TNM Classification and Clinicopathological Factors

What Is Helpful for Adjuvant Chemotherapy Decision after Lung Cancer Resection?

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In the present issue of the *Journal of Thoracic Oncology*, Matsumura et al.[1] reported a retrospective unicentric study assessing the prognostic role of a pathological factor, lymphatic permeation, after non–small-cell lung cancer (NSCLC) resection. Lymphatic permeation was defined by the presence of floating tumor cells in vessels with no supporting smooth muscles or with elastic fibers. The confirmation of the visualization of the lymphatic vessels was confirmed by immunohistochemical staining with anti–D2-40 antibody. Lymphatic permeation was classified as ly0 in case of absence of lymphatic permeation, ly1 in the presence of intratumoral lymphatic permeation, and ly2 in the presence of extratumoral lymphatic permeation. In 1069 patients, lymphatic permeation was detected in 224 (21%), with 134 (12%) ly1 and 90 (9%) ly2. The 5-year overall survival rates of the ly0, ly1, and ly2 groups were 75%, 63%, and 34%, respectively, which were statistically significantly different. In multivariate analyses, ly2 appeared to be an independent poor prognostic factor.

Two questions may arise from those results: Should lymphatic permeation be incorporated in the staging classification? Is lymphatic permeation a potential useful marker for proposing adjuvant chemotherapy? By definition, lymphatic permeation can be today fully assessed only after surgery and requires careful microscopic examination of the removed piece. It is thus a factor to be considered for the pathological staging. This type of factor is not taken into consideration in the present tumor, node, metastasis (TNM) classification,[2] mainly because of lack of data, small number of patients, or inconsistent clinical and pathologic results. As pulmonary nodules or visceral pleura invasion,[3,4] lymphatic permeation might be a new T descriptor for a further revision of the staging system. Other potential changes are related to the size of the primary tumor, the number of positive descriptors within a T, N, or M category, or the number of metastases. This will nevertheless require the careful collection of adequate data with a sufficient number of cases for allowing multivariate analysis, taking into account all other significant descriptors.[5] Data concerning the presence of carcinomatous lymphangitis described in the area of the primary tumor, elsewhere within the lobe of the primary, and involving other areas within the ipsilateral and/or contralateral lung are currently collected in the International Association for the Study of Lung Cancer Staging Project.[6]

In terms of prognosis, multiple factors have been proposed, including tumor characteristics, patients' characteristics, tumor metabolic activity, laboratory parameters, and tumor biological markers.[7] On the basis of the data available in the huge retrospective study performed for the 7th revision of the TNM system, the International Association for the Study of Lung Cancer staging committee proposed clinical extent of disease and

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sex as potentially useful prognostic factors for patients with resectable NSCLC. Performance status and squamous cell type were proposed for stage IIB or superior and for stage IIIA, respectively. Considering pathological staging, age and sex were confirmed as important prognostic factors in addition to pathologic TNM category in surgically resected NSCLC.[8] Standard uptake value maximum (SUVmax) of the primary tumor measured on fluorodeoxyglucose positron emission tomography scan was also included in the list of recommended prognostic factors.[7] The evidence is based on more than 20 studies, all retrospective in nature that have assessed the prognostic value of the primary tumor SUV, a semiquantitative measurement of the tumor metabolic activity. In a literature meta-analysis first published in 2008[9] and updated in 2010,[10] SUV was found to be a potential prognostic factor for survival in the whole group of patients (stages I–IV; hazard ratio, 2.08; 95% confidence interval, 1.69–2.56), as well as for nonmetastatic tumors (stages I–III; hazard ratio, 2.18; 95% confidence interval, 1.83–2.60) (Table 1). To assess the independent value of SUV, the same team performed an individual patient data meta-analysis, the first results of which were presented at the World Lung Cancer Conference 2013. In multivariate analysis, SUV confirmed its prognostic value in addition to age, stage, tumor size, and surgery. Other metabolic criteria are nowadays under investigation in NSCLC, considering the whole tumor burden either by measuring the "metabolic tumor volume" or the "total lesion glycolysis" (TLG). For example, a recent large retrospective study showed that metabolic tumor volume and TLG are independent prognostic factors, at the difference of SUV, in stage III NSCLC,[11] and the same conclusion was drawn for TLG in another retrospective study including only stage IV NSCLC.[12]

