Prognostic factors in stage III non-small cell lung cancer: a review of conventional, metabolic and new biological variables

Thierry Berghmans, Marianne Paesmans and Jean-Paul Sculier

Ther Adv Med Oncol

(2011) 3(3) 127–138

DOI: 10.1177/

1758834011401951

© The Author(s), 2011.

Reprints and permissions:

<http://www.sagepub.co.uk/journalsPermissions.nav>

Abstract: Lung cancer is one of the most frequently occurring neoplasms and usually has a poor prognosis because most of the patients present with advanced or metastatic disease at the time of diagnosis. Numerous prognostic factors (PFs) have been studied, but the two most prominent, having both prognostic and operational values, are disease stage and performance status. Even if the literature on PFs in lung cancer is impressive, the number of publications specifically dealing with PFs in stage III non-small cell lung cancer (NSCLC) is limited. We reviewed the literature on this topic and separated the available information into three groups: conventional PFs, metabolic criteria (standardized uptake value [SUV] measured on ^{18}F -FDG-PET) and new biomarkers. Performance status and the distinction between stage IIIA and IIIB confirmed their prognostic value in stage III NSCLC. Other conventional PFs have been suggested such as age, weight loss, response to treatment and some characteristics describing the locoregional extension of the tumour. There is a place for the SUV as a PF for survival in early NSCLC, but its role in stage III NSCLC has to be further assessed. Some new biomarkers involved in cell cycle regulation or in apoptosis have been shown to have potential value. Their role needs to be confirmed in large prospective studies including conventional PFs to determine their independent value as a PF in stage III NSCLC. In conclusion, few PFs have been well evaluated in stage III NSCLC. New studies, taking into account the modifications derived from the 7th international staging system of the UICC, have to be performed.

Keywords: non-small cell lung carcinoma, prognosis, stage, performance status

Introduction

Lung cancer is one of the most frequently occurring neoplasms and is the leading cause of death by cancer worldwide [Boyle and Ferlay, 2005]. Only 10–15% of the patients will ultimately be cured. Non-small cell lung cancer (NSCLC) accounts for 85% of all cases. There is a large heterogeneity among these patients, even within a specific search leading to the need for the identification of prognostic factors (PFs). We defined a PF as a variable, assessed before any treatment, correlated to an evaluation criterion (i.e. survival), that is useful in estimating the patient's future, independently of the treatment that will be applied. By extension, we also analyse the role of therapeutic variables such as response to treatment.

Literature on PF in lung cancer is exponentially increasing. During the years 1990–2000, the

annual number of publications on this topic rose from less than 50/year to 150/year [Brundage *et al.* 2002]. Disease stage is currently the main PF for survival in patients with NSCLC, having both prognostic and operational values. Other PFs have been commonly reported, mainly performance status, gender, age, histology, haemoglobin level, some primary tumour characteristics such as tumour size or local extension, and mediastinal neoplastic infiltration. Some other variables have been suggested less frequently as PFs in NSCLC. They can be divided into four groups, as follows:

- routinely assessed biological variables (calcaemia, lactate dehydrogenase [LDH] and alkaline phosphatase levels, leukocytosis, neutrophil count);
- patient's characteristics (weight loss, comorbidity, smoking status, body mass index, ethnicity);

Correspondence to:

Thierry Berghmans
Institut Jules Bordet, Rue
Héger-Bordet, 1, B-1000
Brussels, Belgium
thierry.berghmans@bordet.be

Marianne Paesmans
Data Centre, Institut Jules
Bordet, Brussels, Belgium

Jean-Paul Sculier
Department of Intensive
Care Unit and Thoracic
Oncology, Institut Jules
Bordet, Brussels, Belgium

- tumour characteristics (histological grade, number of metastatic sites, cancer-related symptoms, vascular or local invasion, malignant pleural effusion, primary tumour site);
- while not really a PF by definition, treatment parameters (adjuvant chemotherapy to surgery, type of chemotherapy, objective response to treatment).

Stage III NSCLC, for which the interest of a multimodality approach was first recognized, is diagnosed in a heterogeneous group of patients. However, there are large discrepancies in the therapeutics that can be proposed, with some patients receiving surgery as part of the treatment, others are treated with chemoradiotherapy and with a few only receiving palliative chemotherapy. There is obviously interest in finding adequate PFs in stage III NSCLC delineating more homogeneous groups of patients with similar prognosis allowing an appropriate comparison among studies and eventually selecting those patients at higher risk and in need of more intensive therapy.

Our aim was to review and summarize the available evidence about PFs in stage III NSCLC, reviewing the role of 'conventional' PF (anatomical factors, clinical and sociodemographic parameters, therapeutic characteristics) that have been reported in unselected NSCLC, metabolic criteria (standardized uptake value [SUV]) and biomarkers.

Methods

We performed a review of the English-, French- and Dutch-language literature assessing PFs in NSCLC using a Medline search completed by the references found in the selected publications and those known by the authors. The studies dealing specifically with or providing enough information concerning stage III NSCLC were selected, if multivariate analyses were performed. We also searched, among phase III randomised clinical trials involving stage III NSCLC, those reporting analyses for potential survival PFs. Concerning the potential prognostic role of biomarkers for survival, we searched meta-analyses published on this topic in NSCLC and studies specifically designed in stage III NSCLC.

To be homogeneous, only studies for which the authors explicitly used the 4th to 7th versions [Goldstraw *et al.* 2007; Mountain, 1997, 1986] of the International Staging System, or those

performed during the period that these versions were used, were considered for this review. The older classification indeed grouped both locoregionally advanced and metastatic tumours into stage III.

Results

When looking at PF studies in lung cancer, we are facing a large heterogeneity. Selected populations are quite different, some studies incorporating all stage III and others dealing with specific subgroups. Diagnostic criteria, work ups and therapeutics are eminently variable. The statistical analyses that were carried out are also variable: there is no consensus about the variables to take into consideration for adjustment when looking at a new potential PF, there is no consensus on how to manage a continuous variable, there might be differences in the definition of the outcome and some studies do not make use of any multivariate techniques. In some studies, that inclusion of posttherapeutic factors such as objective response rate could have an impact on the conclusion about the role of pretherapeutic PFs. In order to reduce this heterogeneity, we separated the publications into groups of similar significance: conventional PFs, metabolic criteria and new biomarkers.

'Conventional' prognostic factors

By conventional PFs, we mean anatomical factors, clinical and sociodemographic parameters and some routinely assessed biological variables that are commonly used and are not investigational. We also considered therapeutic characteristics, as in various selected publications, while not exactly dealing with our definition of a PF. The main PFs in NSCLC, all stages considered, were stage, performance status, gender, age, histology and some characteristics related to primary tumour (T) or nodal mediastinal (N) extension. Other variables have been considered as potential PFs for survival. They can be grouped into biological factors (e.g. LDH, calcaemia, alkaline phosphatases, leukocytosis and neutrophil counts), patient's characteristics (e.g. weight loss and body mass index, comorbidities, smoking behaviour and ethnicity) and tumour features (e.g. histological grade, number of metastatic sites, related symptoms, vascular or local invasion, malignant pleural effusion and primary tumour location). According to the restrictions defined previously, some treatment parameters (adjuvant chemotherapy after

surgery, chemotherapy type and objective response to the treatment) have also been suggested.

