Follow-up of Patients With Completely Resected Lung Cancer

This year, approximately 177,000 new primary lung cancers will be diagnosed in the United States; approximately 25% of these patients will undergo surgical resection with curative intent. Recurrences after an apparently complete resection may be locoregional, distant, or both, and will develop over the next 5 years in approximately 20 to 30% of patients with stage I disease, in 50% of those with stage II, and in 70 to 80% of those with stage III disease. Early detection of a recurrence may benefit a patient by affording an opportunity for curative re-resection of locoregional disease or instituting noncurative medical therapies as soon as possible to prolong life or to sustain a level of quality of life for as long as possible, or both. Other benefits from ongoing monitoring might include improved management of nononcologic medical problems, detection of new primary malignancies in a population at heightened risk, the opportunity to allay fears about symptoms or physical findings wrongly interpreted by the patient or family as suggesting recurrent disease, and provision to the surgeon with feedback on the effectiveness of surgical management.

It is surprising then that there is little published information, and no consensus opinion (to my knowledge), available to guide the clinician in setting up a schedule for monitoring the patient who has undergone complete resection. An optimal plan would provide for follow-up that is sensitive and specific in detecting recurrent disease, while cost-effective and not unduly onerous for either medical personnel or the patient. The practice that has evolved in the Division of Thoracic Surgery at Memorial Sloan-Kettering Cancer Center for following up patients after resection of a primary lung malignancy has done so without prospective or retrospective evaluation as to effectiveness, and is as follows. After the immediate postoperative period, an office visit is scheduled every 3 months for the first postoperative year, every 4 months for the second, every 6 months for the third and fourth, and yearly thereafter. At each office visit, a careful interval history is obtained. Symptoms that may be specifically sought include recurrent or new chest pain, new persistent cough (generally present for 4 weeks without signs or symptoms associated with infection), hemoptysis, new wheezing, new hoarseness, weight loss and/or anorexia (worrisome for liver metastases), new neurologic symptoms such as unsteadiness, speech disorders, or seizures, or unrelenting and progressive skeletal pain suggestive of osseous metastases. Physical examination is performed to assess probable sites of recurrence, specifically, palpation of the supraclavicular regions for adenopathy, auscultation of the lung for alterations in lung sounds, palpation of the upper abdomen primarily to assess the liver, and inspection of the wound. Further examination is guided by symptoms. Radiologic surveillance for the asymptomatic patient is limited to a posteroanterior and lateral chest radiograph at each office visit. The ordering of additional imaging studies, such as thoracic CT scans, bone scans, brain imaging, or positron emission tomography scans, is guided by changes in the chest radiograph, physical examination findings, or symptoms. We have not found helpful thoracic CT scans performed on the asymptomatic patient without significant changes on postoperative chest radiographs. The postthoracotomy chest always has abnormalities apparent on CT scan that could be interpreted as recurrence but that most often can only be definitively established as such by reoperative thoracotomy. Abnormalities that rise to the level of detection on chest radiographs are far more likely to merit further investigation (and often by less invasive measures than surgery such as a radiographically guided needle biopsy). Blood tests and sputum cytology test are not routinely used. Surveillance bronchoscopy is generally reserved for those patients with tumors resected close to a bronchial margin or having undergone sleeve resections, for patients known to have bronchial mucosa with either severe dysplasia or carcinoma in situ, and possibly, for patients with multiple prior aerodigestive malignancies. This pattern of follow-up is similar to those of other major programs but is considerably less intense than that practiced by others, particularly in Japan.
It should be noted that to the extent that physicians follow up patients after resection and without recurrence, it is done so less because of a belief in the possibility of potentially curative interventions such as reresection than for other reasons such as a desire to “please patients, avoid malpractice suits, and improve patient quality of life.” It is realistic to assume that potentially curative intervention, such as reresection, although being the most desired of all possible goals of follow-up care, is likely to be available to only a fraction of all patients with recurrent disease; a retrospective study of the M.D. Anderson experience suggested that potentially curative management was offered to only 3% of all patients having recurrent lung cancer diagnoses. However, the question of whether other noncurative benefits may accrue to the patient undergoing careful follow-up evaluations is largely unaddressed in the literature. I believe that they are likely to be present, because, for example, it is probable that initiating chemotherapy when a recurrence is asymptomatic is more likely to be beneficial than if given once a patient’s performance status has deteriorated.

