Surgical management of pulmonary large cell neuroendocrine carcinomas: a 10-year experience

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Abstract

OBJECTIVES: Large cell neuroendocrine carcinoma (LCNEC) represents a relatively rare and poorly studied entity whose management is not clearly established. The aim of this study was to assess clinico-pathological characteristics, treatment modalities and outcomes of LCNEC.

METHODS: A retrospective study of patients operated on for LCNEC between 2000 and 2010 was carried out.

RESULTS: Sixty-three patients (49 men, median age 64 years) with pathologically confirmed LCNEC of the lung were operated on between 2000 and 2010. Neoadjuvant chemotherapy was administered in 16 cases. Standard lobectomy, sleeve lobectomy, bilobectomy and pneumonectomy were performed in 63.5%, 9.5%, 1.6% and 15.8% of cases. There were two cases of extended resection. Sublobar resections were performed in four patients. Postoperative mortality was 1.6%. Postoperative staging was IA, IB, IIA, IIB, IIIA, IIIB and IV in 15.9%, 19%, 20.6%, 4.8%, 34.9%, 4.8% and 0% of cases, respectively. Adjuvant treatments were administered in 70% of cases. Overall 5-, and 8- year survival rates were 49.2% (37–61.6%) and 42% (28.8–56.4%), respectively. Multivariate analysis, including age (>64 years), cumulative tobacco consumption, size of tumour, pT and pN parameters showed that only age (P = 0.05, RR 2.1 [0.99–4.43]) and pT parameter (P = 0.0078, RR 2.93[1.33–6.46]) were independent predictors of survival.

CONCLUSIONS: Surgery may achieve satisfactory results in terms of survival, in spite of the similarities of LCNEC with small cell lung cancer. Multimodality management seems necessary.

Keywords: Large cell • Neuroendocrine • Carcinoma • Neoadjuvant therapy • Lung cancer

INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) of the lung represents a relatively rare entity of the pulmonary neuroendocrine tumour spectrum, the management of which remains controversial. Previous classifications had only taken into account typical and atypical carcinoid tumours as well as small cell lung cancer (SCLC), but the 1999 [1] and 2004 WHO classifications of lung tumours recognized, mainly based on Travis’ 1991 study, [2] the entity called LCNEC. LCNEC are classified as a variant of large cell carcinoma with both neuroendocrine morphology (organoid or palisading rosettes, high mitotic rates, abundant necrosis and large cell size) and differentiation (positivity for neuroendocrine markers like chromogranins, synaptophysin, NCAM at immunohistochemistry or neuroendocrine granules at electron microscopy).

Among neuroendocrine tumours, LCNE are generally thought to have a prognosis intermediate between atypical carcinoid tumours and SCLC. The prognostic characteristics of LCNE within the whole population of lung cancer patients have been less extensively evaluated. Because of their classification within large cell tumours, LCNEC have been often treated accordingly. However, in the past 10 years, several reports have shown a behaviour closer to SCLC than non small cell lung carcinoma (NSCLC), raising the question of the place of surgery. On the other hand, other reports have shown more satisfactory results, making current management very controversial. In this paper, we retrospectively evaluated our experience in the surgical management of patients with LCNEC, in order to study the clinical characteristics, treatment modalities and outcomes.

MATERIALS AND METHODS

The clinical and pathological records of all patients operated on for LCNEC in our centre between November 2000 and July 2010 were retrospectively reviewed.

In all cases, a complete staging protocol was applied, which included a clinical examination, computed tomography scan,
fibre-optic bronchoscopy, and (after 2006) a positron emission tomography scan.

Pathological diagnosis was confirmed in each case by a board certified pathologist with a special interest in lung disease. Neuroendocrine phenotype was confirmed by immunohistochemistry through assessment of the expression of chromogranine A or CD56 (ck11). Tumour cell proliferation was analysed by assessing the expression of KI-67. These results are expressed as a percentage of marked cell nuclei, identifying three groups, namely group 1 (<20% with positive cells), group 2 (between 20 and 50%) and group 3 (more than 50%). Clinical and pathological TNM was determined according to the 2010 AJCC classification for lung cancer staging.

