Proffered Papers

Colorectal

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The impact of surgical training workshops on the outcome in rectal cancer in the population of Stockholm

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The Swedish rectal cancer radiotherapy trials have led to an increasing use of short course preoperative radiotherapy in rectal cancer (RC). Despite this the local recurrence (LR) rate after irradiation, with conventional surgery, has been 12–15%. Following reports that Total Mesorectal Excision (TME) may reduce LR to below 5% in curative cases, the Stockholm Rectal Cancer Study Group set up a collaborative project of surgical workshops to introduce TME to the surgeons of Stockholm. Three workshops were held between 1994 and 1997. The aim of the study was to assess if the TME technique could reduce the LR rate after RC surgery in the population of Stockholm and thus if a surgical teaching initiative could have a direct effect on patient outcome.

Material and Methods: Prospectively collected data on postoperative morbidity-mortality and LR rate within two years of surgery in all RC patients in Stockholm 1995–96 were compared to data from patients included in the two Stockholm radiotherapy trials (Stockholm I Trial; 1980–87 and Stockholm II Trial; 1987–93). Patients operated on with a curative abdominal procedure were included in the analysis.

Results: In all, 70% of patients with RC had a curative abdominal procedure in Stockholm 1995–96. In the Stockholm I Trial the corresponding figures were 81% and in the Stockholm II Trial 86%. TME was performed in 83% of the patients in 1995–96. The rate of abdominoperineal resection (APR) was 26% in 1995–96 compared to 60% and 55% in the Stockholm I and Stockholm II Trials ($p < 0.001$). The crude LR rate was 5.5% in 1995–96 compared to 16% and 14% respectively in the two Stockholm Trials ($p < 0.001$).

Conclusion: The rate of LR and APR was reduced in RC patients in Stockholm after the introduction of TME technique. Surgeons can adopt this technique by workshops with active surgical training. Surgical teaching inititiatives like the TME workshops significantly improve outcome in rectal cancer.

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Preop chemoradiation (CTRT) ± postop chemo (CT) in locally advanced rectal cancer. Preliminary results

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Purpose: to report the preliminary results of a multicenter randomized trial on preop CTRT followed or not by postop CT in 583 pts with locally advanced rectal cancer (T3–T4) after 33.6 months mean follow up (Sept. 93–Feb 99).

Materials and Methods: males 388, females 195, median age 61 yrs, tumor stage: T3 401, T4 98; distance from anal verge: <4 cm 109, >=4–8 cm 375, >8 cm 80. Preop CTRT: 45 Gy (180 cGy × 5, weekly) + 5-FU 350 mg/mq and Fol.ac. 10 mg/mq on days 1 to 5 and 29 to 33, of the RT. Postop. CT: 5-FU 350 mg/mq and Fol.ac. 100 mg/mq day 1 to 5 for 6 cycles, 3 weeks apart.

Results: to be considered as preliminary because the forms collection from the partecipating centers is still ongoing. Preop CTRT: forms received 475: completing the preop treatment 466; toxicity >= G3 28 (2 toxic deaths); undergoing surgery 439 (APR 152, LAR 281, palliative 6); interval CTRT-surg: median 39 days; anastomotic deiescence 43, perineal abscess 11, intestinal occlusion requiring surgery 10; perioperative deaths 5. Operative specimen pathology: no residual tumour 74, tumour within the intestinal wall 153, still outside the intestinal wall 195; positive nodes 103; positive margins 12. Postop CT: randomized 299; forms received 135, completing a minimum 6 cycles 110. Follow-up: forms received 391, with 6 months minimum follow-up: local recurrence alone 15; local and distant 10; distant only 75. Postop CT alone not evaluated.

Conclusion: preop CTRT resulted in pathological down-staging in 2/3 of cases (negative specimens 17%) and local recurrence rate of 6%.

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Influence of the interval between pre operative radiotherapy (preop RXT) and surgery on downstaging and sphincter preservation for rectal cancer. The LYON R90 01 randomized trial

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Purpose: The aim of this trial was to evaluate the role of interval between preop RXT and surgery in the treatment of rectal cancer.

Methods: Operable patients with rectal adenocarcinoma accessible to digital recta examination, staged T2-3 Nx M0 were randomized before radiotherapy (39 Gy/13 fractions/17 days – 3 fields technique × 18 MV) into 2 groups: short interval (SI) with surgery performed within 2 weeks after the end of RXT versus long interval (LI) surgery delayed after 6 weeks. Between 1991 and 1995, 205 patients were included and the groups were well balanced (median age 64 Y).

