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Prognosis and Outcome of Patients with Pulmonary Carcinoid Tumors: Experience at the MENA Region

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Abstract

Introduction: Carcinoid tumors are a subset of neuroendocrine tumors, with Pulmonary Carcinoids (PC) being the second most involved type. PC are classified into Typical (TC) and Atypical (AC) subtypes. They have a low incidence, with relatively high survival rates. In this study, we report the characteristics, prognosis, and outcomes of patients with PC at the American University of Beirut Medical Center (AUBMC) to better understand these tumors and their prognostic markers. To our knowledge, this is the first study of its kind in the Middle East and North African (MENA) region.

Materials and Methods: This is a retrospective chart-review based study at our tertiary referral center, with 36 consecutive patients with PC from 1993 till 2017. Information collected encompassed demographics, tumor characteristics, recurrence, and survival. All patients were called as the last follow-up on 24/1/2019.

Results: 39% of patients were asymptomatic at diagnosis. Most patients had early-stage disease. 80% of patients had typical PC, and 20% had atypical PC with both subtypes having good outcomes, except for a higher progression rate among atypical subtype (60%). The median time to disease progression or recurrence was 6 years. Only 2 patients passed away. Immunohistochemical (IHC) markers were not assessed in all patients and those tested showed high sensitivity for chromogranin A (82%) and synaptophysin (100%).

Conclusion: Our study gives insight about patients with PC in Lebanon and the MENA region with a low incidence of disease. Most patients are surgically treated and have a good survival rate. IHC markers should be better implemented. Larger studies are needed to elaborate and verify our results.

Keywords: Carcinoid tumors; Lung; Neuroendocrine tumor; Chemotherapy; Surgery; Radiation

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Introduction

Carcinoid tumors are a subset of neuroendocrine tumors. Most carcinoid tumors arise from the gastrointestinal tract, with a prevalence of around 60%. The pulmonary system is the second most commonly involved system, with a prevalence of around 27% [1,2]. Pulmonary neuroendocrine tumors represent a spectrum that includes the most aggressive variant of Small Cell Lung Cancer (SCLC), Pulmonary Carcinoids (PC), Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH), and other less aggressive forms [3]. PC can secrete various hormones, thus resulting in carcinoid syndrome, variants of carcinoid syndrome, rarely Cushing's syndrome, or other peptide produced endocrine syndromes [4].

Carcinoid tumors of the lung arise from Kulchitsky cells that are present in the bronchopulmonary mucosa [5]. Based on their histological features, PC are generally classified into two subtypes: Typical pulmonary carcinoids (TC) and Atypical pulmonary Carcinoids (AC), with a 9:1 prevalence ratio, respectively [1,2,6]. TC show a high degree of differentiation, rare mitosis (less than 3 mitotic figures per 10 high-power field), and scarce pleomorphism or necrosis. However, AC have increased cellular atypia, intermediate mitotic index (3 to 10 mitotic figures per 10 high-power field), and increased pleomorphism or necrosis [1,6]. AC constitutes 10% of the carcinoid tumors and are located mostly in the lung periphery. AC are larger than TC, more aggressive, and they metastasize more commonly [7].

While their incidence is low at about 5.25 cases per 100,000 in the United States, carcinoid tumors can lead to death in 5% to 25% of patients [1,6]. Typical carcinoids have a better overall

survival rate when compared to atypical carcinoids [8]. The role of chemotherapy and radiation therapy in PC is controversial, and the prognostic significance of the current tumor staging and histologic type remains limited [6].

The diagnostic work-up of PC currently includes the presence of tumor markers. Chromogranin A and synaptophysin are glycoprotein's used as markers for neuroendocrine tumors in serum and tissue, respectively. They belong to the neuron-specific enolase group, considered confirmatory of neuroendocrine origin of tumors. Immunostaining with antibodies to chromogranin A differs depending on the site of origin of carcinoid tumors. For instance, antibodies to chromogranin A fail to stain 40% of hindgut tumors and 12% of foregut carcinoid tumors [8]. Synaptophysin, nevertheless, stains all carcinoid tumors regardless of their site of origin and is very specific and sensitive.

