



Talk at *Cancer Lifeline*, Part 3: Managing Locally Advanced (Stage III) Non-Small Cell Lung Cancer (NSCLC)

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Hello, my name is Dr. Jack West and I'm a medical oncologist specializing in lung cancer at the Swedish Cancer Institute in Seattle, Washington. I also serve as the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

The following video presentation is an excerpt from a lecture I delivered in June 2009 at Cancer Life Line, a Seattle-based nonprofit organization for cancer patients and caregivers.

The information provided here includes my own views and they do not necessarily represent those of the Global Resource for Advancing Cancer Education or Swedish Cancer Institute. The contents of this program do not constitute medical advice and are intended to supplement, but not replace input from an individual patient's medical team.

So I'm going to turn now to locally advanced or Stage III lung cancer. And within the realm of Stage III, there are some patients who can potentially undergo surgery and that is its own lecture, but I'm going to focus really on the patients with Stage IIIB disease that is generally treated not with surgery, but with chemo and radiation. And also the Stage IIIA patients who may not have as bulky or extensive disease, but may have it in a place that makes surgery a less advisable idea or it involves enough of the mediastinal lymph nodes, the lymph nodes between the lungs and the mid-chest, to recommend a non-surgical approach.

This concept of giving chemo and radiation is meant to be curative. We would like the numbers to be higher than they are, but it is important that the combination of chemo and radiation is challenging and pretty aggressive. But we push because we would like to get people to the goal of killing the last cancer cell and actually curing them.

One question over the last several years had been should we give it at the same time chemo and radiation concurrently, or should we give chemo and radiation one at a time. It is easier on patients to give it one at a time. But studies like these two and the one on the left done in Japan, and the one on the right done in North America, compare chemotherapy followed by surgery to chemo and chemotherapy followed by radiation compared with chemo and radiation at the same time. And these studies show an approximate doubling of the long-term survival if we give the chemo and radiation together.

If we talk about the median survivals, which has some real limitations, but it's at least something to give us a handle on how well these treatments performed. Trials done all over the world with various combinations of chemo and doses of radiation have consistently shown an approximately three-month improvement in median survival, and with that we also see better cure rates overall.

The real problem is that it doesn't come free, that acute esophagitis, or inflammation of the esophagus like a sunburn, basically, of the esophagus, which is associated with difficulty swallowing and sometimes difficulty with eating and drinking enough, is much, much more common when you get chemo and radiation together. The chemo works throughout the body, but it also potentiates the effect of radiation when they're given together, which is good in fighting the cancer, but it causes more tissue damage to normal non-cancer tissue and with that you see higher esophagitis rates. And it's about a six-fold difference. So, we do try to give concurrent chemo and radiation when it's feasible. But it's not for everybody.

One of the approaches over the last several years that had been quite popular, had been giving chemo and radiation together for about seven weeks and then giving a few cycles of what's called consolidation chemotherapy. Basically a chemo chaser with a different drug to try to hit the cancer a different way, and this early study showed the median survival in a smallish group of patients, 83 — not the definitive word on it, the median survival was 26 months which as I showed just a couple of slides ago is far better than 17 months and there was a lot of hope that this would be *the* way that we should be treating everyone. In fact, for most of the last few years, the majority of oncologists throughout the country were using this kind of approach, including me here 2-3 years ago.

But in the last few years we've actually gotten larger and clearer studies that do not support adding more chemo after the seven weeks of chemo and radiation together. This is a study done by the Hoosier Oncology Group, which is affectionately known as HOG -- They like it. And this trial gave everyone chemo, good chemo and radiation together and then half the patients got three additional cycles of Taxotere®, a different chemotherapy. And half the patients were watched after that. Now, one thing to point out is that I had mentioned that this is challenging treatment that they started out with just over 200 and a third of the patients dropped off before they got to the part of being randomized to stop or get more. The other third either had progression or side effect problems or just said I'm not interested in anything more and don't come near me again.

So, what we saw are superimposed curves which basically means there was no improvement in survival from adding the additional chemotherapy. In fact, [slide 10] what we did see as a difference were more side effects: more infections in the patients who got Taxotere® additional chemo, higher pneumonitis rates and more treatment-related deaths. And this is showing that 5.5% of patients died from the treatment. And that's actually not some outlier result. In fact, even in the studies that had supported giving the additional chemo, there was a 5-6-7% death rate from the treatment. And it just wasn't highlighted that much. It was really a question of what did you point the

spotlight at. And, these investigators really said we saw no benefit and we saw higher treatment-related death rates from the extra treatment we were doing. So what this suggests is really that we're getting into the "red zone" here where more treatment maybe doing more harm than benefit in a lot of the patients.

