Primary Adenoid Cystic Carcinoma of Lung – An Overview

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Abstract

Adenoid cystic carcinoma of the lung is a rare salivary gland-type neoplasm. Due to the rarity of the disease, its clinicopathological behaviour and management principles are poorly understood. The main evidence has come from institutional experience and retrospective case series. In this current overview, an attempt is made to search the available literature and to summarise the existing evidence.

Introduction

Adenoid cystic carcinoma (ACC) is a distinctive type of malignant epithelial neoplasm that most commonly arises from salivary glands of the head and neck and less commonly from lacrimal glands, breasts, skin, vulva and upper aerodigestive system.Primary ACC of the lung is an extremely rare neoplasm, accounting for only 0.04-0.2% of all primary lung tumours [1]. In the thorax, most of these cancers originate from central airways, such as the trachea and main bronchus, and ACC of the peripheral lung is extremelyrare [2]. Because of their relatively indolent nature, these tumours used to be referred to as benign glandular neoplasms, but are now regarded as low-grade bronchial carcinomas [1]. Because of rarity of the disease, randomised control trials are not possible and the evidence of management is mainly based on institutional experience and retrospective case series/reports. The aim of this overview is to summarise the pattern of the disease, management options and their outcomes.

Clinical features

Cough, wheeze, dyspnoea and haemoptysis are the most common presenting symptoms [3,4]. In a study involving 40 patients with ACC, Molina et al. [5], common presenting symptoms were as follows: cough (70%), dyspnoea (60%), wheezing (42.5%), pneumonia (30%) and haemoptysis (27.5%) In another study of 38 patients, the frequency of presenting symptoms were as follows; shortness of breathing 72%, wheeze 39%, cough 23%, stridor 21% and haemoptysis 18%. Many patients had two or more symptoms [6]. There is often a long interval between the onset of symptoms and diagnosis. Maziak et al. [6] demonstrated that the mean duration of symptoms before diagnosis was 15 months with a range of 1-72 months. This is most likely due to the relatively slow growing nature of the disease and the fact that plain chest radiograph frequently fails to show any abnormality.

Unlike other bronchogenic carcinomas of the lung, smoking is not thought to be a definite risk factor for thedevelopment of primary ACC of the lung [3,4]. However, in one series, over half of the patients with ACC (69.2%) were reported to be current or former smokers. This percentage was higher than that of reported adult smokers in the UnitedStates, even going back to 1970. This may raise a question about the actual relationship between smoking andsalivary gland-type tumours [5].

In another study by Gaissert et al. [7] 135 patients with ACC were evaluated and one third ofpatients were smokers. The presenting symptoms in this group were as follows; dyspnoea 48%, cough 40%, haemoptysis 21%, wheeze 32%, stridor 15%, hoarseness 7% and dysphagia 5%. The mean duration of symptoms was 12.2 months.

Histological features

ACC exhibits three predominant histological growth patterns. The most frequent and predominant pattern is a cribriform pattern (nests of tumour cells containing numerous sharply outlined luminal spaces, sometimes containing mucinous secretion within their lumens). The second most common pattern is a tubular pattern (characterised by singly scattered gland-like spaces with wide-open lumina lined by two to three layers of small cuboidal cells, sometimes

containing a pinkish amorphous secretion within the lumen). The least frequent pattern (and mostaggressive), is a solid pattern (sheets of cells lacking luminal structures that showvesicular nuclei and open chromatin; mitotic activity is occasionally identified within these solid areas) [2,4,8]. Lymphatic or vascular invasion is uncommon although perineural invasion has been reported in few cases [5].

The cells show positive staining for actin and myosin but tend to be negative for neuroendocrine markers CD56, chromogranin and carcinoembryonic antigen [3]. In a detailed immunohistochemical examination on 17 out of a total of 34 patients, Hu et al. [1] demonstrated the following pattern of positive immunostaining; wide-spectrum keratin in 17/17 patients, p63 in 11/12 patients, SMA in 6/9 patients, S-100 in 7/8 patients, vimentin in 10/12 patients, CK7 in 11/11 patients, GFAP in 1/3 patients and CEA in 2/9 patients. Staining was absent for Syn in 7 patients, CD56 in 7 patients, CK20 in 4 patients, CgA in 4 patients and TTF-1 in 14 patients.

Management

Primary ACC of the lung is a rare entity and most of the available data on these tumours come from retrospective case series. As ACC are primarily salivary gland tumours, the management principles have mainly been extrapolated from the clinical management of salivary gland ACC.

Surgery is the mainstay of the treatment. Sleeve resection, lobectomy or pneumonectomyare common surgical procedures depending on the site and extent of disease. In a large retrospective institutional experience from the Mayo clinic (1972 – 2002 study), the most common procedures for patients with ACC (n = 40) were tracheal resection (33.3%), lobectomy (29.2%), and pneumonectomy (29.2%) [5].

