



**INTRAOOP**

# New Treatment New Hope

## The Role of IOERT in Locally Advanced Rectal Cancer

(IntraOperative Electron-beam Radiation Therapy)

### Background

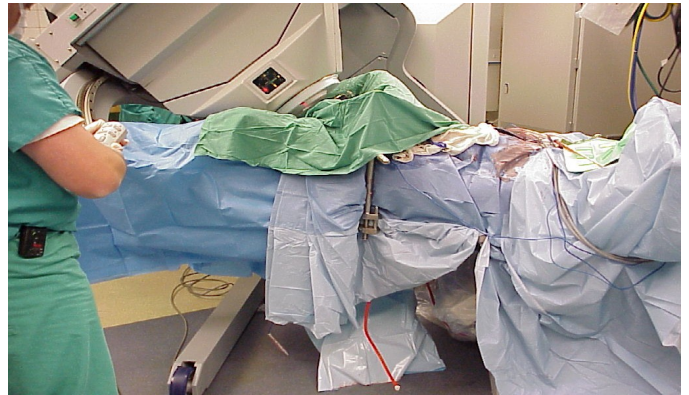
Colorectal cancer is the third leading cause of cancer in both men and women in the United States. If the disease is detected early, the survival rates are upwards of 90% and the morbidity is low. Despite improvements in screening which result in detecting this disease in earlier stages, colorectal cancer remains the second leading cause of cancer death in men and the third in women. Each year more than 50,000 people will succumb to this disease.

Colon cancer and rectal cancer are staged using the TNM system, in which T describes the extent of the cancer and whether or not the tumor has penetrated through the bowel or rectal wall and whether it has adhered to other structures; N describes whether and to what extent there is regional nodal involvement; and M describes whether the patient presents with distant metastases or not. In locally advanced cancer (T3 or T4) the tumor has penetrated through the bowel or rectal wall and may also be adhering to other organs and structures.

The standard treatment practice for locally advanced colon or rectal cancer is to treat the patient with 5-6 weeks of pre-operative chemoradiation therapy in an attempt to downstage and make these potentially difficult tumors easier to resect. After the tissues have healed from the chemoradiation (~ 4 weeks), the patient undergoes surgery. For colon cancer, adequate lengths of bowel must be resected proximal and distal to the primary cancer and the major lymphatic drainage system in the mesentery is also removed. For rectal cancer, the surgical procedure usually performed is a Total Mesorectal Excision (TME), in which the entire rectal mesentery to the sacrum is dissected in an attempt to remove micrometastatic disease. Despite these aggressive surgical procedures, disease may still persist, and local relapse is common. After the patient has recovered from the surgery, maintenance chemotherapy is usually required.

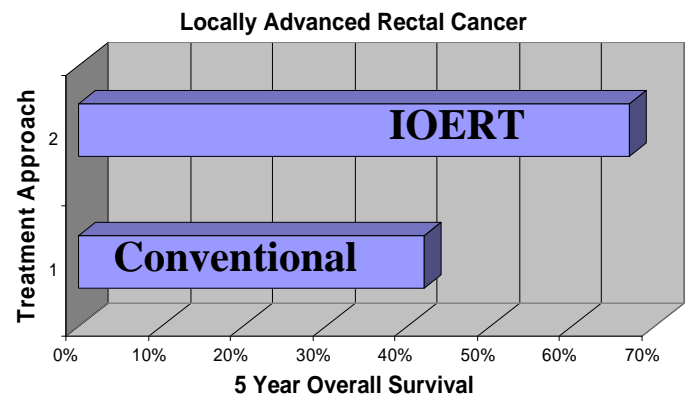
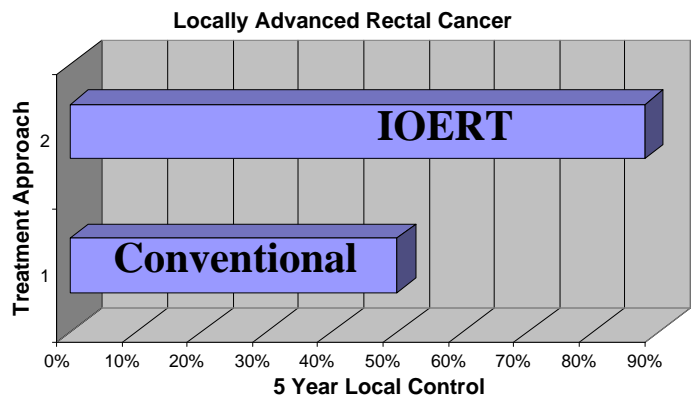
### Rationale for IOERT

