Increasing Age and Carcinoma Not Otherwise Specified

A 20-Year Population Study of 40,118 Lung Cancer Patients

Camilla Maria T. Sagerup, MD,† Milada Småstuen, cand scient,‡ Tom B. Johannesen, MD, PhD,‡ Åslaug Helland, MD, PhD,*†§ and Odd Terje Brustugun, MD, PhD*†§*

Background and Aim: New treatment regimens require a differentiation between histological subsets of non-small cell lung cancer. We aimed to assess how the incidence and prognosis of carcinoma not otherwise specified (NOS) coincide with an aging patient population, disease stage, and diagnostic methods used.

Methods: Complete national data on 40,118 cases (including 6,597 diagnosed with carcinoma NOS) from the Cancer Registry of Norway (1988–2007) are presented.

Results: The proportion of elderly patients (70 years and older) have increased to over half of all patients diagnosed, a trend also evident among carcinoma NOS patients. The proportion of carcinomas NOS reported to the cancer registry in this 20-year period has increased from 12% in 1988 to 19% in 2007. Crude 5-year relative survival in carcinoma NOS was lowest of all non-small cell lung cancer entities throughout the 20-year period; however, patients diagnosed with carcinoma NOS in the period 2003 to 2007 had about 24% lower risk of dying within 5 years after diagnosis compared with patients diagnosed between 1988 and 1992, adjusted for covariates. Most lung cancers are diagnosed by biopsy of the primary lesion; although the proportion is lower among carcinomas NOS than other histological entities. By the last 5-year period studied, carcinoma NOS was the histological entity most commonly diagnosed by cytology (38%).

Conclusion: The proportion of carcinomas NOS has increased to 19% of all lung cancer cases. This histological entity is associated with older age and poor survival.

Key Words: Lung carcinoma, Carcinoma NOS, Age, Survival, Incidence.

(*J Thorac Oncol.* 2012;7: 57–63)

*University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Oslo, Norway; †Department of Genetics, Oslo University Hospital-Radiumhospitalet, Oslo, Norway; ‡Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway; §Department of Oncology, Oslo University Hospital-Radiumhospitalet, Oslo, Norway.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Camilla Maria T. Sagerup, MD, Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Montebello, 0310 Oslo, Norway. E-mail: camilla.sagerup@rr-research.no

ISSN: 1556-0864/12/0701-0057

Lung cancer is not only the most common cancer in the world; it is increasingly a cancer of the elderly. Median age at time of diagnosis is now approaching 70 years,[1] and patients aged 70 years and older currently account for close to 50% of all lung cancers.[1–3] Nevertheless, our knowledge about the optimal treatment for lung cancer in older patients is limited as elderly patients are often underrepresented or excluded from clinical trials.[4,5]

Furthermore, new diagnostic challenges have arisen with the emergence of clinical trials that brought on the advent of histology-specific treatment regimens.[6,7] Until recently, treatment options did not vary between histological entities of non-small cell lung cancer (NSCLC), hence treatment after a diagnosis of NSCLC carcinoma not otherwise specified (NOS) did not differ from that of other non-small cell histologies.

Current changes in treatment practices, however, highlight the importance of monitoring epidemiological data to assess how patient demographics coincide with new diagnostic demands. With access to complete, national cancer registry data encompassing >40,000 patients within the 20-year period 1988 to 2007, we aimed to assess how an aging patient population, disease stage, and diagnostic methods play a role in the incidence and prognosis of carcinoma NOS, a diagnostic entity given over 6,500 patients in this period.

MATRIALS AND METHODS

Population Demographics

Norway has a universal, public health service financed by taxation and a national insurance scheme equally accessible to all residents, independent of geography or social status.

Data Collection

Since 1952, it has been mandatory by law to report all malignant neoplasms to the Cancer Registry of Norway (CRN). In addition, copies of cytology, biopsy, and autopsy reports are submitted from pathology laboratories and death certificate reports from the Cause of Death Register run by the National Statistics Bureau, Statistics Norway. Since 1993, all hospitals have filed discharge summaries electronically to the registry. The system of reporting to CRN was evaluated in 2009, and overall completeness of reporting was estimated at 98.8%.[8]

Data Analysis

We used the CRN database December 2008 submission to analyze patient demographics, including histology, age, stage, and diagnostic method used. When both biopsy and cytology is performed in primary diagnostics, biopsy is registered as primary method. Age-specific incidence rates (IRs) were estimated (per 100,000) with number of cases in each age group in the denominator and the number of person-years of that age group in the numerator.

We calculated 5-year male and female relative survival (RS) stratified by age, stage, and histological type for individuals diagnosed through successive 5-year calendar periods. Not all deaths among cancer patients are because of the primary cancer under study, and deaths resulting from other causes could lead to lower survival estimates. In addition, the cause of death is not always known and reliable. RS provides an estimate of net survival and thus circumvents the above problem. It is defined as the observed survival proportion in a patient group divided by the expected survival of a comparable group in the general population with respect to age, sex, and calendar year of investigation.[9]

The effect of selected covariates (gender, age, stage, and diagnostic period) on survival was modeled using Cox proportional hazards regression. The assumption of proportional hazards was checked by means of visual inspection of log minus log plots. All statistical tests were two sided and p values <0.05 were considered statistically significant. All statistical analyses were performed using STATA version 11 and SPSS version 18.

