6035 POSTER

Post-neoadjuvant anastomotic recurrence in rectal cancer: downsizing, downstaging and distal margin distance correlations

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Background: To analyze the influence of preoperative chemoradiation pelvic effects on the risk of anastomotic recurrence in rectal cancer patients.
Methods: From 4/95 to 1/05, 110 cT_{3-4} or cN+ patients treated with neoadjuvant chemoradiation had radical sphincter preserving surgery. Tumor characteristic were: adenocarcinomas; distance to the anal verge inferior to 3 mm (0.9%) or in the 4 to 6 cm segment (23, 6%); size (maximal clinical dimension) range from 2−13 cm (median 4.8 cm); cT_3 (82.7%), cN+ (44.5%). Neoadjuvant treatment included fluopirimidin modulated pelvic radiotherapy with or without induction Oxaliplatin. Pelvic radiotherapy consisted in 45−50.4 Gy followed by a 10−15 Gy intraoperative presacral electron boost. Surgical procedures performed were: anterior resection (AR) (67%), low AR (31%) ultra-low AR (4.5%).
Results: Downsizing effect was present in 80% of surgical specimens (median size of maximal residual tumor dimension 2.7 cm). T downstaging was 60% and N downstaging 30%. pT_0N_0 category rate was 12.7%. Distance from the lower limit of the residual lesion to the distal surgical margin was: 0−10 mm 26.9%, 11−20 mm 25%, 21−30 mm 25%, >31 mm 23.1%. With a median follow-up of 55.5 months (7–150 months) anastomotic recurrence was diagnosed in 7 patients (6.5%). There were no statistical correlations with downstaging (T or N) or downsizing effects, nor with distance from the lower limit of the residual lesion to the distal margin: 9.3% $\leqslant$2 cm versus 4% >2 cm. Virtual intratumoral surgical section, estimated from the pre-neoadjuvant T longitudinal dimension, was speculated in 21 patients (3 developed anastomotic recurrene 2; 12% vs 5.8%, $p = 0.21909$).
Conclusions: Anastomotic recurrence in rectal cancer patients treated with neoadjuvant chemoradiation is an exceptional event. Virtual intra-tumoral surgical section and anastomosis does not contributes to an excessive risk of recurrence. Data to further impulse the development of policies for ano-rectal complex preservation in rectal cancer patients candidates to neadjuvant treatment.

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The prognostic impact of positive lymph node number in stage III rectal cancer patients treated with surgery followed by radiochemotherapy

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Background: To investigate the prognostic impact of positive lymph node number (LNN) on disease-free survival in stage III rectal cancer patients.
Material and Methods: We retrospectively reviewed the data of 273 consecutive patients who received surgery and 5-FU based postoperative radiochemotherapy for stage III rectal cancer from 1999 to 2004. Lymph node status was evaluated as total number of lymph nodes examined (TLN), positive LNN and lymph node ratio (LNR). Positive LNN was divided into LNN1 (1−3 nodes), LLN2 (4−7 nodes), and LLN3 ($\geqslant$8 nodes). LNR was categorized into three groups, LNR1 to 3, according to cutoff points 0.2 and 0.5. The relationships between survival and clinicopathologic variables, including lymph node status were analyzed.
Results: The median values of TLN, positive LNN, and LNR were 17, 3, and 0.2, respectively. After a median follow-up of 55 months (range, 6–110 months), the disease-free survival, loco-regional failure-free survival, and distant metastasis-free survival were 54.6%, 81.7%, and 58.1%, respectively. In multivariate analysis, LNN was a significant prognostic factor for disease-free survival ($p = 0.01$), whereas TLN, LNR, pathologic tumor stage, patient's age, gender, and sequence of radiochemotherapy (chemotherapy prior to postoperative radiochemotherapy vs. immediate postoperative radiochemotherapy) were not. In patients with LNN3 showed a significant lower disease-free survival rate at 5-years than in patients with LNN2 (28.3% vs. 50.5%, $p = 0.01$), or patients with LNN1 (28.3% vs. 63.2%, $p < 0.001$).
Conclusions: Positive lymph node number was the most significant prognostic factor for the disease-free survival in stage III rectal cancer patients who had treated with surgery and postoperative radiochemotherapy.