Each patient was surgically treated with a curative intent and completeness of resection was systematically checked intraoperatively using frozen sections. Lobar resection and full nodal dissection represented the standard operative procedure. Surgery was performed in a multimodality setting including adjuvant and neoadjuvant treatments. However, our centre is a tertiary referral department caring for patients referred by several hospitals, so applied protocols were not uniform. As a general rule, all patients with suspected N2 disease underwent either mediastinoscopy or trans-bronchial needle aspiration. If mediastinal disease was confirmed, neoadjuvant chemotherapy (mainly platinum–etoposide) was prescribed and surgery performed in case of response or stable disease. Adjuvant chemotherapy was prescribed in cases of stage II–III disease, and was also platinum–etoposide based in most cases. Adjuvant radiotherapy was administered in cases of N2 disease.

Data analysis

Continuous data are expressed as means or medians (when not distributed normally) and categorical variables as percentages. Data on postoperative morbidity and mortality (within the 30th postoperative day or during the same hospitalization) were collected. Follow-up information was obtained by telephone interview of patients or families (in the case of deceased patients) and confirmed by family physicians and referring chest physicians as well as by interrogation of the registers of the municipality of birth. Survival, including postoperative deaths was calculated by the Kaplan–Meier method. Univariate comparisons were performed by the log-rank test. All variables with a P-value <0.2 at univariate analysis were entered in a multistep multivariate Cox model to individuate independent prognostic factors. A P-value <0.05 was considered as statistically significant.

Ethics

The study was carried out according to principles outlined in the Helsinki declaration and in agreement with French laws on biomedical research.

RESULTS

Sixty-three patients with pathologically confirmed LCNEC of the lung were operated on in the studied period. There were 49 males and 14 females; the median age was 64 years (range 58–82). Fifty-six patients (88.8%) were smokers (median consumption 47.5 pack/year) and 18 (28.6%) had a history of known pulmonary disease (bronchial asthma, n = 2 chronic pulmonary disease, n = 16). Clinical signs that helped to discover the disease were cough (22.2%), haemoptysis (11.1%), chest pain (12.7%), dyspnoea (9.5%), weight loss (6.3%) and paraneoplastic syndrome (1.6%). The median time between the onset of symptoms and diagnosis was 4 months. One-third of patients were strictly asymptomatic and a disease was found by a chest X-ray carried out for unrelated reasons.

At fibre-optic bronchoscopy, no endoluminal lesion was found in 31 cases (49.2%). On the basis of clinical work-up, the disease was staged as IA, IB, IIA, IIB, IIIA, IIIB and IV in 30.5%, 22.2%, 7.9%, 11.1%, 20.7%, 7.9% and 0% of patients, respectively. Neoadjuvant chemotherapy was administered in 16 cases (25.4%); 12 patients showed partial responses and two minor responses, whereas one patient had a stable disease and the remaining patient had a progressive disease but was operated on because of a highly symptomatic tumour.

With respect to surgical procedures, standard lobectomy, sleeve lobectomy, bilobectomy and pneumonectomy were performed in 63.5%, 9.5%, 1.6% and 15.8% of patients, respectively. Extended resection was performed in two cases. Sublobar resections were performed in four patients (anatomical segmentectomy and wedge resection, two each). There were no intraoperative deaths. Thirty-seven patients (58.7%) had an uneventful postoperative course. The remaining ones experienced complications including atrial fibrillation, sputum retention and pneumonia. Adult respiratory distress syndrome developed in a single patient and was responsible for their death. Thus, the mortality rate was 1.6%.

At the pathological examination, the mean tumour size was 37.2 mm. Post-operative staging was IA, IB, IIA, IIB, IIIA, IIIB and IV in 15.9%, 19%, 20.6%, 4.8%, 34.9%, 4.8% and 0% of cases, respectively (Table 1).

With respect to KI-67, groups 1, 2 and 3 included 5 (7.9%), 23 (36.5%) and 28 (44.4%) of patients, respectively. KI-67 staining was not available in seven cases.

Adjuvant treatment was administered in 70% of cases, under the care of referring physicians.