A key point in the proper management of pulmonary neuroendocrine tumors is the multidisciplinary approach. Surgical treatment for PC in both primary tumors, as well as oligometastases, should be considered for curative intent or symptom control in patients with advanced or metastatic disease, depending on the individual patient and the site of disease. Furthermore, when considering systemic therapy, both low-grade typical and atypical PC, in some circumstances, have shown to be somewhat responsive to multiple combination chemotherapeutic drugs in historical data such as temozolomide with or without capecitabine, cisplatin or carboplatin combined with etoposide [9,10]. It is usually recommended in progressive metastases with no other treatment options. Another option for symptom control and slowing disease progression in PC would be somatostatin analogs, such as octreotide, lanreotide or pasireotide, as low-grade lung neuroendocrine tumors often show surface over-expression of somatostatin receptors, to which these analogs bind with high-affinity hindering the secretion of peptides and amines responsible for symptoms and tumor growth [11-14]. Furthermore, there exist yet other options for systemic treatment of PC which include Peptide Receptor Radio-ligand Therapy (PRRT). PRRT is a process whereby a radiolabeled agent, such as 90Y-labeled octreotide or 177Lu-DOTATATE is delivered to a specific target, such as somatostatin receptors [15,16]. Moreover, everolimus, an inhibitor of mTOR (mechanistic target of rapamycin), is an approved potential therapy for patients with advanced lung NET, given the increased activation of the mTOR signaling pathway in lung neuroendocrine tumors [17,18]. Interferon alfa, as well as anti-angiogenic drugs such as bevacizumab, have also been suggested to treat patients with advanced progressing lung NETs such as PC [19-22].

In brief, the indolent course of PC disease, on one hand, and the scarcity of randomized clinical trials investigating the optimal management and prognosis of PC, on the other hand, emphasizes the need for a better understanding of these tumors. In this study, we report the characteristics, prognosis, and outcomes of patients with PC at the American University of Beirut Medical Center (AUBMC) to understand these tumors and their prognostic markers better. To our knowledge, this is the first study of its kind in the Middle East and North African (MENA) region.

We present the following article/cases in accordance with the STROBE reporting checklist.

Materials and Methods

Following the approval of the Institutional Review Board (IRB) at the American University of Beirut, we conducted a retrospective search of all medical records to identify patients with pulmonary carcinoid tumors diagnosed and treated at AUBMC between 1993 and 2017. Patients had consented during their clinical visits to their physicians the right to be contacted later for follow-up. We collected information about demographics, tumor characteristics, staging, as well as recurrence from the medical charts. All patients were called as the last follow-up of this study for survival status on January 24th, 2019. All statistical analyses were done using SPSS Statistics version 20.0.

Results

Patients' characteristics

Thirty-six patients were included in this study, 53% of whom were females. The median age at diagnosis was 50 years (19-71). Thirteen patients (36.1%) were smokers. Two patients (5.6%) had asthma or hypersensitive airway disease, and two patients (5.6%) had a positive family history for malignancy.

Disease characteristics and clinical aspects

Fourteen patients (39%) were asymptomatic at the time of diagnosis. Twenty-two patients (61%) had symptoms including cough, dyspnea, and hemoptysis. Twenty-three patients (63.89%) had pulmonary carcinoid tumor involving the right lung. Focality data was retrieved in 34 patients, of which 29 patients (85.3%) had unifocal disease. The largest tumor diameter documented was 2.6 cm. Twenty-eight patient tumors had typical subtype, and 7 had atypical subtype. 87% of patients had localized disease, whereas 13% had metastatic disease. Pathological assessment of the surgical specimens showed that the majority of patients (84.2%) had no Lymphovascular Invasion (LVI), and 22.7% of patients had positive lymph node involvement.

In our patient population, only 17 patients were tested for

Table 1: Patient and tumor characteristics.

