Extratumoral Vascular Invasion Is a Significant Prognostic Indicator and a Predicting Factor of Distant Metastasis in Non-small Cell Lung Cancer

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Introduction: Vascular invasion is thought to be a fundamental step in hematogenous metastasis. The aim of this study was to assess whether the qualitative evaluation of vascular invasion according to its location (intratumoral or extratumoral) could provide an appropriate means of predicting the prognostic outcome and potential patterns of recurrence in non-small cell lung cancer.

Methods: We reviewed the cases of 1000 consecutive patients in whom complete resection of non-small cell lung cancer had been performed. Sections stained by the Victoria blue van Gieson method were examined for the presence of vascular invasion and the evaluation of its location (v0: absence, $n = 540$; v1: intratumoral, $n = 428$; v2: extratumoral, $n = 32$). Survival was estimated using the Kaplan-Meier method. To determine independent prognostic factors, univariate and multivariate analyses were conducted.

Results: The study cohort included 605 men and 395 women, with a mean age of 66 years (range, 20–90 years). The 5-year overall survival rate of the vascular invasion-negative group and the vascular invasion-positive group was 82.5% and 55.1%, respectively ($p < 0.001$), and the 5-year overall survival rates of the v1 group and v2 groups were 55.9% and 44.0%, respectively ($p = 0.010$). Multivariate analysis showed that location of the vascular invasion (v0–1 versus v2) ($p = 0.049$), age ($p = 0.030$), tumor size ($p = 0.004$), lymph node metastasis ($p < 0.001$), and pleural invasion ($p < 0.001$) were significant prognostic factors. The proportion of patients who developed distant metastasis was significantly higher in the v2 group than in the v1 group ($p = 0.026$).

Conclusion: Evaluation of vascular invasion location was a statistically significant predictor of prognosis and potential recurrence patterns.

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Metastasis is a complex, multistep process that ultimately results in the formation of a mature tumor, which leads to the death of almost all cancer patients. Many investigators have elucidated the mechanisms of how tumor cells invade into intratumoral blood vessels within primary cancers and emphasized the biologic importance of this process for tumor metastasis.[1] Vascular invasion (blood vessel invasion) is now considered to be a fundamental step in hematogenous metastasis,[1] and the presence of vascular invasion by cancer cells is one of the most important prognostic factors in many types of cancer including non-small cell lung cancer (NSCLC), and it is also thought to directly represent the metastatic process.[2,3]

On routine histologic examination, vascular invasion was defined as definite tumor cell embolization in the vascular lumen on hematoxylin and eosin and elastic lamina staining. Previous reports have indicated that the existence of intratumoral vascular invasion was associated with unfavorable prognosis in NSCLC[1–16]; however, almost all intratumoral blood vessels are occluded by surrounding tumor cells and stromal cells. This may mean that the intratumoral blood vessels are not functional. Therefore, it is unknown whether tumor cell embolization in intratumoral blood vessels could clearly represent one step of the metastatic process with respect to hematogenous metastasis. However, because extratumoral blood vessels are thought to be functional blood vessels, the existence of extratumoral vascular invasion may be a potential factor of distant metastasis.

Previously, we investigated whether the qualitative evaluation of lymphatic permeation according to its location provides appropriate means of predicting outcomes in consecutive patients with surgically treated NSCLC and found that extratumoral lymphatic permeation showed a significantly shorter recurrence-free survival (RFS) time compared with intratumoral lymphatic permeation.[17] We concluded that extratumoral lymphatic permeation might be an early phase of carcinomatous lymphangiosis.

The objective of this study was to assess whether the qualitative evaluation of vascular invasion according to its

location (intratumoral or extratumoral) could provide an appropriate means of predicting the outcome and potential patterns of cancer recurrence in NSCLC.

PATIENTS AND METHODS

Patients

During the period from August 2001 to October 2005, a total of 1043 patients underwent surgical resection for primary lung cancer at our hospital, and we reviewed the cases of the 1000 consecutive patients in whom complete resection of NSCLC had been possible. Their median follow-up period was 4.1 years. All patients signed the Institutional Review Board-approved informed consent form. Patients who had received preoperative chemotherapy or preoperative thoracic radiation were excluded. The preoperative evaluation included a physical examination, bronchofiberscopy, chest radiography, computed tomography of the chest and abdomen, magnetic resonance imaging of the brain, and an isotopic bone scan. The majority of patients underwent lobectomy or pneumonectomy for resection of the primary lesion. In cases of wedge resection or segmentectomies, lavage cytology at the surgical margin was evaluated by intraoperative rapid cytologic diagnosis and confirmed as negative. Staging was performed according to the tumor node metastasis classification of the International Union Against Cancer. The tumors were histologically classified and graded according to the World Health Organization guidelines, third edition.

