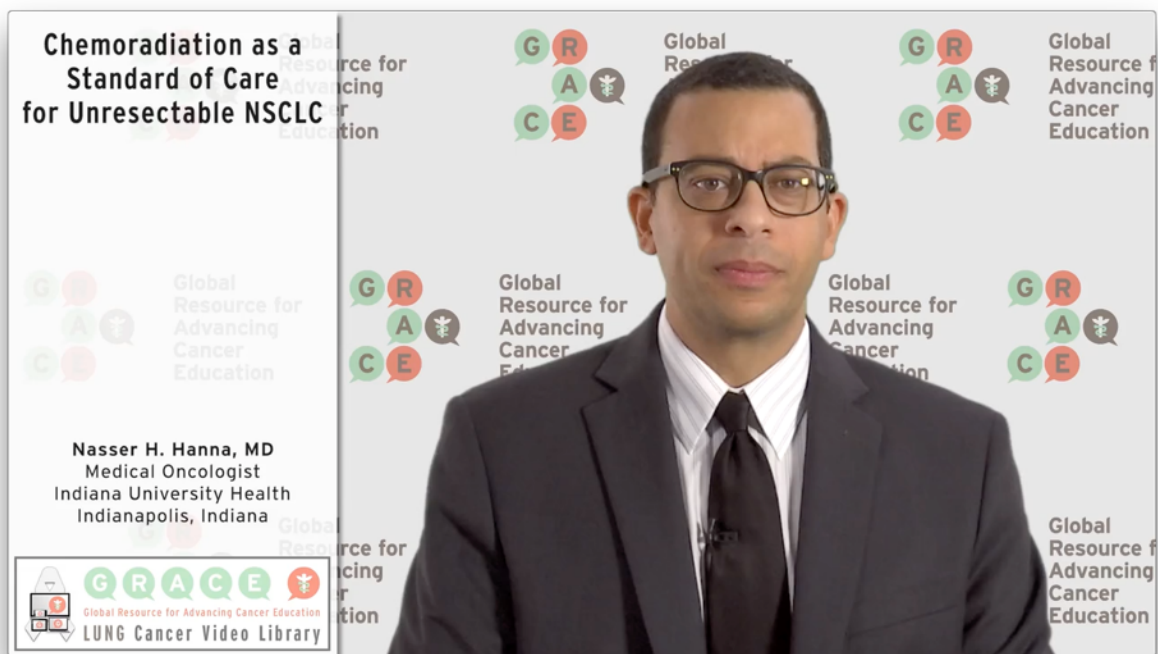




Chemoradiation as a Standard of Care for Unresectable NSCLC



TRANSCRIPT & FIGURES

So what is the standard of care treatment for those who are not going to have surgery for stage III disease that are either medically inoperable or they are surgically unresectable? Well for decades radiation therapy has formed the backbone of treatment. If you can't surgically remove a tumor, you can certainly apply radiation to that tumor; you radiate the tumor, the lymph nodes, and some surrounding tissue where microscopic disease may be. That form of therapy can be effective but by itself oftentimes is not curative. It will shrink tumors and oftentimes patients will have a reduction in symptoms, maybe a tumor was compressing an airway or maybe it was causing them to cough up blood or something like that where the radiation therapy can be effective at relieving some of those symptoms.

Historically radiation therapy alone for stage III disease has resulted in about a 5% cure rate – the vast majority of patients will develop growth shortly thereafter, either outside the radiated field, occasionally in the radiated field, but most commonly distant metastatic disease. That's because even though the disease appears to be confined to the chest, we know that the majority of patients already have microscopic spread of their cancer to other parts of their body. That's not something that you can see on a CT scan, it's not something that you can see on a PET scan, it's certainly not something you can feel on a physical exam, but we know that's the case because historically when you've done surgery alone for this group of patients and successfully removed all the disease you can see, the vast majority of people will still develop distant, recurrent disease usually within about a year's time.

Radiation therapy alone can have some effectiveness for patients, but by and large it's a short term effect and it oftentimes doesn't cure patients.

