6045 POSTER

Comparison of Predictive Models PREMM$_{1,2}$, MMRpro and Wijnen for Mutation Detection Associated With Lynch Syndrome in MLH1 and MSH2 Genes

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Background: Lynch syndrome is the most common inherited cause of colorectal cancer, and is due to germline mutations in mismatch repair (MMR) genes. Most mutations occur in genes MLH1 and MSH2. Currently, clinical and molecular criteria are used for selecting individuals with Lynch syndrome. Several predictive computer models have been development to predict the probability of being a carrier of a mutation in the MMR genes.
Material and Methods: Between 2005–2008, 124 MLH1 (64) and MSH2 (60) analyses in patients with suspected Lynch syndrome were performed. Retrospectively, all patients were applied the predictive models PREMM$_{1,2}$, MMRpro and Wijnen's model. The predictive ability of each model was assessed using the area under the receiver operating curve (AUC). Sensitivity and specificity at different cutoffs were compared for different models.
Results: Pathogenic MMR gene mutations were detected in 20 (16.13%); 6 of MLH1 gene and 14 of MLH2 gene. PREMM$_{1,2}$ had better predictive ability to detect between mutation carriers and noncarriers (AUC 0.698 [95% CI, 0.576 to 0.82]), which MMRpro model (AUC 0.631 [95% CI, 0.502 to 0.76]) ($z = 16.75$, $p < 0.05$). Also, both models were superior to the Wijnen's model (AUC 0.533 [95% CI, 0.386 to 0.679]) ($z = 10.89$ versus MMRpro, $z = 12.69$, $p < 0.05$). From 6% cutoff, PREMM$_{1,2}$ discriminated between individuals carrying germline mutation in the MLH1 and/or MSH2 ($p = 0.028$), for this cutoff point, its sensitivity was 90%, while specificity of 35.82%. The cutoff of PREMM$_{1,2}$ 20% had a sensitivity of 71.64% and specificity of 45%, negative predictive value 81.35% and 32.14% positive predictive value.
Conclusions: The model PREMM$_{1,2}$ has better discriminative power of germline mutation in MLH1 and MSH2 genes that MMRpro models and Wijnen, although its sensitivity and specificity for different cutoff points were low.

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Urological Leaks After Pelvic Exenterations Comparing Formation of Colonic and Ileal Conduits

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Objective: Assess risk factors for urinary leakage of a newely formed urinary conduit after a pelvic exenteration.
Summary Background Data: Pelvic exenterations are a potentially curative treatment for locaaly advanced pelvic cancer. After the creation of an ileal or colonic conduit there is a high risk of urinary leaks. We expect multiple factors would be of influence.
Materials and Methods: Analysis conducted from prospectively collected data of patients who underwent a Pelvic Exenteration with conduit formation for advanced pelvic cancer, in the period from December 1995 until December 2010.
Results: Of 232 patients undergoing pelvic exenteration, 74 (32%) had an ileal (64%) or a colonic (36%) conduit formed. Patients were aged between 14 and 91 years and 74% were male. Twelve (16%) patients developed a leak in total, of which 9 within the first month. The factors significantly associated with a urine leak were involved surgical margins, the magnitude of the exenteration and a current cardiovascular medical history. The 30 day leak rate for colonic conduits was 4% (1/27) compared with 17% (8/47) for an ileal conduit. Survival was not significantly differnt between the patients with or without a leak. The median survival time was however significantly longer for patients without a leak ($P = 0.04$).
Conclusions: Urine leaks after conduit formation in association with exenterations are quite common. Cardiovascular risk facors, positive surgical margins and the magnitude of pelvic exenterations but not radiotherapy were associated with leaks. Colonic conduits had a slightly lower leak rate than ilal conduits.