In addition, we need predictor factors for determining which patients might benefit from adjuvant chemotherapy. Today, the only factor used is the pathological stage on the basis of multiple randomized trials and meta-analyses.[13–18] Some biological markers such as mutS homolog 2 or excision repair cross-complementing 1, although promising in retrospective studies (summarized in Tables 1 and 2), failed mainly because no reproducible cutoff was found to decide which patients should be treated (Table 3). In this optic, anatomical factors such as lymphatic permeation or metabolic factors as measured on the primary tumor by positron emission tomography scan should be assessed in addition to pathological stage by well-designed randomized trials with adequate sample sizes.

TABLE 1. Prognostic Role of SUV in NSCLC

Study	Year of Publication	No. Patients	% ADC	Stage	HR	95% CI
Ahuja	1998	155	?	I–IV	2.05	1.24–3.37
Sugawara	1999	38	50	I–IV	0.56	0.21–1.44
Vansteenkiste	1999	125	25	I–IIIB	2.72	1.50–4.94
Dhital	2000	77	23	?	1.30	0.70–2.60
Higashi	2002	57	67	I–III	6.20	1.34–28.75
Jeong	2002	73	41	I–IV	4.33	1.80–10.45
Downey	2004	100	67	?	2.60	1.02–6.64
Borst	2005	51	25	I–III	3.15	1.59–6.22
Cerfolio	2005	315	31	I–IV	2.65	1.63–4.31
Port	2005	64	88	?	2.36	0.24–22.88
Sasaki	2005	162	46	I–III	7.66	1.41–41.50
Eschmann	2006	137	29	IIIA/IIIB	1.71	1.002.93
Prevost	2006	120	49	I–IV?	2.36	1.34–4.15
Raz	2006	36	0	?	9.90	1.20–79.40
de Jong	2007	66	35	I–IIIA	2.93	1.21–7.09
Downey	2007	487	69	I–IV	1.58	1.05–2.40
Van Baardwijk	2007	102/46	30	I–IIIB	3.40	1.40–8.26
Zhang	2007	82	?	I–III	2.36	1.37–4.06
Goodgame	2008	136	52	I	1.89	1.20–2.99
Hanin	2008	97	47	I/II	2.83	1.52–5.26
Hoang	2008	214	38	IIIA/IIIB/IV	1.29	0.94–1.76
All studies		2591			2.08	1.69–2.56
Nonmetastatic stages		1612			2.18	1.83–2.60

Individual data and meta-analysis (reproduced with permission from the authors).
ADC, adenocarcinoma; HR, hazard ratio; CI, confidence interval; SUV, standard uptake value maximum; NSCLC, non–small-cell lung cancer; ?, unreported.

TABLE 2. Main Studies (Including >100 Patients) Assessing Biomarkers as Predictors of Efficacy for Adjuvant Chemotherapy: Description

