BMJ Open

Patient characteristics, treatment and survival in pulmonary carcinoid tumours: an analysis from the UK National Lung Cancer Audit

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ABSTRACT

Objectives: Pulmonary carcinoid (PC) is a rare tumour with good prognosis following surgical resection. However, little is known regarding patient characteristics and use of other treatments modalities. Our objective was to review patient characteristics, treatment and survival for patients with PC and contrast these results with other forms of non-small cell lung cancer (NSCLC).

Setting: Audit data from UK National Lung Cancer Audit (NLCA) 2008–2013.

Participants: 184 906 lung cancer cases were submitted to the NLCA.

Outcome measures: Primary outcome—survival rates between PC and NSCLC. Secondary outcome—differences in performance status, lung function and treatment modality between PC and NSCLC.

Results: PC histology was recorded in 1341 (0.73%) patients and non-carcinoid NSCLC histology in 162 959 (87.4%) cases. 91% of patients with PC had good performance status (Eastern Cooperative Oncology Group (ECOG) 0–1), compared with only 53% of NSCLC. 66% of PC had localised disease. Of all PC cases, 77% were treated with surgery, 6.2% received chemotherapy and 3.6% received radiotherapy, with the remainder treated with best supportive care. Overall 1-year and 3-year survival rates for PC were 92% and 84.7%, respectively. In contrast, 1-year and 3-year survival rates for NSCLC were 36.2% and 15.6%, However, 3-year survival for PC markedly decreased with worsening performance status and advanced disease to 23.8% for performance status ECOG 3–4 and 33.6% for stage IV disease.

Conclusions: In contrast to other forms of NSCLC, the majority of patients with PC present with good performance status, preserved lung function and early stage disease amenable to surgical resection. However, 1 in 5 patients with PC has metastatic disease which is associated with poor prognosis, as is poor performance status at presentation. We believe these data will help clinicians provide accurate prognostic predictions stratified according to patient characteristics at presentation, as well as guide future clinical trials.

Strengths and limitations of this study

■ Very large data set reviewed.
■ Highly representative and detailed analysis of pulmonary carcinoid tumours.
■ Unable to differentiate between typical and atypical carcinoid tumours.

INTRODUCTION

Pulmonary carcinoid (PC) is a rare tumour which is estimated to account for only around 1–2% of all lung cancers[1] with an incidence in Europe of 0.2 per 100 000 per year.[2] The pathological definition is usually based on the WHO classification first published in 1967 and most recently updated in the fourth edition. An absence of extensive necrosis and a mitotic count of <10 per high power field is used to differentiate PC from high-grade large cell and small cell neuroendocrine tumours. PC can be further subdivided into typical and atypical on the basis of mitotic count and the presence/absence of focal necrosis, although this can only be reliably assessed on a surgical specimen, and there remains interobserver variability in this pathological interpretation.[3]

Overall 5-year survival for lung cancer is poor at 9.5%,[4] but PC is a distinct subgroup of tumours which appear to have a more favourable outcome, especially after surgery with a view to a complete R0 resection.[2] In 2003, a Surveillance, Epidemiology, and End Results (SEER) analysis from the USA reported a 5-year survival of 74% for patients diagnosed with tracheal and bronchial carcinoid from 1973 to 1999.[5] A recent SEER analysis of 441 patients with atypical carcinoid reported a surgical resection rate of 78% with 3-year survival of 67%.[6] A smaller case series which included 142 patients with typical and atypical PC reported a surgical resection rate of 72% with a 5-year survival rate of 89% for typical carcinoid and 75% for atypical carcinoid.[7] Surgical case series tend to report even higher survival rates; a Japanese registry report of tracheal and

bronchial carcinoid tumours reported a postoperative 10-year survival of 82% for typical carcinoid and 59% for atypical carcinoid.[8]

While these case series provide an interesting insight into the management of carcinoid tumours, the relatively small number of patients and retrospective nature of data collection limit general applicability. In addition, relatively little is known regarding patient characteristics in PC and other treatment modalities such as chemotherapy or radiotherapy. To address this, we performed an analysis of patients with PC submitted to the UK National Lung Cancer Audit (NLCA). We report on patient characteristics, treatments and contrast the results with other forms of non-small cell lung cancer (NSCLC).

METHODS
Data source
The NLCA is commissioned by the Healthcare Quality Improvement Partnership (HQIP) and collects data on all patients with lung cancer in England and Wales. It was set up to record information about activity, process and outcomes in lung cancer and explain the wide variations in outcome across the UK.[9] The database includes 112 fields covering patient demographics, referral patterns, investigations, performance status (PS) using the Eastern Cooperative Oncology Group (ECOG) scale, lung function, stage of disease, treatment modalities of surgery (not including endobronchial interventions), chemotherapy and radiotherapy, and survival. Data are collected by an online tool (LUCADA database) from all hospital managing lung cancer in the UK. Annual reports are then sent to all hospital chief executives and medical directors, primary care trusts, cancer commissioners, MDT and network leads.[9]

As this is a review of data from a national audit, no ethical approval is required.

