

# RECTAL CANCER STUDIES

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Randomized rectal cancer studies are always important since they start with two groups of patients treated in different fashion.

Randomized studies mean the patient consents only to participate in this study, not to dictate the type of treatment. Panels within institutions must have reviewed the treatment protocol and accepted it for their patients' consideration. The patient knows fully about which options are available. Many patients and most all physicians find this quite important. Some patients, however, wish to dictate treatment. These patients either won't participate in such a study or will learn to understand their importance - if indeed there is value to it. Every patient should have full knowledge of the informed-consent process and their disease when all risks/benefits and alternatives are explained.

Usually conflicts between physicians' opinions and patient's desires create different proposed approaches and answers that are best resolved by randomized studies. These differences are often due to different approaches used by various centers and physicians.

Physicians usually only propose randomized studies when the obvious answer is unclear. Certain patients have biases which dictate treatment. This bias may not always lead to the best outcome however.

Recently published by Francois et al, in the prestigious Journal of Clinical Oncology was a randomized study analyzing anal preservation for those with rectal cancer. Many patients with rectal cancer lose control of the anal sphincter. Loss means no control of bowel movements and therefore the patient is generally will have a colostomy. This obviously affects the quality of life.

In the United States, radiation is commonly used after the diagnosis and either before or after surgery for rectal cancer. In Europe, many administer radiation before the definitive surgical treatment of rectal cancer.

Fortunately in many centers such as ours pre-surgical radiation is frequently administered in an attempt to shrink the cancer and avoid a more radical operation and colostomy. This requires an informed patient and surgeon working in concert with the medical oncologist and radiation doctor.

Different approaches are used in different countries. A Swedish rectal cancer evaluation study group has shown an improvement in survival if radiation plus surgery is administered compared to surgery alone. They gave 2500 rad in five fractions over one week. This is a much greater dose administered per day than in the United States. Yet, the overall dose is about half from standard treatment here.

The French had previously published literature showing that pre-operative radiation is more effective than post-operative radiation and, thus, in France therefore usually radiation precedes surgery.

Studies between 1980 and 1990 of 158 patients showed that if patients had surgery within two weeks of radiation, the likelihood of complete response - meaning no cancer in the primary site - was 6%. If patients had surgery six or more weeks after radiation there was a 15% likelihood of no cancer in the original location being found at the time of surgery. This is not especially surprising since it is known that radiation continues to work even after the last treatment.

Furthermore, the likelihood of sparing the anal sphincter was 40% if surgery was performed within the first two weeks of radiation and 60% if done so more than 6 weeks after radiation. These

studies led to the thought that a six week wait after radiation is beneficial for patients to maximize radiation effects and help preserve the anal sphincter.

Thus a randomized study was undertaken to randomly allocate patients and determine the best method of treatment. Endorectal ultrasound was performed in 179 cases by a gastroenterologist to stage or determine the extent of cancer. This is performed by placing the ultrasound probe in the rectal area itself to visualize the extent of cancer. Work-up for metastases was performed including CT scan and blood tests. Ultrasound testing is a form of non-invasive radio-wave testing to determine extent of disease.

Radiation treatments included the rectal cancer 4 centimeters below the cancer with the perirectal lymph nodes involved. The anus was not involved unless there was invasion of the upper part of the anus. The field sizes were approximately 14x10cm. There was no shielding of the radiation fields.

In the United States most patients have customized shielding of the radiation fields to minimize harm to healthy normal tissues. Dose in this European study was 300 rad administered in each fraction times 13 for a total dose of 3900 rad at 13 fractions over 17 days. In US, we deliver radiation at a slower rate to minimize adverse effects on healthy tissues.

Before randomization the surgeon had to declare whether he thought the sphincter-conserving therapy would be possible. Between 1991 and 1995, 210 patients were randomly allocated with all but nine eligible for treatment; Overall 201 patients were accessible in 29 centers. One hundred and two patients received radiation with the short interval with 99 patients having the long interval between radiation and surgery.

Unfortunately, 20 patients had distant metastases or unresectable cancer at the time of surgery. Radiation was said to be well tolerated and did not require a hospital stay.

Overall response rate meaning shrinkage of cancer was 51% in the short interval and 71% in the long interval group of patients. This was statistically analyzed and found to be important. One may well expect this since radiation usually keeps on working after the end of the actual treatment.

The likelihood of complete response or no residual cancer cells was greater in the long interval than in the short interval. The short interval group complete response rate was 10.3%. In the long interval group it was 26%. There was no difference in lymph node involvement between the groups of patients.

One hundred and forty four patients had conservative therapy with 67 treated by abdominal - peritoneal resection thus requiring colostomy. The likelihood of preserving the sphincter was greater in the long interval group than in the short interval group. In the short interval group it was 67% and in the long interval group it was 75%. This translated out to 67 compared to 77 patients. Preserving the sphincter also means avoiding the colostomy.

Post-operative complications were said to be similar at 63% at the short interval and 55% of the long interval group. The risk of dying after surgery in the short interval group was 3% and 4% in the long interval group. There was no difference in hospital stays between the two groups.

Complications occurred in 18% of the short interval group and 17% in the long interval group. Re-operation occurred in 13% of the short interval and 10% of the long interval group. Three year overall survival rate was 78% in the short interval group and 73% in the long interval group. There was said to be no difference in survival between the two groups, when analyzed statistically.

Local recurrences occurred in 9% overall of the patients including 11% of sphincter preserving therapy patients and one patient with an abdominal peritoneal resection. In the short interval

group there was 9% local recurrence rate which was identical to the long interval group.

The authors found that there tended to be an increase in rate of patients in the long interval group who had anal conserving therapy but overall no statistical difference in the two groups.

The study did show that a greater interval in time between radiation and surgery increased the likelihood of downstaging or shrinking the cancer since the response rate was 53% in the short interval group and 71% in the long interval group.

Furthermore, tumors with only a few residual cancer cells were more frequent in the long interval group amounted to 26% compared to the 10% in the short interval group. The doctors also felt that the longer interval between radiation and surgery did not increase the complication rate. Overall there was no difference in survival although the time observed was short.

The French researchers concluded, "This multicenter perspective randomized trial including only patients with lower or middle rectal cancers demonstrates that there is an increased probability of downstaging of the tumor when there is a long interval between the completion of radiation therapy and surgery.

Toxicity in early clinical results is not altered by delayed surgery. There was a non-significant trend for increased sphincter presentation with a longer interval."

More sophisticated radiation techniques, sequencing of combined chemotherapy and radiation as well as staging should positively impact more patients as done here currently. Fractionated stereotactic body radiosurgery can even be considered for treatment of recurrent or metastatic rectal cancers.

You may wish to contact our experts at 2112-CHOICES or e-mail questions to [gil.lederman@rsny.org](mailto:gil.lederman@rsny.org). We also have a multidisciplinary panel of experts to review each patient's case. Additionally we hold seminars open to the public on a regular basis.