

Studies For The Adjuvant Use Of Chemotherapy Plus Radiation Versus Radiation Alone In Lung Cancer

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Lung cancer is one of our society's most devastating diseases. When cancer starts in the lung but travels to adjacent lymph nodes, it suggests a more aggressive course.

A randomized study in the treatment of resected lymph node positive lung cancer was recently published in the New England Journal of Medicine. The study is important both because of its quality and its methods.

There are few high quality randomized studies. Many patients do not like to enter randomized studies feeling they know the approach they want to receive. Many commonly feel more aggressive treatment will lead to more beneficial results. Sometimes this is erroneous. Randomized studies help guide us to the best treatment approaches. They can educate a generation of doctors.

It is known that when lung cancer patients have involvement of the lymph nodes in the chest the prognosis worsens compared to when there is no such cancerous lymph node involvement in non-small cell or non-oat cell lung cancer. Lymph node involvement means the patient has more extensive stage disease. These include squamous cell, adenocarcinoma, and large cell carcinomas. The type of cancer is defined by the pathologist after microscopic examination. When cancer is present in the lymph nodes, even if surgically removed, recurrence of the cancer frequently occurs. Thus, there is a need to consider further therapy.

Studies have previously shown that post-surgical treatment for patients with lymph node involvement decreases the likelihood of local recurrence. Of course, local recurrence is detrimental. Many patients if the cancer recurs locally develop severe symptoms including cough, shortness of breath, bleeding, infection and even death.

For Stage II and Stage III non-small cell lung cancer a randomized study by Keller et al is conducted and published in the prestigious New England Journal of Medicine. The purpose was to find the best treatment approaches.

The study commenced in 1991 with patients being enrolled for the subsequent nearly six years. Patients received 5040 cGy (Centigray) 28 fractions of 180 cGy each (centigray is a measure of radiation). This is a traditional radiation approach. Radiation was given, in general, half from the back and half from the front for the first course and the subsequent slightly altered to protect the spinal cord. Concurrent chemotherapy consisting of Etoposide and Cisplatin were used starting concurrently with radiation and then continuing for four cycles of chemotherapy.

All patients had to have lymph node involvement with cancer but no metastases beyond the chest. All patients, at the time of surgery, had sampling or complete removal of multiple levels of lymph nodes. If cancer was in the opposite site of the mediastinum or in multiple levels of lymph nodes or if extended beyond the capsule of the lymph node or if there was cancer beyond the lymph node itself the patient was ineligible for this study.

Four hundred and eighty eight patients from 121 facilities were enrolled with 242 randomly allocated to receive radiation alone and 246 to receive radiation and chemotherapy as described. Some patients did not start the therapy that was assigned to them including 14 that were to receive combine modality and 11 who were to receive radiation alone.

Of those 232 patients who began chemotherapy and radiation, 69% received all or part of the four cycles of chemotherapy. Five percent just three cycles and 13% just two cycles. The main reason

people did not complete chemotherapy was their refusal or excessive toxicity or progressive cancer. Eighty four percent of the patients completed the radiation.

The authors noted that, "Side effects were more common and more severe in the group given chemotherapy and radiotherapy." Side effects included bacteria infection in the blood causing two of the four deaths. The other two deaths included inflammation of the lung and inflammation of the esophagus. Two deaths in the radiation alone group were felt to be due to inflamed lung or pneumonitis with a third due to esophagitis.

How did patients' survival rate compare? The median survival was 39 months in the group receiving radiation alone and 38 months receiving combined modality treatment. There was statistical analysis that showed no difference. Actually the survival was slightly greater in the radiation alone group.

When patients were analyzed by age less than or greater than 60 years, sex, race or stage there was no difference in survival. Recurrence was found in 53% of the patients receiving radiation by itself and 56% of patients receiving chemotherapy and radiation.

Radiation and relapse of the cancer within the radiation field occurred in 13% of those receiving radiation alone and in 12% receiving chemotherapy and radiation. The time to recurrence was 30.4 months in the radiation group and 26.1 months in combined chemotherapy radiation group.

Nevertheless, the authors could not find any advantage of giving chemotherapy and radiation compared to giving radiation alone in preventing local recurrence or increasing survival after the diagnosis and surgical treatment of the cancer.

In fact, the authors suggested that the data revealed radiation alone was superior to chemotherapy and radiation in some aspects.

There were, unfortunately, more side effects in the group getting chemotherapy and radiation combined than radiation alone. It was noted, however, that survival was longer than in previous studies and was suggested that this may be because of better staging. Better staging means the physicians better know the extent of cancer before treatment is undertaken. When patients have metastatic cancer beyond the lymph nodes and are excluded from such a study it would improve the apparent results compared to older era studies. This may, indeed, be the case as radiographic imaging such as CT scan, bone scan, PET scan and MRI's better define the extent of cancer than were available in the past.

The authors concluded that chemotherapy should only be used in a clinical setting and not routinely after surgical resection of lymph node involved cancers.

In an accompanying editorial from Carney and Hansen, they noted, "Patients with advanced metastatic non-small cell lung cancer constitute the largest group of candidates for chemotherapy. Despite its' widespread use, the benefits of chemotherapy in these patients are unclear. The prognosis in this group is grim; the median survival without cytotoxic treatment is less than six months, and even with treatment cures are almost unheard of. Before chemotherapy is initiated in such patients, its effect on quality of life must be considered."

Furthermore, they noted, "Studies indicated that although the rate of response to chemotherapy were only 20 to 30%, 60 to 70% of patients had decreases in disabling symptoms such as cough, hemoptysis and dyspnea. These data led to a new optimism, but unfortunately they have not been substantiated in recent large randomized studies. For these reasons, it is easy to understand the lack of universal acceptance of the use of chemotherapy for all patients with advanced, non-small cell lung cancer."

They emphasize that, "All patients should be informed of the potential benefits, limitations and

adverse effects before embarking chemotherapy, and all suitable patients should be encouraged to participate in clinical trials so that real progress can be made against non-small cell lung cancer."

"Lung cancer is the most preventable of all common cancers. The elimination of cigarette smoking remains the best hope for reducing mortality from this disease. For former smokers and those who continue to smoke, new techniques for the early detection of the disease when it is most curable and methods for preventing lung cancer are promising developments."