Angiographic Findings As Prognostic Factors In Non-small-cell Lung Cancer

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Citation

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Abstract

The aim of this study was to assess the correlation between prognosis and angiographic findings in primary non-small-cell lung cancers (NSCLCs) to determine the relationship between angiographic findings and angiogenesis. The study included 134 primary NSCLCs. Tumor vascularity, bronchopulmonary shunt (B-P shunt)
formation on bronchial arteriography (BAG) and pulmonary arterial perfusion in tumors on pulmonary arteriography were retrospectively reviewed. Patients with tumors that were B-P
shunt-positive and those with adenocarcinomas including large cell carcinomas that were negative for pulmonary arterial perfusion had a significantly shorter survival time compared to those with tumors that were B-P shunt-negative and those who were pulmonary arterial perfusion-positive ($p<0.05$). The survival times of patients with hyper- and hypovascular tumors did not differ significantly ($p>0.05$). B-P shunt in tumors and pulmonary arterial perfusion in adenocarcinomas including large cell carcinomas may represent prognostic factors
in NSCLCs. Tumor vascularity on BAG may not directly indicate angiogenesis in NSCLCs.

INTRODUCTION

Angiogenesis is regarded as essential for tumor growth. An abundance of literature demonstrates that angiogenesis is associated with prognosis in lung cancer. To our knowledge, however, the relationship between angiographic findings and angiogenesis in lung cancer has not yet been described.

We retrospectively investigated the correlation between prognosis and angiographic findings as well as histologic type in primary non-small-cell lung cancers (NSCLCs) for purely scientific purposes.

MATERIALS AND METHODS

PATIENTS

A consecutive series of 134 primary NSCLCs in patients who underwent selective bronchial arteriography (BAG) were retrieved from the angiographic files dated between March 1985 and December 1990. Tumors were pathologically confirmed by surgery and/or biopsy. The mean age of the 95 male and 39 female patients was 63.8 years (range, 26-89 years). Tumors were histologically classified as 68 adenocarcinomas, 56 squamous cell carcinomas and 10 large cell carcinomas.

The clinical stage classification was performed according to the international staging system on the basis of the patient's clinical examination, including chest PA and lateral radiographs, CT scan of the chest, pulmonary arteriography (PAG), radionuclide bone scintigraphy, abdominal ultrasonography and CT scan of the brain: stage I in 25 patients, stage II in 22 patients, stage III in 53 patients and stage IV in 34 patients. The series contained 115 patients underwent PAG.

These patients had been collected to assess the correlation between angiographic findings and histologic type in primary lung cancers (not published). They had given informed consent.

ANGIOGRAPHIC FINDINGS

Tumor vascularity, bronchopulmonary shunt (B-P shunt) formation on selective BAG including magnification stereoscopic angiography ([[[1]]]), and pulmonary arterial perfusion in tumors on PAG were initially reviewed by two radiologists independently. These investigators had no knowledge of the relevant clinical data and any differences in the evaluation were discussed until a consensus was reached.

Tumor vascularity was evaluated by the degree of staining intensity during the parenchymal phase. The intensity of

tumor-staining was classified as either hypervascular tumors upon moderate-intense staining or hypovascular tumors upon weak or no staining. Staining with complicating pulmonary conditions such as inflammatory lung diseases and B-P shunt observed in a secondary inflammatory lesion adjacent to or separated from the tumor were excluded.

Microvessels were stained with anti-CD-31 antibody JC70 (DAKO A/S, Glostrup, Denmark) and/or anti-factor VIII-related antigen polyclonal antibody (DAKO) in some samples. However, microvessels were not counted because of insufficient numbers of samples. Silicone rubber microangiograms of resected specimens after injection into the branch of the pulmonary artery were obtained from only one sample.

None of the patients received chemotherapy or radiation therapy before angiography. The median follow-up time after angiography was 3 years and 9 months (minimum of 15 months). Clinical course was reviewed from the recorded findings at follow-ups in the medical records.

The pathological features of the patients were obtained from the appropriate reports. Tumors were histologically analyzed by experienced pathologists who were unaware of the analytical results.

STATISTICAL ANALYSIS

Survival curves were calculated using the Kaplan-Meier method and analyzed by the log rank test. Statistical significance was determined by applying the unpaired Student's t-test or chi-squared test. A difference was considered significant at the level of $p<0.05$.

RESULTS

Table 1 shows the correlation between histologic type, angiographic findings, clinical stage and the frequency of distant metastasis. Table 2 shows the correlation between pulmonary arterial perfusion and disease-free periods of time in adenocarcinomas and large cell carcinomas. Figures 1-4 show the correlation between histologic type, angiographic findings and survival rate and time.

