Vascular invasion in non-small cell lung carcinoma

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Abstract

Aims: To determine if there is any correlation between vascular invasion and prognosis in non-small cell carcinoma of the lung; and to look specifically at invasion of vascular channels by tumour cells.

Methods: Eighty seven patients undergoing lobectomy or pneumonectomy for adenocarcinoma or squamous carcinoma were followed up for five years. The histological sections were studied for evidence of vascular invasion using an elastic van Gieson stain. The incidence of intimal fibrosis in arteries and veins was noted and the proportion with vascular invasion evaluated using a scoring system. The presence or absence of lymphatic permeation and tumour necrosis were noted. Survival data were analysed using the log rank test.

Results: The overall five year survival was 32%. There were 64 squamous cell carcinomas and 23 adenocarcinomas. Vascular invasion was seen in 77% of patients and lymphatic invasion in 44%. Neither the presence nor absence nor the proportion of blood vessels showing vascular invasion showed any relation to prognosis. Intimal fibrosis and tumour necrosis were unrelated to prognosis. Patients with lymphatic permeation had recurrence and died earlier than those without.

Conclusion: The presence of arterial or venous invasion by adenocarcinoma or squamous carcinoma of the lung was unrelated to survival; lymphatic permeation was associated with poor prognosis. The two common non-small cell lung cancers behaved differently from other solid tumours, where vascular invasion was a significant factor in determination of prognosis. The presence of intimal fibrosis was unrelated to prognosis.

Invasion of the lymphatic or vascular space is a feature of malignant neoplasms, allowing them to metastasise. This has been shown for Wilms' tumour, 1 cervical carcinoma, 2, 3 breast carcinoma, 4, 5 endometrial carcinoma, 6 lung, 7, 8 oesophagus 9 and adenocarcinoma of the colon and rectum. 10, 11 Although by contrast, Jass et al found that invasion of rectal veins did not influence the survival in rectal carcinoma. 12 This study was undertaken to see if there was a similar correlation between vascular invasion and prognosis in carcinoma of the lung and to look specifically at invasion of vascular channels by tumour cells, rather than combining both vascular and lymphatic channels under the same broad heading.
analysis of the contingency tables was performed using the $\chi^2$ test. The median duration of follow up was 92 months (range 14–141 months).

Results
The overall five year survival rate was 32%. The number of tumours of each histological type and the incidence of vascular and lymphatic invasion is shown in table 1. Vascular invasion was found in 26 of 87 patients (30%) and lymphatic invasion was found in 38 of 87 patients (44%). In patients with vascular invasion the pulmonary veins were more frequently affected than the arteries (data not shown).

There was no correlation between side nor site of tumour within the lung ($p = 0.5$, $p = 0.236$, respectively). There was a significant association between the presence of tumour within lymphatic channels and survival. Those patients with lymphatic invasion had recurrence and died earlier than those without ($p = 0.003$). By contrast, neither the presence nor absence nor the proportion of blood vessels invaded by tumour was related to prognosis (table 2). The presence or absence of intimal fibrosis and tumour necrosis were also unrelated to prognosis (table 2).

**Discussion**
This study showed no correlation between presence of vascular invasion and survival in squamous and adenocarcinoma of the lung. However, lymphatic permeation was associated with a poor prognosis. The possibility that intimal fibrosis was responsible for retarding or preventing malignant infiltration and subsequent dissemination of cells was considered by examining the presence or absence of this change in each tumour and relating it to survival. There was no significant correlation. The difference between the observations in our study and those obtained by others with different tumour types may reflect the fact that most of the previous investigators have made no distinction between neoplastic invasion of lymphatics and blood vessels, and thus a strong correlation of survival with lymphatic invasion may have masked a lack of correlation with blood vessel disease. In addition, capillaries, being thin walled, can easily be confused with lymphatics, making their identification difficult in some cases. The five year survival rate of 32% in these patients studied is similar to the 30% reported in a similar cohort by the Edinburgh Lung Cancer Group.

**Table 2** Correlation between histological and physical variables and survival in carcinoma of the lung

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival p value</th>
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<tr>
<td>Lymphatic invasion</td>
<td>0.003</td>
</tr>
<tr>
<td>Blood vessel invasion</td>
<td>0.75</td>
</tr>
<tr>
<td>Intimal fibrosis of vessels</td>
<td>0.93</td>
</tr>
<tr>
<td>Tumour necrosis</td>
<td>0.76</td>
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</tbody>
</table>

Figure  Pulmonary artery (media wall shown between arrows) infiltrated by squamous carcinoma (elastic van Gieson).
Vascular invasion in non-small cell lung carcinoma

There is no way of demonstrating whether tumour cells identified within a vascular lumen are viable in vivo, and should a blood vessel be obliterated by tumour, the malignant cells may be relatively hypoxic and incapable of distant implantation and replication. At 77%, the incidence of vascular invasion in this study of lung cancer is high, compared with 52% in rectal cancer,\textsuperscript{11} 17% of Wilms' tumour,\textsuperscript{4} and 25% of endometrial carcinoma.\textsuperscript{6} However, this figure is similar to that reported in bronchial tumours by Mosely and Dickson (88%)\textsuperscript{5} and Kolin and Koutoulakis (58–87%).\textsuperscript{6} This high incidence may reflect the relatively more vascular nature of the lung compared with other organs, the thin media of pulmonary blood vessels, or the lower intraluminal pressure of the pulmonary arterial bed, predisposing these vessels to invasion. As a practical point it is important that several tumour blocks are examined for presence of blood vessel disease. In a pilot study of 10 patients we found that the incidence of vascular invasion was grossly underestimated if only one tumour block was examined (unpublished data).

The mechanisms whereby tumours may metastasise are complex and not completely understood. The mechanical, enzymatic, and migratory characteristics of the cells seem to be important.\textsuperscript{14} Consequently, access to vascular channels is likely to be only one of many factors which may influence the outcome, and the Edinburgh Lung Cancer Group have shown that performance indices, such as the Karnovsky score, are good prognostic indicators in both small cell and non-small cell tumours.\textsuperscript{7} The results of this study suggest that in terms of bloodborne metastases at least, carcinoma of the lung behaves differently from other common solid tumours.

4 Betelheim R, Munro Neville A. Lymphatic and vascular channel involvement within infiltrative breast cancers as a guide to prognosis at the time of primary surgical treatment. Lancet 1981;i:631.