A list of PFs in advanced NSCLC has been provided in a review by Brundage and colleagues [Brundage *et al.* 2002]. Among them, disease stage, weight loss and performance status were considered essential PFs. The prognostic role of disease stage was recently confirmed in the very large study performed by the International Association for the Study of Lung Cancer (IASLC) [Sculier *et al.* 2008]. Outside of the distinct prognosis of stage III from the other stages, the authors showed a statistically significant survival difference between stage IIIA and IIIB patients. Stage was further confirmed as a statistically independent PF in multivariate analysis ($p < 0.001$), in addition to age, gender, histology and performance status.

From our literature review, we found 39 studies meeting our eligibility criteria, published between 1997 and 2009 and presenting results of multivariate analyses for PF identification for overall survival [Albain *et al.* 2009; Caglar *et al.* 2009; Garrido *et al.* 2009, 2007; Kim *et al.* 2008, 2007; Lee *et al.* 2008; Nakamura *et al.* 2008; Sculier *et al.* 2008, 2004, 1999a, 1999b; Ademuyiwa *et al.* 2007; Riquet *et al.* 2007; Van Meerbeek *et al.* 2007; Vokes *et al.* 2007; Basaki *et al.* 2006; Betticher *et al.* 2006; Stinchcombe *et al.* 2006; Tomita *et al.* 2006; Barlesi *et al.* 2005; Lorent *et al.* 2004; Niizeki *et al.* 2004; Socinski *et al.* 2004; Tanaka *et al.* 2004; Brooks *et al.* 2003; Osaki *et al.* 2003; Choi *et al.* 2002; Firat *et al.* 2002; Kameyama *et al.* 2002; Andre *et al.* 2000; Langendijk *et al.* 2000a; Furuse *et al.* 1999; Martins and Pereira, 1999; Suzuki *et al.* 1999a, 1999b; Vansteenkiste *et al.* 1997; Coen *et al.* 1995; Jeremic and Shibamoto, 1995]. The number of patients ranged from 42 to 836, with 10 studies including less than 100 patients and only 6 studies including more than 500 patients. Only 20 studies considered all stage III NSCLC [Albain *et al.* 2009; Caglar *et al.* 2009; Garrido *et al.* 2009, 2007; Kim *et al.* 2008; Nakamura *et al.* 2008; Ademuyiwa *et al.* 2007; Vokes *et al.* 2007; Stinchcombe *et al.* 2006; Basaki *et al.* 2006; Barlesi *et al.* 2005; Sculier *et al.* 2004, 1999a, 1999b; Socinski *et al.* 2004; Brooks *et al.* 2003; Firat *et al.* 2002; Kameyama *et al.* 2002; Langendijk *et al.* 2000a; Furuse *et al.* 1999; Martins and Pereira, 1999; Suzuki *et al.* 1999b; Coen *et al.* 1995; Jeremic

and Shibamoto, 1995], others dealing with selected populations. More than 50 different variables were considered in these 39 studies, the details of which are presented in Tables 1 and 2. The most frequently reported PFs were disease stage, performance status, age and characteristics describing locoregional extent (primary tumour and/or mediastinal extension). Prognosis was better in less advanced disease, in patients with good performance status and in younger patients. In surgical series, patients presenting with a TN or a mediastinal downstaging, an objective response after induction chemotherapy or a complete tumoural resection had an improved survival. In these series, the importance of mediastinal nodal neoplastic involvement was underlined, the clinical or pathological positive N2 status being associated with poorer prognosis. Outside of stage, performance status was the principal PF in medical series while age, gender and weight loss were less frequently reported.

Metabolic criteria

During the last decade, ^{18}F fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) emerged as a cornerstone in the diagnostic procedure for solitary pulmonary nodules and for the staging of lung cancer. SUV is a semiquantitative measurement of the tumour metabolic activity. In lung cancer, small-size studies have assessed the prognostic role of SUV measured by ^{18}F -FDG-PET on the primary tumour. One meta-analysis [Berghmans *et al.* 2008a], updated recently [Paesmans *et al.* 2010], suggested that high SUV might be a poor prognostic factor for survival in patients with NSCLC. Using a random-effects model, the combined hazard ratio (HR) of 21 eligible retrospective studies was 2.08, significantly different from 1, with a 95% confidence interval (CI) ranging from 1.69 to 2.56. A subgroup analysis taking into account the disease extent was further performed. Fourteen studies gave enough information for meta-analysing nonmetastatic patients. The combined HR was 2.18 (95% CI 1.83–2.60).

Nevertheless, only two studies including stage III patients allowed data extraction [Hoang *et al.* 2008; Eschmann *et al.* 2006]. In the first study [Eschmann *et al.* 2006], 137 patients received induction chemoradiotherapy, eventually followed by surgery, for stage IIIA/B NSCLC. It was unclear from the publication whether some stage IV NSCLC were included into this group.¹⁸ F-FDG uptake was quantified by calculating

Table 1. Conventional prognostic factors in stage III non-small cell lung cancer: surgical series.

Study	Year	ISS	Stage	N patients	Treatment	Significant factors in multivariate analysis
Vansteenkiste <i>et al.</i> [1997]	1997	4th?	IIIAN2	140	Surgery	T, PS, n N stations, histology, cN2
Suzuki <i>et al.</i> [1999a]	1999	5th	pN2	222	Surgery	cN, T size, n N2 stations, R0
Andre <i>et al.</i> [2000]	2000	5th	III	702	Surgery	pT, N2, induction CT
Choi <i>et al.</i> [2002]	2002	4th	pN2	101	Surgery + other	R0, CT use
Kameyama <i>et al.</i> [2002]	2002	5th	III	152	Surgery	Age, R0, pN
Osaki <i>et al.</i> [2003]	2003	5th	T4N0-2	76	Surgery	pN, R0
Lorent <i>et al.</i> [2004]	2004	?	IIIApN2	131	CT → surgery (or RT)	pT, mediastinal downstaging
Niizeki <i>et al.</i> [2004]	2004	5th	cN2-pN0	45	Surgery	Visceral pleural invasion, CEA level
Tanaka <i>et al.</i> [2004]	2004	5th	pIIIAN2	99	Surgery → CT or RT	cN2, n N2 stations, MCV [CD105], PI
Barlesi <i>et al.</i> [2005]	2005	5th	IIIAN2/IIIB	95/60	CT → surgery	IIIA: mediastinal downstaging, post-operative complication IIIB: vascular invasion
Betticher <i>et al.</i> [2006]	2006	5th	IIIApN2	75	CT → surgery	R0, pathological response, mediastinal downstaging
Tomita <i>et al.</i> [2006]	2006	?	pN2	78	Surgery	None
Garrido <i>et al.</i> [2007]	2007	?	IIIAN2/IIIB	136	CT → surgery	R0, response to induction CT, age
Kim <i>et al.</i> [2007]	2007	?	IIIAN2	66	CRT → surgery	ypN
Riquet <i>et al.</i> [2007]	2007	5th	pN2	586	Surgery	Age, pT, one N2 station, adjuvant treatment
Van Meerbeeck <i>et al.</i> [2007]	2007	5th	IIIAN2	332	CT → surgery or RT	Histology
Kim <i>et al.</i> [2008]	2008	5th	IIIAN2/dry IIIB	42	CT → surgery	Downstaging
Lee <i>et al.</i> [2008]	2008	5th	IIIAN2	262	Surgery +/- CRT	Age, adjuvant CT, n N2 stations
Caglar <i>et al.</i> [2009]	2009	?	III	144	CRT +/- surgery	Stage, surgery
Albain <i>et al.</i> [2009]	2009	?	IIIAN2	396	CRT +/- surgery	Weight loss, gender, nN2 stations