In their article, “Follow-up in Lung Cancer,” published in this issue of CHEST (see page 1494), Younes and colleagues provide a retrospective analysis of 130 patients with apparently complete resection of non-small cell lung cancer nonrandomly followed by either a “strict” protocol (consisting of a schedule of office visits, imaging studies, and blood tests obtained even if the patient is asymptomatic) or by clinical visits and radiographic studies not formally scheduled but arranged only on the basis of the patient detecting either worrisome symptoms or new physical findings (“symptom” group). The regimen that the strict group was asked to follow consisted of clinical interviews and physical examinations with chest radiographs every 2 months for 6 months, then interviews and examinations every 3 months for the next 18 months, with chest radiographs and thoracic CT scans alternately being obtained. The authors found that the median survival after diagnosis of recurrent disease was 7.9 months in the strict group and 6.6 months in the symptom group, a difference that was not statistically significant.

This study can be criticized on several points, beginning with the shortcomings common to all retrospective studies, in this case, the lack of any explanation as to how patients were assigned to the strict and symptom groups. It appears that the surgeons assigned higher-risk patients to receive strict follow-up, and that this succeeded in raising their survival rate to the level of the lower-risk symptom group. It is possible that patients known to be less compliant were followed up on a symptom basis, and, being more likely to ignore symptoms once they became apparent, had treatment initiated at a point further along the course of their disease, suggesting that the treatment of recurrent disease is ineffective whenever begun, perhaps to even a greater degree than the authors suggest.

Second, the authors examined only follow-up performed within the first 2 years after resection, even though 50% of recurrences will occur after this period. The benefits of intervention may be more marked for patients with late recurrences, which presumably represent more indolent disease. Third, Younes et al do not provide information on the relative survival of patients with recurrences detected and treated while asymptomatic compared with patients in whom recurrences were detected by the onset of symptoms. A prior study by Walsh et al suggested that the median survival of patients with treated asymptomatic recurrences was 34 months, whereas the survival of patients treated when symptomatic was 19 months, a difference that could be attributed to improved effectiveness of treatment instituted while the patient was asymptomatic or, equally well, to differences in the biology of disease, or to other unknown factors.

Younes et al did find that the strict group appeared to have better general medical care with fewer emergency department visits and that fewer inpatient days were required for management of their nononcologic medical problems, although the documentation is scanty. Although I would be reluctant to use the data in this article to suggest a pattern of clinical follow-up after complete resection of a lung cancer, I believe that the authors should be credited for opening the line of questioning into whether benefits other than potentially curative management of recurrent disease may arise from close management of patients who often have comorbidities, such as COPD or atherosclerotic disease. I believe that the benefits of careful follow-up care are likely to be real and that future studies should look beyond the question of curative management of recurrence to consider other possible benefits as outlined above.

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Cytokines and Pleural Drainage Fluid
Do Local Levels Make a Difference?

There is a mounting body of evidence to support the role of leukocytes and their products, cytokines, in the development of postoperative complications, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome. On the superficial level, one can think of this inflammatory response as “bad.” From a teleologic viewpoint, however, there must be a beneficial function to any enzyme or biological system that is conserved throughout evolution. One of the primary roles of the inflammatory response, in this respect, is to promote healing, thus allowing the organism to return to normal after an injury or stress. This is often forgotten in our quest for the “magic anti-cytokine bullet.” Is it possible that we have gone to the other end of the spectrum and have overlooked the beneficial role of cytokines?

Another fact that is often forgotten when we talk about the role of cytokines in disease is that they are designed to function in cell-to-cell communication, not systemically. Specifically, they have a paracrine function, yet we continue to assess their levels systemically in the serum. Serum levels reflect the “overflow” of the locally produced cytokines into the systemic circulation. This, of course, can have important consequences to the patient. However, the systemic level could represent either an over- or underrepresentation of the actual interstitial levels. Perhaps the serum levels are not related to the interstitial levels, ie, where important cell-to-cell interaction occurs. Is it possible that we are measuring the wrong levels? In this issue of CHEST (see page 1604), Weissflog and colleagues set out to assess the postoperative course of pleural leukocytes and cytokine concentrations in patients with and without malignancy who had undergone thoracic surgery. However, in doing so, they have also addressed the outlined concerns.

