Overview on
Colorectal papers

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Colorectal Cancer

1. Molecular biology

Many different approaches to study molecular biology aspects of colorectal cancer may be found in this three months review. The wide spectrum of markers analyzed would be impossible to be properly discussed here, so that we will present a brief summary of those more frequently studied and an occasional new relevant finding.

Microssatelite instability

Identification of germline mutations in mismatch repair genes is increasingly being used to guide clinical practice in hereditary non-polyposis colon cancer. Ward and cols performed a retrospective assessment of the clinical utility of immunostaining and microsatellite instability testing in a group of HNPCC individuals identified from the records of family cancer clinics in whom germline testing of hMSH2 and hMLH1 had already been performed. Of the 32 assessable tumours, 24 (75%) showed microsatellite instability whilst most of the MSI-H cancers (92%) failed to express either hMLH1 or hMSH2. They concluded that MSI testing and immunostaining are extremely useful tools which significantly improve the clinical interpretation of germline results and that the use of germline genetic testing is indicated for a highly selected group of individuals.

Colombino and cols assessed the microsatellite instability (MSI) in 91 rectal cancers and found that seventeen (19%) of these exhibited a MSI(+) phenotype. While MSI was detected in seven (64%) of 11 familial patients, a lower MSI incidence was observed in sporadic cases (10/80; 12.5%). A significant association with better disease-free survival (DFS) and overall survival (OS) was found for MSI(+) patients compared to MSI(-) ones (P <0.001). They concluded that MSI is a strong molecular prognostic marker in rectal carcinoma, independent of the administered treatment (radiotherapy, chemotherapy or both).

Chapuso and cols analyzed a total of 100 sporadic proximal colon adenocarcinomas comparing the expression of hMLH1, hMSH2 and hMSH6 proteins evaluated by immunohistochemistry (39% positives) to microsatellite instability assessment by PCR (43% positives). After further analyses performed on other tumoural areas, total concordance between the two techniques was observed. They concluded that that

immunohistochemistry may be as efficient as microsatellite amplification in the detection of unstable phenotype.

Lanza and cols evaluated by immunohistochemistry MLH1 and MSH2 protein expression in 132 MSI-H (high-frequency), 23 MSI-L (low-frequency), and 150 microsatellite stable (MSS) colorectal adenocarcinomas. Loss of MLH1 or MSH2 expression was detected in 120 (90.9%) MSI-H carcinomas, whereas all MSI-L and MSS tumors showed normal expression of both proteins. The results of the present investigation strongly indicate that immunohistochemical analysis of MLH1 and MSH2 expression is a practical and reliable method for the routine detection of the vast majority of MSI-H large bowel adenocarcinomas. The authors also pointed out that MSI-H MLH1/MSH2-positive colorectal carcinomas are characterized by distinctive pathological features.

Choi and cols investigated the relationships between the clinicopathological features and microsatellite alterations of 168 colorectal cancers. Twenty-nine (17%) with high-frequency MSI were associated with good survival ($P < 0.05$). The survival curve and multivariate analysis identified high- and low-level chromosomal loss as the most significant predictor of poor and good survival, respectively. They concluded that the classification of colorectal cancer based on chromosomal loss and MSI provides a prognostic index that reflects tumor pathobiology.

Rossi and cols undertook a study searching for mutations in the hMSH2 and hMLH1 genes in 25 unrelated kindreds with suspected hereditary nonpolyposis colorectal cancer (HNPCC). All patients were studied with direct sequencing. Ten mutations were detected (40%) and hMLH1 gene had a higher mutation detection rate than hMSH2 (32% vs. 8%). Only 3 of these 10 positive families fulfilled the Amsterdam criteria. They concluded that hMLH1 gene had a higher mutation detection rate than hMSH2 and that the physician who deals with CRC must take into consideration the heredity issue with patients who present with an early age of onset or a familial history of CRC- or HNPCC-related cancers, including gastric cancer, even if they do not fulfill the former Amsterdam criteria.

