ESOPHAGEAL CANCER

By: Gil Lederman, M.D.

Esophageal cancer is one of the most debilitating of all cancers. It is often diagnosed when a person has difficulty swallowing. This is usually a new symptom. The difficulty swallowing usually starts with solid foods - often meats. Patients facing this discomfort will often drink more fluids and eat softer foods before being seen by a physician.

The physician will frequently ask to have endoscopy performed. Endoscopy is the placement of a flexible fiberoptic scope in the esophagus. This allows direct visualization of the esophagus. If an abnormality is detected, a biopsy can be performed. Anyone with difficulty swallowing should be seen by their physician and have appropriate tests, such as endoscopy, CT scan with contrast or other tests such as barium swallow x-ray performed. Esophageal cancers usually affect the interior of the esophagus.

Sometimes a test called a barium swallow (the swallowing of a liquid in the consistency of a milkshake followed by x-rays of the esophagus) is undertaken. Not infrequently with esophageal cancer, x-rays will show the blockage.

The major treatments for esophageal cancer include chemotherapy, radiation and surgery. Resection of cancer of the esophagus is a difficult operation and survival rates are generally modest - said to be between 5 and 20% at five years when such an operation is undertaken.

In many cases, resection cannot - or will not - be performed for medical or other reasons. Chemotherapy and radiation is given in lieu of surgical resection or prior to the surgical intervention.

Radiation does indeed improve the control rate and many patients respond to chemotherapy with shrinkage of the cancer. Studies have shown an improvement in outcome when chemotherapy and radiation are given simultaneously compared to radiation alone.

Hennequin et al, in the International Journal of Radiation Oncology Biology Physics reported on a study, started in 1988 and completed in 1997, comprised of 304 patients with esophagus cancer referred for radiation. Patients were included if they had a biopsy which showed cancer, locally advanced cancer thought to be a Stage T3 or N1 or regional lymph nodes (those in the celiac, nodes of the abdomen or supraclavicular nodes located above the clavicle). Staging is an agreed upon extent of disease description. Also patients had to have no prior treatment, reasonable function and the ability to undergo chemotherapy and radiation.

Prior to treatment all patients had x-rays and barium swallow as well as CT scans of the chest and abdomen and ultrasound to test the liver to rule out metastatic cancer there. The patients also had endoscopy of the esophagus and in some patients, ultrasound was performed at the time of endoscopy.

Stage T3 is defined by endoscopically directed ultrasound or by CT scan detected mediastinal spread, extension to the tracheal/bronchial respiratory tree or vascular structures. The tracheal/bronchial respiratory tree is part of the breathing system that passes air into the lungs and returns carbon dioxide. Stage T4 is defined as when cancer invaded the tracheal/ bronchial tree. These were excluded. Lymph node involvement was based upon CT scan criteria only. Biopsy of these additional areas was not performed.

While 304 patients were referred to the radiation department, only 112 were included in the analysis. Researchers used two different protocols - one consisting of 5FU chemotherapy as continuous infusion for 72 hours and Cisplatin (50mg/m2 on Day One and Two as IV-bolus)

{mg/m 2 stands for milligrams per meter square of body surface area, a common method of drug calculation} and radiation delivered in 8 fractions of 1.8 Gray each from Day One to Day Twelve, totaling 14.4 Gray with a split between Days Thirteen and Twenty-One. Gray is a unit of radiation dose. Three cycles or 43.2 Gray were given before surgical evaluation. After September 1990, radiation schedule was changed to 10 fractions of 200 rad during each cycle with a total of 40 Gray given before surgical evaluation.

After chemotherapy/radiation, evaluation included physical examination, repeat endoscopy of the esophagus and CT scan. Surgery took place one month after radiation finished or another chemotherapy/radiation cycle was performed with a total dose of 60 to 66 Gray. A complete response was defined as no radiographic or endoscopic evidence of cancer with a negative biopsy. CT scan defined a partial response as more than 50% regression. Some had stable disease or progression of cancer.

Difficulty swallowing and weight were evaluated at the same time. Follow-up was performed every four months for the first year and every six months after. Ninety-eight percent of the patients took the first dose of chemotherapy, 93% the second dose and 78% the third dose. Overall, full dose chemotherapy was given in 83% of the cycles and in all cases, full radiation dose was given. Two patients died of pneumonia.

Improved swallowing occurred after treatment in 58.7% of patients and 31% actually gained weight while 53% saw no change in weight. There were 28 patients who had complete clinical responses to the treatment. This represents 25.7%. Fifty patients (45.9%) had partial responses. Twenty-two patients (20%) had stable disease and 9 patients (8.2%) had progression of cancer. Tumor progressed in organs in five cases and locally in four.

Fifty patients underwent surgery with 38 having their esophagus removed. Of 62 patients, 11 did not have surgery with tumor progression or death before repeat staging, 15 patients had inadequate response, 4 patients refused surgery (eleven physicians suggesting not to go through surgery), and 21 patients had medical contra-indications. Contra-indications included chronic respiratory disease, cardiac disease or cirrhosis.