Results:

	SI (N = 99)	LI (N = 102)	P
Clinical response:	53%	71%	0.04
Sterilized specimen (±)	10%	26%	0.05
Sphincter preservation	68%	76%	N.S
Anastomotic leak	13%	10%	N.S
Local recurrence (3Y)	9%	10%	N.S
3 y. overal survival	78%	74%	N.S

In patients with tumor in the low rectum (5 cm or less above anal verge) the sphincter preservation was only 23% in SI and 41% in LI.

Conclusion: After preop RXT a long interval increases the tumor down staging and in some selected cases many increase the chance of sphincter preservation. No increase in complication or local recurrence is seen with long interval (accepted for publication in J. Clin. Oncol.)

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In vivo monitoring of tumor microcirculation changes during radiotherapy in patients with rectal carcinomas: Preliminary results and possible implications for therapy

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Purpose: This study aimed to measure microcirculatory changes within rectal carcinomas during fractionated radiotherapy.

Material & Methods: Perfusion data were obtained by Magnetic Resonance Imaging (MRI) measurements using a specially ultrafast T1 mapping sequence in a 1.5Tesla whole body scanner. T1 maps were acquired in intervals of 14 sec or 120 sec during and after constant rate infusion of Gadolinum- DTPA (Gd-DTPA). The Gd-DTPA concentration time curve was evaluated separately for arterial blood and tumor over a time course of 40 minutes. The applied method allows a spatial resolution of 2 mm × 2 mm × 5 mm. Patients underwent MR imaging before and at weekly intervals during the entire course of fractionated radiotherapy.

Results: With excellent spatial and temporal resolution dynamic T1 mapping revealed distinct Gd-DTPA accumulation level changes within the tumor during radiation. The perfusion index (Pi) of Gd-DTPA versus radiation dose showed a significant increase in the first or second week of treatment, then either returned slowly to the pretreatment level or rose again after an intermediate drop. The average Pi- value at the beginning was 0.16 (±0.054) and at the highest level was 0.23 (±0.06). In all groups the rise from the Pi-maximum was statistically significant, revealing an increase within a range of 8.06% to 82.55%.

Conclusion: The ultrafast T1 mapping MR-technique described here proved to be a practicable tool for monitoring tumor microcirculation during therapy and offers the potential for customized optimization of therapeutical procedures.

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Disseminated tumor cells detected by CK 20 RT-PCR in the blood and the bone marrow of patients with colorectal carcinoma represent an independent prognostic factor

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Purpose: The prognostic impact of the detection of disseminated tumor cells by molecular technics in patients with gastrointestinal carcinoma is so far not proven. The aim of our study was to evaluate the prognostic impact of the detection in bone marrow and blood by CK 20 RT-PCR in patients with colorectal carcinoma.

Methods: Bone marrow and venous blood samples of 170 patients with colorectal carcinoma were taken preoperatively. A multivariate analysis to detect independent prognostic factors was performed in 122 patients with curative resection (R0) (Cox regression model).

Results: Univariate analysis revealed the lymph node status ($P = 0.0127$) and the detection of tumor cells in the bone marrow ($P = 0.0081$) and in venous blood ($P = 0.0024$) as prognostic factors. The detection of cells in the bone marrow ($P = 0.0405$) as well in the venous blood ($p = 0.0072$) and the combination of both compartments (venous blood and/or bone marrow ($p = 0.0131$)) showed a significance influence on survival in multivariate analysis.

Conclusion: The detection of disseminated tumor cells by CK 20 RT-PCR in bone marrow and/or venous blood of patients with colorectal carcinoma is an independent prognostic factor and should therefore lead to randomized studies with adjuvant treatment modalities in positively tested patients.

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Phase III trial of 5-fluorouracil (5FU) and leucovorin (LV) with or without trimetrexate (TMTX) as first line treatment in advanced colorectal cancer (ACC)

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Purpose: In phase II studies TMTX, a non-classical antifolate, plus 5FU/LV has shown promising response rates but a high incidence of severe diarrhea in untreated ACC patients (pts).

Methods: 364 pts were randomized between LV 200 mg/m^2 in 1 h i.v. and 5FU 600 mg/m^2 bolus i.v. (*arm A*) or TMTX 110 mg/m^2 in 1 h i.v. followed after 24 h by LV 200 mg/m^2 in 1 h i.v. and 5FU 500 mg/m^2 bolus i.v. and LV 7 × 15 mg orally q 6 h starting 6 h after 5FU (*arm B*). Treatment was given weekly x6, q8 wks (one cycle) for a maximum of one year. Primary endpoint was progression free survival (PFS), secondary endpoints were overall survival (OS), response rate, toxicity and quality of life. Eligibility criteria included untreated ACC (adj. therapy with ≥1 yr interval allowed), WHO PS ≤ 2, age ≥ 18 yrs.