Characteristics	N	%
Smoking Status		
Smokers	13	36.1
Non-smoker	23	63.9
Gender		
Male	17	47.2
Female	19	52.7
Focality		
Unifocal	29	85.3
Multifocal	5	14.7
Histologic type		
Typical	28	80
Atypical	7	20
Lymphovascular invasion		
Absent	16	84.2
Present	3	15.8
Status on last follow up		
Stable	29	80.5
Progression	2	5.6
Recurrence	3	8.3
Deceased	2	5.6

Table 2: Distribution of progression or recurrence according to the histologic type.

Histologic Type		Progression or Recurrence	
		Yes	No
Typical	28	3	25
Atypical	7	4	3
Not Available	1	0	1
Total	36	7	29

Table 3: Survival according to the histologic type.

Histologic Type		Deceased on follow-up	
		Yes	No
Typical	28	1	27
Atypical	7	1	6
Not Available	1	0	1
Total	36	2	34

chromogranin A, of whom 14 patients (82.35%) were positive. Only 16 patients were tested for synaptophysin status, all of which were positive (Table 1).

Disease management

Patients were diagnosed by CT guided biopsies or endobronchial ultrasound-guided biopsies. Staging by the primary caring physician was based on the American Joint Committee on Cancer (AJCC) staging system. Twenty-seven patients (75%) underwent surgical resection except those who had stage four diseases. Only 5 patients (14%) received chemotherapy in the metastatic setting. One patient received radiation therapy in the adjuvant setting. Different regimens included cisplatin and etoposide, docetaxel, gemcitabine, and capecitabine.

Patients' follow-up

The median time of follow up was 6.17 years. The median overall survival was 6 years. The average time to progression or recurrence was 9.67 years, and the median time to progression or recurrence was 6.17 years. On last follow-up, dated January 24th, 2019, 34 patients (94.5%) were alive. Twenty-nine patients (80.5%) had no or stable disease, 2 patients (5.5%) had disease progression, and 3 patients (8.5%) had disease recurrence. Finally, in the 2 patients (5.5%) who passed away, death was attributed to disease progression.

Twenty-five of the 28 patients (89.28%) with typical carcinoids did not have disease progression or recurrence. Among the remaining patients, one progressed after 43 months and had stage IV disease since diagnosis. The second patient progressed after 55 months and passed away in progression. The third patient progressed after 80 months and had a stage IA2 disease at diagnosis.

Out of the 7 patients with atypical carcinoid, 4 patients (57%) had disease progression or recurrence. One patient had a stage IV at diagnosis, progressed after 7 months and passed away. Another patient progressed after 43 months and has stage II B at diagnosis. Moreover, the third patient had stage III A at diagnosis and progressed after 74 months, while the fourth patient who had a stage I A1 at diagnosis and progressed after 17 years (Table 2 and 3).

Discussion

Pulmonary carcinoids are a rare entity of neuroendocrine tumors that comprises a number of histopathologic variants differing in tumor biology and prognosis. Age at diagnosis, histopathological type, and the presence of mediastinal or subcarinal lymph nodes represent independent prognostic factors for overall survival, relative survival, and event-free survival of pulmonary carcinoids [8]. Our study, first of its kind in the MENA region, reviews charts of 36 patients with PC, assesses their clinical characteristics, clinical progression, and survival rates over a median follow up of 6 years.

In our study, we found that the Lebanese patients with pulmonary carcinoid have a 5-year survival rate of 94.5%, relatively comparable with that documented in literature reaching 88% studied in the United States of America [23] and 96% in 102 patients with PC studied by Daskalis et al. [24] in Europe.

