cient and is associated with the rapid development of a severe metabolic acidosis. Maintenance of adequate tissue perfusion and oxygenation remains a key objective in the treatment of these patients.

In a provocative article in this issue of CHEST (see page 1301), Kellum and colleagues propose a very different scenario to explain the accumulation of lactic acid in patients who have acute lung injury associated with sepsis or pneumonia. The investigators found that lactate concentrations in the arterial blood slightly exceeded those in the mixed venous blood in each of nine patients with these abnormalities, but not in patients who had no evidence of lung injury. They cite literature that failed to show either tissue hypoxia or systemic lactate production in animal or clinical studies of sepsis, and suggest that lactate generation by the lungs is responsible for metabolic acidosis in these patients.

It has long been recognized that approximately 50% of the glucose consumed by the lungs is converted to lactate and appears in the pulmonary venous outflow. In contrast, less than 25% of glucose consumed in other tissues (e.g., the heart) is converted to lactate. This level of lactate production by the lungs is puzzling since they are exposed to the highest oxygen tensions of any internal organ. Tierney suggested that high pulmonary lactate production can be attributed to the absence of mitochondria in the attenuated portions of the type I pneumocytes and there is little room for mitochondria in the adjacent endothelium. Extrapolating from animal studies, one can estimate that normal human lungs, weighing a total of 1000 g, produce 11 mmol of lactate each hour. It is certainly conceivable that injured lungs containing large numbers of leukocytes, which also produce lactate, may release significantly more lactate into the circulation. Whether they can generate as much as 200 mmol/h remains to be confirmed.

Even if the lungs can produce this much lactate, it cannot be concluded that they are the principal culprits responsible for lactate accumulation, because other organs that metabolize lactate should be able to accommodate this additional metabolic load. It can be estimated that a normal liver can consume a maximum of 140 mmol of lactate each hour and even more can be metabolized by other tissues, particularly skeletal muscle. Liver abnormalities are common in septic patients, and decreased extrapulmonary lactate consumption may play a more important role in the development of lactic acidosis than abnormal pulmonary metabolism.

Detection of excessive pulmonary lactate production theoretically could help grade the severity of lung disease, but these measurements are fraught with technical difficulties. Because the entire cardiac output traverses the lungs, arteriovenous differences tend to be very small. Lactate derived from the heart and entering the left ventricular cavity through thebesian veins may increase arterial lactate levels. It would be difficult to attribute the differences in hemoglobin concentrations reported by Kellum and colleagues to shifts of fluid in the lungs. (An increase in hemoglobin from 14.9 to 15 g/dL at a cardiac output of 5 L/min would require the movement of 33 mL/min between the plasma and lung tissues and could not be sustained for very long.) The collected samples may contain some residual saline from the catheters, which could also dilute lactate. Unless lactate concentrations are measured in whole blood, the relationship between red cell and plasma lactate concentrations must be determined.

Much remains to be learned about both pulmonary and extrapulmonary lactate metabolism in patients with SIRS. Further research in this area should address the question of whether injury to the lungs can alter extrapulmonary lactate metabolism, or whether abnormalities in extrapulmonary lactate metabolism are due to the direct effects of hemodynamic or other disturbances associated with sepsis.

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REFERENCES

Strategies for Treatment of Occult Carcinomas of the Endobronchus

O ccult carcinomas of the lung are a subpopulation defined as carcinomas diagnosed by sputum cytology, and bronchoscopy using brushings, wash-
ings, and/or biopsy. Their defining concept is that they cannot be detected by conventional radiographic means before or immediately after the initial diagnosis.

In 1974, Sanderson et al. published “Bronchoscopic Localization of Radiographically Occult Lung Cancer.” In 1980, Cortese et al. published their study, “Roentgenographically Occult Lung Cancer.” In the same year, Martin and Melamed published “Occult Carcinoma of the Lung.” Initially, the treatment of choice was surgery, whether lobectomy or pneumonectomy. However, as work with photodynamic therapy (PDT) and then endobronchial brachytherapy (EBBT) increased, the “menu” of treatment modalities increased. This issue of CHEST introduces an article by Perot et al. (see page 1417).

This subpopulation of roentgenographically occult carcinomas of the lung is associated with interesting attributes. First, the time interval from the initial abnormal sputum cytology to bronchoscopic confirmation, as reported by the Mayo Lung Project, ranged from 1 to 1,014 days (median, 70 days; 75th percentile, 169 days). Second, the disease is most often T1S, T1 and N0.2 (Saito et al. found that of 94 patients, 17% were T1S and 77% were T1.) Third, most cases are squamous cell carcinomas; in a significant number dysplasia initially had been the only finding. Fourth, no findings are apparent on plain radiography or, when available, on computerized axial tomography. Fifth, no adverse prognostic factors (ie, weight loss) that predict lower cure or survival rates exist, and rarely are symptoms present.5-8 Finally, synchronicity and metachronicity are significant. In a surgical series, Nagamoto et al.9 reported a rate of 1.06 lesions per patient, Kato et al. found 1.21 lesions per patient, and Saito et al.10 found 1.2 lesions per patient. In the Mayo Lung Project Study, a metachronous rate of 5% per year was reported, and in a study by Saito et al.11 a rate of 0.022 lesions per patient-year. In the latter, the rate was 0.041 lesions per patient-year when synchronous and metachronous tumors were combined.

