Carcinoid lung tumors — incidence, treatment and outcomes: a population-based study

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Abstract

Objective: Few published reports have examined the incidence and outcomes for patients with carcinoid lung tumors. The aim of the current study was to explore incidence, type of surgical treatment given, and outcome for patients with typical (TC) and atypical (AC) lung carcinoids in a national cohort (Norway). **Methods:** All lung-cancer patients diagnosed in the period 1993—2005 and who were reported to the Cancer Registry of Norway were identified. Biopsies or resection specimens were reviewed and reclassified according to the World Health Organization (WHO) 2004 classification. Surgically treated patients were staged according to the seventh edition of the pathological tumor—node—metastasis (pTNM) staging system. **Results:** Of 26 665 lung cancers registered during the period, 265 (1%) had carcinoid tumors, of which 11 were diagnosed coincidentally at autopsy. In the remaining 254 patients, TCs were found in 188 cases, and ACs were found in 59 cases; seven cases had unclassifiable carcinoids. Of the 217 resected tumors, 173 (80%) were TCs. General surgeons performed 94 resections, including 11 of 17 pneumonectomies. All six bronchial resections were performed by thoracic surgeons. Of the 33 operated patients who died during follow-up, 18 had metastatic carcinoid tumors, of which 10 (56%) were ACs. In 37 non-resected patients (15 with AC and seven with unclassifiable histology), metastatic or locally advanced disease (N = 21, 12 of which were ACs) was the main cause of inoperability and death. Five-year survival for all patients was 92% for TC and 66% for AC; for resected patients, the survival rates were 96% and 79%, respectively. **Conclusions:** Carcinoids are rare malignant tumors and are, in most cases, resectable; the TC subgroup had better prognosis than the AC in univariate analyses. The main cause of death was metastasis/locally advanced tumor at presentation or recurrent disease following resection; both situations were three times more common in patients with AC.

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1. Introduction

Carcinoid tumors of the lung are neoplasms of neuroendocrine origin that account for approximately 25—30% of all carcinoid tumors [1—4]. Depending on the degree of mitotic activity and necrosis, tumors >5 mm in diameter are further subclassified into typical carcinoids (TCs) and atypical carcinoids (ACs). Based on the World Health Organization (WHO) 2004 classification of bronchopulmonary carcinoids, ACs are distinguished from TCs by the demonstration of necrosis and/or presence of 2—10 mitoses per 2 mm^2 (10 × high-power field)$^{-1}$ [5]. In TC, there are <2 mitoses per 2 mm^2 (10 × high-power field)$^{-1}$, no necrosis is present and the tumor is >0.5 cm in diameter. For both subclasses, studies indicate a relatively good prognosis following surgery in comparison with the prognosis following surgery for other non-small-cell lung carcinomas (NSCLCs), even with tissue-sparing resection [6—9]. However, to our knowledge, there have been no population-based studies of carcinoid tumors that also include all patients in whom surgery was not performed. Even in the series gathered by the International Association for the Study of Lung Cancer (IASLC), most patients had undergone resection [10].

Formerly published data from the Cancer Registry of Norway on survival after resection for primary lung cancer, including carcinoid tumors, demonstrate the 5-year observed and relative survival for carcinoid tumors to be 94% and 99%, respectively [11]. However, a subdivision into TC and AC was not performed at the time, nor were the cases reviewed by pathologists.

Because knowledge regarding the incidence and total outcome in population-based studies of carcinoid tumors is limited, especially with regard to the AC and TC subgroups, the purpose of this study was to explore incidence, treatment given and outcome for all carcinoid lung-cancer patients in a national cohort (Norway) with regard to TC and AC subgroups.

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2. Methods

All newly diagnosed cases of cancer are required by Norwegian law to be reported without patient consent to the Cancer Registry of Norway. Since 1953, the Registry has collected information on all cancer patients in the population from clinical and pathology reports. The Registry also routinely receives death certificates from the Cause of Death Registry of Statistics Norway and is virtually complete (99%) [12]. Inclusion of cases into this Registry occurs according to the International Standards for Cancer Registration published by WHO. Tumors are registered according to location and to morphology. Pulmonary carcinoids are registered as separate malignant entities.

