The Post-Surgical Long-Term Behaviour of Lung Carcinoid Tumours

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Abstract Here, we report a retrospective evaluation of long-term behaviour of lung carcinoids after surgery. A total of 23 patients (17 with typical pulmonary carcinoids and 6 with atypical pulmonary carcinoids) were enrolled in our hospital from April 1994 to July 2009. All patients underwent intervention at the Unit of Surgery and then were followed at the Unit of Oncology. The standard protocol for patient monitoring consisted of follow-up at 3 months after surgery, 6 months after first control and annually for 5 years. The follow-up evaluations consisted in blood tests, imaging of chest and abdomen, bone scintigraphy, and brain computed tomography. In case of disease recurrence, patients underwent chemotherapy (etoposide, carboplatin) and radiotherapy. All patients were followed for a mean of follow-up period of 100 months, ranging between 20 and 203 months. In the group of typical carcinoid, the observed recurrence rate at

5 years was zero, at 10 years was 5.8 %, whereas the observed mortality rate at 5 and 10 years was zero. In the group of atypical carcinoid, both the recurrence rate and the mortality rate at 5 and 10 years were 16.6 %. A statistical significant difference ($p=0.002$) in the recurrence rate between stage I and stage II was observed. The overall prognosis of pulmonary carcinoids was favourable, and the typical carcinoids presented a better prognosis than the atypical ones. The stage at time of diagnosis could be considered as a predictive prognostic factor.

Keywords Carcinoid tumours · Lung cancer · Lymph node metastasis · Tumour behaviour · Long term follow-up

Introduction

Neuroendocrine tumours (NETs) of the lung comprise approximately 20 % of all primary lung cancers and are grouped in four histological categories: typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma and small-cell carcinoma [1, 2].

The small-cell carcinoma accounts for 13–17 % of all primary tumours of lung, and the other three types together account for 3–7 % [1, 2].

NETs of lung could be conceived as a spectrum of malignant tumours with different biological characteristics and different prognosis [1, 3].

Here, we report our experience in a retrospective evaluation of post-surgical long-term behaviour in 23 typical and atypical lung carcinoids affected patients.

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Materials and Methods

A total of 23 patients, 17 with typical pulmonary carcinoid and 6 with atypical pulmonary carcinoid were admitted for intervention at the Unit of Surgery and then followed at the Unit of Oncology of our hospital, from April 1994 to July 2009.

The preoperative evaluation consisted of imaging thoracic study by chest computed tomography or chest magnetic resonance imaging. The location and the size of the nodule and therefore the possibility of its surgical removal were investigated. For central located carcinoids, the bronchoscopy allowed preoperative evaluation of the nodule. All patients underwent blood test for cancer markers analysis and were evaluated by abdominal ultrasound and/or abdominal computed tomography and bone scintigraphy to stage tumour.

Histological examination was made according to the current World Health Organization (WHO) criteria for classifying pulmonary neuroendocrine tumours. Neoplasms with carcinoid morphology, greater than 5 mm in diameter, with less than two mitoses per 2 mm² and lacking necrosis were considered typical carcinoids, whereas neoplasms with carcinoid morphology and with the mitosis number comprised between 2 and 10 per 2 mm² were considered atypical carcinoids [2].

The final pathological stage of all patients was defined using the TNM classification for non-small-cell lung cancer (the seventh edition) [4].

The standard protocol for patients monitoring consisted of follow-up at 3 and 9 months after surgery, and then annually for 5 years. The first controls after surgery were made at our hospital for all patients. Because of the very long follow-up period, some patients (especially those who came from far away) were no longer willing to undergo the controls at our hospital and made them independently. Therefore, at the census time, we contacted by telephone all patients lost from our outpatient department, questioned them about their health and assessed them according our oncological follow-up protocol.

The follow-up protocol comprised medical and radiological evaluations consisting in blood tests, chest computed tomography, abdominal ultrasound scan and/or abdomen computed tomography, bone scintigraphy, and brain computed tomography. In case of disease recurrence, patients underwent chemotherapy by etoposide and carboplatin and radiotherapy.

Two sets of Kaplan-Meier survival curves were generated based on the overall survival (Fig. 1) and the different survival between the two groups of typical and atypical carcinoids (Fig. 2).

A third Kaplan-Meier curve shows the different onset time of relapse between the two groups (Fig. 3).

Because no patients with atypical carcinoid had stage II, the difference in recurrence rate between the stage I and II was

Fig. 1 The Kaplan-Meier curve for the overall survival analysis. Hash marks represent the two patients lost from the study (they died because of a different cause from the carcinoid progression)

evaluated by chi-squared test both in the group of typical carcinoid and in the group of all 23 patients (considering the two groups as one).

Results

A total of 23 patients affected by typical or atypical carcinoid tumour of the lung were enrolled at the IRCCS “Casa Sollievo della Sofferenza” Hospital from April 1994 to July 2009 and were operated and followed at the Units of Surgery and Oncology.

Table 1 shows the clinic-pathological information for each lung carcinoid affected patient.

