



## **Options for Stage IIIA NSCLC: The Outer Limits of Resectability**

**Howard (Jack) West, MD**  
**July, 2009**

Hello and welcome to the GRACE video presentation on Options for Stage IIIA Non-Small Cell Lung Cancer: The Outer Limits of Resectability. My name is Dr. Jack West and I'm a medical oncologist and the Medical Director of the Thoracic Oncology Program at Swedish Cancer Institute in Seattle, Washington. I also serve as the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

This video presentation is sponsored by the Lung Cancer Connection: providing support, education, information and hope to the newly diagnosed and their families.

The information provided here includes my own views and they are not necessarily those of the Global Resource for Advancing Cancer Education, nor those of Swedish Cancer Institute. The contents of this program do not constitute medical advice and they are intended to supplement, but not replace input from an individual patient's medical team.

A transcript as well as a PDF file with copies of figures associated with the program are available at [www.cancergrace.org/GRACEcasts](http://www.cancergrace.org/GRACEcasts).

Among the patients with outward advanced disease and distant spread, those with locally advanced non-small cell lung cancer within the chest are generally treated with curative intent. But our best chance for cure combines at least two of the three main treatments for cancers: surgery, radiation and chemotherapy.

Stage IIIA non-small cell lung cancer generally includes mediastinal lymph nodes, those in the middle of chest and on the same side as the tumor designated as N2 nodes. If lymph nodes are on the side of the mediastinum opposite of the tumor or above the clavicles, they are called N3 nodes and a patient is considered to have Stage IIIB non-small cell lung cancer which is typically not considered a surgically managed disease.

However, one of the more controversial questions in lung cancer management is whether patients with Stage IIIA disease and N2 nodes should routinely undergo surgery after induction therapy of chemo, or chemo with radiation, or alternatively should undergo chemo and radiation without surgery.

One of the reasons this area is so controversial is that there is such a range of patients who fall into this category with different prognoses. This study reviewing outcomes of over 700 patients with Stage IIIA N2 non-small cell lung cancer who

underwent surgery at one of six centers in France shows the differences in outcomes depending on whether patients had lymph nodes in multiple areas of the mid-chest involved, or just a single area; and whether patients had large nodes on CT scans or normal sized nodes, one centimeter or less, but with microscopic involvement of cancer.

Those with non-enlarged nodes and a single area involved had a better prognosis than those with multiple areas and/or with enlarged nodes on CT scans. So part of the problem is that we're pooling results from patients with different prognoses.

Over the past 15 years, we've favored adding at least preoperative chemotherapy rather than just pursuing surgery alone. This has been based largely on a pair of small but impressive studies, one from Spain and the other from M.D. Anderson Cancer Center in Houston. Both of these randomized patients with Stage IIIA N2 non-small cell lung cancer to surgery alone or preoperative chemotherapy followed surgery. Each actually closed early after just 60 patients were enrolled because interim results so strongly favored those who received chemotherapy before surgery.

Though there were major flaws with these trials, and even combined they include only 120 patients, the results were widely considered so convincing that it became standard to add chemotherapy, most commonly before surgery, for patients with Stage IIIA disease.

An alternative approach was used by the Southwest Oncology Group which gave preoperative chemotherapy with cisplatin and etoposide along with concurrent chest radiation to patients with locally advanced non-small cell lung cancer then repeated a CT scan. If patients showed stable disease or tumor shrinkage, which the majority did, then they proceeded to surgery.

As shown in the table on the right, there were long-term survivors consistent with true cures. But the patients who had no viable cancer in their mediastinal lymph nodes after preoperative chemo and radiation had a far superior survival compared with the patients who had residual viable tumor after induction therapy.

This finding of a very significant prognostic effect for so-called mediastinal sterilization has also been found in several other trials and it raises the question that if a patient's outcome is largely predicted by their response before they head to the operating room, perhaps the surgery isn't the critical factor. Perhaps patients would do just as well without surgery if they underwent chemo with radiation delivered at a higher dose more likely to be curative without surgery.