Results: A planned interim analysis was performed on toxicity and PFS in the first 222 pts entered prior to may '98. Pts characteristics were not significantly (NS) different between arm A (110 pts, 186 cycles) and B (112 pts, 233 cycles). Diarrhea was the major toxicity but occurred less frequently as reported previously due to strict guidelines: grade 3/4 in arm A 25% vs. in arm B 15% (NS). Other grade 3/4 toxicities occurred <10% in both arms. Median PFS was borderline significant (p 0.053) in favor of pts treated with TMTX (3.9 vs.5.3 months).

Conclusion: These promising results will be updated together with an analysis on OS in april '99 when the median follow-up will be 17 months. The results will be presented at the meeting.

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Irinotecan (Iri) in combination with high-dose infusional (HDI) 5FU/FA either weekly or bi-weekly: Evidence of survival advantage and quality of life (QoL) improvement in metastatic colorectal cancer (MCRC)

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Single agent IRI has been shown to be active in MCRC with significant survival advantage over best supportive care or best 5FU schedule in patients with prior 5FU failure (Lancet, 1998). As of Feb. 1998, 387 pts were randomized to receive (A): combination of IRI at 180 mg/m^2 day (d) 1 and 5FU 400 mg/m^2 as IV bolus followed by 600 mg/m^2/d as a 22 hours (h) continuous infusion (c.i.) + FA on d1–d2 repeated every 2 weeks (wks) or IRI at 80 mg/m^2 and 5FU 2.3 g/m^2 as a 24-h c.i. + FA weekly × 6 every 7 wks, *versus (vs)* (B): the same regimen of 5FU/FA alone. The main pts characteristics are comparable between groups A (199 pts) and B (188 pts): median age 62 *vs* 59, primary colon/rectum 55/45 *vs* 65/35, performance status 0 52% *vs* 51%, prior adjuvant CT, 26% *vs* 24%, number of organs ≥2 38% *vs* 37%, respectively.

Efficacy: group A *vs* B: response rate (RR) 41% *vs* 23% ($p < 0.001$) time to progression (TTP) 6.7 months (m) *vs* 4.4 m ($p < 0.001$) survival 16.8 m *vs* 14.0 m ($p = 0.029$).

Safety: The main NCI grade 3/4 adverse events by pts in group A *vs* B are: neutropenia 42% *vs* 11%, diarrhea 22% *vs* 10%; other toxicities were <5% and comparable in both groups.

QOL: A better QoL in favor of A was maintained during chemotherapy. Iri in combination with HDI 5FU/FA show a significantly better RR, TTP and survival along with at least an equivalent QoL, as compared to HDI FU/FA alone in pts with MCRC.

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Medical resource use in a phase III trial (SO 14796) of XelodaTM (capecitabine) in previously untreated advanced/metastatic colorectal cancer

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Introduction: XELODA(TM) (capecitabine) is a novel, orally administered, tumor-activated fluoropyrimidine carbamate. A randomized phase III clinical trial comparing XELODA (TM) (2500 mg/m^2/d × 14 d, q3 weeks, n = 301) vs. Mayo regimen (5-FU 425 mg/m^2; LCV 20 mg/m^2 d1-5, q4 weeks, n = 301) resulted in a higher response rate (26.6% vs. 17.9%, p = 0.013), and similar duration of response (7.3 vs 9.6 months) and progression-free survival (5.3 vs 4.8 months). The most remarkable differences in adverse events (AEs) were lower rates for XELODA (TM) patients requiring treatment for stomatitis, vomiting, and diarrhea and a higher rate of hand-foot syndrome (HFS).

Methods: Patients were recruited from 66 centers in 8 EU-countries, Australia, Russia, Israel and Taiwan. Data on hospital use, IV administration visits, AEs requiring medications or procedures, and all physician encounters were collected alongside the clinical trial for all randomized patients and analyzed.

Results: Administration of the Mayo regimen requires 5 visits per monthly cycle for IV administration of 5-FU and LCV. Data were available on 94% (=6,092) of the IV administration visits on the Mayo regimen. 336 of these administrations lasted >24 hours, implying overnight hospitalization for drug administration. 5,718 visits were <8 hours, and 38 visits lasted 8–23 hours. Patients receiving XELODA (TM) required one outpatient visit at the beginning of each cycle and no further visits for drug administration. Total days in hospital for the following AEs – stomatitis/mucosal inflammation, hand-foot syndrome, neutropenia, pyrexia, infections, diarrhea, nausea, and vomiting – was reduced by 184 hospital days (370 vs. 186, −50%) in the XELODA (TM) arm. For these AEs, the use of cephalosporins, quinolones, fluconazole and 5HT3-antagonists was consistently lower (−16%, −39%,