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CA 15-3 TUMOR MARKERS IN DETECTION OF METASTASES IN BREAST CANCER PATIENTS

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The results indicate that there is no significant difference in maximal value that follows the metastases before they are manifested and after they are manifested. Serum concentrations of CA 15-3 were examined at 500 patients surgically treated for breast cancer.

For the period of 12–55 months they were examined every 3 months with border value of 19.30 U/ml.

The sensitivity of Ca 15-3 in detection of distan is 86% with positive predictive value of 77% and 14 months as a mean (S.D.) time of raised marker level value. According to localisation of metastases the highest sensitivity was in hepar, bone and multiple metastases, and lowest with locoregional recurrences.

Colorectal cancer

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TRANSANAL ENDOSCOPIC MICROSURGERY IN EARLY RECTAL CANCER

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In the period from 8/89 to 1/94, 355 rectal tumours were locally excised by TEM, 236 of them have been adenomas and 98 carcinomas. In the group of carcinomas, 53% preoperatively have been judged as adenomas (rectoscopy, histology, endosonography).

In carcinomas, a full wall dissection or a segmental resection is always performed.

The final histology showed the following tumour stages (number of reoperated patients): 54 (8) pTI, low risk and 2 (0) pT1 high risk; 25 (16) pT2, low risk and 2 (2) pT2 high risk; 13 (8) pT3 low risk and 2 (0) pT3 high risk.

Patients with pT1 low risk carcinomas, resected *in toto*, patients treated with palliative intent, high risk patients and those who refused an open operation, were not reoperated. The more advanced tumour stages (pT1 high risk, pT2 and pT3) required another open intervention. Of the 34 reoperated, 3 showed a residual primary tumour (two in pT2 and one in pT3 carcinoma). In 15 reoperated patients, we could see lymph node metastases (only in pT2 and pT3 carcinomas). After a follow up period of 17 months, 2 of 46 patients with pT1 low risk carcinoma, 0 of 2 patients with pT1 high risk carcinema, 0 of 9 patients with only locally excised pT2 carcinomas and 1 of 7 patients with only locally excised pT3 tumour had developed a recurrence. The two patients with recurrence of pT1 low risk tumour, underwent a second procedure for cure.

The zero mortality, the low morbidity rate and the oncological reliability of the TEM makes it the method of choice in the treatment of pT1 low risk rectal carcinoma.

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THE EFFICACY OF RIGS (RADIOIMMUNOGUIDED SURGERY) FOR COLORECTAL CANCER SURGERY

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Radioimmunoguided surgery (RIGS) is an intraoperative diagnostic method based on monoclonal antibodies (MoAb) labeled with a radioactive isotope (^{125}I). Twenty colorectal cancer pts (12 recurrent, 8 primary) were injected with an anti-TAG (tumor-associated glycoprotein) MoAb, CC49 ^{125}I. Workup included colonoscopy, abdominal and chest CTs. Intraoperative traditional surgeon's exploration, including liver US, was followed by a gamma-detecting probe (Neoprobe 1000) survey. The MoAb localized on the tumor in 100% of pts. In addition to the primary lesions, CT identified 6 tumor sites, the surgeon 21 sites, RIGS 48 sites—36 confirmed by Pathology (H&E). In 9/20 pts (45%) RIGS detected occult findings (H&E-confirmed). These included lymph nodes, anastomosis, pelvis, uterus and peritoneum in 8/12 (66.6%) recurrent pts, and 1/8 (12.5%) primary pts, and changed the surgical plan in 10/20 (50%) pts. Thus, RIGS surgery can lead to a non-randomized more rational approach when selecting radical or non-radical surgery for colorectal cancer.

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LOCAL RECURRENCE AFTER TOTAL RECTAL RESECTION, MESORECTUM EXCISION AND COLOENDOANAL ANASTOMOSIS FOR TREATMENT OF LOW RECTAL CANCER

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Globally at the NCI of Milano from March 1990 to March 1995, 112 coloendoanal anastomoses (CEAA) associated with a colic reservoir after total rectal resection (TRR) were done. The present abstract concerns 90 CEAAs performed in 87 consecutive patients affected with primary rectal carcinoma (18 pts Dukes A; 20 pts Dukes B; 42 pts Dukes C and 7 pts Dukes D). All lesions were located in the lower third of the rectum with a distance from the anal verge ranging from 4 to 7 cm. The follow up period ranged from 1 to 53 months (median 22). The distance of the distal tumor margin from the resection edge of the rectum ranged from 1 to 6 cm. All Dukes A and B patients did not show local relapse while only 8 Dukes C patients presented pelvic relapses after TRR and CEAA from 7 to 14 months. Only one case showed this recurrence at the para-anastomotic site. Post-operative morbility due to procedure was low. A perfect continence was documented in 66% of cases after colostomy closure and many patients (63%) referred one or two bowel movements a day. Presently 70 patients of this series are alive, 57 of whom without actual evidence of disease. At present it is unanimously accepted that minimum distance edge from the neoplasm must not be more than 2 cm. However some literature data and our personal experience show that free distal margin from neoplasm is less important than thought in the past, with regard to local relapse and survival time, but a careful total mesorectum excision seems to be the most important factor in reducing incidence of local and pelvic recurrence. We conclude that a conservative surgical approach such TRR and CEAA can be considered a feasible option to the traditional abdomino perineal resection for primary cancers in the low rectum.