Compared to patients with typical carcinoids, those with atypical carcinoids generally have a more aggressive course of disease, worse prognosis, and a greater incidence of lymph node metastasis and recurrence [1]. A study by Song et al. [25] analyzing 68 patients with AC showed 5- and 10-year overall survival rates of 70.6% and 61.8%, respectively. Another study by Chong et al. [3] reported even lower overall survival rates at 5- and 10-years ranging at 35 and 44%. Our study had 7 patients with AC, only 1 patient of which passed away few months after diagnosis, making the 5-year overall survival rate in our AC population 86% which is higher than published data. On the other hand, TC generally has an excellent prognosis, with a 5- and 10-year survival that can reach 90% and 84% respectively. Our patient population showed a TC overall survival rate at 5 years of 96.5%, also better than those in literature. Perhaps, our higher survival rates in both AC and TC patients are because of the high percentage of youth (age range 19-46), healthy status and finally the early stage at diagnosis of most patients in our population, which has previously been correlated with better survival rates [25]. However, regarding progression rates, our results were commensurate with published data, having a recurrence rate of 11% in TC (3 out of 28 patients) versus 57% in AC (4 out of 7 patients) [8,24]. All patients who progressed were non-smokers, and none of them with earlier stages had LVI or LN involvement which may imply the non-relevance of these factors in the prognosis of PC. Nonetheless, patients with earlier disease staging at diagnosis did take a longer duration to progression reaching up to 17 years which suggests correlation with recurrence.

Moreover, the high positive rate of chromogranin A and synaptophysin tested in our patients parallels published data showing high diagnostic sensitivity reaching 82% and 100%, respectively [26]. Unfortunately, not all patients were tested, which may reflect the limited use of these markers in the current practice when diagnosing PC in our region of the world. Another reasonable interpretation may be the delayed incorporation of these markers into clinical use until the new millennium. Other markers with a proven prognostic value such as cyclin A2 and B1 as per Brcic et al. [27], or Spread through Air Spaces (STAS) by Aly et al. [28] or less meaningful prognostic values such as Ki67 were not used in our study population.

Most of our patients underwent surgical resection (n=27, 75%); 14% had chemotherapy and 3% had radiation therapy. Surgical resection remains to be the gold standard treatment for PC, and the vast majority of patients in case-series remain recurrence-free for years following surgery. There is, nevertheless, controversy regarding the most optimal extent of surgery as well as the prognostic significance of systemic chemotherapy and radiation therapy [3,29,30].

In our patient population, 13 patients (36.1%) were smokers, most of typical histopathology. However, AC and not TC are usually reported to be associated with tobacco use [1,4]. Two patients (5.6%) had asthma or hypersensitive airway disease, and 39% of the patients were asymptomatic at the time of diagnosis, whereas 61% had respiratory symptoms, including cough and pneumonia. These findings compare to published data where the clinical presentation includes cough, recurrent pneumonia, dyspnea, hemoptysis, wheezing, and fevers. In contrast, the diagnosis for some patients may be entirely incidental with no presenting symptoms [31,32].

Study Limitations

Our study has several limitations. The first limitation is the retrospective design of the study, which introduced incomplete documentation and retrieval of data, as information relied on chart review. The small sample size, when analyzing specific variables, including histologic type, lymph vascular invasion, and management, is another limitation. However, our study has two significant points of strength. First, the sample size is relatively adequate when taking into consideration the rarity of the disease with an incidence as low as 5.25 cases per 100,000 in the United States [1,6]. Second, to our knowledge, this study is the first of its kind in the Middle East and North Africa (MENA) region, with scarce data regarding the prevalence and management of pulmonary carcinoids in this part of the world.

Conclusion

Pulmonary carcinoids (except SCLC) are rare neuroendocrine tumors with a good prognosis in general. They are under-studied in our part of the world. In our study population, typical and atypical pulmonary carcinoids showed a very good median overall survival of 6 years, with a 5-year overall survival of 96.5%% and 86% respectively. TC were associated with a lower recurrence rate (11% for TC *vs.* 57% for AC). This implies that the Lebanese and MENA population of carcinoid patients is similar in terms of survival, recurrence, and diagnosis of those published worldwide. Smoking, LVI and LN status did not impact outcome, but early stage at diagnosis may have played a role in prognosis. Chromogranin A and synaptophysin are good diagnostic markers and should be used more often in our population. Other prognostic markers including Cyclins and STAS were not used and no conclusion can be drawn from our study about their prognostic impact in the Lebanese and the MENA region population.

In conclusion, more extensive studies are needed to better understand the prevalence of PC, the importance and role of different markers in PC, and the optimal management of such disease in Lebanon and MENA region. Perhaps building a joint collaborative research network between referral centers in our region can help perform more studies and include more patients with this rare disease, as well as fund the use of more prognostic markers.

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