ISS, International Staging System; PS, performance status; R0, complete resection; CT, chemotherapy; CRT, radiochemotherapy; CEA, carcino-embryonic antigen; MCV, microvessel density; PI, proliferative index.

the average standardized uptake value (SUV_{avg}). The prognostic value of SUV_{avg} was assessed dichotomizing the patients according to the so-called 'best' cut-off method (in fact, a minimal p -value approach without adjustment for multiplicity) found by the authors. In multivariate analysis, stage ($p = 0.01$), tumour grading ($p = 0.04$) and SUV_{avg} ($p = 0.05$) were statistically independent PFs for survival. The second study included patients with advanced NSCLC (stages IIIA/IIIB/IV) [Hoang *et al.* 2008]. The maximum standardized uptake value (SUV_{max}) was quantitatively used to determine ^{18}F -FDG PET activity, dichotomizing the patients according to its median value. Overall, SUV_{max} was not a PF in this population with advanced NSCLC ($p = 0.35$). Subgroup analyses were performed, separating the patients with dry stage III from those with wet stage IIIB (now stage IV in the 7th Union Internationale Contre le Cancer (UICC) staging system) and IV. The difference in survival of patients with dry stage III NSCLC stratified by the median SUV_{max} was of borderline statistical significance

($p = 0.067$). The HR that we calculated for the studies by Eschmann and colleagues and by Hoang and colleagues were 1.71 (95% CI 1.00–2.93) and 1.34 (95% CI 0.93–1.95), respectively. The combined HR was 1.45 (95% CI 1.07–1.97) (unpublished results). This is suggestive for a prognostic role of SUV in stage III NSCLC. These results as well as the independent value of SUV need to be confirmed in larger studies within a multivariate analysis taking into account other conventional PFs. An individual data meta-analysis is underway and could perhaps solve the question.

Prognostic role for survival of 'new' biomarkers in stage III NSCLC

We defined as 'new' biomarkers, biological factors that are not used in routine practice and that have not been eventually considered for conventional PF, such as LDH level. The literature on these new biomarkers in lung cancer is impressive. Thousands of articles have been published during the last decade concerning more than

Table 2. Conventional prognostic factors in stage III non-small cell lung cancer: medical series.

Study	Year	ISS	Stage	N patients	Treatment	Significant factors in multivariate analysis
Coen <i>et al.</i> [1995]	1995	4th	III	239	RT+/-CT	RT dose, pleural effusion
Jeremic and Shibamoto [1995]	1995	?	III	169	CRT	Age, stage, gender, PS, weight loss
Furuse <i>et al.</i> [1999]	1999	4th	III	320	CRT	PS, concomitant CRT
Martins and Pereira [1999]	1999	?	III	796	?	PS, weight loss, superior vena cava syndrome, surgery, CT, RT
Sculier <i>et al.</i> [1999b]	1999	4th	III	462	CT <i>versus</i> CRT	PS, age, stage, neutrophils, platelets, response to CT
Sculier <i>et al.</i> [1999a]	1999	4th	III	115	CT → CT or RT	PS
Suzuki <i>et al.</i> [1999b]	1999	5th	pl-IV	836	?	IIIA: T size IIIB: pN2-3
Langendijk <i>et al.</i> [2000a]	2000	4th	III	198	RT	PS, weight loss, N, QOL
Firat <i>et al.</i> [2002]	2002	4th	III	112	RT	PS, co-morbidity
Brooks <i>et al.</i> [2003]	2003	?	III	59	CRT	p53, hMSH2
Sculier <i>et al.</i> [2004]	2004	5th	III	328	CRT	PS, stage, haemoglobin, bilirubin
Socinski <i>et al.</i> [2004]	2004	?	Dry III	694	RT, CRT	Haemoglobin, PS, RT vs RT/CT
Stinchcombe <i>et al.</i> [2006]	2006	?	III	102	CRT	Tumour volume, PS, stage
Basaki <i>et al.</i> [2006]	2006	?	III	71	RT (+/- CT)	Tumour volume, TTV
Ademuyiwa <i>et al.</i> [2007]	2007	5th?	III	203	?	Age, gender, ethnicity, BMI, PS, FEV1, smoking, haemoglobin, SUV, stage
Vokes <i>et al.</i> [2007]	2007	5th?	III	366	CRT	PS, age, weight loss
Nakamura <i>et al.</i> [2008]	2008	5th	III	102	RT+/-CT	Tumour site
Sculier <i>et al.</i> [2008]	2008	7th	IIIA	2048	?	Age, gender, histology, PS
Garrido <i>et al.</i> [2009]	2009	5th	III	139	CRT	Concurrent CRT

BMI, body mass index; PS, performance status; FEV1, forced expiratory volume in 1 second; SUV, standardized uptake value; TTV, target treatment volume; RT, radiotherapy; CT, chemotherapy; CRT, radiochemotherapy; N, node; QOL, quality of life; T, tumour.

200 different biomarkers. The methodological problems encountered with these studies are the same as with conventional PFs including small-sized, underpowered retrospective studies, lack of multivariate analyses and matchless populations (e.g. different work ups and treatment variability). In addition, we are facing the difficulties in comparing laboratory results due to the lack of standardization. The best example came from immunohistochemistry (IHC) with various laboratory protocols for the detection of the same marker and the absence of an international validated definition of tumour positivity.

We first looked at the most published biological factors for whom meta-analyses have been performed. They are summarized in Table 3. They all concerned NSCLC. For most of them, the abnormal expression of the marker at the protein level assessed by IHC or the evaluation of aberration at the gene level were found to be unfavourable factors for survival, except for TTF-1 and Bcl-2 that were found to be favourable PFs in IHC studies. However, we cannot find from these meta-analyses information specifically dedicated to stage III NSCLC, which does

not allow meaningful extrapolation to this population.

