Pulmonary Sarcomatoid carcinoma: a surgical diagnosis and prognostic factors

Les carcinomes sarcomatoïdes du poumon de diagnostic chirurgical et leurs facteursPronostiques

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RÉSUMÉ

Introduction: Les carcinomes sarcomatoïdes pulmonaires constituent un groupe rare de tumeurs représentant environ 0,4% du carcinome pulmonaire non à petites cellules (NSCLC).
Cinq sous-types ont été décrits: le carcinome pléomorphe, le carcinome à cellules fusiformes, le carcinosarcome, le carcinome à cellules géantes et le blastome pulmonaire. Le diagnostic est anatomopathologique mais nécessite un prélèvement de bonne qualité de la tumeur.
Méthodes: Sur une série de 1582 patients opérés pour un cancer du poumon de 1992 à 2016, 43 patients ont été rétrospectivement identifiés comme ayant été traités chirurgicalement pour un carcinome sarcomatoïde pulmonaire.
Résultats: La population était composée de 33 hommes et 10 femmes avec un âge moyen de 55 ans. Les résultats d'imagerie ont montré une masse périphérique dans la majorité des cas (n= 29). Les investigations n'ont pas montré une lésion primitive ailleurs. Six patients ont reçu un traitement d'induction pour une atteinte pariétale. Une lobectomie ou une bilobectomie a été réalisée chez 30 patients et une pneumonectomie chez 11 patients. Un wedge a été réalisé chez un patient et une thoracotomie exploratrice chez un autre. Macroscopiquement, la taille moyenne de la tumeur était de 5,2 cm (1-17,5 cm). Les diagnostics histologiques étaient: carcinome pléomorphe (n = 30), carcinosarcome (n = 5), carcinome à cellules fusiformes (n = 1), carcinome à cellules géantes (n = 3) et blastome (n = 4). Deux patients sont décédés dans un mois de complications chirurgicales et cinq sont morts de leur maladie dans les 17 mois. Un traitement adjuvant a été réalisé chez 6 patients. La récidive s'est produite chez 4 patients dans les 12 mois après l'opération. La survie médiane pour tous les patients était de 8 mois.
Conclusions: La résection du carcinome sarcomatoïde pulmonaire primitif est associée à un taux de survie acceptable si la résection est complète. La taille de la tumeur est le facteur pronostique le plus important. Néanmoins, un suivi attentif est essentiel.

Mots-clés
Cancer du poumon; Carcinome sarcomatoïde, Chirurgie, Pronostic

SUMMARY

Introduction: Pulmonary Sarcomatoid Carcinoma (PSC) is a rare group of tumors accounting for about 0.4% of non-small cell lung carcinoma (NSCLC). Five subtypes were described: pleomorphic carcinoma, spindle cell carcinoma, carcinosarcoma, giant cell carcinoma and pulmonary blastoma. The diagnosis is pathological but requires a good quality sampling of the tumor.
Methods: On a series of 1582 patients operated on for lung cancer from 1992 to 2016, 43 patients were retrospectively identified as having been treated surgically for pulmonary sarcomatoid carcinoma.
Results: The population consisted of 33 males and 10 females with mean age of 55 years. Imaging findings showed a peripheral mass in the majority of cases (n=29). Careful investigation failed to discover a primitive lesion elsewhere. Six patients received induction therapy for wall involvement. Lobectomy or bilobectomy was performed in 30 patients and pneumonectomy in 11 patients. A wedge resection was performed in one patient and an exploratory thoracotomy in another. In macroscopy, the mean tumor's size was 5.2 cm (1-17.5cm). The histologic diagnoses were: pleomorphic carcinoma (n=30), carcinosarcoma (n=5), spindle cell carcinoma (n=1), giant cell carcinoma (n=3) and blastoma (n=4). Two patients died within 1 month of surgical complications and 5 died of disease within 17 months. Adjuvant therapy was performed in 6 patients. Recurrence happened in 4 patients within 12 months after operation. Median survival for all patients was 8months.
Conclusions: Resection of primary pulmonary sarcomatoid carcinoma is associated with an acceptable survival rate if the resection is complete. The size of the tumor is the most important prognosis factor. Nevertheless, a carefully follow-up is essential.