Patient population
All patients from England and Wales submitted to the NLCA between 2008 and 2013 with recorded histology of PC were included in the analysis. The NLCA database only allows the selection of one Systematized Nomenclature of Human Medicine (SNOMed) III code (M8240/3) for PC which equates to carcinoid 'not otherwise specified'. The data set did not differentiate between typical and atypical carcinoid tumours. All cases were primary pulmonary tumours. No extra-PC tumours or pulmonary metastases from other sites were included.

A comparative analysis was performed using patients diagnosed with non-carcinoid NSCLC (all other cell types excluding small cell cancer).

All staging referred to in this paper is preintervention staging.

Statistical analysis
Statistical analysis was performed using SPSS V.19. Continuous variables are presented as mean (SD). Survival was calculated using linked office of national statistics data and is presented as proportions at specified time intervals from diagnosis using Kaplan-Meier methods.

RESULTS
Every hospital in England and Wales participated in the NLCA during the study period and a total of 184 906 lung cancer cases were submitted. PC histology was recorded in 1341 (0.73%) patients and NSCLC (as defined in the methods) in 162 959 (87.4%) cases.

Patient characteristics
The patient characteristics for the two groups are shown in table 1.

Age and gender were recorded in all cases. Mean (SD) age at the time of diagnosis for patients with PC was 62 (15) years with 62% female, whereas mean (SD) age for NSCLC was 72 (11) years, with 44% female. PS was recorded in 88% cases and stage in 81% cases. Ninety-one per cent of patients with PC had good PS (ECOG 0–1) and 66% had localised disease (stage I–II). In contrast, only 53% of patients with NSCLC had good PS and 24% had localised disease. Mean (SD) lung function as measured by the forced expiratory volume in 1 s (FEV_1) was 2.27 L (0.83) in the PC group and 1.71 L (0.72) in the NSCLC group.

Treatment
Treatment data are summarised in table 1. Staging is classified as localised (stage I–II), regional (stage III)

Table 1 Patient characteristics, tumour stage and treatment

N	Carcinoid 1341	NSCLC 161 618
Patient characteristics		
Age—mean (SD)	62 (15)	72 (11)
Female	62%	44%
Performance status 0–1	91.4%	52.6%
FEV_1—mean (SD)	2.27 (0.83)	1.71 (0.72)
Stage		
Localised	65.7%	20.4%
Regional	6.3%	22.3%
Metastatic	8.7%	43.1%
Unknown	19.2%	14.2%
Treatment		
Surgery	76.9%	14.2%
Chemotherapy	6.2%	25.7%
Radiotherapy	3.6%	28.4%
No treatment recorded	13.3%	31.7%

FEV_1, forced expiratory volume in 1 s; NSCLC, non-small cell lung cancer.

Table 2 One-year and 3-year survival rates (%) stratified according to performance status

| ECOG | Carcinoid | | ECOG | NSCLC | |
	1-year	3-year		1-year	3-year
0–1 (n=1003)	93.5	85.2	0–1 (n=72 065)	55.3	26.7
2 (n=70)	75.2	57.4	2 (n=28 499)	26.9	8.3
3–4 (n=24)	41.7	23.8	3–4 (n=36 528)	11.1	2.4

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

and distant (stage IV). Overall, 87% of the patients with PC received anticancer treatment (surgery, radiotherapy or chemotherapy). In contrast, 68.3% of patients with NSCLC received active treatment. The majority of patients with PC (77%) were treated with surgery, 6.2% received chemotherapy and 3.6% received radiotherapy. This is in contrast to NSCLC, where only 14% of patients had surgery, 26% received chemotherapy and a further 28% received radiotherapy.

Survival

Overall 1-year and 3-year survival rates for PC were 92% and 84.7%, respectively. In contrast, 1-year and 3-year survival rates for NSCLC were 36.2% and 15.6%, respectively. Survival rates by PS are shown in table 2. There was a stepwise decrease in survival for PC from 1-year and 3-year survival rates of 93.5% and 85.2%, respectively, for PS 0–1 patients down to 41.7% and 2.4%, respectively, for poor PS (ECOG 3–4) patients. A very similar pattern of survival rates was seen for localised (stage I–II), regional (stage III) and distant (stage IV) PC disease (table 3). Survival in patients with NSCLC also decreased with worsening PS and more advanced stage, but in contrast to carcinoid, survival rates were much lower (tables 2 and 3).