External beam doses necessary to achieve control in cases of microscopic residual disease in colon and rectal cancer are in excess of 60 Gy. However surrounding healthy tissues limit external irradiation doses to 45-50.4 Gy, an insufficient dose to control advanced disease. EBRT boost is often technically difficult to achieve due to the risk of small bowel involvement, and even then is limited to 5.4 Gy which results in a total dose of at most 55 Gy. The gap between the maximal external beam dose and the optimal tumorcidal dose can be overcome by means of IOERT boost to the area at risk. For locally advanced rectal cancer, IOERT is particularly effective as a boost because, in the pelvis, even extended surgery is confined to natural boundaries that often make it impossible to achieve a total resection with clear margins. With IOERT, the area of highest risk for tumor cell persistence and can be safely delivered while dose-limiting structures such as small bowel, bladder and ureters can be mechanically excluded from the radiation field. Furthermore, a boost dose of 10-15 Gy of IOERT is biologically equivalent to 20-30 Gy of fractionated EBRT treatment, thereby enhancing the therapeutic ratio. In the U.S., IOERT boost is generally restricted to T4 disease, while in Europe, T3 tumors, particularly those that do not downstage adequately with the preoperative chemoradiation therapy, are also treated with IOERT. A European study (3) also suggests that dose escalation by IOERT allows a 20-25% reduction of the preoperative EBRT dose (to 41.4 Gy), achieving high local control (93% at 5 years) and survival (69% at 5 years), but with substantial reduced acute and late radiation induced morbidity.



### Dutch Rectal Group Recommendations

The Dutch Rectal Cancer Group, one of the world's most respected expert groups in rectal cancer management, has recently recommended that IORT be considered for all T4 and recurrent rectal cancer patients.



IOERT data: Pooled Analysis

Conventional Survival data: Clinical Radiation Oncology, L.L. Gunderson & J.E. Tepper, 2006, ISBN-13: 9780443068409, p.647

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### European pooled analysis

Numerous studies (1-5) demonstrate that IOERT improves local control and possibly survival in locally advanced cancer. The largest reported series of patients is a pooled analysis from the International Society of IOERT-Europe in which 651 patients with locally advanced rectal cancer received a 10 Gy IOERT boost to the area of risk during resection as part of their treatment. Followup ranged from 0-179 months. At 5 and 10 years, the OS was 67% and 46%, respectively, and the local control rate was 88% and 86%. In a multivariate analysis, circumferential margin positivity was a strong ( $p<0.0001$ ) predictor of survival, as well as local recurrence ( $p<0.01$ ). The use of neoadjuvant radiochemotherapy seemed to improve overall survival (70% versus 64% at 5 yrs,  $p<0.05$ ), but had no impact on local recurrence rate. Patients who responded well to neoadjuvant treatment had significantly better survival and local control than those who did not ( $p<0.0001$ ). The level of the tumor (below or above 5 cm from the anal verge) had no impact on either local recurrence rate or overall survival rate.

### Future directions

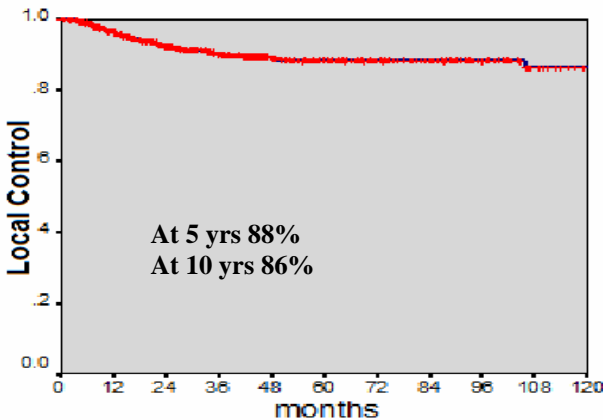
IOERT has demonstrated remarkable local control in locally advanced primary colorectal cancers when used in combination with preoperative radiation chemotherapy to 50.4 Gy and maximal surgery. A recently published study (3) of a large cohort of patients indicates that IOERT in these tumors provides sufficient dose escalation to allow a reduction in EBRT dose, thereby reducing the overall toxicity of the treatment. Further studies to validate this approach are warranted.