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CAUSES AND RISK FACTORS FOR POSTOPERATIVE MORTALITY IN SURGERY FOR RECTAL CANCER, WITH OR WITHOUT PREOPERATIVE RADIOTHERAPY

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The Stockholm Rectal Cancer Study Group has conducted two prospective, radomised trials on preoperative radiotherapy in rectal cancer. The studies have shown a reduced local recurrence rate after radiotherapy but also an increased postoperative mortality in irradiated patients compared to non irradiated. This study analysed causes of death and risk factors in patients dying in the postoperative period.

Patients and methods: In all, 1406 patients were included in the two trials and 1399 of these were operated. All cases of postoperative death within 30 days of surgery were identified (51 patients), and causes of death analysed. To identify patient related risk factors for postoperative mortality a case-control study was performed, with a detailed review of clinical records.

Results: Forty-one of the 692 irradiated patients died postoperatively compared to ten of the non irradiated. The postoperative mortality in irradiated patients was significantly increased only in those irradiated

with a two-field technique. The causes of death were cardiovascular in 16 cases, infectious in 24, pulmonary embolism in 5 and miscellaneous in 6 cases. Preoperative cardiovascular morbidity was an independent risk factor for postoperative death in both irradiated and non irradiated patients.

Conclusion: Preoperative radiotherapy in rectal cancer should be given with an optimised regimen, avoiding two-field techniques and extended fields. Patients with clinically significant cardiovascular disease should probably not be recommended this treatment.

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IMPROVED TREATMENT RESULTS IN RECTAL CANCER BY POSTOPERATIVE RADIOTHERAPY AND 5-FLUOROURACIL

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The purpose was to investigate whether a time-scheduled regimen of postoperative radiotherapy and 5-fluorouracil (5-FU) 30 min. before radiation could reduce local recurrence rate and improve survival in rectal cancer Dukes' B and C. 144 patients with rectal cancer Dukes' B and C were randomized to surgery alone or surgery combined with postoperative radiotherapy 46 Gy and bolus 5-FU. 136 patients were eligible. The treatment was well tolerated. After an observation time of 42–93 months, patients within the adjuvant treatment group had a cumulative local recurrence rate of 12%, compared to 30% in the surgery only group ($P = 0.01$). The 5-year recurrence-free as well as overall survival was 64% in the adjuvant group compared to 46% ($P = 0.01$) and 49% ($P = 0.05$), respectively, in the surgery group. *Conclusion:* The one month combination treatment improved treatment results in rectal cancer Dukes B and C, in terms of local and total recurrence rate and survival, without serious side effects. The timing of 5-FU and radiation is probably important.

700 ORAL

PHASE II STUDY WITH TOPOTECAN (T) ADMINISTERED AS A 21-DAYS CONTINUOUS INFUSION TO PATIENTS WITH COLORECTAL CANCER

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T is a watersoluble semisynthetic analog of camptothecin which exerts cytotoxicity during the S-phase of the cell cycle through specific inhibition of topoisomerase I. Preclinical data have indicated that T is more effective with prolonged exposure. The clinical feasibility of this concept was recently reported by Hochster *et al.* (J.C.O. 1009: 12; 553–559) using a 21-days continuous infusion (c.i.). We performed a phase II study with T 0.6 mg/m^2/d as a 21-days c.i. repeated every 28 days, in patients (pts) with metastatic colorectal cancer, not previously treated with chemotherapy. Dose reductions of 0.1 mg/m^2/d were performed if myelosuppression persisted beyond day 28. If no toxicity worse than grade 2 occurred dose increases by 0.1 mg/m^2/d were allowed. The starting dose was reduced to 0.5 mg/m^2/d after in 5/11 pts the second course was delayed. Response was evaluated every 2 courses according to the WHO criteria, toxicity was scored according to the CTC criteria. To date, 41 pts have entered the study. Patient characteristics included: 22 females, 19 males; median age 57 years (range 37–68); median WHO performance score 1 (range 0–2). Two pts were unevaluable; 39 pts assessable for toxicity up to now received a total of 94 courses, median 3 per pt (range 1–9). The main toxicity was myelosuppression, with neutropenia grade 3–4 occurring in 26% of courses, median nadir of ANC occurring on day 25 (range 8–35), and thrombocytopenia being, relatively mild with the nadir also on day 25. Despite this mild myelotoxicity treatment had to be delayed in 24 courses (26%) mainly because of prolonged myelosuppression. As prescribed by protocol treatment delays mandated dose-reduction in the subsequent course. As a result of this median dose intensity (mg/m^2/wk) decreased in the successive courses 1–9 from 2.62–2.62–2.62–2.1–2.1–1.92–2.1 to 2.1. In addition, a marked inhibition of the erythropoiesis was observed. Non-haematological disease effects were mild, nausea grade 1–2 occurred in 25 courses (26%), vomiting in 15 courses (16%), and asthenia and fatigue in 32 courses (34%). Alopecia being grade 2, except in one, was seen in 8 pts (20%). Steady-state (Css) levels of T were determined by HPLC during the first 2 courses and varied widely: 0.65 ± 0.15 ng/ml (range 0.37–0.91, N = 15). No significant correlation was found between Css and absolute dose. In the 30 pts presently evaluable for response 1 CR and 2 PRs were observed. In conclusion, this dosing schedule is relatively well tolerated but has only modest clinical activity in colorectal cancer.