Weissflog and colleagues assessed the levels of tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, and interleukin 10. They obtained samples of chest tube drainage five times in the first 24 h after surgery and then on postoperative days 1 through 3. Corresponding serum samples were obtained, as well as one preoperative serum sample. They separated the patients based on the presence or absence of malignancy and on whether the thoracotomy was video-assisted or open. They found that in the cancer patients, all of whom had open procedures, cytokine levels were decreased compared to those in patients operated upon for nonmalignant disease. This is especially significant in light of their data showing that patients with nonmalignant disease who had open thoracotomies had increased cytokine levels compared to those who received video-assisted thoracotomies. Thus, the presence of cancer depressed local cytokine production even with the stress of an open thoracotomy, which increased local cytokine production in nonmalignant disease.

More importantly, there were no differences in the serum concentrations of the three cytokines, when the two groups were compared. This lack of difference in the serum concentrations confirms previous work.1,2 The site of production of the cytokines measured in the chest tube drainage is not clear. However, they are locally produced, either by the cancer cells or by local inflammatory cells, and are not secreted or overflowing into the systemic circulation. Thus, by measuring cytokine levels in chest tube effluent, as a surrogate for local, interstitial cytokine levels, the authors have shown a difference between local and systemic levels. This is important information, because as stated, it is at the local level that the cytokines exert their positive and negative effects. Perhaps by knowing the local levels, we can more accurately study the cytokines as markers of disease, as prognostic indicators for morbidity and mortality, and as substances to be manipulated therapeutically to affect patient outcome.

Four patients developed complications: one cardiac arrest, one stroke, one bronchopleural fistula, and one purulent pleural space infection. *Staphylococcus aureus* and *Enterococcus* species were cultured in both of the patients with the latter two...
complications. All of those patients who developed complications had decreased levels of the measured cytokines in the chest tube effluent, but not systemically. Again, this supports the need to measure local, not systemic, levels. All four also had cancer. Cancer is known to be a cause of immunosuppression. The etiology of this immunosuppression is multifactorial. Perhaps one of the reasons is because of the decreased production of cytokines at the local level. Some baseline level of local cytokine production may be necessary or beneficial for healing. When the local level falls below this critical level, complications could be more likely to occur. Obviously, these numbers are too small to draw any definitive cause-and-effect conclusions, but the inference is important.

One caveat to these inferences and the authors’ conclusions: chest tubes can become colonized with bacteria, even if there is not a frank pleural space infection. Although colonization is uncommon in the first 3 postoperative days, it is not impossible. If present, colonization could activate the leukocytes and thus change cytokine levels in the drainage fluid. Obviously, this could affect the results. However, if activation did occur, it would tend to increase the cytokine levels, something that did not occur in these patients. Also, the authors did obtain cultures of the chest tube drainage and there was growth in only the two patients who developed complications.

In summary, Weissflog and colleagues have accomplished their goal of describing the differing cytokine levels in patients with malignant and nonmalignant conditions who undergo thoracic surgery. They have also shed light on the beneficial role of cytokines in wound healing, as well as showing us that future research may need to measure local cytokine levels instead of concentrating on systemic levels.

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Improving Outcomes in the ICU Setting
Are We Effectively Using all of the Information That Is Potentially Available to Us?

The complexity of patients cared for in modern ICUs, along with continuing advances in the technology of critical care and the escalating costs associated with providing that care, have been factors motivating critical care practitioners to identify and implement “best” medical practices. Individual best practices are often determined based on their association with improvements in patient outcomes, increased efficiency and cost-effectiveness of medical care, or both of these criteria. These practices should ideally be determined based on sound medical evidence obtained from rigorously performed clinical trials, the most rigorous being randomized controlled trials. However, such trials have often not been performed for many aspects of critical care medicine, including the optimal utilization of neuromuscular blocking agents in the ICU setting. Outcomes research is an emerging field that attempts, in part, to use variations in medical practices to identify important associations between such practices and clinical outcomes. As reported in this issue of CHEST (see page 1627), Behbehani and coworkers performed a retrospective cohort study to determine the incidence of acute myopathy in asthma patients requiring mechanical ventilation at two medical centers in Vancouver, Canada.