In another effort to reduce treatment toxicity, patients whose tumor was sufficiently downstaged after preoperative chemoradiation therapy of 50.4 Gy were offered laparoscopic resection using TME + IOERT(6). The preliminary indication from this pilot study is that laparoscopic resection provides reduced invasiveness and faster recovery. Further studies are needed to determine which locally advanced patients might benefit from this approach and whether the same high level of local control is achieved using this less invasive surgical approach.

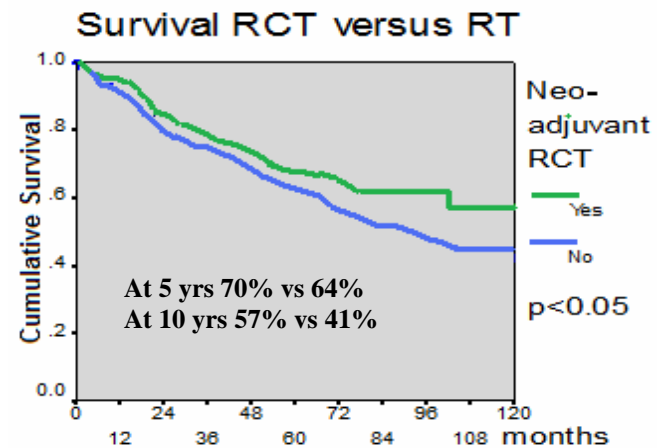
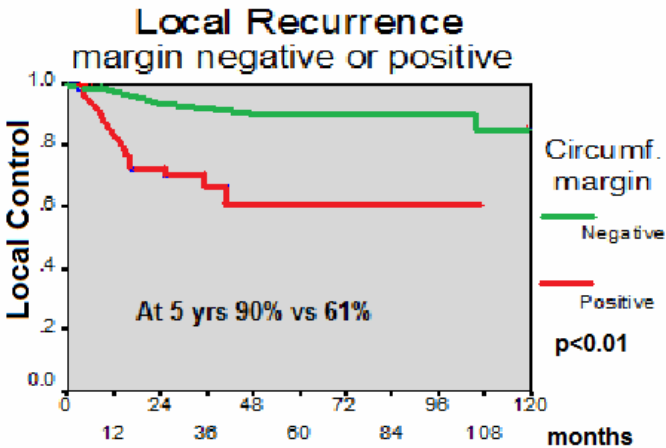
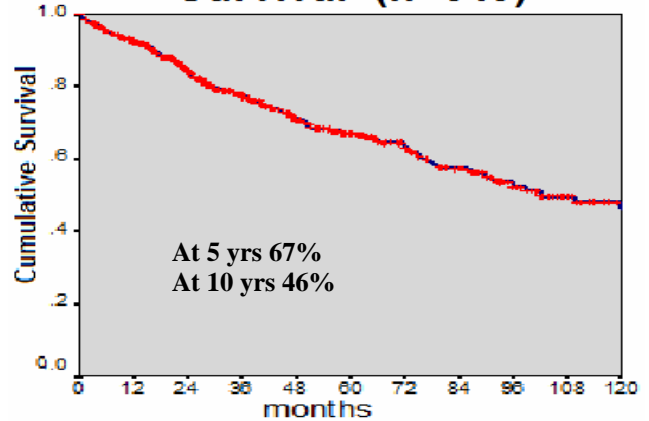
### IOERT DATA FROM POOLED ANALYSIS

Hospital Universitario Gregorio Maranon, Madrid / Catholic University of the Sacred Heart, Rome / University of Heidelberg, Heidelberg / Catharina Hospital, Eindhoven

#### Local Recurrence (58 events in 649 patients)



#### Survival (n=649)



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