All clinical notification forms and pathology reports on biopsies, cytologies, and/or resection specimens with a diagnosis of carcinoid lung tumor during the period 1993—2005 were included and reviewed. Biopsy specimens were revised either by a local pathologist or by one of the authors (EHS, $N = 64$), if local departments were unable to carry out the revisions. All were asked to verify the diagnosis of carcinoid tumor established previously and to subclassify the tumor histology further into TC and AC, according to the WHO 2004 classification based on a study by Travis et al. published in 1998 [13]. To quantify the presence of necrosis and the frequency of mitoses, a diagnostic subdivision into TC or AC may require either surgical specimens or more biopsy material than what is generally obtained by the transthoracic or bronchial route. However, in non-resected tumors with sparse histological material, a diagnosis of AC was made if, in addition to carcinoid features, the biopsies also demonstrated necrosis or mitosis.

Following the collection of clinical data and histology reports, disease extension subsequent to resection was reclassified at the Cancer Registry, according to the seventh edition of the International Classification of TNM [14,15]. For cases in which the clinical information reported to the Registry was insufficient, additional relevant data were obtained directly from the hospitals in charge.

2.1. Statistics

Chi-squared tests were used for descriptive statistics. Observed survival was calculated by the life-table method for descriptive purposes and by Kaplan—Meier for survival plots. Follow-up ended on 31 December 2008. Continuous variables are presented as mean with range. P values less than 0.05 were considered statistically significant. Data analyses were carried out with the Statistical Package for Social Sciences (SPSS) 17.0 and R 2.11.1.

3. Results

During the period from 1993 to 2005, lung cancer was diagnosed in 26 665 patients in Norway, 265 (1%) of whom had carcinoid tumors. In 11 cases, the tumors were diagnosed by coincidence at autopsy in patients, who died from other causes. Four cases initially reported to represent carcinoid tumors were found on revision to represent adenocarcinomas ($N = 2$) and large-cell carcinomas ($N = 2$); they were there-
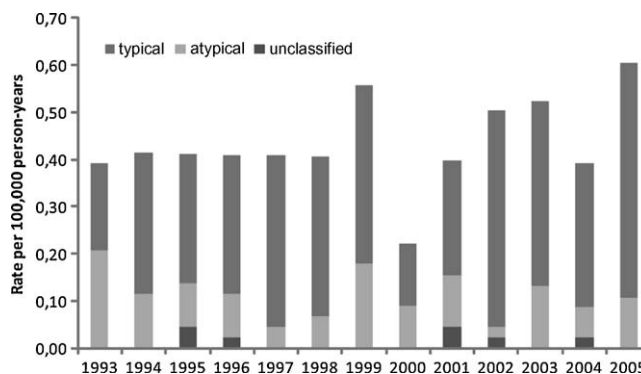

Fig. 1. Incidence of carcinoid lung tumors in Norway.

fore excluded. The incidence of carcinoid tumors in the Norwegian population was quite stable during the study period, ranging from 0.22 to 0.66 per 100 000 person-years (Fig. 1). The number of new cases ranged from 17 to 25, except for 2 years in which there were 10 and 29 new cases, respectively. Seven tumors in non-operated cases were not subclassified due to sparse biopsy specimen material. Of the remaining 247 patients, 188 (76%) had a verified diagnosis of TC; the remaining 59 had AC. Table 1 summarizes the characteristics of these patients. The rate of 5-year observed survival for all patients was 92% for TC and 66% for AC.

3.1. Resected patients

The majority of patients ($N = 217$, 85%) underwent surgical resection. Of these, 129 were women and 88 were

Table 1. Clinical characteristics according to lung carcinoid histological subtype for all patients ($N = 254$) and resected patients ($N = 217$).

	Typical carcinoids	Atypical carcinoids	Unclassified carcinoids
All patients			
Gender			
Women	113 (60.1)	34 (57.6)	5 (71.4)
Men	75 (39.9)	25 (42.4)	2 (28.6)
Age			
<50	85 (45.2)	19 (32.3)	3 (42.9)
50—69	70 (37.2)	26 (44.1)	1 (14.3)
≥70	33 (17.6)	14 (23.7)	3 (42.9)
Treatment			
Conservative (non-surgery)	15 (8.0)	15 (25.4)	7 (100)
Upper lobectomy	32 (17.0)	11 (18.6)	
Lower lobectomy	50 (26.6)	8 (13.6)	
Middle lobectomy	27 (14.4)	6 (10.2)	
Bilobectomy	21 (11.2)	3 (5.1)	
Pneumonectomy	14 (7.4)	3 (5.1)	
Sublobar resection	24 (12.8)	12 (20.3)	
Bronchial resection	5 (2.7)	1 (1.7)	
Resected patients			
pStage 7th edition			
IA	110 (63.6)	22 (50.0)	
IB	39 (22.5)	8 (18.2)	
IIA	17 (9.8)	7 (15.9)	
IIB	4 (2.3)	3 (42.9)	
IIIA	3 (1.7)	2 (4.5)	
IV	0	2 (4.5)	
Location			
Peripheral	63 (36.4)	28 (63.6)	
Central	110 (63.6)	16 (36.4)	

Table 2. Results of preoperative invasive diagnostic tests performed in 116/217 operated patients.