Kang et al. [9] examined a total of 48 patients with primary salivary gland-type lung cancers. Twenty patients had ACC (7 in the trachea, 5 in the main bronchus and the remaining 8 in peripheral lungs). One patient received neoadjuvant chemotherapy and one neoadjuvant radiotherapy. Tracheal resection was performed in 5 patients, carinal sleeve resection in 4 patients, sleeve lobectomy in 6 patients and pneumonectomy in 5 patients. No nodal involvement was found in 11 patients, N1 in 3 and N2 in 3 patients. In the remaining 3 patients, nodal involvement was not mentioned. R1 (positive margin) resection was found in 8 (40%) patients. Nine patients required no adjuvant treatment. Adjuvant radiotherapy was employed in ten patients and one patient required adjuvant chemotherapy. Six of the R1 resection patients received adjuvant radiotherapy, 3 of these showed disease recurrence during the follow-up period (range 15.2 – 137 months). Two patients developed distant metastases and one developed local recurrence. The remaining two patients refused to have adjuvant therapy and they were alive without disease recurrence at the time of publication. Although some studies [5,7,8] have proposed that nodal staging and surgical excision determine the prognosis, in this study, there was no statistically significant difference in survival (p =0.5) and recurrence (p=0.23) rates between lymph node positive and negative patients respectively.The authors also concluded that although it was impossible to evaluate the role of adjuvant radiotherapy in the case of imcomplete surgical resection, R1 resection did not appear to have an adverse effect on recurrence regardless of post operative radiotherapy [9].

Maziak et al. [10] in a clinical study of managing ACC at Toronto hospital (32-year experience) reported outcomes on 38 patients.

Thirty two patients underwent primary surgical resection and six received primary radiotherapy for unresectable disease. Primary resection and anastomosis was performed in 29 patients and prosthetic reconstruction (Marlex mesh) in 3 patients. Three patients (9%) died within 30 days of the operation. Nine patients developed recurrent nerve palsy, 8 were found to have airway granulation and 5 developed wound infection. Dysphagia was present in 4 patients and stenosis in 3 patients. In half of the patients (50%), the surgical margin was incomplete i.e. R1 resection. The median survival for 16 patients with complete resection was 93 months and for 16 patients with incomplete resection margins median survival was 61 months (mean 118 and 90 months respectively). Although there was no statistically significant difference in these two subgroups, there was a trend for increased survival in the group who underwent complete resection particularly at 10 years; complete resection 69% vs. incomplete resection 30%. The median survival for 6 patients treated with primary radiotherapy was 87 months [6].

In a study by Hu et al. [11] 26 of 34 patients were operable (10 patients had R1 resection). Three, 5 and 10-year overall survival in operable patients was 92%, 91% and 70% respectively. Nine of 10 patients with R1 resection received adjuvant radiotherapy and the survival was similar to that of R0 resection. Four patients with R0 resection also underwent postoperative radiotherapy but no additional benefit was yielded.

Gaissert et al. [7] compared thoracic ACC with that of squamous cell carcinoma (SCC) of the trachea/carina (135 patients in each group). 59% of patients with ACC had positive margins in contrast to only 18% with SCC. 74.8% patients with ACC underwent primary resection. Reasons for contraindications to surgery were as follows; extent of airway involvement in 68%, extent of regional disease in 23%, distant disease in 6% and patient choice in 3%. Postoperative radiation was given in 70% of ACC patients as compared to 46% patients with SCC. Mean survival period was 69 months with resected ACC and 41 months with unresected ACC (38 and 8.8 months respectively with SCC). Overall 5-year survival was 52% for resected and 33% for unresected ACC and 10-year survival was 29% and 10% respectively. Complete resection was of prognostic importance but lymph nodal positivity was not found to be of prognostic value.

Radiotherapy

The role of radiotherapy is not well defined in the literature. However; in general, this option is kept in reserve for patients with either incomplete resection margins or in patients with unresectable disease.

Maziak et al. [6] reported that six of a total of 38 patients were found to have unresectable disease at the time of presentation and they received primary radiotherapy. The radiation dose varied from 50 to 75 Gy. Of these 6 patients, one patient could not complete the radiotherapy and two developed local recurrence after 7 and 8 years and went on to have palliative surgery with residual tumour present after the procedure. The survival for these two patients was 33 and 25 months respectively. The median survival for 6 patients treated with primary radiotherapy was 87 months, which was comparable to surgery (93 months for 16 patients with complete excision and 61 months for the remaining 16 patients with incomplete excision). However, five of these six patients ultimately had a fatal local recurrence. In this study, 25 out of 32 patients who underwent primary resection also received pre or post-operative radiotherapy (9 preoperative and

Table 1: A summary of the literature review.