Another study to assess the role of immunohistochemical expression of MSH2 and MLH1 proteins was undertaken by Valentini and cols, who performed this examination in 25 positive MSI by PCR method. They found a high concordance rate between both methods (80%) and proposed immunohistochemical technique as a method to select MSI patients for improved outcome and response to chemotherapy.

Gastrin, Helicobacter pilory and COX-2 in colorectal cancer

As recently growth factors such as gastrin have also been implicated in the carcinogenesis of colorectal cancer, Konturek and cols studied this relationship and found that (1) the CRC and its margin contain large amounts of progastrin and show gene expression of gastrin, CCK(B)-R, and COX-2; (2) removal of the CRC markedly reduces the plasma concentrations of progastrin; (3) the Hp infection rate is higher in CRC, and this may contribute to colorectal cancerogenesis via enhancement of

progastrin and gastrin release; and (4) plasma progastrin concentrations might serve as a biomarker of CRC.

Yao and cols also studied the hypothesis that gastrin possesses potent trophic properties on both normal and neoplastic cells of gastrointestinal origin. They demonstrate that gastrin leads to a dose-dependent increase in colon cancer cell proliferation and tumour growth in vitro and in vivo, and that this increment is progressively reversed by pretreatment with the cyclo-oxygenase-2 inhibitor NS-398. The results of these studies demonstrate that selective cyclo-oxygenase-2 inhibition is capable of reversing the trophic properties of gastrin and presumably might prevent the growth of colorectal cancer induced by hypergastrinaemia.

Angiogenesis and vascular endothelial growth factor (VEGF)

Nakayama and cols studied the hypothesis that vascular endothelial growth factor (VEGF) is the most powerful angiogenic factor and a prognostic indicator in many malignancies. Blood samples were obtained prior to surgery from 33 patients with colorectal cancer, and additional samples were obtained 6 months post-operatively from 15 of the 33 patients. Plasma levels of VEGF were only significantly increased in patients who had recurrence and a worsening of colorectal cancer. In blood samples obtained from 15 patients both prior to surgery and 6 months post-operatively, post-operative mean plasma VEGF tended to decrease relative to the pre-operative level. They concluded that these findings may contribute to detect patients that may require additional immunochemotherapy after surgery.

Uthoff and cols wished to demonstrate vascular endothelial growth factor (VEGF) transcript polymorphism in human colon cancer. They studied 25 colorectal adenocarcinomas and found a variety of mutant angiogenic VEGF suggesting that this may provide a genomic basis for the diversity of tumor-host response and may prove to be important therapeutic targeting, since all the different VEGF isoforms would have to be neutralized to prevent angiogenesis.

Survivin

Rodel and cols report that spontaneous apoptosis has been shown to predict tumor response to preoperative radiochemotherapy in rectal cancer. It remains to be elucidated, however, which genetic profile determines whether a tumor is more or less prone to apoptosis. Recently, a novel member of the inhibitor of apoptosis family, designated survivin, was identified. In the present study, they investigated the impact of survivin on tumor cell apoptosis and the risk to develop distant metastases or local failure after preoperative radiochemotherapy and surgical resection. The expression of survivin and the apoptotic index were evaluated by immunohistochemistry on pretreatment biopsies of 54 patients with locally advanced adenocarcinoma of the rectum. An inversely correlation of survivin expression with the apoptotic index was found. Low survivin expression was significantly related to an increased disease-free survival rate (77% vs 18% at 5 years in tumors with high survivin expression, p = 0.02) and to a reduced risk for distant metastases (18% vs 78% at 5 years in tumors with high survivin expression, p = 0.05) and local failure (6% vs 37% at 5 years in

tumors with high survivin expression, $p = 0.07$). They concluded that survivin expression may provide a novel predictive indicator for disease-free survival after preoperative radiochemotherapy and surgical resection in rectal cancer.

p53 and radiotherapy in rectal cancer

Rebischung and cols studied the influence of p53 mutations on the response to ionizing radiation and survival in 86 patients treated with preoperative radiotherapy for rectal carcinoma. The prevalence of p53 mutations was significantly higher in patients who did not respond to radiotherapy (63%) than in those who did respond (34%) ($p < 0.01$). Presence of a p53 mutation was also associated with significantly shorter 5-year survival compared to patients without mutations ($p < 0.02$). They concluded that p53 status is an independent prognostic factor of response to radiotherapy and survival in rectal carcinoma.