If patients did not go through surgery, one more cycle of chemotherapy and radiation was given. Of the 50 patients who went through surgery, 12 had exploratory surgery (meaning the esophagus was not removed), 38 patients had the esophagus removed. The tumor was not completely removed in one patient and another patient had positive surgical margins meaning the cancer was present at the incision around the esophagus. In 9 patients (23%), there was no evidence of residual cancer. Two patients had post-operative deaths - one patient with liver failure and another with a pulmonary infection.

Of the 12 who had exploratory surgery, chemotherapy and radiation was given to 4 patients and 3 patients died within one year. The patient who survived this group could not have their esophagus removed because of fibrosis, or scarring. At the time of surgery, biopsies were negative and a year later, the patient underwent removal of the esophagus because of stenosis (constriction of the esophagus). There was no residual cancer seen.

The median follow-up for the entire group was 24 months. Fifty-eight patients died of progressive or recurrent cancer. Other causes of death included surgical complications, lung disease and one unknown cause. The median survival for the entire group was 14 months with a one-year survival of 56%, two-year survival of 41% and five-year survival of 28%. Certain indicators such as age, sex, tumor stage, lymph node stage, involvement of the tracheal bronchial tree, length of the cancer or the chemotherapy protocol had no impact on survival, the authors noted.

However, what was significant was the response to treatment and surgery? For patients who underwent esophagectomy, the one-year survival was 75%, two-year survival was 63% and five-year survival was 40%. In non-surgical patients, the one-year survival was 48%, two-year survival

was 31% and five-year survival was 25%. In the 31 patients who did not respond to chemotherapy, the one-year survival was 23% and the five-year survival was 10.3%. Two years later, only one patient is alive without cancer.

Of the 78 patients who responded to chemotherapy, the one-year survival was 69%, two-year survival was 50% and five-year survival was 35%. There was no apparent survival difference between complete and partial response to chemotherapy and radiation. Patients who had complete remission had the same outcome whether or not they had surgery. Survival in patients who had partial response to treatment was better if they underwent removal of the esophagus.

Where did the cancer recur? In 69 patients who developed tumor relapse, 55% had local recurrence only, 27% had distant metastasis and 15.9% had local and distant metastasis. Local control was obtained in 86% of the patients having esophagectomy. In patients having chemotherapy and radiation, local recurrence occurred in the majority with a control rate of only 43.2%.

The authors noted that the major toxicity was to the blood counts. This would be due to chemotherapy. Other toxicity included irritation or mucousitis due to the radiation in 145 of patients. Mild kidney toxicity occurred in 10 patients. Other minor toxicities in a few patients occurred in the lung or infections in the venous access site. One patient had a stroke on chemotherapy.

The authors concluded, "More aggressive pre-operative chemo/radiotherapy might improve results but would also enhance toxicity, which in turn could raise the surgical complication rate. Therefore, it seems more advisable to intensify the post-operative treatment with chemo and/or radiotherapy depending on the histologic findings. For the patients who are not subjected to surgery, new therapeutic approaches must be explored - high dose rate brachytherapy as a boost technique, accelerated radiotherapy, use of radiosensitizers and integration into the protocol of new drugs such as Taxanes or Oxaliplatine. Hyperfractionated irradiation is currently being evaluated as a tool to improve local control. In conclusion, our data showed that combined chemo/radiation and esophagectomy could improve local control and survival rates over those of chemo/radiotherapy alone for partial responses after induction therapy. There is no obvious benefit for the small number of patients treated surgically after complete response to radiation and chemotherapy. This aggressive approach should be proposed to young patients with good performance status. However, randomized studies are needed to determine whether this approach is better than chemo/radiotherapy alone."

Our approach at Radiosurgery New York is to use chemotherapy with stereotactic body radiosurgery. Stereotactic body radiosurgery allows for higher dose of radiation to be given more precisely to the cancerous area. Our stereotactic frame allows immobilization of the patient's body. High dose precisely delivered radiation should result in higher control rates. Our data shows a local control rate for esophageal cancers of 90%. This is far superior to that seen in the reported study. Chemotherapy can be used with radiation and radiosurgery.

Doctors from Radiosurgery New York have studied the use of combined radiosurgery with chemotherapy. Some times we also use radiosurgery itself to the primary or even metastatic lesions. The beauty of stereotactic radiosurgery is it is more precise than standard radiation and helps avoid critical structures around the esophagus like the heart and spine from receiving full doses of radiation. Also, the treatment using a stereotactic frame is a more accurate system so the beam can be more targeted.

Fractionated stereotactic radiosurgery has opened a new world of oncology allowing precise radiation to the primary and metastatic disease. Our control rate with hypofractionated stereotactic radiosurgery is approximately 90%. Control rate is cessation of growth, shrinkage or disappearance of the cancer in the treated field. We have patient seminars open to the public, on a regular basis and also have a physician multidisciplinary panel to review scans, reports and

medical history to provide the best possible treatment. We have set up a hot line at 212-CHOICES and answer e-mail questions through gil.lederman@rsny.org.

Further analysis of all data will be important to enhance survival rates for those with esophageal cancer.