Author	Type of Study	Stage	No. Patients	Treatment	Marker	Technique	Cutoff
Kamal et al.[19]	Retrospective analysis of a randomized trial (IALT)	I–III	673	CDDP-based	MSH2	IHC (H score)	Median
Pierceall et al.[20]	Retrospective analysis of a randomized trial (IALT)	I–III	769	CDDP-based	MSH2, ERCC1, XPF, BRCA1, P53, PARP1, ATM	IHC (Q score)	
Olaussen et al.[21]	Retrospective analysis of a randomized trial (IALT)	I–III	761	CDDP-based	ERCC1	IHC (H score)	Median
Zheng et al.[22]	Retrospective study (hospital series)	I	187	None	RRM1 ERCC1	IHC Score AQUA	Median
Filipits et al.[23]	Retrospective analysis of a randomized trial (IALT)	I–III	782	CDDP-based	MRP1 and 2	IHC (H score)	Median
Sève et al.[24]	Retrospective analysis of a randomized trial JBR10	IB–II	265	CDDP-VNR	β-tubulin3	IHC (H score)	Median
Reiman et al.[25]	Retrospective analysis of four randomized trials (IALT, JBR10, CALGB9633, ANITA)	IA–III	1149	CDDP-based, carbo-taxol	β-ubulin3	IHC (H score)	176 (median from JBR10)
Graziano et al.[26]	Retrospective analysis of a randomized trial (CALGB 9633)	IB	250	Carbo-taxol	Mucin, bcl-2, p53, blood antigen A	IHC (score 0–16)	≥2
Tsao et al.[27]	Retrospective analysis of a randomized trial (JBR10)	IB–II	253	CDDP-VNR	p53 RAS	IHC (H score) + PCR PCR	>15%
Zhu et al.[28]	Retrospective analysis of a randomized trial (JBR10)	IB–II	133	CDDP-VNR	15 gene signature	Microarrays	
Chen et al.[29]	Retrospective study (analysis of other published datasets or randomized trials)	I–III	692	CDDP-VNR + other?	94 gene signature	Microarray	NA
Voortman et al.[30]	Retrospective analysis of a randomized trial (IALT)	I–III	639	CDDP-based	miR 21, 29b, 34a/b/c, 155, let7a	PCR	Median
Suehisa et al.[31]	Retrospective study (hospital series)	I–IIIA	187	Uracil-tegafur	EGFR mutation	PCR	NA

CDDP, cisplatinum; VNR, vinorelbin; carbo, carboplatinum; MSH 2, mutS homologue 2; ERCC1, excision repair cross complementation group1; XPF, xeroderma pigmentsum; BRCA1, breast cancer group 1; PARP-1, poly [ADP-ribose] polymerase 1; ATM, Ataxia Telangiectasia Mutated; RRM1, ribonucleotide reductase M1, MRP1, multidrug resistance protein 1; Bcl-2, B-cell lymphoma 2; PCR, polymerase chain reaction; IHC, immunohistochemistry; N, number; NA, not applicable; ANITA, Adjuvant Navelbine International Trialist Association; EGFR, epidermal growth factor receptor; JBR10, National Cancer Institute of Canada Clinical Trials Group JBR10 Trial; CALBG, Cancer and Leukemia Group B Trial; AQUA, automated quantitative analysis; RAS, rat sarcoma; P53, 53-KD phosphoprotein.

TABLE 3. Main Studies Assessing Biomarkers as Predictors of Efficacy for Adjuvant Chemotherapy: Results Summary

