Visceral Pleural Invasion: Pathologic Criteria and Use of Elastic Stains

Proposal for the 7th Edition of the TNM Classification for Lung Cancer

William D. Travis, MD, Elisabeth Brambilla, MD,† Ramon Rami-Porta, MD,‡ Eric Vallières, MD,§ Masahiro Tsuboi, MD,‖ Valerie Rusch, MD,¶ and Peter Goldstraw, FRCS#; on behalf of the International Staging Committee*

Objective: To define the anatomic extent of visceral pleural invasion (VPI) and to assess whether elastic stains are useful to determine VPI in lung cancer. The elastic layer of the visceral pleura is not mentioned in the current International Union Against Cancer or American Joint Committee on Cancer staging documents.

Methods: A Pub Med search (www.pubmed.gov) of the National Library of Medicine was made for all articles published between 1970 and 2007 in humans under the search terms lung cancer and pleural invasion. These were reviewed for data regarding the pathologic classification of extent of pleural invasion including the use of elastic stains in this assessment.

Results: Six articles that addressed reported survival data using elastic stains to assess for VPI were reviewed. These articles defined P0 (T1) as lack of pleural invasion beyond the elastic layer, P1 (T2) as invasion beyond the elastic layer, P2 (T2) as invasion to the surface of the visceral pleura and P3 (T3) as invasion of the parietal pleura. In five studies, survival was shown to be significantly worse for VPI defined as P1 or P2 compared with P0.

Conclusions: Based on the currently available data, we propose that the next tumor, node, metastasis (TNM) revision by International Union Against Cancer and American Joint Committee on Cancer define VPI as invasion beyond the elastic layer (PL1) including invasion to the visceral pleural surface (PL2). The abbreviation PL for pleura is recommended rather than P to avoid confusion with the existing use of p (pathologic) TNM in distinction from c (clinical) TNM. We also recommend that elastic stains be used in cases when the distinction between PL0 and PL1 is not clear based on evaluation of hematoxylin and eosin sections.

Key Words: Visceral pleural invasion, Lung cancer, Stage, Elastic stain, Pathology, Pleura.

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The anatomic extent of disease, as expressed by the tumor, node, metastasis (TNM) staging system, is the most important prognostic factor for lung cancer. Visceral pleural invasion (VPI) increases the T staging factor from T1 to T2 and upstages a tumor, even if less than 3 cm in size, from Stage IA to IB according to the TNM staging system for lung cancer by the 6th editions of the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC).[1,2] This is important because adjuvant chemotherapy is sometimes considered for patients following complete resection for Stage IB non-small cell lung carcinoma (NSCLC) but has not been shown to be of value in Stage IA NSCLC.[3] However, a precise definition of VPI is not provided in either the UICC or AJCC publications. In the UICC TNM Supplement, it is stated that "invasion of the visceral pleura (T2) includes not only perforation of the mesothelium, but also invasion of the lamina propria serosae."[4] This document does not provide criteria for what is invasion of the "lamina propria serosae" and whether this bears any relationship to the elastic layer of the visceral pleura. The elastic layer of the visceral pleura is not specifically mentioned in either the UICC or AJCC documents. In recent years, the use of elastic stains has been recommended for defining VPI. While this is becoming more accepted, there remains controversy regarding whether tumors that invade beyond the elastic layer but not to the pleural surface should be regarded as T1 or T2.[5–7]

In 1988, Hammar, suggested a classification of pleural invasion that defined P0 as lack of pleural invasion beyond the elastic layer, P1 as invasion beyond the elastic layer, P2 as invasion to the surface of the visceral pleura and P3 as

*Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York City, New York; †Department of Pathology, University of Grenoble, Grenoble, France; ‡Department of Thoracic Surgery, Hospital Mutua de Terrassa, Terrassa, Barcelona, Spain; §Department of Thoracic Surgery, Swedish Cancer Institute, Seattle, Washington; ‖Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan; ¶Department of Thoracic Surgery, Memorial Sloan Kettering Cancer Center, New York City, New York; and #Department of Thoracic Surgery, Royal Brompton Hospital, Imperial College, London, United Kingdom.