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Neoadjuvant Capecitabine-based Chemoradiotherapy in Resectable Rectal Cancer

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Background: Preoperative 5-FU based chemoradiotherapy (CRT) improves local tumour control in resectable rectal cancer. Capecitabine (CAP), an oral fluoropyrimidine, is converted to active 5-FU in tumour cells. CAP has shown to be as effective and well tolerated as 5-FU iv in the adjuvant and metastatic colorectal cancer. Previous studies in rectal cancer have shown that CAP replace 5-FU in this setting. The aim of this retrospective analysis was to evaluate the effectiveness and safety of preoperative capecitabine-based CRT in patients with resectable rectal cancer.
Methods: From February 2004 to May 2010, patients with resectable rectal cancer, age$\geqslant$18, ECOG$\leqslant$2, adequate haematologic, renal and hepatic functions were included in this analysis. Neoadjuvant chemotherapy was CAP (825 mg/m^2/12h, 5 day/w, oral) with RT (50.4 Gy) for a median of 6 weeks. Surgery was performed a median of 6 weeks after RT. Survival curves were estimated by Kaplan–Meier method.
Results: Sixty one patients, 70.7% men and 29.31% women with a median age of 67 (45−82), ECOG 0−1, with locoregional 47.5% uT3N$_X$, 26.2% uT3N$_+$, 10% uT4N$_X$, 11.5% uT4N$_+$ and well-moderately differentiated G1−2(90%) tumours. Performed surgeries were Abdominoperineal amputations (78%) and low anterior resections (21%). Only 7 patients (12.5%) had CAP reductions. Fifty-two patients (85%) did not have any adverse event grade 3−4 treatment-related. Adverse event consisted of diarrhea and anemia (2 patients each), skin toxicity (1 patient), mucositis and medullar aplasia with DPD deficiency subsequently confirmed (1 patient). After resection, pathological stages were pT0N0 (10.5%), pT1N0 (3.5%), pT2N0 (23%), pT2N1−2 (5.2%), pT3N0 (30%), pT3N1−2 (24.5%), Pt4N0 (3.5%), histological tumour grades were G1 23% (13 pts), G2 62% (35 pts), G3 3% (2 pts), and tumour regression TRG1−2 (15%), TRG3−4 (50%). After surgery, 98% of the pts received adjuvant treatment. At 4-year follow-up there were 8 deaths, being survival from diagnosis to death 85.4% (95% CI, 73.0–92.4) with 3 progressions, and survival from diagnosis to progression 94.5% (95% CI, 84.0–98.2).
Conclusions: Efficacy and tolerance of Neoadjuvant capecitabine-based chemoradiotherapy in patients with well-moderately differentiated locoregional rectal cancer is similar to concurrent RT+5-FU as previous studies had suggested. Long-term follow-up demonstrated high rates of survival from diagnosis, with few disease progressions.

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Colorectal Cancer Resectable Liver Metastases Patient 5-year Survival After Preoperative Transarterial Chemoembolization With Oxaliplatin Followed by Liver Resection

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Background: Liver resection (LR) is a standard treatment option in resectable colorectal cancer (CRC) liver metastases patients. Perioperative chemotherapy has allowed to raise reccurence-free survival by 9% but role of neoadjuvant therapy hasn't been learned yet.
Material and Methods: Prospective nonrandomized trial, including 66 synchronous and metachronous CRC resectable liver metastases patients, has been completed. Resectability criteria were removal of all metastases with reservation of more than 30% liver parenchyma; portal vein, more than 2 hepatic vein and inferior cava invasion absence. LR has been performed in group 1 ($n = 40$, average age-59 years old, 25 men, 15 women). Transarterial chemoembolization (TACE) with 50–100 mg oxaliplatin, followed by LR in 4−6 weeks, has been carried out in group 2 ($n = 10$, 58, 2/8). TACE with 30−50 mg doxorubicin, followed by LR in 4−6 weeks, has been conducted in group 3 ($n = 16$, 56, 8/8).
Results: Median and 5-year recurrence-free survival (RFS) have amounted to 13.1 months and 22.3$\pm$6.6% in group 1; 36.9 months and 40.0$\pm$15.0% in group2; 13.8 months and 5.9$\pm$5.7% in group 3, respectively ($p = 0.015$). RFS was hgher in group 2 versus group 1 ($p = 0.033$) and group 3 ($p = 0.003$). Median and 5-year survival (OS) have amounted to 32.8 months and 30.3$\pm$7.4% in group 1, median hasn't been obtained and 5-year survival has amounted to 58.3$\pm$16.1% in group 2, 31.1 months