Despite the large number of publications concerning the prognostic role of biomarkers on survival in patients with lung cancer, few are specifically dealing with stage III NSCLC. They are summarized in Table 4. Some series included at least some comparable biomarkers in their analyses. Langendijk and colleagues assessed the role of p53, Bcl-2, topoisomerase α and apoptotic index in a series of 161 patients treated by exclusive chest radiotherapy at a dose of 60 Gy [Langendijk *et al.* 2000b]. Only the apoptotic index was a statistically independent PF in multivariate analysis. Hwang and colleagues assessed the apoptotic index, p53, Bcl-2 and c-Myc in 68 patients receiving chest radiotherapy [Hwang *et al.* 2001]. In multivariate analysis, Bcl-2, apoptotic index and objective response to radiotherapy were statistically independent PFs for survival. Brooks and colleagues evaluated p53, Bcl-2, EGF-R, c-erbB2 and markers involved in tissue repair and vinorelbine activity, MDR, GST, hMLH and hMSH2 (mismatch repair [MMR] genes) [Brooks *et al.* 2003]. Fifty nine

Table 3. Summary of meta-analyses assessing the prognostic role of new biomarkers in non-small cell lung cancer.

Study	Biomarker	N studies	Results	95% CI	Prognostic value
Huncharek <i>et al.</i> [1999]	K-RAS	8	RR 2.35 at 2 years	1.61–3.22	Unfavourable
Huncharek <i>et al.</i> [2000]	p53 gene	8	RR 1.52	1.07–2.16	Unfavourable
Mitsudomi <i>et al.</i> [2000]	p53	43	$p < 0.05$	–	Unfavourable
Choma <i>et al.</i> [2001]	Aneuploidy	35	OR 0.67 at 4 years	0.57–0.78	Unfavourable
Steels <i>et al.</i> [2001]	p53	50	HR 1.44	1.20–1.72	Unfavourable
Meert <i>et al.</i> [2002a]	EGF-R	11	HR 1.14	0.94–1.39	Not a prognostic factor (Pejorative in subgroup)
Delmotte <i>et al.</i> [2002]	VEGF	18	HR 1.48	1.27–1.72	Unfavourable
Meert <i>et al.</i> [2002b]	MVD	7–9	HR 1.80–1.99	1.10–2.96	Unfavourable
Meert <i>et al.</i> [2003]	c-ERB2	20	HR 1.55	1.29–1.86	Unfavourable
Martin <i>et al.</i> [2003]	Bcl-2	18	HR 0.72	0.57–0.86	Favourable
Martin <i>et al.</i> [2004]	Ki-67	16	HR 1.56	1.30–1.87	Unfavourable
Mascaux <i>et al.</i> [2005]	K-RAS	28	HR 1.35	1.16–1.56	Unfavourable
Nakamura <i>et al.</i> [2005]	c-ERB2	20	$p = 0.0001$	–	Unfavourable
Nakamura <i>et al.</i> [2006]	EGF-R	18	HR 1.14	0.97–1.34	Not a prognostic factor
Mascaux <i>et al.</i> [2006]	COX2	10	HR 1.39	0.97–1.99	Not a prognostic factor (Pejorative in subgroup)
Berghmans <i>et al.</i> [2006b]	TTF-1	8	HR 0.64	0.41–1.00	Favourable
Trivella <i>et al.</i> [2007]	MVD	17	HR 1.03	0.97–1.09	Not a prognostic factor (Pejorative in subgroup)
Fan <i>et al.</i> [2008]	Surviving	8	RR 1.88	1.31–2.70	Unfavourable
Zhan <i>et al.</i> [2009]	VEGF		HR 1.46	1.38–1.54	Unfavourable

RR, relative risk; OR, odds ratio; HR, hazard ratio; CI, confidence interval; MVD, microvessel density.

Table 4. Summary of studies assessing the prognostic role of biomarkers in stage III non-small cell lung cancer.

Study	N patients	Treatment	Investigated biomarkers	Independent biomarkers PF in multivariate analysis
Langendijk <i>et al.</i> [2000b]	161	RT	p53, Bcl-2, topoisomerase 2 α , apoptotic index	apoptotic index
Hwang <i>et al.</i> [2001]	68	RT	apoptotic index, p53, Bcl-2, c-myc	apoptotic index, Bcl-2
Graziano <i>et al.</i> [2001]	132	CT $\rightarrow$ RT	p53, c-erbB2, NSE, chromogranin A, Leu-7, synaptophysine	None
Brooks <i>et al.</i> [2003]	59	CRT	p53, Bcl-2, EGF-R, c-erbB2 MDR, GST, hMLH1, hMSH2	p53, hMSH2
Berghmans <i>et al.</i> [2005a]	93	Various	p53	None
Morero <i>et al.</i> [2007]	33	CT $\rightarrow$ RT or surgery	p53, Bcl-2, p21, p27, Ki67, apoptotic index	None
Berghmans <i>et al.</i> [2005b]	99	Various	EGF-R	None
Grossi <i>et al.</i> [2010]	87	Surgery	EGF-R, c-erbB2, c-kit, COX2, surviving, Bcl-2, cyclin D1, cyclin B1, MMP-2, MMP-9	Cyclin D1
Uramoto <i>et al.</i> [1999]	91	Surgery	Fas	Fas (univariate)
Broermann <i>et al.</i> [2002]	28	CT $\rightarrow$ surgery	K-ras mutation	None
Spierings <i>et al.</i> [2003]	87	RT +/- CT	rhTRAIL + DR4-5	DR5
Chang <i>et al.</i> [2005]	102	CRT	Blood lymphocyte mutagen sensitivity assay	Mutagen test
Berghmans <i>et al.</i> [2006a]	108	Various	TTF-1	None
Berghmans <i>et al.</i> [2008b]	84	Various	Mdm-2	None
Kreuter <i>et al.</i> [2009]	142	Various	MVD	None

RT, radiotherapy; CT, chemotherapy; PF, prognostic factor; CRT, radiochemotherapy; MDR, multidrug resistance; GST, glutathione-s-transferase; hMLH1, human MutL homolog 1; hMSH2, human MutS homolog 2; COX2, cyclooxygenase 2; MMP, metalloproteinase; rhTRAIL, recombinant human tumour necrosis factor-related apoptosis-inducing ligand; MVD, microvessel density; PF, prognostic factor.

patients from two therapeutic studies were included. They received a concomitant chemoradiotherapy with vinorelbine or carboplatin plus vinorelbine. In multivariate analysis, high p53 and low hMSH2 expressions were significantly associated with a poorer overall and cancer-specific survival rates. Morero and colleagues searched in a small group of 33 patients treated by induction chemotherapy before surgery or radiotherapy if p53, Bcl-2, p21, p27, Ki67 or apoptotic index have a prognostic role [Morero *et al.* 2007]. No significant factor was found. Graziano and colleagues reported on immunohistochemistry assessment of p53, c-erbB2, NSE, chromogranin A, Leu-7 and synaptophysin [Graziano *et al.* 2001]. Patients with unresectable stage III NSCLC, included in three prospective Cancer And Leukemia Group B (CALGB) studies, were treated with a sequential combination of chemotherapy (cisplatin plus vinblastine) followed by chest radiotherapy with or without concomitant carboplatin administration. None of the considered factors was found to be a PF either in univariate or multivariate analyses. We assessed the prognostic role of EGF-R and p53 [Berghmans *et al.* 2005a, 2005b]. None of the markers was individually associated with survival. Lastly, Grossi and colleagues looked at multiple biomarkers in 87 patients with stage IIIA pN2 NSCLC treated with radical surgery [Grossi *et al.* 2010]. Only cyclin D1 was a statistically independent PF in multivariate analysis.