Overall 1-, 5- and 8-year survival rates were 73% (95% CI 61.0–87.6%), 49.2% (37–61.6%) and 42% (28.8–56.4%) of cases, respectively (Fig. 1).

Sex was not associated with long-term survival (P = 0.92). Age ≥64 years was associated with a trend towards a worse prognosis (5-year survival of 38.1 vs. 58.1, P = 0.15). Cumulative tobacco consumption ≥45 pack/years was associated with a worse 5-year survival (34.6 vs. 64.9%, P = 0.048). The presence of associated

| Table 1: Re-partition of pathological TNM classification of tumours in the studied population |
|---------------------------------|-------|-------|-------|
| pTNM | pT (%) | pN (%) | pM (%) |
| 0    | 29 (46) | 63 (100) |       |
| 1a   | 21 (33.3) | 15 (23.8) |       |
| 1b   | 26 (41.2) |       |       |
| 2a   | 9 (14.2) | 19 (30.2) |       |
| 2b   | 3 (4.8)  |       |       |
| 3    | 8 (12.7) | 0 |       |
| 4    | 4 (6.3)  |       |       |
illnesses ($P = 0.36$), the duration of symptoms before surgery ($P = 0.4$), the extent of resection ($P = 0.45$) and occurrence of postoperative complications ($P = 0.56$) were not associated with long-term survival.

The administration of neoadjuvant chemotherapy (which was associated with a higher stage, $P = 0.00014$) was associated with a trend towards a worse 5-year outcome in the whole population (35.2 vs. 53.8%, $P = 0.14$). As the great majority of patients had a clinical response to chemotherapy, no comparison was possible with patients having stable or progressive diseases.

pT parameters influenced the outcome: 5-year survivals of pT1-2 and pT3-4 tumours were 55.6% (41.76–68.64) and 22.2% (6.90–52.43) ($P = 0.089$), respectively (Fig. 2). The presence of mediastinal nodal disease was associated with a trend ($P = 0.2$) towards a worse prognosis, with 5-year survival figures of 37.9 vs. 54.1% in N0-1 disease. As a consequence, when survival was analysed per stage, a trend (not reaching significance) towards a worse prognosis was observed in stage IIIA and B disease when compared with stage I–II disease (5-year survivals of 33.3 vs. 56.3%, $P = 0.06$).

KI-67 staining was not associated with 5-year survival, with figures of 60% (23.07–88.24), 52.2% (31.33–72.29) and 50% (32.63–67.37) for groups 1, 2 and 3 ($P = 0.84$), respectively.

Multivariate analysis, including age of >64 years, cumulative tobacco consumption, administration of neoadjuvant chemotherapy, and pT and pN parameters, showed that only the pT parameter ($P = 0.0091$, RR 2.78 [1.29–5.98]) was an independent predictor of survival.

**DISCUSSION**

LCNECs account for ~3% of lung cancers. The criteria for pathological diagnosis are widely accepted nowadays and applied, making comparisons of surgical series more reliable than in the past.

Although LCNEC is classified as a variant of large cell carcinoma, it shares several biological features with SCLC, in terms of frequency of loss of heterozygosity, [3] telomerase activity [4] and expression of neuroendocrine markers [5]. In contrast, differences do exist, for example, in terms of both genomic profile [6] and of the expression of other markers such as CK7 and E-cadherin [7]. These biological features might probably explain why LCNEC finally shares clinical and pathological characteristics with both SCLC and NSCLC.

Nowadays, clinical and radiological examinations do not provide very useful information to help distinguish LCNEC from other cell types [8]. Octreotide scans could suggest the neuroendocrine character of a lung tumour, but is not completely accurate and is unable to distinguish LCNECs from carcinoid tumours or SCLCs [9].