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Bevacizumab – Capecitabine – Oxaliplatin – Radiation – REctal Cancer Trial (A-CORRECT) for locally advanced and low rectal cancers

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Background: Capecitabine (Cap) and oxaliplatin (Ox) have been given safely in phase I/II trials concurrently with radiation with promising pathological complete response (pCR) rates of 15−24% compared with historical rates of 8−14% with 5-FU alone. The aim of this multicenter phase II trial is to evaluate the efficacy and safety of bevacizumab (Bev), Cap and Ox given concurrently with radiotherapy in patients (pts) with locally advanced or low-lying rectal cancer.
Materials and Methods: Pts with histologically confirmed locally advanced mid, upper (fixed/tethered T3/4 or bulky N+) or low ($\geqslant$T3NX) rectal adenocarcinomas received i.v. Bev 5 mg/kg (d −14, 1, 15, 29), oral Cap 825 mg/m^2 bid (d1−14, 22−35), i.v. Ox 50 mg/m^2 (d1, 8, 22, 29) and radiation 50.4 Gy/28 fractions (d1−35, Mon-Fri). Surgery was performed 7−9 weeks after completion of radiation. Study endpoints are: pCR rate, rate of sphincter-sparing surgery, complete resection (R0) rate, safety, 1-month post-surgical complication rates. The planned sample size is 37 evaluable pts.
Results: As of 16 April 2009, 37 pts have been enrolled. Baseline data is available for 30 pts: M/F 23/7; median 59 (range 38−84) years; ECOG 0/1 22/8; T3/4 23/7; median distance from anal verge 5 cm (range 0.4−18 cm). 29 pts are evaluable for toxicity and 16 pts are evaluable for response. *Preoperatively:* the most common adverse events (# of pts: all grades/grade 3+) were pain 22/1, fatigue 19/1 and diarrhea 19/4. 4 infection/abscess, 1 fistula and no bleeding complications or perforations reported. *Postoperatively:* the most common adverse events were pain 13/1, fatigue 12/1, hypertension 6/1 and insomnia 6/0. Pre-defined post operative toxicities, including Serious Adverse Events, were infection/abscess 4/1, anastomotic leaks 4/2, wound healing complications 4/1, fistula 1and no bleeding complications or perforations. Treatment modification was required in 12/74 cycles (16%). 22 of 24 pts who completed radiation received full dose radiation, 50.4 Gy/28. At cut-off, postoperative data were available for 16 pts: sphincter-sparing surgery ($n = 9$); R0 ($n = 14$); pathological staging pT0/1/2/3/4: 3/2/3/7/1 with 3 pts (19%) achieving a pCR.
Conclusions: Pre-operative therapy with Cap, Ox and Bev was well tolerated allowing planned delivery of radiation. 38% of pts (6/16) had post-operative complications grade 3+ consistent in frequency with other studies.
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6038 POSTER

Pilot study of preoperative involved field radiotherapy in rectal cancer

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Background: The success of total mesorectal excision (TME) surgery in reducing local recurrence rates in rectal cancer, suggests that the majority of cells leading to local recurrence reside within the mesorectal fascia. If correct, RT to the entire pelvis in rectal cancer patients may not be needed. We hypothesize that preoperative RT to the rectal tumor with a margin to encompass the mesorectal tissue and adjacent lymph nodes (involved field) will lead to equivalent local control as the standard RT volume but with less morbidity and improved quality of life.
Methods and Materials: Thirty MRI or endorectal ultrasound staged T3 and/or N1/M0 rectal cancer patients accrued. Preoperative RT to a dose of 45 Gy to PTV1 (GTV+ mesorectum + presacral space + lateral lymph nodes + 3.5 cm superior and inferior) +/− a boost of 9 Gy to the GTV +