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COMPARISON OF HISTOLOGIC TYPE, CLINICAL STAGE AND PROGNOSIS

Significantly more patients classified with stage III-IV tumors were found in the adenocarcinoma group than in the squamous cell carcinoma group ($p=5.8X10^{-4}$). The frequency of distant metastasis was significantly higher in adenocarcinomas than in squamous cell carcinomas ($p=2.7X10^{-7}$) (Table 1). The survival times of patients with adenocarcinomas were significantly shorter than for those with squamous cell carcinomas ($p<0.05$) (Fig. 1). There was no statistical difference between large cell carcinomas and adenocarcinomas and between large cell carcinomas and squamous cell carcinomas with respect to the clinical stage, frequency of distant metastasis and survival times.

COMPARISON OF TUMOR VASCULARITY, CLINICAL STAGE AND PROGNOSIS

The clinical stage and frequency of distant metastasis of hyper- and hypovascular tumors on BAG did not statistically differ ($p=0.27$, 0.54, respectively) (Table 1). The survival times of patients with hyper- and hypovascular tumors were also not significantly different ($p>0.05$) (Fig. 2). Figure 5 shows an example of a hypervascular tumor on BAG.

Figure 5. Patient 1. Squamous cell carcinoma in a 26-year-old male.

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COMPARISON OF B-P SHUNT, CLINICAL STAGE AND PROGNOSIS

Patients with stage III-IV B-P shunt-positive tumors significantly outnumbered those with stage III-IV B-P shunt-negative tumors ($p=9.0 \times 10^{-5}$). The frequency of distant metastasis was significantly higher in B-P shunt-positive tumors than in negative tumors ($p=0.01$) (Table 1). Survival times were significantly shorter for patients with B-P shunt-positive tumors than for those with negative tumors ($p<0.05$) (Fig. 3). Figure 6 shows a B-P shunt-positive tumor on BAG.

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COMPARISON OF PULMONARY ARTERIAL PERFUSION, CLINICAL STAGE AND PROGNOSIS

Pulmonary arterial perfusion was observed in 57.1% of patients with adenocarcinomas 15.4 % of those with squamous cell carcinomas and 42.9% of large cell carcinomas.

The clinical stage and frequency of distant metastasis of pulmonary arterial perfusion-positive and negative tumors did not statistically differ (p=0.23, 0.078, respectively) (Table 1). The survival times of patients with pulmonary arterial perfusion-positive and negative tumors did not statistically differ (p>0.05).

On the other hand, in the group of adenocarcinoma including large cell carcinoma patients with stage III-IV pulmonary arterial perfusion-negative tumors significantly outnumbered those with stage III-IV positive tumors (p=0.014) (Table 1). Although there was no statistical difference between the frequency of distant metastasis of pulmonary arterial perfusion-positive and negative tumors (p=0.57) (Table 1), the disease-free periods of time of pulmonary arterial perfusion-positive tumors were significantly longer than those that were negative in this group (p=0.01) (Table 2). In addition, the survival times were significantly shorter for patients with pulmonary arterial perfusion-negative tumors than for those with positive tumors in this group (p<0.05) (Fig. 4). Figures 7 and 8 show pulmonary arterial perfusion-positive tumors on PAG.

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*Mean±standard deviation. **Calculated by Student's t -test.

Figure 7. Patient 3. Adenocarcinoma in a 78-year-old female.

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Figure 8. Patient 4. Adenocarcinoma in a 65-year-old male.

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DISCUSSION

Angiogenesis is required for the growth and metastasis of solid tumors ([[[2]]], [[[3]]]). Numerous studies of various cancers have shown a statistically significant correlation between tumor angiogenesis and metastasis or prognosis when measuring microvessel density (MVD) in carcinoma using anti-factor VIII-related antigen polyclonal antibodies, anti-CD-31 antibodies, CD-34 antibodies, or by the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) ([[[4]]]).

Several studies of lung cancer have also shown a statistically significant correlation between prognosis and tumor angiogenesis ([[[5]]], [[[6]]]). Conversely, other reports indicate that neither MVD nor VEGF expression are significant prognostic factors of metastasis or survival among patients with NSCLCs ([[[7]]], [[[8]]]). These contradictory results may be due to heterogeneity in MVD among tumors, or inter-and intra-observer variation associated with quantifying MVD ([[[9]]]).

The prediction of tumor angiogenesis prior to surgery would aid clinicians in the provision of optimized treatment and estimation of prognosis. Furthermore, it would help to distinguish those patients who require surgery from those who do not. However, to date, published studies have examined angiogenesis using tumor tissues obtained at surgical resection only. One report described that the preoperative measurement of serum VEGF concentrations was significantly associated with the T stage of lung cancer. However, VEGF expression and serum VEGF concentrations were not significantly associated ([[[10]]]).

Some investigators have described a relationship between tumor vascularity on angiography and angiogenesis only in cases of hepatocellular carcinoma (HCC). Mise et al ([[[11]]]) reported that VEGF mRNA levels in HCC correlate with tumor staining on angiography. On the contrary, El-Assal et al ([[[12]]]) reported that tumor vascularity on angiography is not statistically correlated with the MVD of HCC, and suggested that angiographic findings do not directly reflect the MVD of HCC, because many factors could contribute to the degree of angiographic tumor enhancement, such as the arterial blood supply, MVD, the

selectivity of arterial cannulation and the volume of contrast materials. The present study did not identify a significant association between the frequency of distant metastasis, clinical stage or the survival times of patients with hyper- and hypovascular tumors on BAG (Figs. 2, 5). We cannot account for this. However the same reason suggested by El-Assal et al may also hold true for lung cancer. Therefore, we consider that tumor vascularity on BAG does not directly reflect angiogenesis in lung cancer. Further studies are needed to clarify these issues.