and 8.8±8.7% in group 3, respectively. Statistically significant differences of overall survival haven't been obtained (p = 0.06). The influence of TACE with oxaliplatin on RFS and OS has been demonstrated by Cox regression analysis (HR 0.24 [95% CI 0.09–0.64], p = 0.003 for RFS and HR 0.28 [95% CI 0.09–0.86], p = 0.014 for OS).
Conclusions: Using TACE with oxaliplatin and LR in CRC resectable liver metastases patients has improved recurrence-free survival and has reduced disease recurrence and death risks. Phase III of clinical trial is under consideration.

6049 POSTER

Phase II Study of Neoadjuvant Chemoradiotherapy With Oxaliplatin-Containing Regimen in Locally Advanced Rectal Cancer

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Background: Preoperative fluorouracil (FU)-based chemoradiotherapy was associated with improved local control and less toxicity but did not improve overall survival. Oxaliplatin also has radiation sensitization properties. Patients with pathological complete response (ypCR) following chemoradiation have better survival than do those without ypCR.
Purpose: The aim of this study was to assess tolerance of this regimen and evaluate the response of rectal cancer following chemoradiotherapy containing oxaliplatin preoperatively.
Methods: Between August 2008 and August 2010, thirty patients with clinical T3/T4 or N+ rectal adenocarcinoma located in mid or lower rectum without metastasis were entered onto the study in single institute. Data were analyzed according to the intention-to-treat principle. Leucovorin was administered at 20 mg/m^2 followed by continuous infusion of 5-FU of 350 mg/m^2 on days 1 to 5 and 29 to 33. Oxaliplatin was administered at 130 mg/m^2 on days 1 and 29 simultaneously with leucovorin. Radiation dose was 180 rad/fraction to a total dose of 50.4 Gy (28 fractions). Surgery was scheduled 6 to 8 weeks after completion of chemoradiotherapy. Adverse effects were graded according to the Common Toxicity Criteria of the National Cancer Institute. Tumours following surgery were graded by tumour regression. All statistical analyses were conducted using SPSS 18.0. This study was approved by the institutional review board of our institution.
Results: Thirty one patients were entered onto the study. Six patients (19.4%) experienced grade 3 diarrhea. Grade 2 nausea and vomiting occurred in 5 and 2 patients, respectively. Severe neurotoxicity was not observed: grade 1 sensory neuropathy occurred in 10 patients (32.3%). Myelosuppression was mild and grade 2 anemia, neutropenia, and thrombocytopenia occurred in 2, 2, and 1 patient, respectively.
All patients underwent surgical resection: 23 underwent low anterior resection, 6 had coloanal anastomosis, and 2 received Hartmann's procedure. Sphincter-saving surgery was performed in 28 patients (93.5%). Mean distance of the tumour from anal verge was 5 cm. Anastomotic leakage occurred in 4 of 29 (13.8%) patients with anastomosis. Mean number of harvested lymph nodes was 8.4. Mean distal margin of tumour was 1.5. The circumferential resection margin was involved in two patients (6.5%). Overall 24 patients (77.4%) responded to the treatment. Four of the 31 patients (12.9%) taken to surgery had ypCRs. When ypCR was combined with only few residual cells, the rate was 22.6%.
Conclusion: The overall toxicity of combined oxaliplatin to continuous infusion of 5-FU and radiation was well tolerable. The neoadjuvant chemoradiation with oxaliplatin-containing regimen for patients with locally advanced rectal cancer was associated with higher rates of sphincter preservation and down-staging. Further prospective randomized trials are necessary to better define the benefits as oncologic outcomes.

