Elevated Preoperative C-reactive Protein Predicts Poor Cancer Specific Survival in Patients Undergoing Resection for Non-small Cell Lung Cancer

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Background: Although only the minority of patients with non-small cell lung cancer (NSCLC) are suitable for surgical resection, it offers the best possibility of cure. The aim of this study was to examine the relationship between the clinicopathological status, the preoperative systemic inflammatory response, and survival in patients undergoing potentially curative resection for NSCLC.

Methods: Data from 96 patients who underwent resection of NSCLC between 2000 and 2003 were collected retrospectively and that for 2004–2006 prospectively.

Results: All patients had Eastern cooperative oncology group performance status 0 or 1. No patient had T4, unresectable nodal or metastatic disease, and all macroscopic tumors were removed, with subsequent negative surgical margins. The majority of patients were older than 60 years (71%), men (57%), underwent a lobectomy (65%), and had tumor, node, metastasis stage I disease (66%). Of the markers of the systemic inflammatory response, white cell count, C-reactive protein, and albumin, only an elevated C-reactive protein (>10 mg/L) was associated with cancer-specific survival. On multivariate analysis, only tumor, node, metastasis stage (hazard ratio 1.88, 95% confidence interval 1.34–2.63, $p < 0.001$) and preoperative C-reactive protein (hazard ratio 1.67, 95% confidence interval 1.01–2.83, $p < 0.05$) retained independent significance. Those patients with a preoperative C-reactive protein concentration >10 mg/L had a median survival of 26.2 months compared with 75.9 months in those patients with a C-reactive protein ≤10 mg/L ($p < 0.05$).

Conclusion: The results of this study indicate that the presence of a systemic inflammatory response predicts poor outcome in patients who have undergone potentially curative resection for lung cancer.

Key Words: Non-small cell lung cancer, Surgery, Tumor stage, C-reactive protein, White cell count, Albumin, Survival.

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Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death in North America and Western Europe. Most patients present with advanced inoperable disease and the majority die within 12 months.[1] Although only suitable in the minority of patients, approximately 11% in the UK,[2] surgery confers the greatest chance of long-term cure.

Despite careful selection, in terms of tumor, node, metastasis (TNM) stage and fitness, approximately 30% of patients with early-stage disease, who undergo surgical resection, will develop metastatic spread and die of their disease.[3] Therefore, there has been a longstanding interest in identifying those patients with apparently early-stage disease most likely to die of lung cancer. Ideally, a factor or combination of factors would clearly stratify patients who will remain disease free and are "cured" from those who will ultimately die of their cancer.[4] Currently, TNM stage is the most widely used tool to predict the likely outcome. However, despite revisions, there is considerable "overlap" in survival between the stages.[3,5,6]

The systemic inflammatory response, as manifest by alterations in white cell count and circulating concentrations of the acute-phase proteins, C-reactive protein, and albumin, has been shown to be an independent prognostic factor in various advanced cancers[7–9] including non-small cell lung cancer.[10–13]

More recently, it has been reported that when various tumors were resected with curative intent, an elevated C-reactive protein concentration has been shown to be associated with poorer cancer-specific survival, independent of pathologic stage.[14–17]

Therefore, it is of interest that Hara et al.[18] recently reported that, in 203 patients who had undergone potentially curative resection for NSCLC, an elevated preoperative C-

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reactive protein concentration was associated with poorer cancer-specific survival independent of TNM stage. In addition, it has been reported that an elevated preoperative C-reactive protein concentration was associated with a poorer complete resection rate,[19] larger tumors size, and lymphovascular invasion.[20] However, the prognostic value of C-reactive protein has not been shown in other studies.[21,22]

The aim of this study was to examine the relationship between clinicopathologic status, systemic inflammatory response (measured before surgery), and cancer-specific survival in patients undergoing potentially curative resection of NSCLC.

PATIENTS AND METHODS

Patients

Patients with histologically proven NSCLC who, on the basis of surgical findings and/or preoperative chest and abdominal computed tomography, were considered to have undergone a potentially curative resection and had routine laboratory measurement of albumin and C-reactive protein in the 2 months before surgery, between March 2000 and November 2006 in a single unit in the North Glasgow NHS Trust, were included in the study. Patients who died within 30 days of surgery were excluded from the analysis. During this period, data were collected for 96 of 108 patients who underwent resection for non-small cell lung cancer. Data for 2000–2003 were collected retrospectively and that for 2004–2006 prospectively.

