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Sphincter preservation in rectal cancer after radiotherapy

J.P. Gerard, P. Romestaing, F. Mornex, O. Chapet. *Département de Radiothérapie, Centre Hospitalier Lyon Sud, Pierre Benite, France*

Purpose: To present clinical data supporting the hypothesis that radiotherapy (RXT) can play a role in the sphincter saving treatment of rectal cancer.

Methods: RXT can provide sphincter saving approach in 2 situations. (1) Radiotherapy alone in T1 N0 (contact x-ray) or T2-3 N0-1 lesions in inoperable patient (combined contact x-ray + External RXT + iridium Brachytherapy). (2) Preoperative RXT with long interval (5 weeks) before surgery in T2-3 lesions. Randomized trial comparing immediate v.s delayed surgery.

Results: 1) T1 N0 contact x-ray: 116 patients treated between 1980–1998: local control 89% overall 5 year survival rate 83%. T2-3 combined irradiation: 1986–1997, 63 patients: local control: 71% overall 5 year survival: 64% (Gérard Sem. Rad. Oncol. 1998, 8: 13).

2) Lyon R90.01 phase III trials. Between 1990–95, 203 patients included short interval () long interval (). The long interval showed a significant increase in complete sterilization of the operative specimen (15% vs 5%) and a trend toward more sphincter saving surgery for low lying tumor (41% vs 22%). Updata analysis after 5 year follow up showw no difference in term of local control and 5 year survival (François J.C.O 1999, 17: 2396).

Conclusion: 1) High dose of RXT in small volume can give long term control of T1-2 (3) rectal cancer. 2) Preoperative RXT and delayed surgery may increase the chance of sphincter saving surgery.

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How mandatory is preoperative short term radiotherapy in addition to TME-surgery for rectal cancer

Cornelis J.H. van de Velde. *Dutch Colorectal Cancer Group; On Behalf of the Participating Groups; LUMC, Department of Surgery, P.O. Box 9600, 2300 RC Leiden, The Netherlands*

Both short term preoperative radiotherapy and total circumferential mesorectal excision have independently demonstrated to improve local control and rectal cancer. The combination of the two treatment modalities without radiotherapy has never been evaluated in the structure of a multicenter randomized clinical trial. The Dutch Colorectal Cancer Group jointly with the Nordic Gastro Intestinal Tumor Adjuvant Therapy and the EORTC conducted a randomized trial to answer the question whether preoperative short term radiotherapy is beneficial in TME treated patients.

Methods: Between January 1996 and January 2000 1861 patients with resectable rectal cancer were randomly assigned to preoperative 5 × 5 GY radiotherapy followed by TME of TME alone. In the trial standardization and quality of surgery, pathology and radiotherapy was achieved, where-as no postoperative chemotherapy was given due to the result of an earlier clinical trial of this group in which no beneficial effect of chemotherapy was found, however in non-standardized surgery.

Results: Of 1861 patients, 57 patients were ineligible and excluded from analysis. Overall two-year local recurrence rate was 5.8% after local radical resection. The two-year local recurrence rates were 8.5% in the TME alone group and 2.9% in the preoperative radiotherapy plus TME-group. Preoperative radiotherapy reduced local recurrence rate for tumors located below 10 centimeter of the anal verge. A significant effect of radiotherapy was found only in TNM stages II and III. The survival in both randomized groups was similar. Quality assurance led to a major improvement of quality of life through reduction of abdominal perineal resections and nerve preservation. Quality assurance of pathology could identify poor surgical specimens with a direct relationship with recurrence and survival, but overall short-term preoperative radiotherapy at this time of analysis has an effect on local recurrence without an effect on survival. Detailed analysis of all subgroups including quality of life will be presented. The current study of the Dutch Colorectal Cancer Group (PROCTOR-study) evaluates after preoperative radiotherapy and TME-surgery the value of postoperative chemotherapy in stage II and III rectal cancer.