Now, the Southwest Oncology Group or SWOG which is a group that most of the oncologists in this area who do clinical trials participate in, were involved with this study which gave everybody the chemo and radiation followed by three cycles of Taxotere® and then asked the question of is there a benefit of giving maintenance therapy, an oral drug like gefitinib (or Iressa®) an EGFR inhibitor, versus placebo to improve survival.

And this study also had a hard time getting people through it. We saw that a little more than a quarter of the patients dropped off before getting to the Taxotere® portion. And then more than half of the patients dropped off either because of progression or side effect issues, before they got to the maintenance randomization.

Now, I'd said that we like in Oncology to see the separation of the curves. That's only when the treatment is better than the last thing we had. And in this case, unfortunately, the curve on top is the placebo, okay. So, there is a 12-month worse median survival with Iressa®, gefitinib, compared with placebo. And, these are very important, clinically significant and borderline statistically significant differences. And, really what this highlights is that this is why we need to do clinical trials because I would say that no one in the field of oncology, lung cancer oncology, expected that Iressa® could be detrimental. We thought it would either be neutral or it would be better. And a lot of oncologists were generally giving this to people. But, if we didn't do the trial, we would be hurting patients without knowing the harm we were doing and that's why it's important to actually ask these questions in an important way and not just kind of think you know and guess.

So, what are the questions, what are the things we're doing now? Well, I had said that we don't have proof that giving more chemo after the chemo and radiation portion improves results. That has not stopped the Oncology community from still doing that in some of the larger trials.

This is a study done by the Radiation Therapy Oncology Group or RTOG. And the RTOG is asking whether we can get a benefit from increasing the dose of radiation from what's called 60 Gray to 74 Gray. So escalating the dose, can we do that safely and improve survival. And also half the patients are going to get another targeted drug called Erbitux® (or cetuximab), which is a monoclonal antibody given weekly during treatment, and it's targeted against the epidermal growth factor receptor.

So everyone gets the standard chemo, everyone gets radiation. Half the patients will also get this monoclonal antibody and half the patients will get a higher dose of radiation and we'll see how that turns out. But after the end of the seven-week period, everyone is assigned to get more chemotherapy which we really don't have proof for, but frankly a lot of oncologists and, in this case, the National Cancer Institute is involved with

blessing these trials before they move forward saying that we still think people need to get more.

This is another study being done by Eli Lilly which makes a drug called Alimta® which is FDA-approved for advanced metastatic disease. Alimta® is a drug that can be given at the same time as radiation and many of the drugs that we have for chemo, are not safely given at full dose with radiation without causing problems. But you can do that with Alimta®. And so, this study is giving half the patients, cisplatin and Alimta® with radiation; and half of the patients an older perfectly good standard of cisplatin and etoposide with radiation. But then after that, we're still giving consolidation either with Alimta® as a single drug, or various two-drug combinations and trying to see which one is better.

These studies are actually now ongoing. But as you can see, oncologists and the National Cancer Institute are not eager to drop the additional chemotherapy. And really I think that is because we have a hard time accepting that just six or seven weeks of chemotherapy is going to be enough. And, in fact, in the postoperative chemo trials for a stage II patient for instance, we routinely give three or four cycles very commonly. So, it's hard to envision why we would do we would standardly give four cycles for a stage II patient, but somebody with a bulky stage III cancer should just get two and then we just cross our fingers.

So, this is a situation where even though we have some evidence that doesn't prove a benefit, we are not eager to just settle with what we've got. So concurrent chemo and radiation is consistently superior, despite encouraging results in the early study that showed the benefit of a consolidation chemo, we haven't got proof that that adds a benefit. What we do see is that adding an EGFR inhibitor like gefitinib, Iressa®, did not help and it actually hurt people. So we really don't favor giving that at least to a general population that doesn't have a molecular target like the EGFR mutation I'll talk about.

But we're still asking the question of whether six or seven weeks of treatment is really enough or whether we should be giving more. And we're looking at higher radiation doses, new drugs like Alimta®, cetuximab, etc.