All patients had Eastern cooperative oncology group performance status 0 or 1. No patient had T4, unresectable nodal or metastatic disease, and all macroscopic tumor was removed, with subsequent negative surgical margins. All patients underwent thoracotomy, and no patient underwent video-assisted thoracoscopic surgery. Patients were staged according to the 1997 TNM classification of lung tumors.[5] No patient had computed tomography-positron emission tomography scanning because this study predated routine computed tomography-positron emission tomography scanning in the staging of radically treatable patients with lung cancer. Preoperative white cell count was available in 73 patients.

After surgery, patients were considered to have undergone adjuvant treatment if they received chemotherapy (mainly cisplatin based) and/or radical radiotherapy.

The Research Ethics Committee of North Glasgow NHS Trust approved the study.

Methods

Serum concentrations of albumin and C-reactive protein were measured by a bromcresol green dye-binding method and turbidometric assay, respectively, using an autoanalyzer (Abbott Diagnostics, Abbott Park, IL). The limit of detection for C-reactive protein was 6 mg/L. The inter- and intra-assay variability of white cell count, albumin, and C-reactive protein were less than 10% as assessed by routine quality control procedures. A C-reactive protein concentration of >10 mg/L was considered to indicate the presence of a systemic inflammatory response.[7,8]

Statistics

Grouping of the variables age, tumor type, operation, white cell count, and albumin was carried out using standard thresholds.[9,11,22] C-reactive protein concentrations were also grouped ($\leq 10/>10$ mg/L) as previously described.[7] Values from groups of patients were compared using contingency table analysis (χ^2) as appropriate. Survival was analyzed using the Cox proportional hazards model; deaths up to the end of January 2009 were included in the analysis. For multivariate survival analysis, a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival was used. To remove a variable from the model, the corresponding p value had to be >0.10. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL).

RESULTS

The clinicopathological characteristics of patients with operable NSCLC at diagnosis are shown in Table 1. The

TABLE 1. Clinicopathological Characteristics and Cancer-Specific Survival of Patients Undergoing Potentially Curative Resection for NSCLC

		Univariate Survival Analysis		Multivariate Survival Analysis	
	Patients $n = 96$	Hazard Ratio (95%CI)	p	Hazard Ratio (95%CI)	p
Age ($<60/\geq 60$ yr)	26/70	1.08 (0.59–1.97)	0.807		
Sex (female/male)	40/56	1.45 (0.85–2.47)	0.170		
Type (adeno/squamous/other)	47/39/10	1.21 (0.84–1.74)	0.310		
Operation (lobectomy/pneumonectomy/wedge resection)	64/23/9	1.42 (1.00–2.02)	0.048		0.102
TNM stage (I/II/III)	65/19/12	1.94 (1.39–2.70)	<0.001	1.88 (1.34–2.63)	<0.001
White cell count ($<8.5/8.5$–$11.0/>11 \times 10^9$/L)	43/16/14	0.84 (0.56–1.24)	0.375		
Albumin ($\geq 35/<35$ g/L)	90/6	0.85 (0.26–2.71)	0.780		
C-reactive protein ($\leq 10/>10$ mg/L)	49/47	1.73 (1.02–2.98)	0.041	1.67 (1.01–2.83)	0.047
Adjuvant treatment (yes/no)	12/84	0.56 (0.22–1.40)	0.215		

TNM, tumor, node, metastasis.

majority of patients were older than 60 years (73%), men (58%), underwent a lobectomy (67%), and had TNM stage I disease (68%). Nineteen percent patients had an elevated white cell count, 7% patients had a low albumin concentration, and 48% patients had an elevated C-reactive protein concentration. Thirteen percent of patients received adjuvant treatment.

The minimal follow-up period was 28 months; the median follow-up period of the survivors was 75 months. In

