'hot-spots' and manually counting the stained labelling or 2. random counting of stained labelling in the prespecified volume [15]. Our centre used the former technique. A prospective study evaluating Ki-67 using a standardised counting approach is needed to reliably assess its value in disease behaviour and outcomes.

In our investigation, an important observation was a higher-than-expected prevalence of non-local disease for TC (14/58 [24%]). In the literature, incidence of nodal or metastatic involvement with TC varied between 4-15% [2,4]. Ki-67% was low in 12/14 (86%) of these patients, suggesting it was not a useful marker in predicting the extent of disease at presentation in patients with TC.

This study highlights the ongoing uncertainty surrounding Ki-67 as a prognostic marker in pulmonary carcinoid tumours. Studies evaluating this to date have been retrospective and the Ki-67 counting method has been heterogenous. Prospective studies with a standardised counting method and an adequate period of follow-up are needed to accurately determine Ki-67's ability to prognosticate survival.

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