Key-words
lung cancer; Sarcomatoid carcinoma, Surgery, Prognosis

INTRODUCTION

Pulmonary sarcomatoid carcinoma (PSC) is a rare form of cancer in which the cells show properties characteristic of both epithelial and mesenchymal tumors. It account for 0.1%-0.4% of all pulmonary malignant tumors[1].The 2004 world Health organisation (WHO) classification defined them as poorly differentiated non-small cell carcinoma that contains a component of sarcoma or sarcoma-like elements (at least 10% spindle and/or giant cells) or a carcinoma consisting only of spindle and giant cells [2]. PSC has histological variants that include pleomorphic carcinoma, giant cell carcinoma, spindle cell carcinoma, carcinosarcoma, and blastoma [1]. It can occur in multiple organs, counting skin, bone, thyroid, breast, liver, pancreas, urinary tract, and lung [3]. Clinical presentation may differ, including chest pain, dyspnea, cough, and hemoptysis. Sarcomatoid carcinoma is very aggressive, with an overall 5-year survival rate of approximately 20% [4]. Limited data has shown that most cases of sarcomatoid carcinomas occur with advanced local disease and metastasis. Because of the rarity of presentation, the prognosis and the appropriate treatment for these tumors remain uncertain.
We aimed in this study to evaluate the prognostic factors after surgical resection of sarcomatoid carcinoma.

METHODS

On a period of 24 years, 1582 patients were operated on for lung cancer from 1992 to 2016, 43 patients were retrospectively identified as having been treated surgically for primary pulmonary sarcomatoid carcinoma. Clinical data, surgical reports and microscopic results were available for all patients.

Preoperative Assessment: Complete clinical history, physical exam, hematological and biochemical tests, bronchoscopy, CT scan of the chest, the brain and the upper abdomen, electrocardiography and spirometry were practiced for every patient before undergoing surgery. PET scan is not available in our institution it was not performed for our patients.
Bone scan was performed in the presence of bone pain.

Postoperative assessment: Histologically, the tumors were classified according to the WHO histological classification of lung tumors published in 2004. The cancer stage was defined according to the TNM staging system proposed in 2009. It was recommended for all patients to be seen by the surgeon at one month and every 3 months after the surgery.
Unfortunately, finding exact year survival for all patients was difficult; first because we are the unique thoracic surgery department in the country which made it hard to join all patients and second because 20% of patients were operated on in the two last years.
Statistical analysis: Follow-up information was obtained by direct telephone interview with patients or, in case of deaths, with families. Referring physicians were also contacted to confirm data obtained from patients or the families interview. Overall survival rates (including non cancer-related deaths) were calculated by the Kaplan-Meier method and compared by the log-rank test. Results were considered significant at a value of $p < 0.05$.

RESULTS

There were 33 male (77%) and 10 female (23%) with a median age of 55 years (range 12-75).
Twenty seven patients (63%) were smokers. All patients presented with thoracic symptoms such as chest pain in twenty nine patients, hemoptysis in 27 cases, cough in 24 cases, shortness of breath in 11 cases, and weight loss in 1 case.
Only 12 patients had visible endobronchial tumours. The majority of neoplasms presented as large peripheral masses (Figure 1). The tumour location was peripheral in 36 (83.7%) and central in 7 (16.3%) cases. Also 65% of the tumours were located in the upper lobes (right upper lobe in 38%, left upper lobe in 27%), followed by the right and left lower lobe with respectively 15% each, and the middle lobe 5%.
Typical pulmonary resection was performed on 41 patients (95%). In most of cases (70.8%), it consisted on a lobectomy or bilobectomy whereas a pneumonectomy was undergone in 11 patients (25%). In one patient a wedge resection was performed and an exploratory thoracotomy was performed on another. Thirty six patients underwent surgery without having preoperative treatment. Induction chemotherapy was performed for 6 patients because of a mediastinal invasion. There was partial response in 4 unresectable patients allowing a complete resection in all of them. In one patient, the preoperative chemotherapy did not stop nor reduce the progression of the tumor. One patient had had preoperative platin-based chemotherapy

associated to radiation therapy in front of a parietal invasion. Post operative chemotherapy was made for 6 patients; because of lymph nodes invasion in 3 cases and parietal invasion in 3 others.