In contrast, accurate evaluation of angiogenesis in brain tumors, and breast and cervical cancers can be made using color doppler ultrasonography and contrast-enhanced MRI ([[[13]]],[[[14]]],[[[15]]],[[[16]]]). Although reports indicate that benign and malignant tumors can be distinguished using contrast-enhanced CT or MRI in lung cancer ([[[17]]],[[[18]]],[[[19]]],[[[20]]]), no reports have addressed the issue of angiogenesis. Tumor enhancement as observed upon CT and MRI reflects contrast material distribution from the capillaries to the tumoral interstitium ([[[21]]]). Further investigations are required to clarify the relationship between angiogenesis and tumor enhancement on CT and MRI.

To the best of our knowledge, the relationship between pulmonary arterial perfusion on PAG and prognosis has not been described to date. The frequency of distant metastasis and survival times of patients with pulmonary arterial perfusion-positive and negative tumors did not statistically differ in the present study. This result may be due to the low frequency of pulmonary arterial perfusion-positive tumors in squamous cell carcinomas (15.4%). In squamous cell carcinomas the tumors invade the submucosal and peribronchial connective tissue more commonly ([[[22]]]). Thus, pulmonary arterial perfusion may not be prognostic factor in squamous cell carcinomas because encasement of pulmonary artery was observed frequently.

On the contrary, the clinical stage was significantly more advanced and the disease-free periods of time were significantly shorter when tumors were pulmonary arterial perfusion-negative, compared to those that were positive in the group of adenocarcinoma including large cell carcinoma. In addition, the survival times of patients with pulmonary arterial perfusion-negative tumor were significantly shorter than those with positive tumors in this group (Tables 1, 2) (Figs. 4, 7). Pezzella et al (8) identified two vascular profiles associated with angiogenesis in lung cancer: either tumors destroy and replace normal tissue, producing their own associated stroma and vessels; or intratumor vessels are recognizable as normal lung vessels because they maintain alveolar features. They noted that patients with the first type of tumor have shorter survival times and disease-free intervals. Although this study was based on histopathologic descriptions, the first and second group may correspond to our pulmonary arterial perfusion-negative and positive tumors on PAG, respectively (Figs. 7, 8). Thus, our results would be compatible with those of Pezzella et al.

Only one report appears to describe the relationship between B-P shunt and prognosis. Namio et al ([[[23]]]) reported that the prognosis of patients who had a B-P shunt formed in the tumor was extremely poor irrespective of histologic type, and they noted the metastatic spread of tumor cells through the B-P shunt. The present study also confirmed that the clinical stage was significantly more advanced and prognosis was significantly worse among patients with B-P shunt-positive tumors compared to those with negative tumors (Fig. 3).

Yoshimura ([[[24]]]) reported that the prognosis of patients with adenocarcinoma and epidermoid carcinoma of the lung is the same. Nakanishi et al ([[[25]]]) reported that the prognosis of squamous cell carcinoma of the lung after surgical intervention was fairly good. The prognosis of patients with resectable early stage squamous cell carcinoma of the lung might be better than those with adenocarcinoma. Imoto et al (10) reported that the positive ratio of VEGF was significantly higher in patients with adenocarcinoma than in those with squamous cell carcinoma. Although we studied only a relatively small number of patients, the clinical stage of the patients with adenocarcinoma was significantly more advanced and the prognosis was significantly worsened compared to those with squamous cell carcinomas (Fig. 1). Taken together, these findings might indicate that adenocarcinoma has a higher angiogenic potential than squamous cell carcinoma.

The present study did not identify a significant association between large cell carcinomas and adenocarcinomas and between large cell carcinomas and squamous cell carcinomas with respect to the clinical stage, frequency of distant metastasis and survival times. This result may be due to insufficient numbers of patients with large cell carcinomas.

A limitation of our study is that the patient series we reviewed was relatively old. Pulmonary angiography has not been routinely employed as a diagnostic tool in recent years

and we have performed BAG or PAG as the preferred diagnostic procedure prior to interventional radiology for advanced cases in which surgery is contra-indicated since 1990. Consequently, to avoid selection bias towards any specific diagnostic procedure and to represent a general lung cancer population, we investigated these patients.

In conclusion, B-P shunt formation on BAG and pulmonary arterial perfusion in adenocarcinomas including large cell carcinomas on PAG were significantly correlated to the clinical stage, occurrence of distant metastases or disease-free periods of time, and survival times. Therefore, these signs may be prognostic factors for primary NSCLCs. Tumor vascularity on BAG was not related to the clinical stage or prognosis, and accordingly it does not directly indicate angiogenesis in primary NSCLCs.

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