Study	Number of patients with Lung ACC	Outcome/comments
Pandey et al. [17]	4	Total 7 patients; three with muco-epidermoid carcinoma All but one (unresectable disease) had complete excision six patients are alive after a median follow up of 5 months (range 1-30)
Hu et al. [1]	34	26 patients underwent primary resection (R0 in 16 patients and R1 in 10 patients; Lymph nodes positive in 5 patients) Of 10 patients with R1 resection, 9 received postoperative radiotherapy (50-75 Gy) Survival in R0 resection group and R1 section + postoperative radiotherapy yielded similar outcome. Post op RT in R0 resection did not improve survival Various chemotherapy regimes in metastatic settings were given, only one case showed sensitivity to cis-platinum and paclitaxel chemotherapy
Kang et al. [9]	20	20 patients with ACC (7 in trachea, 5 in main bronchus and remaining in peripheral lungs) No nodal involvement in 11 patients, N1 in 3 and N2 in 3 patients (not mentioned in 3) R1 (positive margins) resection in 8 (40%) patients and six of these patients received adjuvant radiotherapy Aggressive surgical resection (irrespective of nodal staging) is more important prognostic factor, regardless of the postoperative radiotherapy
Molina et al. [5]	40	Total 62 patients (remaining patients with muco-epidermoid carcinoma and mixed type) 30.8% of ACC patients presents with lymph nodal involvement at presentation For patients with ACC, 85% at 1 year, 73% at 3 years, 57% at 5 years, and 39% at 10 years Clinical staging and complete surgical excision were the determinant prognostic factors
Chopra et al. [10]	3	Three (2 with central bronchial and 1 with peripheral lesion) patients treated with surgery and postoperative radiotherapy 2 patients had R1 resection and 1 R2 resection No local recurrences found (follow up range: 14 months to 10 years)
Yang et al. [18]	7	3 patients received surgery followed by postoperative radiotherapy (OS was 1-10 years) 1 patients underwent pneumonectomy only (OS 5 months) 2 patients received radiotherapy only (OS was 1 and 2 years) 1 patient received combination chemotherapy (5FU, etoposide and cisplatin). The patient survived for 2 years
Gaissert et al. [7]	135	A comparative study of ACC and SCC of trachea/carina (135 patients in each group) 74.8% patients with ACC were resected. 59% of patients with ACC had positive margins Postoperative radiation was given in 70% of ACC Overall 5-year survival was 52% for resected and 33% for unresected ACC and 10-year survival was 29% and 10% respectively Complete resection was determinant prognostic indicator but lymph nodal involvement was of no prognostic significance.
Maziak et al. [6]	38	32 patients were treated with primary resection and 6 with primary radiotherapy 16 patients had R1 resection. Although there was no statistically significant difference in outcome of R0 and R1 subgroups but there was tendency of better survival (median survival of 91 vs. 63 months; 10 year survival was 69% vs. 30%) Survival in primary radiotherapy group was comparable to that of surgery but five out of six patients had ultimate local recurrences
Moran et al. [4]	16	No etiological risk factors (e.g. smoking history) was identified in any of the patients Three patients were metastatic at presentation (Two patients died with widespread metastases after 2 and 12 months respectively) Three patients were alive without disease recurrence at 5, 10 and 12 years Three patients developed recurrence/contralateral lung metastases from 2-15 years after initial diagnosis Three patients died of unrelated conditions Clinical staging at the time of presentation is the main prognostic parameter
Grillo et al. [19]	60	Of patients treated with surgery (and usually postoperative radiotherapy) 7 died of carcinoma and 38 were alive being disease free 12 patients are treated with radiotherapy alone; 9 died of disease and 3 alive without evidence of disease The authors concluded that resection should probably be followed by full dose mediastinal radiotherapy in most cases
Markel et al. [20]	3	Unresectable disease at time of diagnosis. All died 7 months – 2 years after diagnosis
Weiss et al. [21]	4	Two patients had unresectable tumours and died with extensive residual disease or distant metastases
Payne et al. [22]	13	In 12 patients, histological extension of tumour was found into trachea/adjacent mediastinal structures (five of these patients died with extensive residual disease and five with distant disease)

ACC: Adenoid Cystic Carcinoma; OS= Overall Survival.

16 post-operatives). In this subgroup treated with dual modality, the median survival in 23 patients (excluding two operative deaths) was 88 months (range 11 – 263 months) and in the remaining six patients (excluding one patient with operative death) who did not receive adjuvant radiotherapy, the median survival was 131 months (5 – 352 months). The difference was not significant, however it is logical to assume that adjuvant radiotherapy was reserved for high risk patients and is likely to delay or reduce the incidence of local recurrence [6].