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Address for correspondence: William D. Travis, MD, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10021. E-mail: travisw@mskcc.org

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TABLE 1. Survival of NSCLC by Assessment of Viscral Pleural Invasion Using Elastic Stains

Author, Year	Resected NSCLC Cases Studied	Frequency of VPI	Definition of VPI	Survival Data	Favor Elastic Stains
Bunker ML 1999[38]	26	P0: 12 (46%) P1: 8 (31%) P2: 6 (23%)	Hammar method[5]	Significantly worse survival with greater degrees of pleural involvement (p = 0.0000)	Yes
Manach 2001[29]	1281 430 T1: 851 T2	VPI: n = 245 (19%)	Hammar method[5]	Significantly worse 5 & 10 yr survival in VPI (35% and 28%) compared to no VPI (52% and 34%), P = 0.000002; VPI also independent factor in multivariate analysis	Yes
Kang JH 2003[28]	439 T2: 234 IB; 95 IIB, 110 IIIA & B	VPI: 114 (26%)	Hammar method[5]	VPI assoc higher frequency of N2 or N3 (p = 0.009) VPI worse survival: (p = 0.0006) even with multivariate analysis	Yes
Osaki T 2004[30]	474 T1 & T2	P0: 345 (73%) P1: 110 (23%) P2: 19 (4%) VPI in 129 (27%)	Hammar method[5]	Degree of VPI independent prognostic factor by multivariate analysis (p = 0.033); P1 & P2 worse than p0, but survival for P1 vs. P2 not different	Yes Recommend P1 and P2 be designated as T2
Shimizu K 2004[7]	1653 T1, T2 and T3	P0:1055 (64%) P1: 271 (16%) P2: 81 (5%) T3: 246 (15%) VPI in 352 (21%)	Japanese Lung Cancer Society[6]	Survival identical for P1 or P2–significantly worse than for P0 disease for either ≤3 cm or >3 cm Worse survival for P1/P2 vs. P0	Yes Data supports p0 as non-VPI and P1 or P2 as VPI
Shimizu K 2005[31]	1704 T1 and T2	VPI in 288 (27%)	Japanese Lung Cancer Society[6] But used P0* as non-VPI and P1 or P2 as VPI similar to Hammar	5 & 10 yr survival No VPI: 76 & 53% vs. VPI: 50 and 37% (p < 0.0001) VPI also significant by multivariate analysis	Yes VPI significant and independent for prognosis

VPI, visceral pleural invasion; yr, year; NSCLC, non-small cell lung cancer.

invasion of the parietal pleura and/or chest wall.[5,8] Hammar also included a category of Px that applied to tumors situated within the lung parenchyma with no relationship to the pleura. According to this scheme, P0 corresponds to T1, P1 or P2 correspond to T2 and P3 corresponds to T3. This approach has been used by several recent studies (Table 1) and the same levels of pleural invasion (except for Px) are recognized by the Japan Lung Cancer Society.[6] However, according to the Japan Lung Cancer Society, it is required that the tumor invade to the surface of the visceral pleura (P2) to qualify for T2 and tumors that invade beyond the elastic layer but not to the pleural surface (P1) remain T1.[6] In one study, visceral pleural involvement was defined as tumor extending to within 1 mm of the visceral pleural margin or involving the margin.[9] So there is need for some clarification of the definition of pleural invasion in the staging of lung cancer.

Many pathologists are not inclined to do elastic stains in assessing the pleura for VPI. In a survey of lung cancer surgical pathology reports from the year 1991 performed by the College of American Pathologists (CAP), Gephardt et al.[10] found that VPI was addressed in only 65% of cases. However, more recently Taube et al.[11] surveyed members of the American Association of Directors of Anatomic and Surgical Pathology who consist of many of the leaders in the field of surgical pathology. Of 49 pathologists who responded, 51% never use elastic stains, 29% use them sometimes, and 20% use them routinely to assess for VPI in lung cancer specimens. Butnor et al.[12] recently used an internet based questionnaire to assess interobserver variability for VPI with a set of photomicrographs of the pleura with elastic stains in lung cancer specimens. The kappa statistic for agreement was "fair" with a value of 0.35. The majority of participants regarded invasion of the elastic layer as necessary for VPI.

In preparation for the Seventh edition of the UICC and AJCC TNM Classification for lung cancer staging, a series of white papers are being published by the International Association for the Study of Lung Cancer staging committee.[13–18] Extensive statistical analysis of data from 67,725 cases of NSCLC submitted to the project forms the basis for most of the recommendations. As there was no detailed pathologic information regarding VPI submitted to the project the T Factor Committee was unable to perform an analysis of primary data on this subject. Because VPI is becoming established as an important T factor for lung cancer, this article makes recommendations regarding pathologic as-