2 cm is given. Small bowel dose is not to exceed 50 Gy point dose. A 3 or 4 field box technique is utilized. All patients receive prolonged venous infusion 5 Fluorouracil with the RT, followed by postoperative chemotherapy for 4 cycles.
Results: 22 of 30 patients have been accrued. Preoperative stage shows 14 T3N0 and 8 T3N1 patients. One patient did not complete chemotherapy due to Grade 3 GI toxicity. Postoperative pathology of the first 18 patients shows 3 complete responses − T0N0, 1 T1N0, 5 T2N0, 4 T3N0, 3 T3N1. One patient developed distant metastases and did not have surgery. One patient declined recommended surgery and had local excision alone, which showed no residual disease. One patient whose pathology showed incomplete TME has had a local recurrence. In total, two patients have developed distant liver metastases.
Conclusions: Involved field rectal RT is feasible. The dose to small bowel and bladder is reduced. Data from the remainder of the patients will be presented with discussion of dosimetric and clinical toxicity data.

	Mean Dose			
	Small Bowel (cGy)		Bladder (cGy)	
Patient	Involved Field	Standard	Involved Field	Standard
2	36.4	387.0	1,575.1	3,550.8
3	1,179.3	2,357.6	2,804.1	4,028.1
4	973.2	2,644.9	3,754.9	4,052.0
5	338.5	388.2	3,458.9	4,183.3
6	2,289.3	3,146.5	3,942.6	4,273.9
7	352.0	225.0	3,808.0	3,796.0
8	2,998.6	3,118.4	3,785.0	3,872.0
9	2,105.8	2,241.4	4,009.9	4,534.9
10	187.7	1,102.4	3,601.3	4,394.1
11	1,231.6	1,562.6	4,205.5	4,415.4
12	270.4	1,030.6	4,076.1	4,353.4
13	912.2	4,722.9	3,289.0	3,988.8
14	272.5	1,369.4	3,694.9	4,346.6
15	279.1	253.3	3,931.5	4,302.1
16	2,237.5	2,084.6	3,518.4	4,489.4
17	1,015.4	1,295.2	3,946.6	4,398.4
18	788.2	755.5	4,890.7	5,062.9
20	407.0	2,078.4	4,508.3	4,458.4
Average	993.0	1,709.1	3,711.2	4,250.0

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Pathologic Complete Response (pCR) after preoperative radiochemotherapy in cT3M0 rectal cancer patients: an analysis from a large database

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Background: Many studies reported that patients responding with a pathologic complete response (pCR) after preoperative radiochemotherapy have very good long-term outcome. Predicting a pCR at diagnosis will be important in an attempt to modulate the treatment for each patient (i.e. less invasive surgery).
The purpose of this analysis is to retrospectively evaluate the impact of progressive intensified schedules of preoperative radiochemotherapy on pT0N0 in rectal cancer patients treated in our institution since 1985.
Matherial and Methods: from a large database containing 1420 patients, a group of 405 patients between 1985–2008 was collected retrospectively. The patients were diagnosed with rectal cancer with cT-stage 3 and cM-stage 0 and were treated with preoperative chemoradiotherapy (CRT: 45−55 Gy, 1 or 2 drugs). Surgery was performed 6−10 weeks after treatment and pathologic reports were reviewed for complete response (ypT0N0). Collected pre-treatment variables included sex, age, cN-stage, tumor distance from the anorectal ring, number of involved rectum quartiles (Qrt), tumor length, volume index (Qrt × tumor length), and concomitant chemo type. Post-treatment were collected for 408 patients: the volume index and the relative difference between pre- and post treatment evaluations of tumor distance, Qrt, tumor length and volume index. Multivariate analysis was performed with a 2-norm support vector machine (SVM). Performance of the model was expressed as the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curves and assessed with leave-one-out (LOO) cross-validation. A nomogram was build from the model output.
Results: CRT resulted in a ypT0N0 for 20% of the patients. Based on the AUCs (Mean ±SD) of the ROC-curves we found that the pre+post-treatment model has the highest performance (AUC = 0.65±0.04) compared to pretreatment alone (AUC = 0.62±0.03). Predictive pretreatment variables ranked to importance (i.e. weights): chemo type (0.11), cT (−0.097), tumor length (−0.065) and cN-stage (−0.053). Post-treatment the volume index was most important (−0.17).
Conclusions: the analysis shows the presence of predictive pT0N0 risk factors related to the intensification of the treatments, to some tumor characteristics at the diagnosis (cT, tumor length and cN-stage), and to the response to radiochemotherapy. A nomogram to predict pCR in cT3M0 patients after radiochemotherapy will be proposed.