Precise pathological classification has often been quite obscure because of frequent overlapping between LCNECs and other neuroendocrine tumours, with similar morphology or differentiation, but different postoperative management and prognosis [10]. With the new 2004 classification, the criteria to define LCNEC became clearer, and many studies continued, allowing refinements in pathological diagnosis and molecular assessment.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Overall 5 years survival (%)</th>
<th>Number of patients with LCNEC (n)</th>
<th>Percentage of pTNM stage &gt;IIB (%)</th>
<th>Points to be stressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dresler et al. [17] 1997</td>
<td>13</td>
<td>40</td>
<td>22.5</td>
<td>20% of non-typical carcinoid tumours included</td>
</tr>
<tr>
<td>Takei et al. [5] 2002</td>
<td>57</td>
<td>87</td>
<td></td>
<td>Significant difference in survival for early stages between LCNEC and other NSCLCs</td>
</tr>
<tr>
<td>Paci et al. [18] 2004</td>
<td>21</td>
<td>50</td>
<td>16.7</td>
<td>Only 27% of 5-year survival in stage I</td>
</tr>
<tr>
<td>Casali et al. [19] 2004</td>
<td>51</td>
<td>33</td>
<td>21.2</td>
<td>No patient with c or p stage &gt;IIIa</td>
</tr>
<tr>
<td>Battafarano et al. [20] 2005</td>
<td>30.2</td>
<td>45</td>
<td></td>
<td>Non-significant worse overall survival in LCNEC when compared with other NSCLCs ($P = 0.13$)</td>
</tr>
</tbody>
</table>
pathological analysis is even more difficult, mainly because of the frequently small size of samples [11], which often leads to primary surgery in patients considered resectable (half of the patients in our series). This explains the almost complete absence of non-surgical series as well as the difficulties of enrolling patients in specifically designed neo-adjuvant treatment protocols. In spite of these difficulties, some attempts at the evaluation of preoperative chemotherapy have been performed, and some authors have reported encouraging rates of objective response [12], but could not conclude because of the small cohort of patients. In our series only 16 out of 63 patients had an induction treatment, which was administered in almost all the cases for stage III disease. Interestingly, the majority of them had an objective response to chemotherapy. Thus, currently there is no strong argument to suggest routine preoperative chemotherapy, whose effectiveness is not clearly established, over primary surgery (at least in non-N2 patients) which remains the best evaluated treatment option.

From a prognostic point of view, opinions are quite variable. In a Japanese multicentre study, there was no significant difference in survival between LCNEC and SCLC [13], leading to the idea that the rare cases of LCNEC might be better treated as SCLC. On the other hand, results of other teams were not so disappointing: for example, in stage IA disease, Ioda and co-workers reported 5-year survival rates of 54.5 and 89.3% in LCNECs and other NSCLCs, respectively, suggesting that small LCNECs also have a mediocri prognosis, although they remain accessible to potentially curative treatment [14]. Overall, in series studying merely LCNEC (without comparison with other histological types) 5-year survival rates ranged from 13% to 57% in surgically treated patients (Table 2). Our experience was quite satisfactory as the overall 5-year survival was 49.2%. Probably the low percentage of stage III disease accounts for this relatively favourable outcome.

With respect to prognostic factors, we found that only the pT parameter was an independent predictor of survival. We failed to affirm the independent prognostic value of the pN parameter, probably because of the relatively small number of effects.

Which patients should receive adjuvant treatment can be a matter of discussion. Although LCNECs are surgically treated as NSCLCs in several surgical series, as well as in our experience, global less satisfactory prognosis of this kind of tumours [15] would suggest that management should not be exactly the same as for NSCLCs and adjuvant treatment should probably be proposed, also in the initial stage of the disease. Unfortunately, our data are insufficient to provide new insights into this topic.

With respect to chemotherapy drugs (in either a neo-adjuvant or adjuvant setting), some authors recommended the doublet cisplatin-VP-16, as for SCLC, with satisfactory results in terms of overall survival and recurrence-free survival [16]. However, as LCNEC is a rare entity, the series were small and, in almost all instances, retrospective, like ours.

In conclusion, LCNEC is a rare entity. Surgery may achieve satisfactory results in terms of survival, in spite of pathological and molecular similarities with SCLC. A multimodal treatment including ‘SCLC chemotherapy’ seems necessary, although individualization of patients necessitating such combined treatment remains mandatory.

Conflict of interest: none declared.