Starting really about three or four decades ago, chemotherapy was beginning to be incorporated in the treatment of patients with stage III disease. In the 1970s it was demonstrated that chemotherapy could shrink cancers that had already metastasized, and perhaps if it could shrink cancers that were large enough to see on x-rays, maybe it would be effective enough to treat that microscopic disease that patients have with stage III lung cancer.

So beginning in the 1970s and really going in full force in the 1980s, chemotherapy was incorporated with radiation strategies and a whole host of different strategies were tried. The most common strategy was to give a couple of courses of chemotherapy first, try to shrink the cancer, try to treat that microscopic metastatic disease early on, and then follow that with radiation therapy. Early efforts into that approach were not terribly successful, and that's for several reasons. Number one, our staging tools weren't very good, so oftentimes even though we thought patients have stage III disease, they oftentimes already had stage IV disease and they weren't going to be cured with that type of strategy. Secondly, many patients who participated in those clinical trials were already not doing well. They had what we call a low performance status, in other words, they had already become very debilitated by their disease and their ability to tolerate therapy wasn't very good. Thirdly, our radiation techniques were fairly crude at the time, radiation planning was very crude at the time as well. Fourth, our chemotherapy actually was not terribly active; although it was modestly active, it probably wasn't the most effective therapy that patients could receive. Lastly, it really wasn't recognized, the clinical significance of having weight loss. So oftentimes patients will have suffered a lot of weight loss which is really a signal that they truly have systemic disease, and when you

include all those types of patients on clinical trials, you're really setting yourself up for failure.

The initial attempts at trying to treat patients with both chemotherapy and radiation therapy really would be considered failures. Outcomes were not very good, we really didn't seem to improve cure rates over radiation therapy alone, and this was in an era in which chemotherapy was not very well tolerated. That really started to change in the mid-1980s, and really a landmark trial was conducted by a United States cooperative group. In this trial, patients were excluded if they had a really poor functional status, if they had significant weight loss, and so it really narrowed the group of patients who could potentially benefit from this therapy. In this study, patients received two courses of chemotherapy, and then that was followed by six weeks of radiation therapy. For the first time, we were able to demonstrate an improvement in cure rates. It was fairly modest, we went from about a 5% cure rate to about a 15% cure rate.

Because that was the first time that was really ever demonstrated, a second trial was required to really make sure that this was a real finding. So a second trial was done in the United States by other cooperative groups; this was a much larger trial and they essentially replicated that data.

Well in the 1980s and in the 1990s, this strategy of giving chemotherapy and radiation therapy at the same time was becoming a standard approach in many different cancers. This included cancers of the pancreas, of the esophagus, of the head and neck, of the rectum, and so that sort of idea was attempted in lung cancer. Now we weren't sure if we could actually give

chemotherapy and radiation at the same time to somebody who had lung cancer. It's a bit different radiating the mid-chest area where the heart is going to get radiation, the lungs are exposed to a lot of toxicity from radiation, the esophagus would oftentimes be in the field of radiation. So the first thing we had to do was prove that it was safe and feasible to do, and indeed investigators did demonstrate that. The next step was to determine whether that strategy of giving chemotherapy and radiation at the same time would truly be more effective than giving them separately - there were a lot of theoretical advantages to doing that. First, you would not delay the radiation therapy. Secondly, you might be able to give both therapies at the same time which would work to kill cancer cells in different ways simultaneously, but we knew that it would come at a risk.

We knew that it would come at a risk of increased side effects when you give the treatments together versus giving them separately. Several randomized trials were conducted in the United States, in Japan, in Europe, that looked at comparing the concurrent administration of chemotherapy and radiation to the sequential administration of those two. Those trials by and large demonstrated that while it was more difficult on patients and there were certainly more side effects, you could improve cure rates by giving the treatment concurrently.

So really through the 1990s and into the early 2000s, the standard of care treatment for those who were well enough and fit enough for this type of therapy was to give concurrent chemotherapy and radiation therapy.

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