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American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: A randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non–small cell lung cancer

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Abstract

During the past decade, tremendous interest has arisen in the use of nonoperative therapies for patients with non–small cell lung cancer. Of these therapies, stereotactic body radiotherapy has become established as an effective modality for treating peripheral cancer in medically inoperable patients. Toxicity is low, and the treatment is effective, with excellent local control rates. Several investigators have suggested that stereotactic body radiotherapy could be effective for high-risk operable patients (usually treated with sublobar resection) and even perhaps for standard-risk operable patients (usually treated with lobectomy); however, this is less accepted. A direct comparison of stereotactic body radiotherapy and sublobar resection is difficult for a number of reasons. These include different definitions of recurrence, different populations of patients in these studies (with those undergoing stereotactic body radiotherapy tending to be the medically inoperable group), and different methods of classifying morbidity in the surgical and radiation oncology studies. Imaging follow-up has also not been standardized among the studies. Thus, a randomized study is necessary and timely. Investigators from the American College of Surgeons Oncology Group and the Radiation Therapy and Oncology Group have collaborated to develop a phase III randomized study comparing stereotactic body radiotherapy and sub-lobar resection (with or without brachytherapy) for high-risk operable patients with non–small cell lung cancer. This study (American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021) has recently opened for accrual. It is hoped that this will help to better define the role of these therapies for patients with non–small cell lung cancer.

In general, patients with stage I non–small cell lung cancer (NSCLC) can be classified into 3 groups: standard-risk patients who are usually treated with lobectomy, high-risk operable patients who are usually treated with sublobar resection (SR), and medically inoperable patients who are considered too high risk for surgery and are usually treated with external beam radiotherapy or 1 of the newer approaches for lung cancer such as stereotactic body

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radiotherapy (SBRT) or radio-frequency ablation.[1–4] During the past decade, there has been significant interest in these alternative approaches to surgery, in particular with the use of SBRT.

There has been tremendous success in the development of SBRT. The initial studies focused on the safety and feasibility of SBRT for patients with lung cancer.[5,6]

One problem when interpreting these studies has been the existence of several different types of SBRT systems and the different protocols used to treat NSCLC at different centers. Currently, from the work from the Indiana University and the Radiation Therapy and Oncology Group, a dose of 54 Gy in 3 fractions has been established as optimal for the treatment of peripheral NSCLC using SBRT.[3,7]

A common theme in the reports of SBRT has been that of excellent primary tumor control, even approaching that of lobectomy.[8–10] This has led some investigators to suggest that SBRT might be preferable to surgical resection, in particular, to SR, because of the increased incidence of local recurrence reported with resections less than lobectomy.[1]

This has led to the development of a randomized study that recently opened for accrual. The study is being undertaken by investigators from both the American College of Surgeons Oncology Group (ACOSOG) and the Radiation Therapy Oncology Group. We provide a brief overview of the ACOSOG Z4099/Radiation Therapy Oncology Group 1021 study and its importance to physicians treating patients with NSCLC.

BACKGROUND

There are a number of considerations when comparing 2 very different approaches such as SR and SBRT for treating localized NSCLC, particularly when applied to patients who are at greater than average risk of undergoing surgery. These include oncologic concerns such as recurrence and survival, differences in morbidity between these therapies, the ability to deliver the therapy uniformly (which is of particular significance for SBRT), and the effect of these therapies on a patient’s quality of life.

Although SBRT has been reported to have excellent local control rates, it must be remembered that the definitions of recurrence have been dissimilar between the surgical and SBRT series. In the surgical data, local recurrence usually includes recurrence occurring within the same lobe as the SR and, sometimes, another lobe within the ipsilateral lung, as well as recurrence within the hilar and, sometimes, ipsilateral mediastinal lymph nodes.[2,11,12] In the SBRT data, local recurrence is usually synonymous with primary tumor control only.[13–15] From a surgical standpoint, if a complete resection has been achieved, the only form of recurrence that would be equivalent to failed primary tumor control would be staple line recurrence. For the ACOSOG Z4099 study, a uniform classification for local recurrence will be used, defining local recurrence as a confirmed post-treatment tumor appearing at the primary site, the staple line or chest wall, or within the involved lobe. In addition, specified realms of regional recurrence and distant progression will be collected. This will help us to better understand the differences and similarities between SR and SBRT

with respect to the recurrence patterns and to identify the general strengths and weaknesses of each therapy.

It is often difficult to definitively diagnose local recurrence when it is suspected. Technical and patient challenges exist to obtaining a tissue diagnosis. Additionally, it could be that the presence of recurrence could be of less significance in a higher risk patient with medical comorbidities. Thus, the primary endpoint of the study is the 3-year overall survival. Previous studies of SR have involved both standard-risk and high-risk operable patients, with survival for stage I patients appearing to be 60% to 90% after SR. SBRT studies have generally involved medically inoperable patients but have also included high-risk operable patients.[10,16] Overall survival appears to be about 55% at 3 years.

Another factor to consider is that the patient populations in SBRT and SR studies that have previously been reported are clearly dissimilar. The advantage of a randomized study such as the ACOSOG Z4099 is that the patients will be similar in terms of their comorbid disease and surgical risk.