TABLE 1. Definition of Vascular Invasion According to Location

Grade	Definition	*n* (%)
v0	Absence of vascular invasion	540 (54.0)
v1	Presence of intratumoral vascular invasion	428 (42.8)
v2	Presence of extratumoral vascular invasion	32 (3.2)

Histopathology

The available pathology slides from all 1000 surgical specimens were reviewed in this study. After fixing the specimens with either 10% formalin or cold methanol and embedding them in paraffin, serial 4-μm sections were stained with hematoxylin and eosin and by the Victoria blue van Gieson to visualize elastic fibers. Sections stained by Victoria blue van Gieson were examined for the presence of vascular invasion and pleural invasion. The presence of vascular invasion was determined by identifying conspicuous clusters of intravascular cancer surrounded by an elastic layer. Since August 2001, we have been recording the location of vascular invasion according to our histologic criteria. The presence or absence of vascular invasion and its recorded location are shown in Table 1: v0, absence of vascular invasion; v1, presence of intratumoral vascular invasion (Figures 1*A*, *B*), and v2, presence of extratumoral vascular inva-

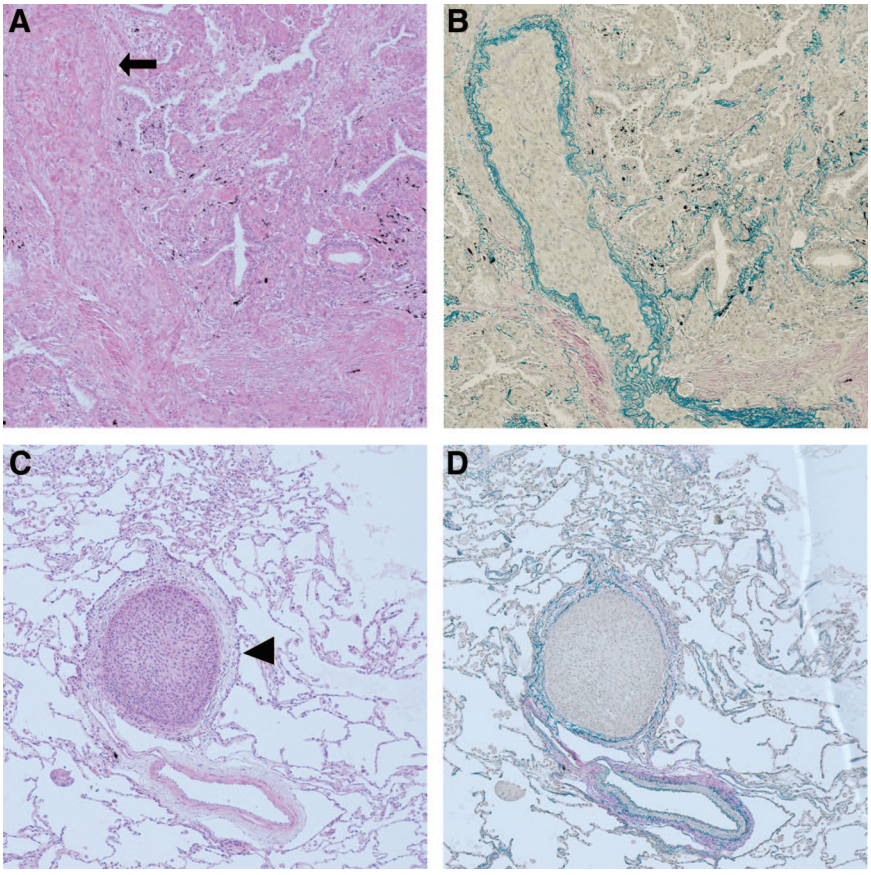

FIGURE 1. Vascular invasion in a Victoria blue van Gieson (VvG)-stained section of non-small cell lung cancer. These figures show intratumoral vascular invasion (v1) within a tumor nest in hematoxylin and eosin (HE) staining (*A*; arrow) and VvG staining (*B*). Findings of extratumoral vascular invasion (v2) in HE staining (*C*; arrow head) and VvG staining (*D*) are shown.