Author	Prognostic for Survival	*p*	Predictive for Survival	*p*	Interaction Test	Comment
Kamal et al.[19]	High MST 58 mo Low MST 42 mo	0.01	Low HR 0.76 High HR 1.12	0.03 0.48	0.06	High expression is a prognostic factor for survival; borderline effect MSH2 expression on the predictive effect of CT efficacy (trend to better survival in ACT in low expression group)
Pierceall et al.[20]	No	NS	No	NS		
Olaussen et al.[21]	ERCC1 neg MST 42 mo ERCC1 + MST 55 mo	0.009	ERCC1 neg HR 0.65 ERCC1 + HR 1.14	0.002 0.40	0.009	High expression is a prognostic factor for survival and low expression is predictive of ACT efficacy
Zheng et al.[22]	RRM1 low MST 60.2 mo RRM1 high MST >120 mo ERCC1	0.02 uni 0.11 multi 0.01	NA	NA	NA	
Filipits et al.[23]	MRP1 neg MST 49 mo + MST 50 mo MRP2 neg MST 54 mo + MST 45 mo	0.47 0.007	MRP1 neg HR 0.79 + HR 0.95 MRP2 neg HR 0.93 + HR 0.82	0.09 0.75 0.59 0.22	0.37 0.56	High expression MRP2: worse prognosis No predictive effect of both MRP
Sève et al.[24]	HR 1.72 (high < low)	0.04	TUBB3 low HR 1.00 TUBB3 high HR 0.64	0.99 0.07	0.25	High expression: worse prognosis; no predictive effect of ACT efficacy
Reiman et al.[25]	HR 1.41	0.005	TUBB3 low HR 1.03 TUBB3 high HR 0.83	0.82 0.11	0.2	High expression: worse prognosis; no predictive effect of ACT efficacy
Graziano et al.[26]	p53 HR 1.92	0.036			>0.05	Few data for no CT arm (only p53) No interaction with treatment
Tsao et al.[27]	p53 (IHC neg >+) HR 1.89 p53 and RAS mutation status not prognostic	0.03	p53 IHC neg HR 1.4 p53 IHC + HR 0.54 p53 mut HR 0.78 p53 wt HR 0.67 RAS mut HR 0.91 RAS wt HR 0.69	0.26 0.02 0.35 0.04 0.7 0.03	0.02 0.65 0.29	p53 is a prognostic and a predictive factor when assessed by IHC. Mutation status of p53 and RAS are neither prognostic nor predictive
Zhu et al.[28]	HR 18 (validated in four independent data sets)	<0.001	High-risk HR 0.33 Low-risk HR 3.67	0.0008 0.021	0.001	High-risk group: worse prognosis and signature is predicting of ACT efficacy
Chen et al.[29]	High MST 3.77 yr Low MST infinity	<0.001	Opposite data according to the investigated cohort			No adequate information on the predictive value of the signature
Voortman et al.[30]	No	All >0.05	No	All >0.05	All >0.05	miR-21: deleterious prognostic effect of lowered expression
Suehisa et al[31]	HR 0.81 (whole group, NA in the control group)	0.48	wt HR 0.34 Mut HR 0.52	0.013 0.28	ND	Mutation EGFR is not predictive of response to UFT but well wtEGFR

MST, median survival time; HR, hazard ratio; ERCC1, excision repair cross complementation group1; RRM1, ribonucleotide reductase M1; uni, univariate; multi, multivariate; neg, negative; IHC, mmunohistochemistry; RAS, rat sarcoma; TUBB3, β-tubulin3; mut, mutation; wt, wild type; ND, not done; NS, not significant; ACT, adjuvant chemotherapy; NA, not applicable; EGFR, epidermal growth factor receptor; UFT, tegafur-uracil.