The correct histological diagnosis of PSC was established postoperatively in all cases. The postoperative pathological examination revealed a mean tumor size of 5.2 cm (1-17.5cm). Histological and immunohistochemical studies revealed 30 cases (70%) of pleomorphic carcinoma, 5 cases (11.6%) of carcinosarcoma, 1case (2.3%) of spindle cell carcinoma, 3 cases (7%) of giant cell carcinoma and 4 cases (9.3%) of blastoma. The tumor cells were positive for epithelial membrane antigen (EMA), cytokeratin (CK), and vimentin (figure 2). They were negative for thyroid transcription factor-1 (TTF-1), smooth muscle actin (SMA) and cytokeratin 5/6. The postoperative tumour stages were IA in 4 (9.3%), IB in 10 (23%), IIA in 11 (25.6%), IIB in 12 (28%) and III in 6 cases (14%). In 12 patients, lymph nodes were found at levels N1 (n=8) and N2 (n=4).

No peroperative death was noted. 3 patients died within 30 days after the surgery. Until completion of the study, 4 patients were lost to follow up and 12 patients died of cancer after discharge. The cumulative 5 year survival for all the series was 8.56% (Figure 3). According to the histological type, the cumulative 3-year survival curves was 14.3% for pleomorphic carcinoma, and 4.76% for other histological types; there was no statistical difference between the 2 groups (p= 0.73) (Figure 4). According to the stage of tumor, the 3 year survival was 13 for patients with stage I and II and it was 0% for stages III. There was a difference between two groups but it was non-significant statistically (p=0.099) (Figure 5).

DISCUSSION

Primary sarcomatoid carcinomas represent between 0.3% and 1.3% of all pulmonary malignant tumors [5]. The sarcomatoid pulmonary carcinomas are defined by the association of a carcinomatous contingent with little differentiation to sarcomatous (or pseudosarcomatous) elements of spindle cells and giant cells [6]. They include five subtypes: pleomorphic carcinomas, spindle cell carcinomas, giant cell carcinomas, carcinosarcomas and pneumoblastomas in adults [7]. In our series, pleomorphic carcinoma was the most frequent subtype, accounting for 30 cases. It corresponds to the association of fusiform cells (or giant cells) with an epidermoid, glandular, or large cell epithelial component [8].The sarcomatoid component (which must represents more than 10% of the tumor) is organized into a fascicular or storiform aspect. Given that the lung is one of the favored metastatic sites for soft tissue sarcomas, care must be taken to exclude the possibility of an alternate primary source by means of thorough clinical history and imaging evaluation [9]. Compared with other histological subtypes, PSC behaves in an aggressive way [4] increasing rapidly and commonly involving the adjacent lung, chest wall, diaphragm, pericardium and other tissues at the time of diagnosis [10].

PSC appears frequently in men and in patients aged more than 60 years, apart from the pulmonary blastoma subtype, which occurs in younger patients [11,12].

Several risk factors have been associated with PSC of the lung, such as smoking cigarettes, cigars, or pipes, and exposure to asbestos in building construction and electrical insulation [13].

Nearby the locally aggressive character of these tumors, no specific signs or symptoms have been found for PSC when compared with other typical NSCLCs [14,15]. As reported in other series, thoracic symptoms are essentially similar to those seen in lung carcinomas, and it depends on the location of the tumor rather than the histologic subtype [16]. However, no paraneoplastic syndrome was reported to accompany PSC, although such symptoms occurred in about 15–20% of small cell lung carcinomas (SCLCs) and 5–8% of NSCLCs [17].