Intuitively, patients undergoing SBRT should have lower morbidity than patients undergoing SR, and, certainly, a review of previous studies would suggest that this is the case. However, a few caveats should be considered. With SR, the complications will typically occur early. With SBRT, the complications will usually occur later, even months and years after therapy. Many surgical series did not use the Common Terminology Criteria for Adverse Events version when reporting morbidity.[17] The Common Terminology Criteria is a broad classification of adverse events (AEs) with several defined categories. Within each category, the AEs are listed and accompanied by a description of severity (or grade). Grade 1 is mild, grade 2 moderate, grade 3 severe, grade 4 life-threatening or disabling, and grade 5, death related to the AE. Typically, grade 3 and greater complications are reported in oncologic studies. The ACOSOG recently reported the incidence of grade 3 and greater AEs from another study of 224 patients with high-risk lung cancer undergoing SR.[18] Grade 3 or greater AEs occurred in 62 (29.7%) of 222 patients eligible for analysis at 30 days. Perioperative mortality occurred in 3 (1.4%) of 222 patients. In comparison, in a phase II study of 55 patients treated with SBRT, grade 3 and 4 AEs occurred in 16% of the patients. No grade 5 toxicities occurred in that study. In the ACOSOG Z4099 study, AEs will be recorded using the Common Toxicity Criteria classification and will be monitored throughout the follow-up period. It might be possible when ACOSOG Z4099 is eventually completed to identify groups of patients who might be more appropriately treated with 1 approach or another because of their risk profile. For instance, in the recently completed ACO-SOG study of SR, grade 3 AEs were more likely to occur in patients with a diffusing capacity of carbon dioxide of 46% or less.[18]

STUDY OVERVIEW

The ACOSOG Z4099 is a randomized phase III study that will compare SR and SBRT for high-risk operable patients with NSCLC. Eligible patients will have clinical stage I disease with tumors 3 cm or less in the maximum diameter. Invasive lymph node staging will not be mandatory for all patients. Only those patients with clinically suspicious lymph nodes

(defined as>1 cm on short axis by computed tomography and/or positive by positron emission tomography) will require biopsy before registration to confirm N0 status. Biopsy methods can include mediastinoscopy, anterior mediastinotomy, endoscopic ultrasonography, endobronchial ultrasonography, computed tomography-guided techniques, and video-assisted thoracic surgical biopsy. It is possible that in the surgical arm of the study the disease of some patients will be upstaged. However, the primary analysis will be an "intent-to-treat" analysis, and all patients registered and randomized will be included in that analysis.

The tumor will need to be in a location that will permit sublobar resection and also not be within 2 cm of the proximal bronchial tree in all directions. Tumors in close proximity to the bronchial tree have previously been demonstrated to have a high incidence of grade 4 and 5 toxicity with standard-dose SBRT.[7] Additionally, tissue diagnosis confirming NSCLC will be required for all patients before registration.

Eligible patients will be defined as high risk using the same criteria used for ACOSOG Z4032.[18,19] ACOSOG Z4032 was a randomized study undertaken to compare SR alone with SR plus brachytherapy for stage I lung cancer. Although closed to accrual, the primary endpoint data for ACOSOG Z4032 is not yet available; thus, it is unclear whether the use of brachytherapy should be routinely recommended. For this reason, brachytherapy is not a requirement in the surgical arm of ACOSOG Z4099, and the decision to use brachytherapy will be determined by institutional preference.

The primary endpoint for the study will be the 3-year overall survival. The secondary endpoints will include comparisons of locoregional recurrence (using a uniform definition), disease-free survival, grade 3 or greater AEs during a 1-year period, the effect of therapy on pulmonary function, and a comparison of AEs and pulmonary function test results in patients with a high or low Charlson comorbidity index.

In addition, some correlative studies will be undertaken to consider patients' quality of life, and molecular studies using tissue obtained at resection and blood. The target accrual for ACOSOG Z4099 is 420 patients.

CONCLUSIONS AND CHALLENGES

A major challenge when undertaking a study using 2 therapies with very different toxicity profiles is to ask a patient to consider randomization to 1 of these approaches. Additionally, physicians could have their own biases regarding what they believe is the optimal therapy. The study will require commitment by investigators as they meet and council their patients and close collaboration between surgeons and radiation oncologists. It is likely that longer and more detailed consultations will be required compared with simply presenting a plan for therapy.

Surgeons understand that the extent of resection can affect ultimate control. As such, not all SRs are the same. Segmentectomy or wide wedge resection is probably superior to close wedge resection. If no lymph nodes are removed, it might be that a close wedge would not be that different from SBRT. In contrast, the results of SBRT have continued to be

encouraging. Local control (using nonsurgical definitions) has been excellent and the morbidity almost certainly lower. Because the cancer is not removed with SBRT, serial imaging will be needed to search for areas of new growth or persistent disease within the scar left after SBRT. An issue when interpreting the results of earlier studies of SBRT is that these were often undertaken in medically inoperable patients with significant comorbid disease. Such patients can die from noncancer-related causes before any coexisting locally recurrent cancer is identified. Thus, in the absence of a randomized study, it would not be appropriate to apply SBRT to patients with better risk.

The time for the ACOSOG Z4099 study is now. If a randomized study is not undertaken, it is possible that very effective surgery will be relegated to a salvage option for patients in whom SBRT fails, which would likely be a disservice to our patients. We believe that the optimal patients to undertake the ACOSOG Z4099 study would be those believed to be in the high-risk surgical category, for which physicians are more likely to have equipoise and be willing to randomize their patients. A less-invasive approach can be justified for these patients, because this should allow for better quality of life and lower morbidity but, perhaps, at a cost of poorer cancer control. Careful documentation of the risk factors such as the Charlson comorbidity index, pulmonary function, and tumor size, could also help us to define the subgroups that would benefit from 1 approach or another.

Abbreviations and Acronyms

ACOSOG	American College of Surgeons Oncology Group
AE	adverse event
NSCLC	non–small cell lung cancer
SBRT	stereotactic body radiotherapy
SR	sublobar resection

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