Sublobar Resection with Brachytherapy Mesh for Stage I Non-Small Cell Lung Cancer

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Lobar resection is currently the standard approach for the treatment of stage I non-small cell lung cancer. Sublobar resection is generally considered a compromise, reserved for high-risk patients because of greater rates of local recurrence compared with lobar resection. Adjuvant radiation therapy may decrease these increased local recurrence rates, but because of respiratory motion and difficulties in identifying the staple line, radiation delivery can be challenging with an external beam approach. Adjuvant intraoperative brachytherapy with the use of low-dose rate iodine-125 seeds placed alongside the surgical staple has been used with success in several centers. A randomized multicenter North American study has also recently completed accrual, but the results of this are not yet available. In the following review, we outline the techniques used, safety considerations, and currently available outcomes of sublobar resection with adjuvant brachytherapy for non-small cell lung cancer.

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The ability to achieve durable local control has traditionally been considered the major shortcoming of sublobar resection (SR) in the treatment of non-small cell lung cancer (NSCLC). The Lung Cancer study Group reported the only randomized study comparing SR with lobar resection in 1995,[1] and the principal finding was a 3-fold increase in local recurrence, from 6.4% to 17.2%, in patients in the SR arm. One potential explanation for the increased observed locoregional recurrence is the presence of residual tumor cells at or close to the resection margin. Other factors include the presence of occult nodal disease and satellite tumors within the same lobe that are not seen on preoperative imaging.

Although the incidence of occult lymph node disease is less with smaller peripheral tumors, it is not zero. This finding was emphasized in a study involving 100 patients with solitary NSCLC tumors measuring 1 cm or less.[2] Ninety-four of the patients had complete mediastinal lymph node dissection performed, with 7 patients found to have lymph node metastases. Therefore, surgeons should strive to perform lymph node sampling or dissection whenever resection is performed. Additionally, anatomical segmentectomy should be undertaken when feasible because this will allow better resection of parenchymal nodes, perhaps allow superior margin, and certainly has been associated with better local control than wedge resection.[3-5] With respect to the issue of adequate treatment margin, Goldstein et al[6] reported a pathologic study of 31 patients who underwent wedge resection followed by subsequent lobectomy for peripheral T1N0 NSCLC. Microscopic growth beyond the visible gross perimeter of the tumor occurred at a mean distance of 7.4 mm. Residual malignancy in the lobectomy specimen was observed in 45% of patients. A significant difference ($P < 0.001$) in the microscopic margin was seen in patients with residual disease in the lobectomy specimens at 0.7 mm compared with those without disease at 2.4 mm.

The effect of margin distance on local recurrence after SR was reported in another study of 81 patients with pulmonary compromise.[7] In this series, rates of local recurrence were significantly increased when a margin of less than 1 cm was obtained (14.6% vs 7.5%; $P = 0.04$). A subsequent study of 49 patients undergoing segmentectomy for T1NO NSCLC showed a similar impact of margin distance, with no local recurrence in patients with a 1 cm or greater margin compared with a 23% relapse rate when mar-

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gin was less than 1 cm.[8] In another study involving 182 anatomical segmentectomies, the investigators demonstrated that if the margin/tumor ratio was less than 1, there was a significantly ($P = 0.0014$) greater recurrence rate of 25% versus 6.2%.[9]

Sawabata et al[10] used a slide brushed along the staple line to examine resection margins, finding malignant cells in 47% of patients undergoing sublobar resection, including some with histologically negative margins. There was a 57% rate of margin recurrence in patients with cytologically positive tumors compared with 0% in patients who had negative margins by staple line cytology. Clearly the issue of adequate margin is an important factor in the greater local recurrence rates reported after SR. It may not always be feasible to obtain an adequate margin for either anatomical reasons or patient-related reasons during surgery. One option that has been reported previously is the use of adjuvant brachytherapy in conjunction with SR.[11] In the following discussion we review the techniques, safety information, and currently available outcomes of SR with brachytherapy.

ADJUVANT EXTERNAL BEAM RADIATION

The addition of adjuvant radiation is by no means a new concept in cancer treatment. Adjuvant external beam radiation therapy has long been used to limit loco-regional spread after resection in solid organ malignancy. The most widely practiced example is the use radiation in protocols for breast conserving therapy in early stage breast cancer. However, application of this principle in the treatment of NSCLC has proven more difficult. Respiratory variation and the subsequent motion of the resection margin make the specific targeting of focused radiation difficult. Radiation damage to surrounding lung parenchyma also poses a potentially significant problem particularly because the patients in whom SR will be used will likely have impaired pulmonary function.

Miller and Hatcher[12] published the first modern series detailing the use of adjuvant radiotherapy after sublobar resection. They described results from 32 patients with stage I and stage II NSCLC treated by wedge resection or segmentectomy caused by pulmonary compromise. Of this group, 18 patients had postoperative radiotherapy delivered to the resection margin and the pulmonary hilum in a cone-down fashion. Lower relapse rates (6.25% vs 35%) were seen in patients treated with adjuvant radiation at 2-year follow-up.

The Cancer and Leukemia Group B (CALGB) conducted a prospective multicenter phase 2 trial in which they examined the use of thoracoscopic wedge resection and local radiotherapy in high-risk patients with clinical T1 lesions.[13] Patients were stratified to a high-risk group on the basis of preoperative pulmonary function testing and underwent thoracoscopic wedge resection followed by 56 Gy of local radiation delivered to the staple line with a 2-cm margin. A total of 65 patients accrued to the study, and thoracoscopic resection was successfully performed in 78% of patients with pathologic T1 lesions and 50% of those with T2 lesions. Overall, only 32 of the 65 patients had pathologically verified T1 NSCLC and had a thoracoscopic resection performed. Of these 32 patients eligible for study completion, 28 went on to receive the fully planned course of radiation, with 3 patients refusing radiotherapy and 1 patient death before planned radiation. Complication rates with adjuvant radiation treatment were relatively low; pneumonitis in 4% and dyspnea in 11%. The experience of this CALGB study underscores the difficulty encountered in the delivery of adjuvant external beam radiation to a compromised patient population.

BRACHYTHERAPY

Brachytherapy, the use of radiation delivery systems placed directly on the desired target tissue during surgery, is being used in some centers to overcome some of the problems encountered using external beam radiation. Brachytherapy offers several theoretic advantages when compared with traditional radiotherapy. Direct surgical placement of the radiation source allows for specific targeting and uniform delivery of radiation to the resection margin, minimizing the amount of normal lung included in the treatment field. This limits the potential for radiation-induced injury to adjacent healthy lung. Preservation of surrounding parenchyma may be especially important in patients with compromised pulmonary function. Internal placement of the radiation source also greatly reduces the treatment distance and the total radiation dose required to achieve adequate treatment of the target area. Brachytherapy also offers an advantage in patient compliance. Ensuring delivery of adjuvant treatment can be difficult when multiple treatments are required following resection. Patients who are limited because of severe emphysema may be reluctant to make several visits to their radiation center for treatment. Poor compliance was an issue in the CALGB study, where 9.4% of patients failed to complete protocol radiation treatment.[13] By contrast, most brachytherapy modalities involve intracorporeal placement of the radiation source at the time of definitive resection, resulting in universal compliance.