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A pilot study of neoadjuvant chemoradiation with higher dose enteric-coated tegafur/uracil plus leucovorin for locally advanced rectal cancer

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Background: Neoadjuvant chemoradiation (CRT) with tegafur/uracil (UFT) 200–350 mg/m^2/day plus leucovorin (LV) 25−75 mg/day for 5 days a week with 45 Gy radiation (RT) for locally advanced rectal cancer (LARC) was known to be efficacious and tolerable, but higher dose UFT/LV and RT may improve pathologic response rate. We have performed a pilot study to evaluate pathologic response rate and toxicity profile of neoadjuvant CRT with higher dose enteric-coated tegafur-uracil (UFT-E)/LV.
Materials and Methods: Patients (pts) were planned to be treated with UFT-E 400 mg/m^2/day plus LV 90 mg/day for 7 days a week during RT 50.4 Gy. Main eligibility criteria were histologically proven rectal adenocarcinoma; T2−4 lesions; age >18 years; ECOG PS 0−1; no prior chemotherapy or pelvic irradiation. Total mesorectal excision was planned to be performed 4−8 weeks after completion of CRT.
Results: Between June 2008 to January 2009, 39 pts were enrolled; median age 57 years (40−92); M/F 26/13; PS 0/1 37/1; cT2/T3 2/33; N0/N+ 6/29; median tumor location from anal verge 6.0 cm (2.0−9.0). The median relative dose intensity of UFT-E was 95.0% (51.6–111.7). Three pts were given reduced dose RT (1 with 27 Gy, 2 with 45 Gy) due to grade 3/4 diarrhea; 5 pts needed UFT-E dose interruption due to toxicities. Grade 3/4 toxicities included leucopenia (2, 5.1%), neutropenia (3, 7.7%), hyperglycemia (4, 10.3%), elevated transaminase level (2, 5.1%), diarrhea (4, 10.3%), nausea (2, 5.1%), and pain (2, 5.1%). Of 36 pts who underwent surgery (all R0 resection), 22 (91.7%) were treated with sphincter saving procedure. Pathologic T0 and N0 were observed in 8 (22.2%) and 29 (80.6%) pts, respectively. Downstaging in T stage was achieved in 24 pts (66.6%). Pathologic complete responses were observed in 8 (22.2%) pts and another 7 (19.4%) pts had only minimal microscopic residual tumor.
Conclusions: Neoadjuvant CRT with higher dose UFT-E/LV showed favorable efficacy and tolerability. A phase II trial of CRT with higher dose UFT-E/LV is ongoing.

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Evaluation of folate derivates in the neoadjuvant treatment of resectable rectal cancer with the antifolate pemetrexed

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Background: Understanding the role of different folate derivates is essential in the understanding of the physiology of tumor growth. To our knowledge this is the first study introducing a sensitive liquid chromatography-mass spectrometry (LC-MS/MS) method to analyze folate levels in tumor and adjacent mucosa.
Methods: Between June 06 and January 08, 37 patients with a histologically proven diagnosis of operable rectal adenocarcinoma were enrolled. Pemetrexed was dosed at 500 mg/m^2 every 3 weeks, during