REFERENCES

1. Matsumura Y, Hishida T, Shimada Y, et al. Impact of extratumoral lymphatic permeation on postoperative survival of non-small cell lung cancer patients. *J Thorac Oncol* 2014;9:337–344 .
2. Goldstraw P, Crowley J, Chansky K, et al; International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. 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* 2007;2:706–714.
3. Rami-Porta R, Ball D, Crowley J, et al; International Staging Committee; Cancer Research and Biostatistics; Observers to the Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:593–602.
4. Travis WD, Brambilla E, Rami-Porta R, et al; International Staging Committee. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2008;3:1384–1390.
5. Rami-Porta R, Goldstraw P. Strength and weakness of the new TNM classification for lung cancer. *Eur Respir J* 2010;36:237–239.
6. Giroux DJ, Rami-Porta R, Chansky K, et al; International Association for the Study of Lung Cancer International Staging Committee. The IASLC Lung Cancer Staging Project: data elements for the prospective project. *J Thorac Oncol* 2009;4:679–683.
7. Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P; International Staging Committee and Participating Institutions. 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* 2008;3:457–466.
8. Chansky K, Sculier JP, Crowley JJ, Giroux D, Van Meerbeeck J, Goldstraw P; International Staging Committee and Participating Institutions. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. *J Thorac Oncol* 2009;4:792–801.
9. Berghmans T, Dusart M, Paesmans M, et al; European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. 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* 2008;3:6–12.
10. Paesmans M, Berghmans T, Dusart M, et al; European Lung Cancer Working Party, and on behalf of the IASLC Lung Cancer Staging Project. 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* 2010;5:612–619.
11. Hyun SH, Ahn HK, Kim H, et al. Volume-based assessment by (18) F-FDG PET/CT predicts survival in patients with stage III non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2014;41:50–58.
12. Zaizen Y, Azuma K, Kurata S, et al. Prognostic significance of total lesion glycolysis in patients with advanced non-small cell lung cancer receiving chemotherapy. *Eur J Radiol* 2012;81:4179–4184.
13. Traitement des cancers bronchiques non à petites cellules et résécables. Recommandations de pratique clinique de l'European Lung Cancer working Party. *Rev Med Brux* 2006;27:29–38.
14. Winton T, Livingston R, Johnson D, et al; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589–2597.
15. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719–727.
16. Alam N, Darling G, Shepherd FA, Mackay JA, Evans WK; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Postoperative chemotherapy in nonsmall cell lung cancer: a systematic review. *Ann Thorac Surg* 2006;81:1926–1936.
17. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol* 2010;28:29–34.
18. Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, Le CT, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 2010;375:1267–1277.
19. Kamal NS, Soria JC, Mendiboure J, et al; International Adjuvant Lung Trial-Bio investigators. MutS homologue 2 and the long-term benefit of adjuvant chemotherapy in lung cancer. *Clin Cancer Res* 2010;16:1206–1215.
20. Pierceall WE, Olaussen KA, Rousseau V, et al. Cisplatin benefit is predicted by immunohistochemical analysis of DNA repair proteins in squamous cell carcinoma but not adenocarcinoma: theranostic modeling by NSCLC constituent histological subclasses. *Ann Oncol* 2012;23:2245–2252.
21. Olaussen KA, Dunant A, Fouret P, et al; IALT Bio Investigators. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006;355:983–991.
22. Zheng Z, Chen T, Li X, Haura E, Sharma A, Bepler G. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. *N Engl J Med* 2007;356:800–808.
23. Filipits M, Haddad V, Schmid K, et al. Multidrug resistance proteins do not predict benefit of adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: International Adjuvant Lung Cancer Trial Biologic Program. *Clin Cancer Res* 2007;13:3892–3898.
24. Sève P, Lai R, Ding K, et al. Class III beta-tubulin expression and benefit from adjuvant cisplatin/vinorelbine chemotherapy in operable non-small cell lung cancer: analysis of NCIC JBR.10. *Clin Cancer Res* 2007;13:994–999.
25. Reiman T, Lai R, Veillard AS, et al; LACE-Bio Group. Cross-validation study of class III beta-tubulin as a predictive marker for benefit from adjuvant chemotherapy in resected non-small-cell lung cancer: analysis of four randomized trials. *Ann Oncol* 2012;23:86–93.
26. Graziano SL, Gu L, Wang X, et al; Cancer and Leukemia Group B; North Central Cancer Treatment Group; Radiation Therapy Oncology Group. Prognostic significance of mucin and p53 expression in stage IB non-small cell lung cancer: a laboratory companion study to CALGB 9633. *J Thorac Oncol* 2010;5:810–817.
27. Tsao MS, Aviel-Ronen S, Ding K, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. *J Clin Oncol* 2007;25:5240–5247.
28. Zhu CQ, Ding K, Strumpf D, et al. Prognostic and predictive gene signature for adjuvant chemotherapy in resected non-small-cell lung cancer. *J Clin Oncol* 2010;28:4417–4424.
29. Chen DT, Hsu YL, Fulp WJ, et al. Prognostic and predictive value of a malignancy-risk gene signature in early-stage non-small cell lung cancer. *J Natl Cancer Inst* 2011;103:1859–1870.
30. Voortman J, Goto A, Mendiboure J, et al. MicroRNA expression and clinical outcomes in patients treated with adjuvant chemotherapy after complete resection of non-small cell lung carcinoma. *Cancer Res* 2010;70:8288–8298.
31. Suehisa H, Toyooka S, Hotta K, et al. Epidermal growth factor receptor mutation status and adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *J Clin Oncol* 2007;25:3952–3957.