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Regulation of p53 activity: the cancer connection

M. Oren, S. Kahan, M. Shutan, J. Zhurinsky, B. Geiger, A. Ben-Ze'ev, A. Damalas. *Weizmann Institute of Science, Department of Molecular Cell Biology, Rehovot, Israel*

The p53 tumor suppressor gene is a major target for inactivation in human cancer. In colorectal cancer (CRC), over 80% of the tumors carry mutations in the p53 gene, which are believed to occur late during tumor progression. Aberrant activation of beta catenin, either by inactivation of the APC tumor suppressor or by mutation of the beta catenin gene itself, occurs very early in colorectal carcinogenesis and plays an important role in tumor initiation.

We investigated whether there is a connection between the activation of beta catenin and the inactivation of p53. We report that deregulated beta catenin leads to accumulation of stable, transcriptionally active p53. This is due to inhibition of Mdm2-mediated degradation of p53, which is responsible for maintaining low levels of p53 in normal cells. Induction of p53 by beta catenin is mediated by the ARF tumor suppressor, and ARF is essential for this induction. Deregulated beta catenin stimulates the transcriptional activity of the ARF promoter. In primary fibroblasts the induction of p53 by excess beta catenin elicits a senescence-like growth arrest; this does not occur in cells lacking either p53 or ARF. It is proposed that these observations underscore an anti-tumor mechanism where deregulation of beta catenin evokes a p53-response, which arrests cell proliferation and prohibits further tumor progression. When p53 function is lost, the oncogenic effects of deregulated beta catenin are unleashed and are enabled to drive tumor progression.

Importantly, cells derived from CRC exhibit constitutive activity of the ARF promoter, which can be blocked by inactivation of beta catenin-mediated signaling. Furthermore, recent work from several groups indicates that ARF transcription is abrogated in a substantial fraction of CRC cases by promoter methylation. This silencing, occurring early during tumorigenesis, is predicted to abrogate the induction of p53 by deregulated beta catenin, thereby overcoming a major obstacle to tumor progression

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The p53 family: What implications in human carcinogenesis?

Sabrina Strano[1], Giulia Fontemaggi[1], Antonio Costanzo[2], Maria Giulia Rizzo[1], Massimo Levrero[2], Ada Sacchi[1], Moshe Oren[3], Giovanni Blandino[1]. *[1] Molecular Oncogenesis Laboratory, Dept. of Experimental Oncology, Regina Elena Cancer Institute, Via delle Messi d'Oro, 156, 00158-Rome; [2] Laboratory of Gene Expression, Fondazione Andrea Cesalpino, University of Rome "La Sapienza" 00160-Rome, Italy; [3] Molecular Cell Biology Department, The Weizmann Institute of Science, Rehovot 76100, Israel*

Many tumors overexpress mutant forms of p53. A growing number of studies suggest that the nature of a p53 mutation in a cell can impact upon cellular properties, clinical responses to therapy and prognosis of a tumor. We and others have previously reported that conformational p53 mutants such as p53His175, but not DNA contact mutants, can increase the resistance to etoposide or contribute to genomic instability by abrogating the mitotic spindle checkpoint and consequently leading to polyploidy of human cells. The molecular mechanisms underlying such effects of mutant p53 remain to be elucidated. We may depict the two following scenarios: A) mutant p53 can transactivate or repress target genes through the binding to specific DNA consensus different from those bound by wt-p53 or through the physical association with DNA binding proteins and utilization of the p53 transactivation domain to turn on/off specific genes; B) mutant p53 can associate with and sequester proteins that are required for anti-tumor effects such as growth inhibition and apoptosis. The recent identification of two p53 relatives, such as p73 and p63 holds new perspectives in studying gain of function of mutant p53. p73 and p63 share a significant homology each other and with p53. Several p73 and p63 isoforms are present in cells. They result either from the use of a cryptic promoter or by alternative splicing. Ectopic expression of p73 or p63 in p53 +/+ or p53 −/− cancer cells can recapitulate the most characterized p53 biological activities such as growth inhibition, apoptosis, and differentiation. The existence of heterodimers between mutant p53 and p73 or p63 has recently been reported. We have previously shown that mutant p53 binds in vitro and in vivo to different isoforms of p73 and markedly reduce their transcriptional activity. Here we report that human tumor-derived p53 mutants can associate in vitro and in vivo with p63. This association is mediated by the core domain of mutant p53 and the DNA binding domain of p63 respectively and may occur directly. We show that overexpression of mutant p53 impairs *in vitro* and *in vivo* sequence specific DNA binding of p63 and consequently affects