2. Risk factors, staging, follow-up and screening

Well-done meat consumption

Le Marchand and cols report that heterocyclic amines (HAAs) and polycyclic hydrocarbons are suspected colorectal cancer (CRC) carcinogens that are found in well-done meat. They require metabolic activation by phase I enzymes, such as the smoking-inducible CYP1A isoenzymes. N-acetyltransferase 2 (NAT2) also play a role in the further activation of HAAs. They interviewed 727 Japanese, Caucasian or Native Hawaiian cases and 727 matched controls. HAA intake was estimated based on consumption of meat and fish for each of several cooking methods and doneness levels. A subgroup of 349 cases and 467 controls was phenotyped for CYP1A2 by a caffeine test. They found that preference for well-done red meat was associated with a 8.8-fold increased risk of CRC (95% CI: 1.7-44.9) among ever-smokers with the NAT2 and CYP1A2 rapid phenotypes, compared to ever-smokers with low NAT2 and CYP1A2 activities and who preferred their red meat rare or medium. These data provide support to the hypothesis that exposure to pyrolysis products through consumption of well-done meat increases the risk of CRC, particularly in individuals who smoke and are genetically susceptible (as determined by a rapid phenotype for both NAT2 and CYP1A2).

Similar results were found by Nowell and cols, who performed a case-control study consisting of 157 cases and 380 matched controls to explore the associations between environmental exposure, metabolic polymorphisms and cancer risk. Data was analyzed using a reference database of heterocyclic amine (HCA) exposure based on the food preferences chosen from the atlas. Data regarding individual food items cooked to different levels of doneness, as well as summary variables of foods and of food groups cooked to different degrees of doneness were also evaluated in a univariate analysis for association with colorectal cancer case status. While higher exposure to HCAs was strongly associated with colorectal cancer risk, increased consumption of five red meats cooked well done or very well done

produced comparable odds ratios (OR) for colorectal cancer risk (OR=4.36, 95% CI 2.08-9.60) for the highest quartile of exposure. Individual measures of specific HCAs provided little improvement in risk assessment over the measure of meat consumption, suggesting that exposure to other environmental or dietary carcinogens such as nitrosamines or undefined HCAs may contribute to colorectal cancer risk.

Smoking and colorectal cancer

Sharpe and cols performed a study to assess the effects of smoking on the risk of colorectal cancer according to anatomic subsite. A total number of 585 patients with colorectal cancer (176 in the proximal colon, 179 in the distal colon and 230 with rectal cancer) were compared to a control group consisted of 405 cancer controls, whose tumor types were considered unrelated to smoking, and 500 population controls. They concluded that cigar smoking seems to be associated with the development of rectal cancer. A weak positive association was also found between cigarette smoking and cancer of the proximal colon. If this last finding is real, the authors suggest that it might partially explain the proximal shift in of colorectal cancer due to the increasing prevalence of cigarette smoking during the middle of the 20th century.

Obesity and colorectal cancer risk in women.

Terry and cols undertook a study using proportional hazards analysis to estimate hazard ratios relating obesity to colorectal cancer risk among 89,835 women aged 40-59 years at recruitment into the Canadian National Breast Screening Study. During an average 10.6 years of follow up (936,433 person years), a total of 527 women were diagnosed with incident colorectal cancer (363 colon and 164 rectal). They found that obesity (body mass index > or = 30 kg/m(2)) was associated with an approximately twofold increased risk of colorectal cancer among women who were premenopausal at baseline. There was no association among postmenopausal women and there was only a weak positive association in the entire cohort.

Amsterdam Criteria in colorectal cancer: how frequent is it?

