



**Optimal Treatment for Locally Advanced NSCLC
Video Podcast Presentation
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Hello and welcome to the GRACE video presentation of Optimal Treatment of Unresectable Locally Advanced Non-Small Cell Lung Cancer. My name is Dr. Jack West and I'm a medical oncologist and 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.

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When we talk about unresectable stage III, also termed locally advanced non-small cell lung cancer, we are referring to patients with multiple or bulky lymph nodes in the mid-chest, or mediastinum, or else patients with nodes on both sides of the mediastinum involved. These patients are most typically treated with a combination of chemo and radiation. Mediastinal lymph nodes on the same side of the chest as the main tumor are called N2 nodes, and those on the opposite side of the chest or are above the clavicle are known as N3 lymph nodes. A cancer is also considered locally advanced and unresectable if the main tumor involves structures that cannot be surgically removed, such as the critical blood vessels or heart, spine, or sometimes trachea. Somewhere in the range of 40% of patients with non-small cell lung cancer have stage III disease, so this is a very common clinical setting.

One of the central questions over the last decade was whether the combination of chemo and chest radiation should be given sequentially or concurrently. This issue has largely been answered, initially by a Japanese study, shown on the left, that gave an older combination chemotherapy regimen before radiation, or together with that radiation. As shown in the bottom left, the patients receiving concurrent chemo and radiation had a long-term survival rate that was twice as high as that seen in patients receiving chemo followed by chest radiation. This was despite the concurrent chemo and radiation giving a break in the radiation course, which is a clearly inferior way to deliver radiation. The right side of the slide shows that a large North American trial with nearly 600 patients with stage III, unresectable non-small cell lung cancer also showed the same findings, though with a different cisplatin-based chemotherapy combination,

and with radiation given without a treatment break. As shown in the bottom right of the slide, there was again a significantly superior survival in the patients receiving concurrent chemo and radiation. The third arm, with results shown with a purple vertical bar, represent results with twice daily radiation, known as hyperfractionation, which was not associated with better results and was associated with severe esophagitis, or inflammation of the esophagus.

In fact, over the last several years many trials from around the world and using many different chemotherapy regimens have consistently shown an approximately three month higher median survival.

While this hasn't been associated with a significantly higher risk of long-term side effects, concurrent chemo and radiation is consistently associated with a much higher rate of moderate to severe esophagitis during treatment, about a six-fold increase from about 4% to nearly a quarter of patients. For some, this requires supplemental IV fluids or rarely even tube feedings temporarily. It can certainly be a challenging approach for many patients.

A strategy that had been widely adopted in North America was based on a modest-sized trial of 83 eligible patients with stage IIIB disease who received cisplatin and etoposide chemotherapy along with radiation to a potentially curative dose of 61 Gray over about 7 weeks, then followed by an additional three cycles of a different chemotherapy called taxotere, or docetaxel, given every three weeks. This was associated with a very promising long-term survival that far exceeded the results seen in other trials.

The value of the additional, or so called consolidation, taxotere chemotherapy was directly tested in a trial conducted by the Hoosier Oncology Group, affectionately known as the HOG, and based in Indiana. This trial of just over 200 patients with unresectable stage III NSCLC gave all patients cisplatin and etoposide with concurrent potentially curative chest radiation and then randomized patients who hadn't progressed to either an additional three cycles of consolidation taxotere or observation alone, with no further treatment. Highlighting the difficulty of concurrent chemo and radiation, only two thirds of the patients got to the point of being randomized without showing progression or having problems with side effects that prohibited their continuing on the trial.

As shown in the completely superimposed survival curves from the trial, there was no evidence of any survival benefit from the additional chemotherapy.

Unfortunately, the additional taxotere was associated with a significantly higher rate of infectious complications and lung tissue inflammation known as pneumonitis, as well as a nearly significant increase in the frequency of treatment-related deaths.

The Southwest Oncology Group, or SWOG, also tested this approach further, but in the SWOG 0023 trial, which gave all patients chemo and radiation concurrently and then followed by taxotere consolidation. Following that, patients were randomized to either

the EGFR inhibitor iressa, also known as gefitinib, as maintenance therapy, or a placebo pill daily. The trial closed early on the advice of the Data Safety Monitoring Committee, after a large trial with iressa showed no significant survival benefit in patients with metastatic non-small cell lung cancer, and an early look at the trial data showed that the arm receiving iressa could never emerge as significantly better than the placebo arm. One important thing to note is the drop-out rate as the trial progressed, as shown in the lower part of the slide. This was difficult treatment, with more than a quarter of patients dropping off before the maintenance taxotere, and over half of the patients progressing or experiencing prohibitive side effect issues that kept them from proceeding to the maintenance iressa or placebo portion of the trial.

When we look at the trial results, we do see a difference in the two arms of the trial, but unfortunately it's in the direction opposite what we'd have hoped to see. The iressa arm, in blue, shows a modestly worse progression-free survival and a significantly worse overall survival, a full twelve month lower median overall survival with iressa compared to the recipients of a placebo. These results are still not understood, but they highlight the fact that we can't reliably predict the outcome of unproven ideas ahead of time and emphasize the need to test new ideas in proper clinical trials.

Despite the lack of any clear evidence that there is a value in administering additional chemotherapy after completing 6-8 weeks of chemo and concurrent chest radiation, the oncology community has been reluctant just stop and observe patients at that point. Several current clinical trials still incorporate consolidation chemotherapy as a core part of the treatment approach. For instance, this nationally conducted trial from the Radiation Therapy Oncology Group, or RTOG, is testing two different doses of chest radiation as well as the potential value of Erbitux, also known as cetuximab, which is a monoclonal antibody to EGFR. But as shown in the far right of the figure, we can see that all patients receive two additional cycles of carbo and taxol chemotherapy after completing their concurrent chemo and radiation, with or without Erbitux.

Similarly, a new trial by Eli Lilly is testing cisplatin and alimta with radiation, compared with an older standard, but both arms receive a form of additional consolidation chemo, despite the fact that we don't have evidence that this improves patient outcomes. This is partly because oncologists and patients are often reluctant to just stop and accept the modest survival rates we've been able to achieve thus far.

In summary, the general principles of managing unresectable stage III non-small cell lung cancer are shown here. Concurrent chemo and chest radiation has been shown to be associated with consistently superior long-term survival results compared with a sequential approach of one followed by the other, but at a cost of higher rates of acute esophagitis. While the results from a single clinical trial known as SWOG 9504 demonstrated very promising results associated with adding so-called consolidation taxotere after several weeks of concurrent chemo and radiation, subsequent larger trials have not supported a clear survival benefit from this additional chemotherapy. The SWOG 0023 trial also illustrated the unsuspected but clear finding that the oral EGFR

inhibitor Iressa was associated with a significant worsening of survival when given as a maintenance therapy.

Despite these issues, we remain ambivalent about stopping our treatments after 6-8 weeks of chemotherapy with concurrent chest radiation, even though the evidence shows that this approach is as good as more intensive strategies and with lower risk of severe side effects and even potentially treatment-related deaths. There are several new trials being conducted that are testing newer agents, such as alimta and erbitux in locally advanced non-small cell lung cancer, and these have actually incorporated additional consolidation chemotherapy despite the absence of clear benefit. This is still a field in evolution.

You can find additional details on several of these topics within the subject archives at the web address www.cancerGRACE.org/lung. Members of GRACE can also leave comments and questions about this presentation at the web address in the middle of this slide. Thank you for your interest.