6050 POSTER

A 12-week Regimen With Interdigitating FOLFOX Chemotherapy and Pelvic Chemoradiation for Simultaneous Primary and Metastatic Rectal Cancer

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Background: Chemotherapy dose used during chemoradiation is adequate for radiosensitization but suboptimal for systemic control. The aim of this study was to evaluate tolerability, and local and systemic benefits of a new treatment regimen delivering intensive chemotherapy and radical radiotherapy in an interdigitating manner. (ClinicalTrials.gov Identifier: NCT00422864)
Materials and Methods: This was a single arm prospective study for patients presenting with untreated simultaneous symptomatic primary and metastatic rectal cancer. The treatment regimen was 12 weeks long. FOLFOX chemotherapy (oxaliplatin 100 mg/m^2 day 1, leucovorin 200 mg/m^2 day 1, 5-FU 400 mg/m^2 bolus day 1, then continuous infusion 2.4 g/m^2 over 46 hours) was given in week 1, 6, and 11. Pelvic radiotherapy (25.2 Gy in 3 weeks in 1.8 Gy/fr with concurrent oxaliplatin 85 mg/m^2 day 1 and 5-FU continuous infusion 200 mg/m^2/day) was given in week 3−5, and week 8−10. In total, patients received, in 12 weeks, 3 courses of FOLFOX and pelvic radiation 50.4 Gy with concurrent oxaplatin and 5-FU. All patients were staged with CT, MRI and PDG-PET before and after treatment.
Results: Twenty-six patients were treated in this study. The mean age was 61 (range 33−82) years. 69% were male. MRI stage of the rectal primary was T2 4%, T3 81% and T4 15%. Liver, lung, and extra-pelvic nodal metastases were present in 81%, 35% and 23% of patients, respectively. 38% of patients had more than one site of metastatic disease. Twenty-four patients (92% [95% CI:75%-99%]) completed the 12-week treatment regimen. All patients received the planned radiation dose. 65% (95% CI:44%-83%) of patients received the planned number of courses of oxaliplatin with 88% of patients receiving at least 75% of the protocol oxaliplatin dose. In this 12-week period, grade 3 toxicities were neutropenia 23%, diarrhoea 15%, and radiation perineal skin reaction 12%. All grade 4 toxicity was due to neutropenia 15%. There was no febrile neutropenia. PET metabolic response (CR+PR) rate for rectal primary was 96% (95% CI:80%-100%). Overall PET metabolic response rate for metastatic disease was 60% (95% CI:39%-79%) (CR rate 16%).
Conclusions: It is feasible to deliver intensive chemotherapy and radiotherapy to treat primary and metastatic rectal cancer simultaneously. High completion and response rates are encouraging. This regimen is the subject of a current phase II neoadjuvant trial for resectable rectal cancer (TROG 09.01).

6051 POSTER

Combined Modality Treatment in Anal Canal Carcinoma − Impact of Full Dose Treatment and Clinical Stage Category on Outcomes

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Background: Since N Nigro's report in 1974, combined modality treatment, chemo-radiotherapy (CCRT), has been the standard in anal canal carcinoma. We report the results of this treatment with regard to compliance, toxicity, clinical outcomes and we intent to determine if full dose treatment and clinical stage has an impact in this patient group.
Material and Methods: Between 1999 and 2009, 42 patients received CCRT with no planned gap (45 Gy at 1.8 Gy/fraction +/− boost 9 Gy at 1.8 Gy/fraction; 5-fluorouracil, 1000 mg/m^2, Days 1−4 and 29−32, mitomycin C, 10−15 mg/m^2, Days 1 and 29). Median age 62 years (28−83); 11 (26%) males (6 HIV positive), 31 (74%) females; Stage I = 6 (14%), II = 13 (31%), IIIA = 8 (19%), IIIB = 15 (36%). Median overall treatment time (OTT) was 35 (14−53) days, 36 (81%) patients received full dose treatment (FDT), 2 patients had grade 4 toxicity, and 1 treatment related death. Median follow up was 63.8 months with a minimum of 25 months.
Results: For the whole study sample Kaplan–Meier 5-year rate of loco-regional control (LRC) was 78%, colostomy free survival (CFS) 73%, distant metastases free survival (DMFS) 76%, disease free survival (DFS) 65% cancer-specific survival (CSS) 69% and overall survival (OS) 46%. The