Tumor type	Bronchoscopic biopsy/cytology (N) (%)	Transthoracic needle biopsy/cytology (N) (%)
Carcinoid	80 (90.9)	16 (57.1)
Squamous cell carcinoma	1 (1.1)	1 (3.6)
Adenocarcinoma	2 (2.3)	5 (17.9)
Small-cell carcinoma	4 (4.5)	0
Adenosquamous cell carcinoma	0	3 (10.7)
Unclassified malignant tumor	1 (1.1)	3 (10.7)
Total	88 (100)	28 (100)

men, and mean age was 46 (16—80) and 54 (14—81) years, respectively. TC was the dominant histology, diagnosed in 80% of the resected cases (Table 1).

Before surgery, preoperative bronchoscopic (N = 88) or transthoracic (N = 28) biopsy/cytology was performed in 116 cases (53%); the samples were diagnosed as carcinoid tumors in 96 cases (83%). A total of 20 cases (17%) were preoperatively diagnosed as other subgroups of primary bronchogenic carcinomas (Table 2). Thus, 101 patients (47%) were subjected to surgery without a preoperative morphological diagnosis. Of patients with TC, 64% of tumors were located centrally in the lung while the same percentage of AC tumors were located peripherally (P = 0.002).

Surgical procedures were performed by both thoracic (N = 123) and general surgeons (N = 94). Tumor access was obtained by thoracotomy in all cases. Lobectomy was the most frequently performed procedure (Table 1); pneumonectomy was performed in 17 cases (8%), 11 of which were carried out by general surgeons. All but one pneumonectomy were performed in patients with centrally located tumors, eight of which had infiltrated more than one lobe. All six bronchial resections were performed by thoracic surgeons.

Peri-/postoperative mortality was nil. In one male patient, perioperative hemorrhage necessitated pneumonectomy. In another male in whom bilobectomy was performed, completion pneumonectomy had to be done 2 days later because of persistent air-leakage. Furthermore, one patient developed bronchopleural fistula 9 months after pneumonectomy. At the end of the observation period, 16 of 17 patients (94%) treated by pneumonectomy were alive; one died from unrelated causes 3 years after resection. Corresponding survival figures were 79% for bilobectomy, 88% for lobectomy and 74% for sublobar resection.

Postoperatively, the majority of cases (N = 179, 82%) were classified as stage I according to the seventh edition of International Classification of TNM. Observed 5-year survival rates were for TC 96% and AC 79%. By stage the survival was 94% for stage IA, 91% for IB and 88% for IIA (24 patients). The number of patients in the more advanced stages was too small to yield valid data on survival. Stage-specific survival for stage IA for surgically treated AC and TC revealed 5-year survival of 81% (95% confidence interval (CI) 66—100%) versus 97% (95% confidence interval (CI) 94—100%), respectively.

None of the patients being treated with resection received adjuvant chemotherapy postoperatively.

Of the 33 resected patients, who died during follow-up, 18 died from metastases giving a total recurrence rate of 8%. Of these patients, 14 had AC, giving a postoperative recurrence rate of 17% for this tumor subgroup, compared with a postoperative recurrence rate of 4% among patients with TC. Two patients with AC and liver metastases underwent combined liver and lung resection. Both died from metastases 1 and 2 years later.

Other causes of death included myocardial infarction (N = 5), secondary cancer other than carcinoids (N = 3), pneumonia/septicemia (N = 3), and cerebral stroke (N = 3). The cause of death in two patients was unknown.

3.2. Non-resected patients

At the time of diagnosis, 37 patients (23 females) had various reasons for not undergoing resection, the most prevalent of which were distant metastasis (N = 16) and locally advanced tumors (N = 5) (Table 3). Mean age was higher than in the resected group of patients, and males were older than females; 68 (range 34—83) versus 62 years (range 38—86), respectively.