The group of typical carcinoid included 17 patients and the group of atypical carcinoid included 6 patients; the males were 12, the females 11 and the mean age was 56.7 years (range 29–

Fig. 2 The Kaplan-Meier curves show the different survival between the two groups of typical and atypical carcinoids. Hash marks represent the two patients lost from the study (they died because of a different cause from the carcinoid progression)

Fig. 3 The Kaplan-Meier curve for disease recurrence, showing the disease recurrence in typical vs atypical lung carcinoid tumours. The analysis shows a more delayed in the first carcinoid group than in the second one and the recurrence probability in the atypical carcinoid group (16.6 % at 5 years) greater than in the typical one (5.8 % at 10 years). Hash marks represent the two patients lost from the study (they died because of a different cause from the carcinoid progression)

79 years). The mean follow-up period was 100 months ranging between 20 and 203, and the median was 108 months. In the group of typical carcinoid, the recurrence rate at 5 years was zero, at 10 years was 5.8 %; the mortality rate at 5 and 10 years was zero. In the group of atypical carcinoid, both the recurrence rate and the mortality rate at 5 and 10 years were 16.6 %.

In the group of atypical carcinoid 1 out of 6 patients (16.6 %) had disease recurrence and subsequently died. He developed brain metastases 12 months after surgery and then was subjected to radiotherapy on the brain and chemotherapy with carboplatin and etoposide; he died 23 months after surgery and 11 months after progression of neoplasm.

In the group of the typical carcinoid, 1 out of 17 patients (5.8 %) had disease recurrence and he was still alive at the time of the census. He developed lymph node metastasis of the chest 84 months after surgery and then was subjected to radiotherapy on the thorax and chemotherapy with carboplatin and etoposide; at the time of the census, i.e., 120 months after surgery and 36 months after progression, he was still alive and without further recurrence.

Furthermore, at the time of the census, in the group of typical carcinoid, two patients had died because of a different cause from the current study disease progression: the first one died (67 years old) after 92 months of follow-up for an ovarian tumour, she had no progression of carcinoid tumour; the second one died (81 years old) after 132 months of follow-up for senescence, without any progression of disease. For the period they lived, these last two patients were considered disease free because they did not die for carcinoid progression.

In the group of typical carcinoid, the patient who had progression was the only one with stage IIA because of chest lymph nodes involvement at diagnosis; the chi-squared test for the difference in recurrence rate between stage I and stage II resulted significant ($p=0.001$).

Furthermore, considering the two groups as a single group of 23 patients because no patient with atypical carcinoid had stage II, the chi-squared test for the difference in recurrence rate between stage I and stage II resulted significant ($p=0.002$).

In conclusion, both the typical and the atypical carcinoid tumours of lung had a favourable prognosis at a long-time follow-up period (Fig. 1); the typical carcinoid showed a better prognosis than the atypical one (Fig. 2) because it had a more delayed relapse (Fig. 3).

The stage at diagnosis time could be considered a predictive prognostic factor ($p=0.001$ and $p=0.002$).

Discussion

The bronchial carcinoids are tumours that originate from diffuse neuroendocrine system cells (amine precursor uptake decarboxylase [APUD] cell system), include the typical carcinoids and the atypical ones and represent 1–2 % of all pulmonary tumours [1, 5–7].

Incorrectly termed ‘bronchial adenomas’, they are malignant uncommon primary neoplasms that characteristically involve the central airways and typically exhibit well-defined margins and bronchial-related growth [1, 5, 6].

Moreover, they are classified as neuroendocrine tumours because of their potential to form and sometimes secrete a variety of chemical substances even if a carcinoid syndrome, due to ectopic hormone production, is rarely presented [6].

Overall, 75 % of them arise in the lobar bronchi, 10 % in the main-stem bronchi, and 15 % in the periphery of the lung [6].

The typical carcinoids present a well-differentiated histology, a low aggressiveness and constitute almost 90 % of all bronchial carcinoids, instead atypical carcinoid tumours have a higher malignant potential and then are more aggressive [1, 5, 6, 8].

The treatment of choice for lung carcinoids is surgical resection even if the debate about the type of surgery to be performed is still open especially for peripheral tumours [5, 9–11]. In fact, in case of central nodules a lobectomy or pneumonectomy is mandatory for anatomical reasons, instead in case of peripheral nodules, given the lack of aggressiveness of carcinoids, a sub-lobar resection could be taken into consideration [9, 10].