Chest CT scan is crucial because the tumor often invades the contiguous thoracic structures (pleura, pericardium, vessels, and chest wall), and it allows the determination of local extension [18].

Preoperative pathological diagnosis failed to identify this tumor type in most cases, mainly due to the excessive cellular heterogeneity. In our series, preoperative pathological diagnosis was NSCLC in all patients who were destined for surgical resection. The diagnosis can be established only after clinical and imaging investigations have failed to identify an alternative primary source. In addition, only detailed immunohistochemistry (IHC) allows exclusion of other primary spindle cell neoplasms. In fact IHC presently allows a better classification of sarcomas, based on the predominant histological pattern of growth and/or cytological composition. Immunohistochemistry is also crucial for diagnosing the much more frequent pulmonary sarcomatoid carcinomas [6]. Immunohistochemical investigations can be used to

help determine the histological type of non-small lung carcinoma. In general, CK5/6 and p63 are markers of squamous cell carcinoma, whereas SP-A and TTF-1 are markers of adenocarcinoma. Staining with CK7 and CK20 antibodies can help discriminate between primary lung carcinoma and metastatic lung carcinoma. In addition, pan cytokeratin (CAM 5.2 and LP 34) has been reported to be present in sarcomatoid carcinoma of the lung [19]. In this series, the most frequently identified tumor of the lung was pleomorphic carcinoma (70%).

In case of localized tumor, surgery is an adequate option for treatment. In contrast, since no data are at present available for the metastatic disease, patients are treated as having non-small cell lung cancer [20]. Vieira et al. showed in their study that the progression-free survival was not statistically significantly different between patients who received platinum-based chemotherapy versus those who did not. Moreover, there was no statistically significant difference in overall survival (7 months with platinum versus 5.3 months without; P=0.096) [21].

Italiano et al. [22] reported the short-term outcomes of using doxorubicin and ifosfamide in the treatment of metastatic PSC. Half of their patients with metastatic PSC qualified an initial response to chemotherapy with doxorubicin and ifosfamide. But, all patients finally died of disease despite continued treatment [23]. Consequently, due to the limited treatment, the five-year survival rate for patients with PSC was relatively worse than for patients with other forms of NSCLC. Tumor size and grade are additional factors that may influence the outcome. The influence of the size on prognostic has been debated. Huang et al.[4] found that tumor size is an independent prognostic factor. In our series, neither the histological type (pleomorphic or not) nor the tumor stage had an influence on survival. For that reason, we believe that aggressive resection of centrally located PSC is justified in otherwise healthy patients. The aim of surgery is to achieve negative margins, and perform a thorough mediastinal lymph node dissection in an effort to adequately stage the patient. Treatment strategies concerning conservative therapy of PSC have changed over the last decade; nowadays PSC patients are appropriate candidates for adjuvant and even for neo-adjuvant treatment. Postoperative chemo- and radiation therapy is now routinely given if resection margins or lymph nodes were positive. In our study, adjuvant therapy was performed in 6 patients. Recurrence happened in 4 patients within 12 months after operation and the survival rate was low.

In conclusion, we report a series of 43 patients with primary sarcomatoid carcinoma of the lung diagnosed after resection of pulmonary tumors miming a lung cancer in our thoracic surgery department over a 24-year period. However, the question should be asked is whether surgery alone is sufficient for local tumor control, bearing in mind the high rate of local recurrence after R0 resection. Moreover, because of the low survival rates even in early stages, combination of extensive surgical intervention resection with aggressive postoperative chemotherapy, radiotherapy, or both might be a reasonable consideration to improve survival.

In consideration of the rarity of this tumor, the multidisciplinary approach in referral centers is highly recommended; the contribution of the radiologist and the pathologist, as well as of the surgeon and the medical and radiation oncologist, could lead to a better diagnostic definition of this rare entity and indicate the more appropriate therapeutic approach.

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