Other various biomarkers have been the subject of small retrospective studies. Uramoto and colleagues looked at the Fas expression among 220 resected tumours [Uramoto *et al.* 1999]. In a subgroup analysis of 91 patients, Fas expression was associated with prolonged survival in stage III NSCLC in univariate analysis. Broermann and colleagues assessed the prognostic role of K-ras mutation (codon 12) after induction chemotherapy on surgical samples [Broermann *et al.* 2002]. Forty patients were initially included of whom 28 went to surgery. A trend to reduced survival was observed in the presence of a mutation, without reaching statistical significance. Spierings and colleagues studied the role of the recombinant human tumour necrosis factor-related apoptosis-inducing ligand (rhTRAIL) and its receptors DR4 and DR5 among 87 patients treated in a randomized trial comparing radiotherapy with or without carboplatin chemotherapy [Spierings *et al.* 2003]. In their analysis including conventional variables (histology, N

status, stage, follow-up duration, gender), the authors found an increase in the risk of death with DR5 expression. Chang and colleagues investigated the relationship between the sensitivity of peripheral blood lymphocytes to a mutagen bleomycin sensitivity assay and further survival of 102 patients treated by a combination of radiotherapy and chemotherapy [Chang *et al.* 2005]. High bleomycin sensitivity correlated with poor overall survival and disease-specific survival. Kreuter and colleagues studied the microvessel density (MVD) from mediastinal lymph node biopsies of 142 stage IIIA/B NSCLCs [Kreuter *et al.* 2009]. They found no association with survival in the whole group while high MVD was a statistically independent favourable PF for survival in the subgroup of patients with stage IIIA having a complete surgical resection of the tumour ($p = 0.04$). We also assessed the prognostic role of TTF-1 and Mdm2 [Berghmans *et al.* 2006a, 2008b] which displayed no prognostic significance.

Outside of the individual prognostic role of the biomarkers, some authors suggested that a combination of some factors could be helpful in defining groups of patients with distinct survival within stage III NSCLC. Based on a hierarchical clustering analysis of their immunostaining data, Grossi and colleagues identified two subsets of patients with better (clusters 1 and 2) and worse (clusters 3, 4 and 5) prognoses (median survival times of 51 and 10 months, $p < 0.0001$) [Grossi *et al.* 2010]. In univariate analyses, we found that patients whose tumour was positive for EGF-R and negative for TTF-1 had longer survival than the others (median survival times 450 and 346 days, $p = 0.11$) [Berghmans *et al.* 2008b]. The difference reached statistical significance in the subgroup of squamous cell carcinoma ($p = 0.02$). Also, the EGF-R/TTF-1 status was of statistical significance for cancer-specific survival ($p = 0.04$), while it was even more pronounced in squamous cell carcinomas ($p = 0.004$). In multivariate analysis, the EGF-R/TTF-1 status was only of borderline statistical significance ($p = 0.06$) for cancer-specific survival.

Discussion

Following this review, we observed that the subgroup of stage, performance status, age, gender, weight loss and some characteristics describing the tumoural locoregional extension are the most prominent prognostic factors in

stage III NSCLC. We suggest that there is a potential prognostic role for new metabolic (SUV) and biological factors (biomarkers) such as p53, Bcl-2, the apoptotic index, hMSH2, cyclin D1 or the DR5 receptor of the rhTRAIL.

While the number of publications on PFs in lung cancer is impressive, studies involving specifically stage III NSCLC are, in comparison, relatively limited. The difficulties in comparing the studies are due to the heterogeneity of this literature. Studies are frequently of limited size and therefore underpowered to identify PFs with a moderate to small effect. The variables taken into consideration are fairly different from one study to another, leading to final multivariate models with few overlaps in the selected covariates preventing us to assess a true independent value of a new PF. Measures of goodness of fit or of the prognostic ability of the models are rarely provided. There are large discrepancies among the patients recruited according to the disease extent, the diagnostic and extension work up or the administered treatment that could influence further survival. To reduce this variability, we separated studies of conventional PFs into surgical and medical series. In these two groups, stage and performance status confirmed their prognostic value.

The same problems are present in the biomarkers literature. Only small-size retrospective studies are available in which the statistical power was limited. They suggested that some factors involved in the cell cycle regulation or the apoptosis could be of prognostic value. There are some explanations to the divergent results found in these publications. While multivariate analyses were performed, few studies included conventional PFs, clinical and biological variables in their model, and those included were also different among the publications [Berghmans *et al.* 2008b, 2006a, 2005a, 2005b; Chang *et al.* 2005; Spierings *et al.* 2003; Broermann *et al.* 2002; Hwang *et al.* 2001; Langendijk *et al.* 2000b]. There was no standardization in the immunostaining techniques as for the use of different antibodies for the same marker. Positivity thresholds were variable. For example, two distinct scores [Brooks *et al.* 2003; Graziano *et al.* 2001], a separation into three groups [Langendijk *et al.* 2000b] or a threshold at 10% positive cells were used for p53 [Morero *et al.* 2007; Berghmans *et al.* 2005a]. The distribution of histological subtypes

was not homogeneous, the different proportion of adenocarcinoma potentially influencing the prevalence of markers as EGF-R or TTF-1. Treatments proposed to the patients were difficult to compare. Some groups have systematically given a cisplatin-based chemotherapy [Morero *et al.* 2007; Graziano *et al.* 2001] while exclusive radiotherapy [Hwang *et al.* 2001; Langendijk *et al.* 2000b] or non conventional chemotherapy regimen were administered by others [Brooks *et al.* 2003]. Lastly, never the role of the biomarkers was confirmed in a validation series, so that the independent role of these potential PF remains to be validated in further large prospective studies.