In the mid 1990s, multiple cancer research groups in North America conducted a trial together that directly compared a surgical to a non-surgical approach. Known as intergroup trials 0139, it enrolled 439 patients with Stage IIIA N2 non-small cell lung cancer many with fairly bulky nodal disease. Everyone received initial chemo with cisplatin and etoposide and chest radiation to an induction dose, then a repeat CT scan. Those who didn't progress received either surgery after that or continued without a break

to a higher more likely curative radiation dose. Both groups were intended to receive a total 4 cycles of cisplatin and etoposide, although many patients especially on the surgical arm did not actually receive all of their intended chemotherapy.

The results were presented several years ago at national oncology meetings but still haven't been published. As shown on the left, the progression-free survival was superior for patients who underwent surgery. On the other hand, the overall survival, as shown on the right, was not significantly better with surgery. Instead the pattern was that the patients assigned to surgery had an earlier detriment and then over time have a trend toward better survival after several years.

Here the results are in numeric form. Again, the progression-free survival is convincingly better with surgery though there was a non-significant 7% higher survival at five years with surgery. Overall, the results suggest that there is an initial higher risk from the trimodality approach with chemo and radiation followed by surgery; but survivors beyond the initial high risk period may do better long term.

The investigators actually noted that the majority of surgical risk was in patients who underwent a pneumonectomy -- surgical removal of an entire lung -- as opposed to lobectomy -- removal of just one major section of lung. They then did an analysis in which they matched patients who had surgery versus chemo and radiation alone by pairing them by performance status, age, sex, and tumor stage, but they did not include nodal stage in this matching.

In patients who underwent a pneumonectomy, those who underwent chemo and radiation without surgery did convincingly better than those who underwent surgery.

In contrast, those who had an extensive disease that allowed a lobectomy did better with trimodality therapy that included surgery compared with chemo and radiation alone.

Though these results as broken down by the type of surgery received have been widely discussed and suggest a clear difference, in fact this was an unplanned and somewhat controversial analysis.

Some believe that the overall results still essentially say that there is no significant difference in outcomes for Stage IIIA patients between trimodality therapy with surgery, or chemo and definitive radiation.

Putting this altogether, it's worth emphasizing how heterogeneous Stage IIIA non-small cell lung cancer really is. Most experts favor individualizing recommendations based on the extent of mediastinal involvement, the bulk of disease, the health of the patient, and the anticipated need for a pneumonectomy or lobectomy.

Nevertheless, the limited available evidence suggests overall comparable survival for induction chemo and radiation followed by surgery versus chemo with definitive

higher dose radiation and no surgery. However, progression-free survival is better in patients undergoing surgery and with longer follow-up, there is a trend toward overall survival being modestly but not statistically superior in the surgically arm. Risk of death is higher early on with surgery and this was particularly true for patients who underwent a pneumonectomy.

An unplanned retrospective analysis that matched patients for multiple characteristics supports the conclusion that those patients needing a pneumonectomy did better with the non-surgical approach; while those with disease that could be resected with a lobectomy had a better survival with the surgical strategy.

It is important to note, however, that we cannot always predict the type of surgery a patient will need prior to them getting to the OR. My own perspective is that fit patients with a single nodal area of non-bulky mediastinal node involvement are strong candidates for surgery as long as that surgery wouldn't be expected to require a pneumonectomy.

On the other hand, patients who have multiple lymph node areas involved, have bulky disease, are not particularly fit, and/or would need a pneumonectomy are not likely well served by an aggressive trimodality approach with surgery because the aggressiveness of this strategy may add more risk than benefit.

Chemo and radiation without surgery is still a very appropriate and potentially curative approach.

You can find additional details on several of these topics within the Subject Archives at the web address [www.cancerGRACE.org/lung](http://www.cancerGRACE.org/lung). Members of GRACE can also leave comments and questions about this presentation at the web address in the middle of the slide.

Thank you for your interest.