In this study of Saito et al.,12 if a patient had a second lesion, there was a 47% probability that within 5 years, a third lesion would be identified, at a rate of 0.11 lesions per patient-year. The 5-year survival rate for patients with a single lesion and no evidence of synchronous or metachronous lesions was 90%. If, however, there were more than one other metachronous or synchronous lesion, the 5-year survival rate was 59%.

Many studies have found that lesions ≤10 mm in size are associated with the most favorable outcomes. In a surgical study of 127 patients,5 55 patients had lesions of this size, and no metastatic lymph nodes could be identified. Of 46 patients with lesions >10 mm but ≤20 mm, there were 4 patients (9%) with nodal metastasis. Of 26 patients with lesions that were ≥20 mm but ≤55 mm, four patients (15%) had metastatic disease. In summary, there was no evidence of nodal metastasis with lesions ≤10 mm. For lesions >10 mm, however, the incidence was 11%. Thus, lesion size could be used to determine which patients had little probability of having metastasis to the lymphatic system.

In an earlier study by Saito,4 extrabronchial invasion was documented by pathological analysis in 16 (17%) of 94 patients. Five (31%) of these 16 patients had metastatic disease to nodes. Only 1 (1%) of 78 patients had nodal disease without evidence of extrabronchial invasion. No recurrences were identified in 75 patients who had intrabronchial disease, had no lymphatic spread, and who underwent a complete resection. Overall, the cause-specific 5-year survival rate was 93.5%, and 80.4% for all causes combined.

In 108 patients who underwent surgical resection for occult carcinoma, Nagamoto et al.10 identified 10 (9.2%) who had additional squamous cell carcinomas <1 mm in size. In turn, these lesions were associated with either dysplasia or marked atypia.

Kato et al. treated 45 lesions fulfilling the criteria for occult carcinomas in 40 patients (1.13 lesions per patient). PDT was the only treatment used for 30 lesions in 20 patients, and the complete response rate was 100%. Three patients (15%) had recurrences, one (5%) of whom later died of the disease. An additional nine patients (45%) died of unrelated causes.

Considerably fewer patients with occult carcinomas are treated with EBBT than with PDT or surgery. Sutedja et al.14 reported two patients with T1 squamous cell carcinoma who were treated with high-dose rate EBBT. Three fractions of 10 Gy were delivered at a 1-cm depth. Both patients were alive without disease at follow-up examinations, at 54 and 25 months, respectively.

Trédaus et al.15 treated 29 patients with a diversity of lesions, whose common denominator was that their carcinomas were limited to the bronchus, and were therefore radiographically occult. Consequently, the disease could be encompassed by intraluminal brachytherapy. In contrast to all other reported series, however, these patients had undergone prior treatment, which included surgery, external radiation, and/or chemotherapy. The patients were treated with high-dose rate EBBT using a dose of 7 Gy calculated at a 1-cm depth for 6 fractions (42 Gy). The median actual survival of these patients had not been reached after 23 months of follow-up.

Saito et al.14 treated 49 occult carcinomas in 41 patients (1.2 lesions per patient) with external beam
Ten patients had undergone surgical treatment for a previous lung carcinoma. Six patients had pneumonectomy, and five of these also had mediastinal irradiation. Another two were treated for previous carcinoma of the lung by radiation therapy alone. One patient was in cardiac failure at the time of treatment, and another patient had HIV infection with severe immunodepression. Of four patients without previous carcinoma of the lung, two were treated before the EBBT, one with cryotherapy and the other with chemotherapy, but without affecting the endobronchial lesion. Thus, this group of patients, with their adverse medical history of either prior lung carcinoma (treated by surgery and/or radiation) or severe medical problems, had respectable 1- and 2-year actuarial survival rates.

If we postulate that these patients had a “field defect,” that is, their entire bronchial mucosa was at risk and had a high probability of developing more than one lesion (ie, synchronous or metachronous lesions), then our strategy of treatment must include this as a basic assumption. (While a pneumonectomy will cure a certain percentage of patients, the remaining lung would continue to be at risk.) Therefore, properly selected lesions (ie, those <10 mm, no evidence of extrabronchial extension, and squamous cell histology) should be considered for therapies designed to preserve pulmonary function (PDT or EBBT). Lesions >10 mm or with evidence of occult extrabronchial extension or nonsquamous histologies should be considered for surgery, if patients are medically operable. If they

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**Occult Lung Carcinoma**

![Diagram](image)

- **Squamous Cell**
  - Size
  - ≤ 10 mm
  - Randomize
  - PDT
  - EBBT

- **Non Small, Non Squamous Cell**
  - Extrabronchial Extension
  - > 10 mm &/or
  - Operable
  - Inoperable
  - Operable

1) N0 Assumed
2) PDT - Photodynamic Therapy
3) EBBT - Endobronchial Brachytherapy
4) Ext. - External Radiation

**Figure 1.** Suggested strategy for occult lung carcinoma.
are inoperable, then prophylactic nodal external radiation plus EBRT should be used.

A suggested strategy is outlined in Figure 1. Although I have categorized it as a strategy, I have no doubt that it will be criticized as a stratagem. The caveat to this proposal is that it must be implemented in a multi-institutional fashion (no single institution will have sufficient patients to launch such a study) with a well-defined protocol. Finally, one arm of the study should be randomized. I have elected to randomize lesions \( \leq 10 \) mm with squamous cell histology to the two therapeutic modalities most conserving of pulmonary function.

Where do we go from here? We will need to organize a group, which may be as easily performed as getting eagles to fly in formation. Be that as it may, it will be necessary to form such a group, so that we will be able to proceed logically and systematically to determine answers to these questions.

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