In conclusion, disease stage and performance status remain the most prominent prognostic factors in stage III NSCLC while other clinical and therapeutic variables have some prognostic value. New biological (biomarkers) and metabolic (SUV) variables are promising prognostic factors. Their definitive role needs to be confirmed in large, well-designed, prospective studies in stage III NSCLC taking into consideration the modification provided in the new international staging classification.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Ademuyiwa, F.O., Johnson, C.S., White, A.S., Breen, T.E., Harvey, J., Neubauer, M. *et al.* (2007) Prognostic factors in stage III non-small-cell lung cancer. *Clin Lung Cancer* 8: 478–482.
- Albain, K.S., Swann, R.S., Rusch, V.W., Turrisi III, A.T., Shepherd, F.A., Smith, C. *et al.* (2009) Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 374: 379–386.
- Andre, F., Grunenwald, D., Pignon, J.P., Dujon, A., Pujol, J.L., Brichon, P.Y. *et al.* (2000) Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol* 18: 2981–2989.
- Barlesi, F., Doddoli, C., Torre, J.P., Giudicelli, R., Fuentes, P., Thomas, P. *et al.* (2005) Comparative

- prognostic features of stage IIIB non-small-cell lung cancer patients treated with surgery after induction therapy. *Eur J Cardiothorac Surg* 28: 629–634.
- Basaki, K., Abe, Y., Aoki, M., Kondo, H., Hatayama, Y. and Nakaji, S. (2006) Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume. *Int J Radiat Oncol Biol Phys* 64: 449–454.
- Berghmans, T., Dusart, M., Paesmans, M., Hossein-Foucher, C., Buvat, I., Castaigne, C. *et al.* (2008a) Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol* 3: 6–12.
- Berghmans, T., Mascaux, C., Haller, A., Meert, A.P., van Houtte, P. and Sculier, J.P. (2008b) EGFR, TTF-1 and Mdm2 expression in stage III non-small cell lung cancer: a positive association. *Lung Cancer* 62: 35–44.
- Berghmans, T., Mascaux, C., Martin, B., Ninane, V. and Sculier, J.P. (2005a) Prognostic role of p53 in stage III non-small cell lung cancer. *Anticancer Res* 25: 2385–2389.
- Berghmans, T., Mascaux, C., Martin, B., Ninane, V. and Sculier, J.P. (2006a) Prognostic role of thyroid transcription factor-1 in stage III non-small cell lung cancer. *Lung Cancer* 52: 219–224.
- Berghmans, T., Meert, A.P., Martin, B., Ninane, V. and Sculier, J.P. (2005b) Prognostic role of epidermal growth factor receptor in stage III nonsmall cell lung cancer. *Eur Respir J* 25: 329–335.
- Berghmans, T., Paesmans, M., Mascaux, C., Martin, B., Meert, A.P., Haller, A. *et al.* (2006b) Thyroid transcription factor 1—a new prognostic factor in lung cancer: a meta-analysis. *Ann Oncol* 17: 1673–1676.
- Betticher, D.C., Hsu Schmitz, S.F., Totsch, M., Hansen, E., Joss, C., von Briel, C. *et al.* (2006) Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. *Br J Cancer* 94: 1099–1106.
- Boyle, P. and Ferlay, J. (2005) Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 16: 481–488.
- Broermann, P., Junker, K., Brandt, B.H., Heinecke, A., Freitag, L., Klink, F. *et al.* (2002) Trimodality treatment in Stage III nonsmall cell lung carcinoma: prognostic impact of K-ras mutations after neoadjuvant therapy. *Cancer* 94: 2055–2062.
- Brooks, K.R., To, K., Joshi, M.B., Conlon, D.H., Herndon, J.E., D'Amico, T.A. *et al.* (2003) Measurement of chemoresistance markers in patients with stage III non-small cell lung cancer: a novel approach for patient selection. *Ann Thorac Surg* 76: 187–193.
- Brundage, M.D., Davies, D. and Mackillop, W.J. (2002) Prognostic factors in non-small cell lung cancer: a decade of progress. *Chest* 122: 1037–1057.
- Caglar, H.B., Baldini, E.H., Othus, M., Rabin, M.S., Bueno, R., Sugarbaker, D.J. *et al.* (2009) Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. *Cancer* 115: 4156–4166.
- Chang, J.Y., Komaki, R., Sasaki, R., Liao, Z., Stevens, C.W., Lu, C. *et al.* (2005) High mutagen sensitivity in peripheral blood lymphocytes predicts poor overall and disease-specific survival in patients with stage III non-small cell lung cancer treated with radiotherapy and chemotherapy. *Clin Cancer Res* 11: 2894–2898.
- Choi, Y.S., Shim, Y.M., Kim, J. and Kim, K. (2002) Recurrence-free survival and prognostic factors in resected pN2 non-small cell lung cancer. *Eur J Cardiothorac Surg* 22: 695–700.
- Choma, D., Daures, J.P., Quantin, X. and Pujol, J.L. (2001) Aneuploidy and prognosis of non-small-cell lung cancer: a meta-analysis of published data. *Br J Cancer* 85: 14–22.
- Coen, V., Van Lancker, M., De Neve, W. and Storme, G. (1995) Prognostic factors in locoregional non-small cell lung cancer treated with radiotherapy. *Am J Clin Oncol* 18: 111–117.
- Delmotte, P., Martin, B., Paesmans, M., Berghmans, T., Mascaux, C., Meert, A.P. *et al.* (2002) VEGF et survie des patients avec cancer pulmonaire: une revue systématique de la littérature avec méta-analyse. *Rev Mal Respir* 19: 577–584.
- Eschmann, S.M., Friedel, G., Paulsen, F., Reimold, M., Hehr, T., Budach, W. *et al.* (2006) Is standardised (18)F-FDG uptake value an outcome predictor in patients with stage III non-small cell lung cancer? *Eur J Nucl Med Mol Imaging* 33: 263–269.
- Fan, J., Wang, L., Jiang, G.N., He, W.X. and Ding, J.A. (2008) The role of survivin on overall survival of non-small cell lung cancer, a meta-analysis of published literatures. *Lung Cancer* 61: 91–96.
- Firat, S., Byhardt, R.W. and Gore, E. (2002) Comorbidity and Karnofsky performance score are independent prognostic factors in stage III non-small-cell lung cancer: an institutional analysis of patients treated on four RTOG studies. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 54: 357–364.
- Furuse, K., Fukuoka, M., Kawahara, M., Nishikawa, H., Takada, Y., Kudoh, S. *et al.* (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 17: 2692–2699.
- Garrido, P., Gonzalez-Larriba, J.L., Insa, A., Provencio, M., Torres, A., Isla, D. *et al.* (2007)