TC and AC were each diagnosed in 15 patients, while seven patients presented with unclassified carcinoid tumors (UCs).

Of 20 patients presenting with metastasis and locally advanced tumors, 11 (55%) had AC and three displayed unknown histological subtypes. The proportion of patients with AC and metastasis at the time of diagnosis was higher than the proportion of patients with TC and metastatic disease—62% versus 15%, although not statistically significant (P-value = 0.06).

All but one of these patients died from carcinoid disease during follow-up. Survival in these patients was poor compared with survival among those who were operated upon, only 42% after 5-year (95% confidence interval (CI) 28—61%) (Fig. 2).

Altogether, 10 females (two with AC and five with TC) and one male were alive at the end of the follow-up period. We

Table 3. Causes of non-surgical treatment in 37 lung carcinoid patients.

	Men			Women			Total (N) (%)
	TC (N) (%)	AC (N) (%)	Unclassified (N) (%)	TC (N) (%)	AC (N) (%)	Unclassified (N) (%)	
Distant metastasis	2 (33.3)	5 (83.3)	2 (100)	1 (11.1)	5 (55.6)	1 (20.0)	16 (43.2)
Advanced local disease (T4)	1 (16.7)	1 (16.7)	0	2 (22.2)	1 (11.1)	0	5 (13.5)
Laser therapy	1 (16.7)	0	0	3 (33.3)	2 (22.2)	2 (40.0)	8 (21.6)
Advanced age	0	0	0	1 (11.1)	0	1 (20)	2 (5.4)
Refused surgery	1 (16.7)	0	0	0	0	0	1 (2.7)
Heart failure	0	0	0	1 (11.1)	0	0	1 (2.7)
Unknown	1 (16.7)	0	0	1 (11.1)	1 (11.1)	1 (20)	4 (10.8)
Total	6 (100)	6 (100)	2 (100)	9 (100)	9 (100)	5 (100)	37 (100)

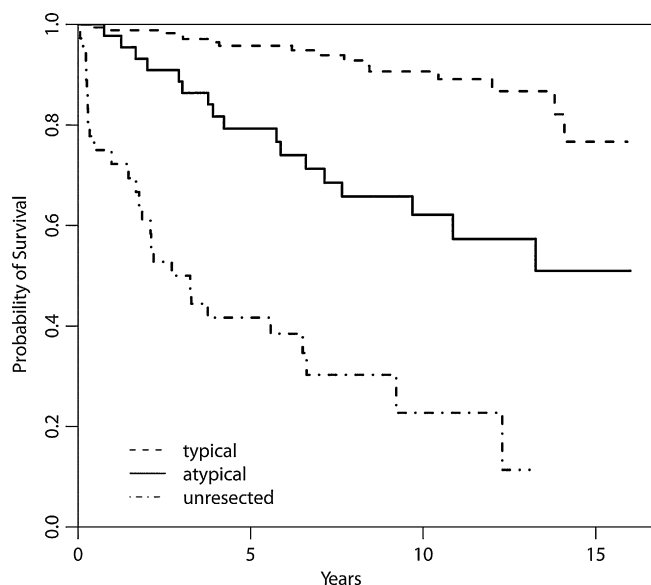TC: typical carcinoid tumor; AC: atypical carcinoid tumor.

Fig. 2. Probability of survival in patients with operated TC and AC and non-resected patients (*n* = 254).

have limited information regarding the extent of use and type of chemotherapy or radiotherapy administered to these patients. A total of eight patients were treated with endobronchial laser therapy; seven were treated with curative intent. Of these, five are still alive, while three died more than 6 years following the procedure.

4. Discussion

In the present study, carcinoid tumors were found in 1% of malignant pulmonary tumors, the majority of which were TCs (74%). As the present study is population based and includes both operated and non-operated patients, we have been able to indicate a more complementary picture of the difference between AC and TC given that the groups are comparable to each other. While the resection rate for all lung cancers in Norway has been steady at 17% during this study period, a number which corresponds well with other comparable countries, roughly 82% of carcinoids were resected.