DISCUSSION

We analysed data submitted to the NLCA to more clearly define patient characteristics, treatment modalities and survival of this subgroup of lung cancers, which we contrasted to patients with non-carcinoid NSCLC. We confirmed that PC is a rare tumour and constituted <1% of all lung cancers in our data set. We demonstrated that the majority (68%) of patients with PC are female, which is in keeping with the previous SEER database reports,[5] [6] but higher than smaller case series[10] [11] which likely reflects the more representative nature of the

NLCA and SEER databases. We report, for the first time, that patients with PC have excellent PS at presentation and well-preserved lung function. In addition, the majority (66%) of patients with PC in this study presented with early stage (localised) resectable disease, although 10% had metastatic disease at presentation. These findings are largely consistent with the stage distribution reported in the SEER analysis of tracheal and bronchial PC[5] where two-thirds of patients had localised disease at presentation; however, the proportion of patients with metastatic disease in this study was only 0.5% for the period 1992–1999. This could be explained by selective submission of surgical cases, whereas data submitted to the NLCA are for all patients with lung cancer, irrespective of treatment modality. The patient characteristics for the PC group were in stark contrast to the NSCLC group. The mean age for the patients with NSCLC was 10 years older than the PC group and only half of patients had good PS. The lung function, as measured by FEV_1, was 25% lower than the PC group. Similarly, only one in four patients in the NSCLC group presented with localised disease and over 40% had metastatic disease at presentation.

Surgery is recommended as first-line treatment in locoregional PC.[3] [12] In our study, three-quarters of patients with PC underwent surgery, reflecting the stage distribution and fitness of this group of patients. The treatment of metastatic PC is less clearly defined. Systemic therapy is generally recommended for metastatic disease; however, the results with chemotherapy have been largely disappointing.[3] Given that chemotherapy is not routinely used or recommended in the adjuvant setting as it does not improve survival,[13] we can infer from our results that most patients with metastatic disease are treated with chemotherapy, despite the poor reported response rates with this treatment. To the best of our knowledge, this is the first time that the use of chemotherapy has been reported on a large scale for

Table 3 One-year and 3-year survival rates (%) stratified according to stage

| STAGE | Carcinoid | | STAGE | NSCLC | |
	1-year	3-year		1-year	3-year
Localised (n=429)	96.4	87.7	Localised (n=33 040)	73.0	44.4
Regional (n=85)	75.8	63.1	Regional (n=26 070)	40.9	12.5
Metastatic (n=117)	54.9	33.6	Metastatic (n=69 598)	16.7	3.5

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

patient with PC tumours. Similarly, there is very little in the literature relating to radiotherapy treatment in PC and recent guidelines do not refer to this treatment modality.[3] The recent report by Steuer and colleagues found that 12.5% of patients with atypical PC received radiotherapy which is higher than the 3.6% radiotherapy treatment rate found in our study and is likely due to the more aggressive nature of atypical PC tumours.

Our data confirm that the prognosis for PC is generally excellent, with overall 1-year and 3-year survival rates of 92% and 84.7%, respectively. Once again, this is in stark contrast to other forms of NSCLC where the 1-year survival rate was only 36.2%. We found that stage at presentation in PC is an important determinant of survival which is in keeping with the findings of previous studies,[5][6] but we also report that PS is an equally important predictor of survival for patients with PC. This complements recent work from the European Association of Thoracic Surgeons (ESTS) who found PS was a predictor for mortality in this group.[14] Although the majority of our patients with PC have good PS at presentation, the small proportion with poor PS in our study had a 1-year survival of only 42%. This group of patients may have had other comorbidities rendering them unfit for any form of active anticancer treatment which could explain the poor survival.

The current study has a number of strengths but also potential limitations. The data set provided by the NLCA is large, with mostly excellent levels of data completeness, but there are some missing data; and also no data were available on patients presenting with carcinoid syndrome. Additionally no information was available on regional control rates or treatment failure. Although the missing data could impact on results, we feel this is likely offset by the size of the data pool. A further limitation is the inability to discriminate between typical and atypical carcinoid tumours in this data set.

However, it is felt that overall it provides a highly representative and detailed analysis of all forms of PC tumours, irrespective of treatment given. However, the inability to record typical versus atypical carcinoid histology limits the study's ability to differentiate treatment and outcomes by these two cell types. Also, the data available categorise cancer by stage rather than T, N, M status. In addition, the details of chemotherapeutic regimens and radiotherapy dosing schedules were not recorded in the NLCA during the time of this analysis.

In conclusion, our large and detailed data set demonstrate that, in contrast to other forms of NSCLC, the majority of patients with PC present with good PS, well-preserved lung function and early stage disease leading to high rates of surgical resection. However, one in five patients have local or regional metastatic disease which is associated with a poor prognosis, as is poor PS at presentation. We believe that these data will help clinicians provide more accurate prognostic predictions stratified according to patient characteristics at presentation. The data shown here provide reassurance to patients and

clinicians that patients with carcinoid with early disease who have surgery enjoy high levels of survival; however, clinical trials are needed of newer treatment in metastatic disease.

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