- Long-term survival associated with complete resection after induction chemotherapy in stage IIIA (N2) and IIIB (T4N0-1) non small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. *J Clin Oncol* 25: 4736–4742.
- Garrido, P., Rosell, R., Massuti, B., Cardenal, F., Alberola, V., Domine, M. *et al.* (2009) Predictors of long-term survival in patients with lung cancer included in the randomized Spanish Lung Cancer Group 0008 phase II trial using concomitant chemoradiation with docetaxel and carboplatin plus induction or consolidation chemotherapy. *Clin Lung Cancer* 10: 180–186.
- Goldstraw, P., Crowley, J., Chansky, K., Giroux, D.J., Groome, P.A., Rami-Porta, R. *et al.* (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2: 706–714.
- Graziano, S.L., Tatum, A., Herndon, J.E., Box, J., Memoli, V., Green, M.R. *et al.* (2001) Use of neuroendocrine markers, p53, and HER2 to predict response to chemotherapy in patients with stage III non-small cell lung cancer: a Cancer and Leukemia Group B study. *Lung Cancer* 33: 115–123.
- Grossi, F., Spizzo, R., Bordo, D., Cacitti, V., Valent, F., Rossetto, C. *et al.* (2010) Prognostic stratification of stage IIIA pN2 non-small cell lung cancer by hierarchical clustering analysis of tissue microarray immunostaining data: an Alpe Adria Thoracic Oncology Multidisciplinary Group study (ATOM 014). *J Thorac Oncol* 5: 1354–1360.
- Hoang, J.K., Hoagland, L.F., Coleman, R.E., Coan, A.D., Herndon, J.E. and Patz Jr, E.F. (2008) Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography imaging in patients with advanced-stage non-small-cell lung carcinoma. *J Clin Oncol* 26: 1459–1464.
- Huncharek, M., Kupelnick, B., Geschwind, J.F. and Caubet, J.F. (2000) Prognostic significance of p53 mutations in non-small cell lung cancer: a meta-analysis of 829 cases from eight published studies. *Cancer Lett* 153: 219–226.
- Huncharek, M., Muscat, J. and Geschwind, J.F. (1999) K-ras oncogene mutation as a prognostic marker in non-small cell lung cancer: a combined analysis of 881 cases. *Carcinogenesis* 20: 1507–1510.
- Hwang, J.H., Lim, S.C., Kim, Y.C., Park, K.O., Ahn, S.J. and Chung, W.K. (2001) Apoptosis and bcl-2 expression as predictors of survival in radiation-treated non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 50: 13–18.
- Jeremic, B. and Shibamoto, Y. (1995) Pre-treatment prognostic factors in patients with stage III non-small cell lung cancer treated with hyperfractionated radiation therapy with or without concurrent chemotherapy. *Lung Cancer* 13: 21–30.
- Kameyama, K., Huang, C.L., Liu, D., Okamoto, T., Hayashi, E., Yamamoto, Y. *et al.* (2002) Problems related to TNM staging: patients with stage III non-small cell lung cancer. *J Thorac Cardiovasc Surg* 124: 503–510.
- Kim, K.J., Ahn, Y.C., Lim do, H., Han, J., Park, K., Park, J.O. *et al.* (2007) Analyses on prognostic factors following tri-modality therapy for stage IIIa non-small cell lung cancer. *Lung Cancer* 55: 329–336.
- Kim, S.H., Cho, B.C., Choi, H.J., Chung, K.Y., Kim, D.J., Park, M.S. *et al.* (2008) The number of residual metastatic lymph nodes following neoadjuvant chemotherapy predicts survival in patients with stage III NSCLC. *Lung Cancer* 60: 393–400.
- Kreuter, M., Kropff, M., Fischaleck, A., Junker, K., Gerss, J., Heinecke, A. *et al.* (2009) Prognostic relevance of angiogenesis in stage III NSCLC receiving multimodality treatment. *Eur Respir J* 33: 1383–1388.
- Langendijk, H., Aaronson, N.K., de Jong, J.M., ten Velde, G.P., Muller, M.J. and Wouters, M. (2000a) The prognostic impact of quality of life assessed with the EORTC QLQ-C30 in inoperable non-small cell lung carcinoma treated with radiotherapy. *Radiother Oncol* 55: 19–25.
- Langendijk, H., Thunnissen, E., Arends, J.W., de Jong, J., ten Velde, G.P., Lamers, R. *et al.* (2000b) Cell proliferation and apoptosis in stage III inoperable non-small cell lung carcinoma treated by radiotherapy. *Radiother Oncol* 56: 197–207.
- Lee, J.G., Lee, C.Y., Park, I.K., Kim, D.J., Cho, S.H., Kim, K.D. *et al.* (2008) The prognostic significance of multiple station N2 in patients with surgically resected stage IIIA N2 non-small cell lung cancer. *J Korean Med Sci* 23: 604–608.
- Lorent, N., De Leyn, P.R., Lievens, Y., Verbeken, E., Nackaerts, K., Dooms, C. *et al.* (2004) Long-term survival of surgically staged IIIA-N2 non-small-cell lung cancer treated with surgical combined modality approach: analysis of a 7-year prospective experience. *Ann Oncol* 15: 1645–1653.
- Martin, B., Paesmans, M., Berghmans, T., Branle, F., Ghisdal, L., Mascaux, C. *et al.* (2003) Role of Bcl-2 as a prognostic factor for survival in lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 89: 55–64.
- Martin, B., Paesmans, M., Mascaux, C., Berghmans, T., Lothaire, P., Meert, A.P. *et al.* (2004) Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis. *Br J Cancer* 91: 2018–2025.
- Martins, S.J. and Pereira, J.R. (1999) Clinical factors and prognosis in non-small cell lung cancer. *Am J Clin Oncol* 22: 453–457.
- Mascaux, C., Iannino, N., Martin, B., Paesmans, M., Berghmans, T., Dusart, M. *et al.* (2005) The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 92: 131–139.