We also have described the difference between AC and TC in terms of tumor aggressiveness: AC is more likely to leave a higher percentage of patients inoperable at presentation, to metastasize following surgery, and to be associated with a poorer survival rate. More than 20% of patients with AC presented with advanced tumor disease at the time of diagnosis, but this was true for less than 4% of patients with TC. All but one of these 21 unresected patients (95%) with advanced disease died from carcinoid tumors during follow-up. Long-term survival was highest in resected patients. Further, 17% of patients with AC developed recurrent disease that resulted in death, while this pattern was observed in only 4% of resected patients with TC. However, due to an incomplete dataset, the study lacks final proof that the two arms in the study are, in fact, comparable.

In a study by Rea et al. [9], an univariate analysis of prognostic factors showed the most important ones to be typical histology and N0 disease at diagnosis. An Icelandic population-based study reported similar findings in 2008 [16]. However, the number of patients included in that study was too low to allow general conclusions to be drawn (64 patients whereof 10 had AC). While our study is larger, we omitted multivariate analysis because too few prognostic factors were known to carry out meaningful interpretations.

When comparing the prognosis of carcinoids to that of other subgroups with NSCLC, both short- and long-term survival are far better for patients with carcinoids [11,17]. In a Norwegian population-based study of 3211 resected patients with primary lung cancer (16% of all lung-cancer cases) diagnosed from 1993 to 2002, the average 5-year relative survival rate was 46%, varying from 58% (stage I) to 21% (stage IV) [11].

The Surveillance, Epidemiology and End Results (SEER) database reported that carcinoid tumors represented 1% of the 463 338 bronchial carcinomas; with an increase during the last 30 years of about 6% per year, this figure was 1.57 of 100 000 in 2003. This increase was thought to reflect the use of more refined pathologic methods [4]. In this database, AC occurred in 10—20% of carcinoid tumors. As shown in the present article, we did not observe a corresponding steady increase in incidence over the time period studied in Norway.

The main surgical procedures performed in Norway were anatomic resections such as lobectomy/bilobectomy (*N* = 158, 73%) and pneumonectomy (*N* = 17, 8%). More recent publications have advocated conservative resections with preservation of as much parenchymatous tissue as possible for peripherally located lesions or bronchial resections for more centrally located tumors [4—7]. Possibly, such tissue-sparing resections should have been performed more frequently in our group of patients rather than mutilating operations such as pneumonectomy. A possible explanation for the prevalence of these more dramatic operations may be that many patients were operated upon by general surgeons, who lacked experience with more sophisticated resections. However, the proportion of pneumonectomies in Norway decreased substantially from 31% to 23% during the time period from 1993 to 2005 [11], a finding, which may be associated with an increasing tendency toward the centralization of thoracic surgery to larger centers during that time.

Because few patients are diagnosed with carcinoid tumors each year, we feel that these cases ought to be referred to centralized institutions that receive a larger volume of such cases. This move could improve preoperative diagnosis and treatment planning. In the present investigation, nearly 50% of patients did not have a preoperative diagnosis and for those who had, several were classified with other histological subtypes. We do not know how many carcinoid tumors were classified as other lung-cancer subtypes and thus not included in this study.

To optimize treatment for patients with carcinoid tumors when the subgroups AC and TC have different prognoses, correct preoperative morphology should be a prerequisite for surgical planning. On the other hand, the subclassification of small biopsies from non-resected patients into TC and AC still presents a challenge to pathologists and may necessarily be associated with some uncertainty.

Carcinoid tumors differ from NSCLC in that the malignant potential and prognosis of the latter is governed mainly by stage, while tumor subtype plays a less important role (with

the exception of true bronchioloalveolar cell carcinomas) [15]. However, in the case of carcinoid tumors, both increasing stage and AC subtype have been suggested as predictors for poorer prognosis. This pattern was also observed in the present investigation, as demonstrated by the poorer cumulative survival rates for patients operated on for AC versus TC, the high proportion of patients with un-resectable tumors due to advanced disease at the time of diagnosis (19% AC vs 5% TC) and the reduced proportion of patients with AC in pathologic (p)Stage I (54% AC vs 81% TC).

The survival rates at 5 years (stages IA and IB patients) were appropriate for the new seventh edition of the TNM system; the number of patients with late-stage tumors was too low to allow for conclusions to be drawn. We chose to apply the seventh edition of the TNM staging system to explore survival because it is the first edition that explicitly recommends the staging of carcinoid tumors [14]. Clarification on this matter can be obtained only by collecting data from the planned International Registry of Pulmonary Neuroendocrine Tumors. For selecting the optimal treatment approach with regard to staging and prognosis, our findings highlight the need for such a registry.

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