Chopra et al. [10] reported three cases of Lung ACC treated with surgery followed by postoperative radiotherapy. In two patients, the disease was in the central bronchus/trachea and in one patient; the lesion was in the peripheral lung. In the patients with central tumours, there was an R1 resection, one was treated with 72 Gy in 60 fractions and the second patient received 50.4 Gy in 28 fractions followed by a brachytherapy boost of 12 Gy in 2 fractions. The patient with peripheral lesion required external beam radiotherapy (EBRT) 45 Gy in 25 fractions and a further boost of 20 Gy in 10 fractions after R2 resection. There were no local recurrences found (follow up range: 14 months to 10 years) although one patient developed a benign tracheal stenosis one year after the treatment. The authors concluded that postoperative radiotherapy can effectively eradicate residual disease after incomplete resection and it may improve the probability of cure.

In the palliative setting, radiotherapy can provide satisfactory palliation of symptoms. A case report described fast and good

symptomatic response to bony metastases in a patient with aggressive metastatic lung ACC who was resistant to several systemic chemotherapeutic agents [12].

Chemotherapy/Targeted Therapies

The role of palliative chemotherapy is not well described in the literature. A case report described sensitivity to uracil-tegafur and cisplatin plus radiotherapy [13]. In another case report, several chemotherapeutic agents including 7 cycles of weekly paclitaxel combined with cisplatinum, 2 cycles of docetaxel and subsequently gefitinb was tried but there was no response [14]. In a clinical study by Hu et al. [15] only one case showed markedreduction in disease after two cycles of paclitaxel and cisplatin chemotherapy, but six months later, the disease progressed. Various other chemotherapy regimens, including gemcitabine and cis-platinum, navelbine and cis-platinum and single-drug chemotherapy with pemetrexed were tried with no benefit. One patient, with anunknown EGFR mutation status, received an oral epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), erlotinib. The primary tumour was stable after one month but mediastinal disease progressed three months later. In this study, EGFR mutation status (exon 18-21) was examined on 2 patients, including a young female who had never smoked, but no mutations were detected. One case of TTF-1 positive ACC in peripheral lung has been described in the literature [16]. A summary of the studies discussed has been provided in Table 1.

Metastatic disease

Distant metastasis is uncommon, although in some studies the incidence of metastasis was up to 40.5% [5]. In this study of 40 patients with ACC, 15 developed distant metastases: (the main site of metastases was lung; in 14 out of 15 patients) [17]. Maziak et al. [18] reported haematogenous metastatic spread in 17 of the total 38 patients (lung metastases in 13 patients, liver in 4, bone in 3 and brain metastasis in 2 patients). The authors stated that 'to date, there is no evidence that chemotherapy is useful in the management of these metastases' so it can be assumed that these patients with haematogenous metastatic spread did not receive any systemic therapy. However these patients survived for as long as 7 years after the metastatic spread was established with a mean survival interval of 37 months [19].

Survival/Prognosis

Prognosis depends on staging, histological pattern (solid pattern having the worst prognosis and tubular having the best prognosis) and complete resection [2,4,5,14]. In the Mayo clinic study, the survival for patients with ACC was reported as follows; 85% at 1 year, 73% at 3 years, 57% at 5 years, and 39% at10 years. It was compared to that of non-small cell lung cancer treated at the same centre from 1997-2002 (n = 5024) which showed 58% at 1 year, 31% at 3 years and 21% at 5 years. The outcome of patients with ACC was significantly poorer (5- and 10-year survival rates, 55% and 39%, respectively, compared with 87% at both 5 years and 10 years in patients with mucoepidermoid carcinoma (MEC) yet remained better than the outcome of patients with typical lung carcinoma [20].

Future Directions

Response to chemotherapy remains poor. There has been increasing interest in exploiting the over-expression of c-kit protein in salivary gland ACC (in upto 80-90% of cases), but the clinical outcome remains limited. In a phase II study of cisplatin and imatinib

in advanced head and neck salivary gland ACC, 8 out of 28 patients showed partial response and 19 patients had useful stabilisation of disease. The median time to progression and overall survival was 15 months (range 1-43) and 35 months (range 1-75) [21], although in another phase II study of Imatinib for ACC of head and neck salivary glands, it had no major effect on the disease [22].

Conclusion

ACC of the lung, although rare, is an important type of lung cancer that is encountered. The evidence to date from retrospective case series, suggests that most ACC of the lung are indolent and slow growing.

Smoking may be related to the incidence of ACC of the lung. Further data needs to be collected to establish a more definite relationship. The main stay of curative treatment is with surgery. The role of radiotherapy remains unclear and further studies are needed to establish the need for radiotherapy in the radical treatment setting and in the palliative setting too. Chemotherapy has not shown any benefit in the majority of patients. The role of oral targeted therapies such as TKIs and immunotherapy need to be investigated in this subset of lung cancer patients.

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