In the 86 patients who were evaluated, there were 94 episodes of near-fatal asthma requiring mechanical ventilation. Based on their study results, a total of nine patients (10.5%) developed myopathy. The incidence of myopathy was significantly greater in patients receiving neuromuscular blocking agents than in patients not receiving these agents: 30% vs 0%, respectively (p < 0.001). A multivariate analysis demonstrated that the duration of neuromuscular blocking agent administration was the only variable significantly associated with the development of myopathy. Although similar findings have been demonstrated previously by other investigators, Behbehani et al also showed that the occurrence of myopathy varied between the two hospitals examined. This discrepancy, to a large extent, appeared to be due to the different ways that the neuromuscular blocking agents were used at the two centers. One center had 8 of 20 patients (40%) develop myopathy after receiving neuromuscular blocking agents, while
the other center had only 1 of 10 patients (10%) develop this same complication after receiving these agents (p = 0.09).

The most obvious explanation for the difference in the occurrence of myopathy between these two institutions is provided by the discussion in the article. The hospital with the greater occurrence of myopathy primarily administered the neuromuscular blocking agents as continuous IV infusions, while the other hospital appeared to administer them as intermittent boluses. This resulted in a longer duration of administration at the center with the greater rate of myopathy: 3.8 ± 2.3 vs 2.0 ± 1.6 days (p = 0.04). The relatively small sample size of this investigation probably accounted for the authors’ inability to identify the treating center as a variable independently associated with the occurrence of myopathy in their multivariate analysis. Indeed, it appears that the main finding of this investigation is the identification of a variation in practice between the two study institutions, suggesting that continuous IV administration of neuromuscular blocking agents should be avoided. An important extension of these findings would be to show that the practices changed at the hospital with the greater incidence of myopathy (i.e., a decreased utilization of continuous IV administration of neuromuscular blocking agents), resulting in a lower incidence of this complication.

Other investigators have relied on similar types of comparative outcome studies to identify optimal medical practices at specific institutions. These studies have focused on outcomes such as hospital mortality, ICU resource utilization, and the occurrence of specific complications. Similarly, studies performed at single institutions using before-after study designs have attempted to identify the benefits or potential harms of practice changes between two different time periods. In general, these studies lack the rigor of randomized controlled trials because of the absence of randomly selected concurrent control groups exposed to the same study conditions; however, they do provide the local medical community with potentially important clinical data regarding their own unique environments. When compared to clinical studies performed at outside institutions, these locally performed studies may also assist hospitals in implementing practice changes, by more readily facilitating buy-in from practitioners.

The potential benefits of having similar types of data available for other institutions cannot be underestimated. Although report cards for hospitals are becoming increasingly popular, they do not necessarily convey useful information regarding the individual practices within those institutions. Moreover, such report cards usually do not provide appropriate data for carrying out improvements or for testing the impact of practice changes on clinical outcomes. Several attempts at implementing large-scale quality improvements or practice changes in the hospital setting recently have been made. The results of specific evaluations and comparisons of heart surgery in parts of New England and New York have led to changes in practices within individual hospitals that resulted in improved clinical outcomes. Similarly, private organizations such as the Institute for Healthcare Improvement have attempted to produce similar improvements in practices at the individual institutional level.

At the present time, there are no systematic approaches available for the comparison of practices and outcomes within ICUs across the United States. Project IMPACT, supported by the Society of Critical Care Medicine, has attempted to be a first step in providing such an approach to quality improvement. Future clinical investigation should reveal if such databases can help identify institutions with the best practices and outcomes and thereby stimulate change in institutions having inferior medical practices and outcomes. Until that time, local efforts should continue to be undertaken to improve the quality of medical care at the individual hospital level, using either historical controls (i.e., before-after study design) or other available databases for comparison. Only by carrying out such efforts can we hope to maintain the quality of medical care in our ICUs under current cost-cutting pressures.