The lymph node status has to be always considered because of its impact on the prognosis; therefore, a hilar and

Table 1 Analytical data of each lung carcinoids affected patient

Number	Gender (M/F)	Age (years)	Histo	Tumour size (cm)	T	N	M	Stage	Surgery	Progression	Chemotherapy	Radiotherapy	Status	ObP (months)	DFS (months)
1	M	50	Typical	1.7	1a	0	0	IA	RML	No	No	No	Alive	91	91
2	F	67	Typical	1.5	1a	0	0	IA	RML	No	No	No	Alive	130	130
3	F	57	Typical	2.8	1b	0	0	IA	LLL	No	No	No	Alive	36	36
4	F	70	Atypical	2.5	1b	0	0	IA	LUL	No	No	No	Alive	124	124
5	M	54	Atypical	1.5	1a	0	0	IA	LLL	No	No	No	Alive	203	203
6	M	71	Atypical	3.0	1b	0	0	IA	LLL	Yes (brain)	Eto + carbo ^a	Brain ^a	Dead ^b	23	12
7	F	29	Typical	3.5	2a	0	0	IB	RLL	No	No	No	Alive	157	157
8	M	48	Typical	3.3	2a	0	0	IB	RLL	No	No	No	Alive	172	172
9	M	52	Typical	2.8	1a	1	0	IIA	RML	Yes (chest)	Eto + carbo ^a	Chest ^a	Alive	120	84
10	F	70	Typical	2.5	1b	0	0	IA	RMLL	No	No	No	Dead ^c	132 ^c	132 ^c
11	M	57	Typical	4.0	2a	0	0	IB	RMLL	No	No	No	Alive	180	180
12	F	36	Typical	2.5	1b	0	0	IA	LUL	No	No	No	Alive	124	124
13	F	59	Typical	3.0	1b	0	0	IA	PNEU	No	No	No	Dead ^d	92 ^d	92 ^d
14	M	69	Typical	3.0	1b	0	0	IA	RLL	No	No	No	Alive	66	66
15	M	47	Atypical	4.0	2a	0	0	IB	RLL	No	No	No	Alive	67	67
16	M	49	Atypical	1.8	1a	0	0	IA	LLL	No	No	No	Alive	124	124
17	F	67	Atypical	4.0	2a	0	0	IB	RMLL	No	No	No	Alive	142	142
18	M	71	Typical	2.0	1a	0	0	IA	LUL	No	No	No	Alive	108	108
19	F	35	Typical	3.5	2a	0	0	IB	PNEU	No	No	No	Alive	52	52
20	F	30	Typical	2.9	1b	0	0	IA	RUL	No	No	No	Alive	50	50
21	M	70	Typical	1.5	1a	0	0	IA	RLL	No	No	No	Alive	47	47
22	F	68	Typical	3.0	1b	0	0	IA	ATYP	No	No	No	Alive	40	40
23	M	79	Typical	3.5	2a	0	0	IB	LUL	No	No	No	Alive	20	20

ObP observation period, DFS disease-free survival, LUL left upper lobectomy, LLL left low lobectomy, RUL right upper lobectomy, RML right middle lobectomy, RLL right low lobectomy, RMLL right middle and low lobectomy, PNEU pneumonectomy, ATYP atypical resection

^a The patient underwent chemotherapy (eto + carbo = etoposide and carboplatin) and radiotherapy after progression disease

^b The patient dead for carcinoid progression

^c The patient had no carcinoid progression and dead for senescence; therefore, she was considered disease free for the period she lived

^d The patient had no carcinoid progression and dead for ovarian tumour; therefore, she was considered disease free for the period she lived

mediastinal lymphadenectomy have to be always associated to the lung resection [5, 10].

Endoscopic resection is considered a safe treatment only in case of pedunculated and polypoid endobronchial carcinoids without extension through the cartilaginous wall of the bronchus; therefore, it has been described in highly selected cases and requires a frequent follow-up [7, 12, 13].

In the other hand, some authors argue the endoscopic resection may represent a bridge therapy before surgery, permitting to improve the respiratory function and to accurately define the implant basis of the tumour [7].

The treatment by somatostatin analogues represents the specific therapy of syndromic patients, i.e., those with carcinoid syndrome, acromegaly, or Cushing's syndrome. Interferon therapy was only indicated when the somatostatin analogue fails [14–18].

There is no role for adjuvant and neoadjuvant chemotherapy in typical and atypical carcinoid; nevertheless, a first-line chemotherapy treatment has been described effective in cases of progression after somatostatin analogues and interferon. In these cases, the most frequently used drugs are cisplatin and etoposide, and some studies show the effectiveness of other drugs such as the combination of capecitabine and oxaliplatin, or the combination of capecitabine and temozolomide [19, 20].

Limited series studies show that a combined chemo-radiotherapeutic treatment can be performed with cisplatin and etoposide in the absence of a therapeutic alternative [21].

The prognosis of bronchial carcinoid is favourable despite their potential to spread with local recurrences and distant metastases of liver, brain and skeleton [1, 3, 5, 6, 8].

Conclusion

To sum up, our study about the long-term follow-up of pulmonary carcinoids demonstrated an excellent overall survival after adequate surgery even if they are malignant neoplasms.

Specifically, both typical carcinoids and atypical ones have tendency to metastasize, but the typical carcinoids manifest a less aggressive behaviour and a better prognosis than the atypical ones because they have a better survival, a more delayed relapse and a more slow progression after recurrence.

Furthermore, in our institutional experience, the lung carcinoid prognosis was found strictly related to the stage of the disease, in fact different stages (I or II) at diagnosis time significantly impacted the recurrence rate ($p=0.001$ and $p=0.002$); therefore, it could be considered a predictive prognostic factor.

Conflict of Interest None declared.

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