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'TOMUDEX' (ZD1694) HAS A HIGHER RESPONSE RATE, SIGNIFICANTLY LESS LEUCOPENIA AND MUCOSITIS AND A SIMPLER DOSING REGIMEN THAN 5-FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) FOR ADVANCED COLORECTAL CANCER (CRC): FIRST RESULTS OF A PHASE III STUDY

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'Tomudex' (T) (ZD1694) is a direct and specific thymidylate synthase (TS) inhibitor. From November 1993, 439 patients (pts) with previously untreated advanced CRC were randomised in a Phase III trial to either (T) 3 mg/m^2 iv given 3 weekly (n = 222) or to LV 20 mg/m^2 plus 5-FU 425 mg/m^2 given 4–5 weekly (n = 212) on 5 consecutive days. Five pts did not receive protocol therapy. Pts were evaluated weekly for toxicity and 12 weekly for objective response. The median follow-up was 5.3 months. The response rate was higher for pts receiving (T) (20%) than for those receiving 5-FU-LV (13%) ($P = 0.059$, odds ratio 1.7, 95%CI 0.981 to 2.818) indicating that pts receiving (T) were approx 1.7 times more likely to respond. There was no evidence of a statistical difference between (T) and 5-FU-LV for time to progression or survival. (T) was associated with statistically significantly lower incidences of grade 3 and 4 leucopenia and mucositis ($P = <0.001$) and statistically significant higher incidence of increased transaminases, although the latter were generally reversible and self-limiting. Slightly more pts in the (T) group demonstrated an improvement in performance status and weight gain. (T) pts spent less time in hospital for dosing visits and the simpler dosing regimen offers the opportunity for economic benefits of reduced number of outpatient visits, pharmacy time and resource and pt travel costs. (T) therefore appears to be at least as effective as standard therapy for advanced CRC, but has a higher response rate, provides equivalent palliative effects and offers a more convenient administration schedule requiring less time in hospital.

'Tomudex' is a trademark, the property of ZENECA Limited.

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RANDOMIZED PHASE III TRIAL COMPARING 5FU BOLUS AND LOW DOSE LEUCOVORIN VERSUS 5FU BOLUS PLUS CONTINUOUS 5FU INFUSION AND HIGH DOSE LV IN METASTATIC COLORECTAL CANCER

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Monthly 5 day course of 5FU bolus infusion with low dose Leucovorin (FUFOL 1d) has the best therapeutic index for 5FU modulation in metastatic colorectal cancer.

Delivering 5FU protracted continuous infusion has also a better index than 5FU bolus. The bi-monthly combination of 5FU bolus followed by 5FU continuous infusion and high dose (LV 5FU2) has show a good efficacy with low toxicity in several phase II studies. The current study compares FUFOL1d and LV 5FU2.

From March 1991 until April 1994, 437 patients (pts), stratified according to performance status, presence of measurable disease, and synchroneous or metachroneous disease, were randomized to (A) FUFOL1d: IV bolus 5FU 425 mg/m^2 d1-5 with folinic acid 20 mg/m^2 IV d1-5 q 4 wk or (B) LV 5FU2: folinic acid 200 mg/m^2 2-hour infusion followed by IV bolus 5FU 400 mg/m^2 and 22-hour infusion FU 600 mg/m^2 d1-2 q 2 wk. Therapy was continued until disease progression and second-line chemotherapy including 5FU continuous infusion was allowed in both arms. Response rate (306 evaluable pts), progression-free survival (PFS) and overall survival (OS) are as follows:

Treatment	Pts	Response	Pts	PFS (wk)	OS (wk)
FUFOL1d	147	17%	218	22.8	57.2
LV5FU2	159	34%	219	29.5	61.4
		P = 0.002		*P = 0.008*	*P = 0.006*