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A Stuck Pig—Even on Warfarin—Doesn’t Always Bleed

As reported by Brickey and Lawlor in this issue of CHEST (see page 1667), a porcine experimental model was established to observe iatrogenic hemor-
rhage following transbronchial forceps biopsy (TBBx) in animals having a prolonged international normalized ratio (INR) as a result of receiving warfarin. Their porcine model has proved to be physiologically similar to the human cardiopulmo-
nary vascular anatomy and physiology, as well as to the hemostatic system. In their first phase, these Air Force intensivists set out to determine at which INR level the animals bled following TBBx. In the second phase, they planned to determine what therapeutic maneuvers would be efficacious in the treatment and/or reversal of hemorrhage when that threshold INR level was reached and TBBx carried out. This was done in a manner in which the bronchoscopist was blinded to all therapeutic and laboratory data. Of interest to this hematologist, a preconceived notion had infiltrated its way into the design: Brickey and Lawlor were intuitively sure that there would be an answer to phase 1 which would permit them to move on soon to the more important phase 2.

Most hematologists have wrestled with the problem of patients with extraordinarily strong indications for warfarin (eg, patients with prosthetic heart valves, those with extreme hypercoagulability, or those with ongoing thrombotic episodes1 who have their anticoagulation stopped by some practitioner before an invasive procedure, whether it is cardiac catheterization, esophagogastroduodenoscopy, colonoscopy, liver biopsy, bronchoscopy, or dental extraction.2) Such practitioners are absolutely convinced that patients who are on modern therapeutic anticoagulation will experience massive uncontrolled hem-
orhage following an invasive procedure, even though there are no reports to substantiate that prejudice. While it is true that there is a baseline underlying hemorrhage rate with any of these procedures, there are no data to attribute that rate to therapeutic anticoagulation. Most bleeding that occurs is either technical or, especially, related to biopsy of a tumor, which is known to be the primary culprit when one analyzes patients who hemorrhage following biopsy.3 On the other hand, there are several reports of serious thrombosis following cessation of anticoagulant therapy in patients who are anticoagulated for good reason.1,4 When interventionists are asked for justification to either attenuate or stop anticoagulation, the only argument given is, “this is the way we have always done it.” This approach is no longer tolerable in the era of evidence-based medicine.

The report by Brickey and Lawlor involves experimental animals, yet it complements an earlier article in CHEST5 in which humans undergoing TBBx did not experience hemorrhage, despite their abnormal prothrombin and partial thromboplastin times. In the Brickey and Lawlor study, the animals did not experience bleeding from the biopsies despite the supratherapeutic INRs. Two animals did exsanguinate (one with an INR of 11.2, the other with an INR of 13.6) but spontaneously from bleeding ovarian cysts. Therefore, these INRs were of hemorrhagic concern but not because of the TBBx. This is most likely due to an intense amount of local tissue factor that is generated from traumatized tissue near the biopsy, which results in generation of thrombin sufficient to cause effective hemostasis despite decreased levels of vitamin K-dependent factors.

It is a leap to go from studies using animals that are otherwise well—and are not aged, atheroscle-
rotic, or riddled with metastases—to the clinical bedside, yet articles such as this by Brickey and

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8 Giraud T, Dhainaut JF, Vaxelaire JF, et al. Iatrogenic complications in adult intensive care units: a prospective two-
9 Joiner GA, Salisbury D, Bollin GE. Utilizing quality assurance as a tool for reducing the risk of nosocomial ventilator-

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10 Kelleghan SI, Salemi C, Padilla S, et al. An effective contin-
uasive quality improvement approach to the prevention of ven-
Lawlor and the one by Kozak and Brath\textsuperscript{5} certainly go a long way towards denting the heretofore immutable stance of most bronchoscopists that the INR must be normal. This hematologist is certain that far more morbidity and mortality have occurred by stopping anticoagulant therapy than by the biopsy of patients who are using anticoagulants and have INRs within the therapeutic range or particularly the lower end of the therapeutic range. It is already clear that major orthopaedic surgery\textsuperscript{6} can be done when the patient has an INR of 1.5 to 2.0. Therefore, it is appropriate not to cancel TBBx simply because the patient is receiving therapeutic anticoagulants. Indeed, as stated by Brickey and Lawlor, patients will continue to bleed with TBBx at a rate somewhere between 1 and 10\%, but that baseline hemorrhagic rate is a technical, not hemostatic, fact.

The final point is that Brickey and Lawlor were unable to go to phase 2 of their experiment because they were unable to find any INR within a reasonable range that correlated with enough hemorrhage to determine what therapeutic maneuvers would decrease bleeding if it occurred.

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