

RADIATION AND CHEMOTHERAPY FOR ESOPHAGEAL CANCER

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One of the more common cancers that are diagnosed in America is that of the esophagus. The esophagus is the organ between the mouth and the stomach. It appears as part of the gastrointestinal tract. Early symptoms include pain, difficulty swallowing and weight loss. Of course, early diagnosis is important and usually is made by direct examination by gastroenterologist.

Despite a variety of advances, the vast majority of people with esophageal cancer succumb to their disease. A group of researchers from Sloan-Kettering, led by Minsky, evaluated a new treatment approach of using combined chemotherapy and radiation. The difference in the two arms of the study was the radiation dose. In the standard arm the dose was 5040 rad and in their high dose program the high dose was 6480.

Part of the analysis of the study was based upon an RTOG, which is Radiation Therapy Oncology Group, study that started in 1985 and randomized patients between chemotherapy and radiation at a dose of 5000 rad versus radiation alone at 6400 rad. There was an improved survival as well as locoregional control in the group that received chemotherapy and radiation together compared to radiation alone. Yet even those with better survival the local failure rate was 47%.

In an attempt to improve survival an inner group study took place using chemotherapy plus radiation at one of two different doses. Because of treatment related complications further evaluation of this randomized study between chemotherapy and radiation yet at two different doses was not followed.

Based upon national radiation trial groups, a variety of institutions across America were allowed to enroll up to sixteen patients for this program. The program opened in mid-1995 and was supposed to collect two hundred and ninety-eight patients. There was an interval analysis in 1999, which showed that the group of higher dose radiation did not have a significant survival difference to warrant continuing the study.

The study was to include patients with T1 through T4 stage cancer of the esophagus with either no lymph node or lymph node involvement but any metastasis. The cancer could be the cervical mid or distal esophagus.

There needed to be a bronchoscopy to exclude tracheal esophageal fistula at the time of diagnosis if the cancer in the esophagus was less than 30cm from the front teeth. Also a CT scan of the chest and abdomen was asked for to exclude metastatic disease. Patients were not included if their cancer was within 2cm of the gastroesophageal junction. The reason for this was concern about damage to the stomach. The vast majority of patients had cancers that were called squamous cell cancers.

Patients were excluded; if there were multiple cancers of the esophagus, invasion of the tracheal/bronchial tree, fistula or metastatic disease other than local lymph nodes, a cancer of the gastroesophageal junction, prior chemotherapy, prior radiation to the thorax, surgical resection of the primary or serious underlying medical conditions.

Patients with lymph node involvement of the supraclavicular nodes were felt to be eligible if the cancer was of the cervical esophagus - otherwise they were excluded.

Patients received 5FU and Cisplatin chemotherapy with radiation simultaneously. Radiation was started on day one. The chemotherapy included Cisplatin at 75mg./m² over thirty minutes on day one. 5FU was given at a dose of 1000mg./m² over twenty-four hours by continuous infusion on

days one through four each. These cycles were repeated every twenty-eight days. Dose per body surface area is a common method of prescribing chemotherapy.

The radiation was used with multiple fields and was given five days a week. The authors noted that at least two fields were treated each day and that treatment could include treatment from what would be called the front and back or anterior/posterior, oblique or lateral fields. The superior/inferior borders of the radiation field were 5cm beyond the primary tumor and the lateral, anterior and posterior borders were at least 2cm from the border of the primary tumor. For the remaining 1440 rad, patients received cone down radiation to treat the primary only and not the lymph nodes. Superior and inferior borders were 2cm beyond the tumor with lateral borders the same as the initial margin. This would be considered standard radiation techniques, which have been in use for many, many years.

Follow-up included physical examination, history, blood test, chest x-ray, and barium swallow x-rays with quality of life analysis at twenty-eight days after completion, repeated every four months for one year and then every six months for two years and then annually.

While patients were informed as to the nature of the study the randomization process took place so that the patient did not choose what dose was given. The institution would randomly allocate the dose as part of the study. In the so-called high radiation dose arm, four patients were excluded because of no bronchoscopy, or two tumors within 2cm of the stomach in three patients and medically unable to tolerate combined modality treatment was one patient. In the standard radiation dose arm four patients were excluded because of no bronchoscopy and one patient because the tumor extended within 2cm of the stomach. Also three patients were excluded because of no esophagram and one patient had prior chest radiation.

Overall there were eleven treatment related deaths or 10% in the high dose arm and 2% in the standard dose arm. In the high dose arm they included cardiac in three, respiratory in one, fistula in one, urinary in one and the remainder infection or genitourinary. In the standard dose two patients had treatment related deaths that were infectious in nature.

Statistical analysis did not show a difference in outcome between the lower and higher dose radiation.

At two years the incidence of local failure was 56% for the high dose arm and 52% for the standard dose arm. There was no statistical difference between those patients.

The authors note, "The reason for the lack of benefit in the high dose arm is unclear. When comparing the high dose versus low dose arms, there was a significant prolongation of treatment time because of toxicity breaks when correcting for the number of radiation treatments as well as a significant lower actual dose of 5FU as a percentage of protocol dose. These factors may have contributed, in part, to the lack of benefit for patients who received high dose versus standard dose treatment."

It is interesting to note that in the high dose arm patients received only 65% of the dose they were supposed to for 5FU and 75% for Cisplatin. Interestingly, only 61% of the patients in the high dose arm and 59% of the patients in the standard dose arm had complete information available for review about the chemotherapy at the time of analysis. Obviously a lack of data would impair analysis significantly.

What is also interesting is that seven of the eleven treatment related deaths in the high dose arm occurred in patients who actually received the low dose. The low dose was 5040 rad.

Thus the authors themselves wrote, "It is unlikely that the higher dose of radiation was responsible for the increased mortality." It seems odd that this treatment program was stopped because of the toxicity at the high dose when in fact the majority of the toxicities occurred at the

lower dose of treatment. Of the thirteen toxicities - nine of them occurred in patients who actually received 5040 rad or not.

While that group continues to recommend a dose of 5040 rad, our group feels differently.

The major difference between radiation techniques at Radiosurgery New York and those described in this combined approach from elsewhere is the technique of radiation. Their technique is one of standard approaches of radiation that does not use conformal and certainly not body radiosurgery techniques.

The beauty of stereotactic body radiosurgery is that in our hands we outline the tumor location and boost the dose to significantly greater techniques. By doing this technique we shield the lungs, heart and other surrounding structures from the highest dose yet our local control rate is 90%. That means that 90% of the patients treated for esophageal cancer have control in the treated area. That is in marked distinction where the majority of patients who received standard radiation have failure.

Most radiation oncologists are aware that higher doses lead to higher control rates. The real question is how to deliver the higher control rates safely.

What has been part of the great appeal of body radiosurgery is that the vast majority of patients are treated safely with higher control rates. Higher control rates should translate into higher survival rates.

We have established a hot line at 212-CHOICES and also answer questions on e-mail: gil.lederman@rsny.org.

Body radiosurgery may offer a great appeal for treatment of esophageal cancers. There is a more focused beam than standard therapy. The stereotactic frame allows a great degree of precision and guidance of beams more precisely to attack the tumor while trying to minimize dose to healthy normal tissues. We have seminars open to the public on a regular basis.