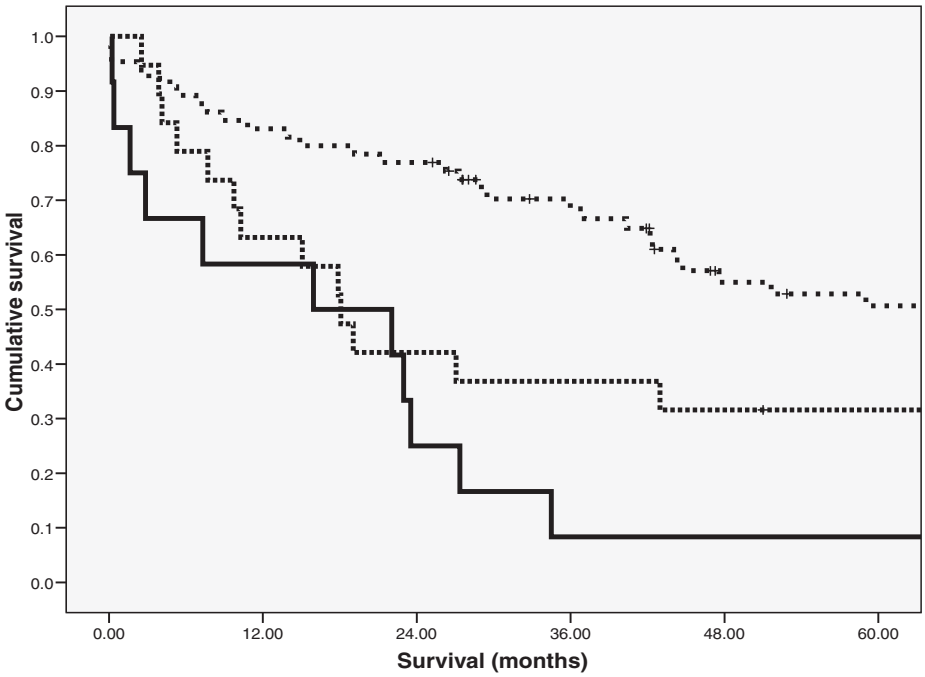

FIGURE 1. The relationship between tumor, node, metastasis stage (I, II, and III from top to bottom) and cancer-specific survival in patients with non-small cell lung cancer.

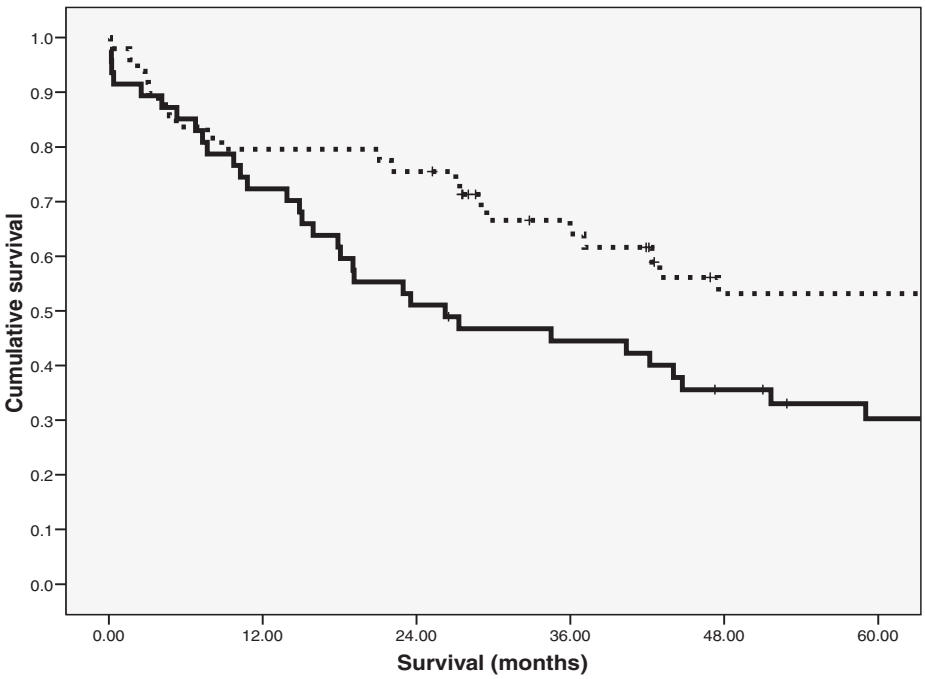

FIGURE 2. The relationship between preoperative C-reactive protein (≤10 mg/L/>10 mg/L from top to bottom) and cancer-specific survival in patients with non-small cell lung cancer.

TABLE 2. The Relationship Between Preoperative C-reactive Protein (≤10/>10 mg/L) and Clinicopathological Characteristics and Cancer-Specific Survival of Patients Undergoing Potentially Curative Resection for NSCLC

	C-reactive Protein (≤10 mg/L, $n = 49$)	C-reactive Protein (>10 mg/L, $n = 47$)	p
Age (<60/≥60 yr)	13/36	13/34	0.901
Sex (female/male)	20/29	20/27	0.864
Type (adeno/squamous/other)	28/16/5	19/23/5	0.210
Operation (lobectomy/ pneumonectomy/wedge resection)	34/8/7	30/15/2	0.740
TNM stage (I/II/III)	37/7/5	28/12/7	0.154
White cell count (<8.5/ 8.5–11.0/>11 × 10^9/L)	25/5/6	18/11/8	0.166
Albumin (≥35/<35 g/L)	49/0	41/6	0.010
Adjuvant treatment (yes/no)	45/4	39/8	0.192
Survival (mo)[a]	75.9 (37.7–114.1)	26.2 (5.8–46.7)	0.038

[a] Median (95% confidence interval).
TNM, tumor, node, metastasis.

the follow-up period, 58 patients died of their disease. On univariate analysis, operation ($p < 0.10$), TNM stage ($p < 0.01$, Figure 1), and preoperative C-reactive protein concentrations ($p < 0.05$, Figure 2) were significantly associated with cancer-specific survival (Table 1). On multivariate analysis of these significant variables, only TNM stage (hazard ratio 1.88, 95% confidence interval 1.34–2.63, $p < 0.01$) and preoperative C-reactive protein (hazard ratio 1.67, 95% confidence interval 1.01–2.83, $p < 0.05$) retained independent significance.