Diagnosis and Staging

We included only cases of carcinomas NOS with histopathological reports that had a final conclusion from the pathologist of carcinoma NOS. Cases where the diagnostic method was unknown or listed as noninvasive (radiology) were not included ($n = 3682$).

CRN uses a condensed staging system for lung cancer reporting, based on the TNM classification system, in that T1-2N0M0 is "Localized," M1 is "Metastatic," and the others are "Regionally advanced." Tumor localization was through 1992 coded according to ICD-7, and tumor histology was coded according to Manual of Tumor Nomenclature and Coding (1968).[10] Since 1993, both topography and morphology have been coded according to ICD-O.[11] A standardized national treatment protocol for the treatment of lung cancer was implemented in 2000. We collected data from 1988, since after that time point, computerized tomography was in widespread use, implying that diagnosis and staging should be uniform throughout the country.

RESULTS

Patient Characteristics

A total of 40,118 cases were included in the study, in which 6,597 cases (16.4%) were carcinomas NOS; 4,284 (65%) men and 2,313 (35%) women. Clinicopathological characteristics for all patients are reported in supplementary Table 1 (http://links.lww.com/JTO/A156) and for carcinoma NOS patients in Table 1.

Age-Specific Incidence and Survival

Among all 40,118 patients, annual average rates in age-specific incidence in males increased slightly (+1.6%) in the age group 70 to 79 years and more notably (+4.4%) in the age group 80 years and older (Figure 1*A*) in the period 1988 to 2007. The proportion of patients in this age group (80+) increased from 11% in 1988 to 19% in 2007 (Figure 1*B*). In women, age-specific IRs increased in all age groups, 50 years and older, and were most pronounced in those aged 60 years and older, which recorded average annual increases from 4.2% to 5.3% (Figure 1*C*). Similar to what was observed in men, the largest increase in proportion of cases was seen in

TABLE 1. Carcinoma NOS Patient Characteristics Stratified by Diagnostic Period and Sex

	1988–1992		1993–1997		1998–2002		2003–2007		Total (1988–2007)	
	M	F	M	F	M	F	M	F	M	F
Carcinoma NOS (%)	752 (68)	356 (32)	1035 (67)	507 (33)	1096 (64)	617 (36)	1401 (63)	833 (37)	4284 (65)	2313 (35)
5-yr relative survival (95% CI)	3.8 (2.4–5.9)	5.9 (3.5–9.2)	5.4 (3.9–7.2)	7.4 (5.1–10.3)	3.8 (2.6–5.3)	5.7 (3.9–8)	7.1 (4.9–9.9)	7.8 (5.3–11)	5.1 (4.2–6)	7.1 (5.9–8.5)
Stage (%)										
Localized disease	254 (34)	112 (31)	323 (31)	156 (31)	223 (20)	124 (20)	253 (18)	173 (21)	1053 (25)	565 (24)
Regional disease	350 (47)	180 (51)	486 (47)	253 (50)	593 (54)	349 (57)	710 (51)	439 (53)	2139 (50)	1221 (53)
Metastatic disease	129 (17)	60 (17)	212 (20)	87 (17)	268 (24)	142 (23)	424 (30)	208 (25)	1033 (24)	497 (21)
Unknown	19 (3)	4 (1)	14 (1)	11 (2)	12 (1)	2 (0)	14 (1)	13 (2)	59 (1)	30 (1)
Age (%)										
0–49 yr	36 (5)	21 (6)	50 (5)	46 (9)	40 (4)	46 (7)	36 (3)	36 (4)	162 (4)	149 (6)
50–59 yr	100 (13)	51 (14)	127 (12)	83 (16)	174 (16)	136 (22)	190 (14)	163 (20)	591 (14)	433 (19)
60–69 yr	249 (33)	121 (34)	332 (32)	149 (29)	286 (26)	168 (27)	404 (29)	222 (27)	1271 (30)	660 (29)
70–79 yr	292 (39)	115 (32)	392 (38)	169 (33)	447 (41)	202 (33)	500 (36)	295 (35)	1631 (38)	781 (34)
Aged 80 years and older	75 (10)	48 (13)	134 (13)	60 (12)	149 (14)	65 (11)	271 (19)	117 (14)	629 (15)	290 (13)
Diagnostic methods (%)										
Biopsy metastasis	88 (15)	52 (12)	153 (15)	68 (13)	146 (13)	89 (14)	156 (11)	106 (13)	543 (13)	315 (14)
Biopsy primary tumor	501 (67)	238 (67)	670 (65)	333 (66)	635 (58)	344 (56)	883 (63)	518 (62)	2689 (63)	1433 (62)
Cytology	163 (19)	66 (22)	212 (20)	106 (21)	315 (29)	184 (30)	362 (26)	209 (25)	1052 (25)	565 (24)

M, male; F, female; NOS, not otherwise specified; CI, confidence interval.