

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's tumour,¹ cervical carcinoma,^{2,3} breast carcinoma,^{4,5} endometrial carcinoma,⁶ lung,^{7,8} oesophagus⁹ 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.

Methods

Eighty seven patients who had resections for lung cancer between 1979 and 1983, and for whom there was complete follow up data, were studied retrospectively. The operations were all carried out by a single surgeon (RAML) and in each there was no clinical or radiological evidence of metastasis at the time of surgery. The number of histological blocks taken from each tumour ranged between two and six (mean four). In most of the cases studied at least one tumour block had some adjacent lung tissue in the histological section.

Slides from each block were stained conventionally with haematoxylin and eosin and elastic van Gieson to permit clear visualisation of blood vessel laminae.¹³ Only patients with squamous cell and adenocarcinoma were studied as it is well recognised that small cell tumours invade the pulmonary vasculature early.¹⁴ Undifferentiated tumours were also not considered as it was felt that they comprise a very mixed group and should be studied separately. Lymphatic invasion was recorded as being present only if tumour cells were seen within areas which had a definite and clearly identifiable endothelial lining.

Vascular invasion was identified if tumour was seen within pulmonary arteries (figure) or veins. Blood vessels with invasion of the media but with an intact intima were not considered to have true vascular invasion. Two pathologists (PSH, CM) independently recorded tumour type and the nature of the vessels involved, together with the presence or absence of intimal fibrosis and tumour necrosis. They also evaluated, semiquantitatively, the proportion of vascular invasion using the following scale: 0 = no vessels involved, 1 = < 33% vessels involved, 2 = 50% vessels involved, and 3 = > 66% vessels involved. Where there was disagreement between the two pathologists the case was reassessed jointly under a double headed microscope. Care was taken to exclude intrabronchial tumour spread. This was done by referring to the haematoxylin and eosin sections as well as insistence on an arterial or venous histological structure. Arterioles or venules which could be confused with lymphatics were not counted on this study.

In addition to the foregoing histological features for each patient, survival data were analysed using the log rank test. Statistical

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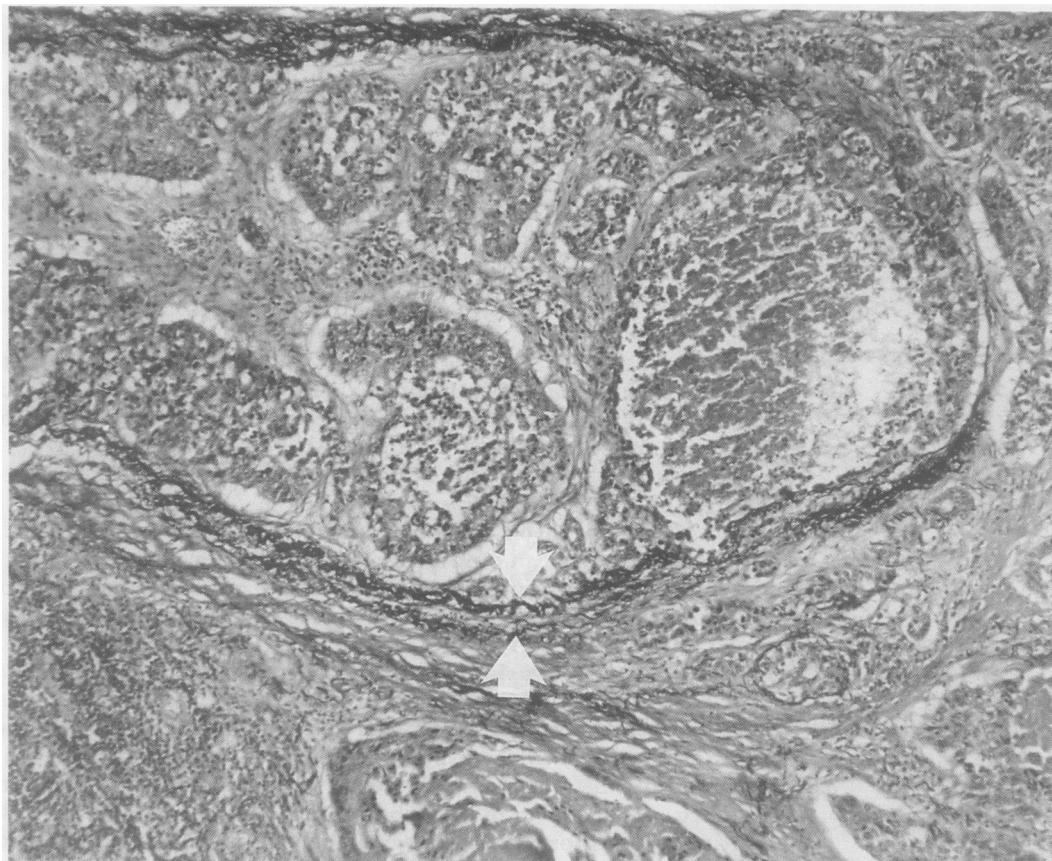


Figure Pulmonary artery (media well shown between arrows) infiltrated by squamous carcinoma (elastic van Gieson).

analysis of the contingency tables was performed using the χ^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 67 of 87 patients (77%) 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).

Table 1 Tumour type

	Squamous Adenocarcinoma	
No of cases	64	23
No with vascular invasion	49	18
No with lymphatic invasion	26	12

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.¹⁵

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

Variable	Survival p value
Lymphatic invasion	0.003
Blood vessel invasion	0.75
Intimal fibrosis of vessels	0.93
Tumour necrosis	0.76

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,¹¹ 17% of Wilms' tumour,¹ and 25% of endometrial carcinoma.⁶ However, this figure is similar to that reported in bronchial tumours by Mosely and Dickson (88%)⁷ and Kolin and Koutoulakis (58–87%).⁸ 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.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 Karnosky score, are good prognostic indicators in both small cell and non-small cell

tumours.¹⁵ 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.

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