The relationship between the presence of an elevated preoperative C-reactive protein concentration and clinicopathological characteristics are shown in Table 2. There were no significant associations with the clinicopathological characteristics with the exception of albumin, which was lower in the elevated C-reactive protein group ($p \leq 0.01$). The patient group with a normal preoperative C-reactive protein concentration (≤10 mg/L) had a median survival of 75.9 months compared with 26.2 months in the elevated C-reactive protein group ($p < 0.05$, Table 2).

DISCUSSION

Surgical resection remains the best prospect for long-term survival in patients with NSCLC. Currently, in patients undergoing surgery, prognostic factors are mainly based on the pathologic findings from the resected tumor. However, this means that the assessment of prognosis occurs after a major operation with significant morbidity and mortality. Therefore, it is of considerable interest that in this study, an elevated circulating concentration of C-reactive protein (>10 mg/L) was associated with poor survival independent of TNM stage. Those patients with a normal preoperative C-reactive protein concentration (≤10 mg/L) had a median survival of 72.5 months compared with 26.2 months in those patients with an elevated C-reactive protein concentration.

Dichotomised variables were used in the analysis based on previous work on the value of systemic inflammatory response markers in predicting survival in operable cancer.[23] The value of standardized threshold (≤10/>10 mg/L) for C-reactive protein is that it can have routine clinical utility. Although continuous variables may have a more close association with outcome, they are rarely useful in clinical decision making.

It has been previously shown that, in patients with primary operable gastrointestinal cancers, approximately one-third to one-half of patients had an elevated circulating concentration of C-reactive protein preoperatively and that these patients had a significantly poorer outcome independent of tumor stage.[14–17] It may be that because C-reactive protein concentration is independent of tumor stage, it might form the basis of a new prognostic score that reflects not only the tumor anatomy but also the host response. Indeed, this approach has recently been used to improve the prediction of outcome in patients who underwent potentially curative resection for esophageal and colorectal cancer.[24,25]

Acute-phase proteins are just one aspect of the systemic inflammatory response.[26] There are cellular components of the systemic inflammatory response and an elevated white cell count has been reported to have prognostic value in patients with a variety of common solid tumors.[9,27,28] However, in this study, elevated white cell count seemed to have no prognostic value in patients with primary operable NSCLC.

The results of this study may also offer insight into the nature of the relationship between the systemic inflammatory response and survival in patients with primary operable NSCLC. C-reactive protein may play a pivotal role in the tumor-host relationship because it is recognized to be not only an activator of innate immunity but also a modulator of adaptive immunity.[29] Moreover, the increase of C-reactive protein seems to be a precursor to tumor dissemination and progressive involuntary loss of weight and lean tissue,[30,31] which are key factors in determining cancer survival.

In this study, there were a number of limitations. The degree of comorbid disease and the smoking history of the patients were not accurately recorded. Recently, Koch et al.[32] reported that the combination of smoking and an elevated C-reactive protein independently predicted poor survival in patients with advanced-stage lung cancer. However, no patients had comorbid disease significant enough to preclude surgery, and all patients were advised to stop smoking before surgery. Therefore, it is unclear whether smoking would have independently predicted survival in this study. This study did not examine the relationship between tumor pathologic feature other than tumor type and TNM stage. However, Jones et al.[33] reported that fibrinogen and C-reactive protein concentrations were directly associated with tumor size in patients undergoing resection of non-small cell lung cancer.

This relatively small study requires verification in larger prospective cohorts, particularly within the context of randomized controlled trials. However, if an elevated C-reactive protein concentration is confirmed to predict a poorer outcome, it may be the case that patients with resected

NSCLC, yet a high inflammatory profile preoperatively, undergo more intensive follow-up and/or adjuvant treatment. Alternatively, it would be important to consider whether modulation of the systemic inflammatory response may be a useful approach in these patients in the perioperative period.

In summary, the results of this study indicate that, in patients who have undergone potentially curative resection for NSCLC, the presence of an elevated C-reactive protein predicts poor outcome.

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