- Mascaux, C., Martin, B., Paesmans, M., Berghmans, T., Dusart, M., Haller, A. *et al.* (2006) Has Cox-2 a prognostic role in non-small-cell lung cancer? A systematic review of the literature with meta-analysis of the survival results. *Br J Cancer* 95: 139–145.
- Meert, A.P., Martin, B., Delmotte, P., Berghmans, T., Lafitte, J.J., Mascaux, C. *et al.* (2002a) The role of EGF-R expression on patient survival in lung cancer: a systematic review with meta-analysis. *Eur Respir J* 20: 975–981.
- Meert, A.P., Martin, B., Paesmans, M., Berghmans, T., Mascaux, C., Verdebout, J.M. *et al.* (2003) The role of HER-2/neu expression on the survival of patients with lung cancer: a systematic review of the literature. *Br J Cancer* 89: 959–965.
- Meert, A.P., Paesmans, M., Martin, B., Delmotte, P., Berghmans, T., Verdebout, J.M. *et al.* (2002b) The role of microvessel density on the survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 87: 694–701.
- Mitsudomi, T., Hamajima, N., Ogawa, M. and Takahashi, T. (2000) Prognostic significance of p53 alterations in patients with non-small cell lung cancer: a meta-analysis. *Clin Cancer Res* 6: 4055–4063.
- Morero, J.L., Poleri, C., Martin, C., Van Kooten, M., Chacon, R. and Rosenberg, M. (2007) Influence of apoptosis and cell cycle regulator proteins on chemotherapy response and survival in stage IIIA/IIIB NSCLC patients. *J Thorac Oncol* 2: 293–298.
- Mountain, C.F. (1986) A new international staging system for lung cancer. *Chest* 89: 225S–233S.
- Mountain, C.F. (1997) Revisions in the International System for Staging Lung Cancer. *Chest* 111: 1710–1717.
- Nakamura, H., Kawasaki, N., Taguchi, M. and Kabasawa, K. (2005) Association of HER-2 overexpression with prognosis in nonsmall cell lung carcinoma: a metaanalysis. *Cancer* 103: 1865–1873.
- Nakamura, H., Kawasaki, N., Taguchi, M. and Kabasawa, K. (2006) Survival impact of epidermal growth factor receptor overexpression in patients with non-small cell lung cancer: a meta-analysis. *Thorax* 61: 140–145.
- Nakamura, T., Fuwa, N., Kodaira, T., Tachibana, H., Tomoda, T., Nakahara, R. *et al.* (2008) Clinical outcome of stage III non-small-cell lung cancer patients after definitive radiotherapy. *Lung* 186: 91–96.
- Niizeki, H., Morikawa, T., Okushiba, S., Kondo, S. and Kato, H. (2004) Survival and prognostic factors in resected cN2-pN0 non-small cell lung cancer. *Ann Thorac Cardiovasc Surg* 10: 9–13.
- Osaki, T., Sugio, K., Hanagiri, T., Takenoyama, M., Yamashita, T., Sugaya, M. *et al.* (2003) Survival and prognostic factors of surgically resected T4 non-small cell lung cancer. *Ann Thorac Surg* 75: 1745–1751.
- Paesmans, M., Berghmans, T., Dusart, M., Garcia, C., Hossein-Foucher, C., Lafitte, J.J. *et al.* (2010) Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. *J Thorac Oncol* 5: 612–619.
- Riquet, M., Bagan, P., Le Pimpec Barthes, F., Banu, E., Scotte, F., Foucault, C. *et al.* (2007) Completely resected non-small cell lung cancer: reconsidering prognostic value and significance of N2 metastases. *Ann Thorac Surg* 84: 1818–1824.
- Sculier, J.P., Chansky, K., Crowley, J.J., Van Meerbeeck, J. and Goldstraw, P. (2008) The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 3: 457–466.
- Sculier, J.P., Lafitte, J.J., Berghmans, T., van Houtte, P., Lecomte, J., Thiriaux, J. *et al.* (2004) A phase III randomised study comparing two different dose-intensity regimens as induction chemotherapy followed by thoracic irradiation in patients with advanced locoregional non-small-cell lung cancer. *Ann Oncol* 15: 399–409.
- Sculier, J.P., Paesmans, M., Lafitte, J.J., Baumohl, J., Thiriaux, J., van Cutsem, O. *et al.* (1999a) A randomised phase III trial comparing consolidation treatment with further chemotherapy to chest irradiation in patients with initially unresectable locoregional non-small-cell lung cancer responding to induction chemotherapy. European Lung Cancer Working Party. *Ann Oncol* 10: 295–303.
- Sculier, J.P., Paesmans, M., Lafitte, J.J., Baumohl, J., Thiriaux, J., van Cutsem, O. *et al.* (1999b) Prognostic factors analysis for response to chemotherapy and survival in a prospective cohort of patients with unresectable locoregional non small cell lung cancer initially treated by induction chemotherapy. *Rev Oncologia* 1: 92–100.
- Socinski, M.A., Zhang, C., Herndon, J.E., Dillman, R.O., Clamon, G., Vokes, E. *et al.* (2004) Combined modality trials of the Cancer and Leukemia Group B in stage III non-small-cell lung cancer: analysis of factors influencing survival and toxicity. *Ann Oncol* 15: 1033–1041.
- Spierings, D.C., de Vries, E.G., Timens, W., Groen, H.J., Boezen, H.M. and de Jong, S. (2003) Expression of TRAIL and TRAIL death receptors in stage III non-small cell lung cancer tumors. *Clin Cancer Res* 9: 3397–3405.
- Steels, E., Paesmans, M., Berghmans, T., Branle, F., Lemaitre, F., Mascaux, C. *et al.* (2001) Role of p53 as a prognostic factor for survival in lung cancer: a systematic review of the literature with a meta-analysis. *Eur Respir J* 18: 705–719.

- Stinchcombe, T.E., Morris, D.E., Moore, D.T., Bechtel, J.H., Halle, J.S., Mears, A. *et al.* (2006) Post-chemotherapy gross tumor volume is predictive of survival in patients with stage III non-small cell lung cancer treated with combined modality therapy. *Lung Cancer* 52: 67–74.
- Suzuki, K., Nagai, K., Yoshida, J., Nishimura, M., Takahashi, K. and Nishiwaki, Y. (1999a) The prognosis of surgically resected N2 non-small cell lung cancer: the importance of clinical N status. *J Thorac Cardiovasc Surg* 118: 145–153.
- Suzuki, K., Nagai, K., Yoshida, J., Nishimura, M., Takahashi, K., Yokose, T. *et al.* (1999b) Conventional clinicopathologic prognostic factors in surgically resected nonsmall cell lung carcinoma. A comparison of prognostic factors for each pathologic TNM stage based on multivariate analyses. *Cancer* 86: 1976–1984.
- Tanaka, F., Yanagihara, K., Otake, Y., Kawano, Y., Miyahara, R., Takenaka, K. *et al.* (2004) Prognostic factors in resected pathologic (p-) stage IIIA-N2, non-small-cell lung cancer. *Ann Surg Oncol* 11: 612–618.
- Tomita, M., Matsuzaki, Y., Shimizu, T., Hara, M., Ayabe, T. and Onitsuka, T. (2006) Preoperative prognostic factors for pN2 non-small cell lung cancer. *Ann Thorac Cardiovasc Surg* 12: 15–20.
- Trivella, M., Pezzella, F., Pastorino, U., Harris, A.L. and Altman, D.G. (2007) Microvessel density as a prognostic factor in non-small-cell lung carcinoma: a meta-analysis of individual patient data. *Lancet Oncol* 8: 488–499.
- Uramoto, H., Osaki, T., Inoue, M., Taga, S., Takenoyama, M., Hanagiri, T. *et al.* (1999) Fas expression in non-small cell lung cancer: its prognostic effect in completely resected stage III patients. *Eur J Cancer* 35: 1462–1465.
- Van Meerbeeck, J.P., Kramer, G.W., Van Schil, P.E., Legrand, C., Smit, E.F., Schramel, F. *et al.* (2007) Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 99: 442–450.
- Vansteenkiste, J.F., De Leyn, P.R., Deneffe, G.J., Stalpaert, G., Nackaerts, K.L., Lerut, T.E. *et al.* (1997) Survival and prognostic factors in resected N2 non-small cell lung cancer: a study of 140 cases. Leuven Lung Cancer Group. *Ann Thorac Surg* 63: 1441–1450.
- Vokes, E.E., Herndon, J.E., Kelley, M.J., Cicchetti, M.G., Ramnath, N., Neill, H. *et al.* (2007) Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol* 25: 1698–1704.
- Zhan, P., Wang, J., Lv, X.J., Wang, Q., Qiu, L.X., Lin, X.Q. *et al.* (2009) Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: a systematic review with meta-analysis. *J Thorac Oncol* 4: 1094–1103.

Visit SAGE journals online
http://tam.sagepub.com

SAGE JOURNALS
Online