Estimates of the colorectal cancer associated with HNPCC vary from less than 1 % to more than 5 %. Amsterdam criteria fulfilled within a kindred (classic Amsterdam and Amsterdam II criteria) are widely used to identify patients prone to HNPCC. In the present study, Raedle and cols assessed the frequency of the Amsterdam criteria within a regional German cohort of 154 patients. A total of 843 first degree relatives have been identified within the kindreds of whom 121 had verified cancers. In 28 of 154 families (18 %), at least one first degree relative of the index patient had CRC. With respect to a typical family history, five kindreds (3.2 %) were likely to suffer from HNPCC on a clinical basis (4 kindreds met the classic Amsterdam criteria and one kindred the Amsterdam II criteria). Based on the classic Amsterdam and Amsterdam II criteria, the authors concluded that approximately 3 % of a regional German cohort of patients with CRC are likely to suffer from HNPCC. However, the final diagnosis of HNPCC can only be established by detection of pathogenic germline mutations within the DNA mismatch repair genes.

CEA antibody scan x CT scan

Garcia and cols presentes a study to assess the utility of nuclear imaging with labelled monoclonal antibody against CEA and the computed tomography (CT) in the follow-up of colorectal cancer after therapy and his accuracy in the detection of recurrent disease. A comparison between both methods was undertaken in 45 patients followed after colorectal cancer treatment. Histological confirmation of the lesions was obtained in 12 patients and the rest was assessed by an average of evolution time of 26 months, CT and blood CEA levels. The values of sensitivity, specificity, PPV and NPV obtained for the CEA- scan were of 91%, 76%, 77% y 90% respectively; 78%, 80%, 78% y 80% respectively for the CT and 65%, 42%, 88% y 74% respectively for the blood CEA levels. The CEA-scan and blood CEA levels combination showed the best results 100%, 95%, 93% y 100% respectively. The authors concluded that CEA-scan showed the highest sensitivity and NPV and that the combination of different techniques showed better results than an individual value.

Screening: when and how ?

Pignone and cols performed a systematic review of the cost-effectiveness of colorectal cancer screening for the U.S. Preventive Services Task Force, from January 1993 through September 2001. Among 180 potential articles identified, 7 were retained in the final analysis. Compared with no screening, cost-effectiveness ratios for screening with any of the commonly considered methods were generally between 10, 000 dollars and 25, 000 dollars per life-year saved. No one strategy was consistently found to be the most effective or to have the best incremental cost-effectiveness ratio. Currently available models provided insufficient evidence to determine optimal starting and stopping ages for screening. They concluded that screening for colorectal cancer appears cost-effective compared with no screening, but a single optimal strategy cannot be determined from the currently available data.

In another paper, Pignone and cols assessed the effectiveness of different colorectal cancer screening tests for adults at average risk, based on recent systematic reviews, Guide to Clinical Preventive Services and focused searches of MEDLINE from 1966 through September 2001. The authors also conducted hand searches, reviewed bibliographies, and consulted context experts to ensure completeness. They concluded that for average-risk adults older than 50 years of age, colorectal cancer screening reduces death from colorectal cancer and can decrease the incidence of disease through removal of adenomatous polyps. Several available screening options seem to be effective, but the single best screening approach cannot be determined because data are insufficient.

Selvachandran and cols described a practical scoring method to predict colorectal cancers based on a weighted numerical score derived from weighting of primary symptoms and symptom complexes which was calculated automatically when the questionnaire data were entered into the computer program. This scoring method was tested in 2268 patients with distal colonic symptoms, referred by general practitioners. Ninety-five had colorectal cancer. The average weighted numerical score was

significantly higher for patients with cancer than for non-cancer patients (mean 76.5 vs 44.5; $p<0.0001$). They concluded that the patient consultation questionnaire depends on history alone and is easily reproducible. In conjunction with the weighted numerical score, which removes operator bias, it can be used as an accurate system for prediction of symptomatic colorectal cancer.

Pre-operative staging

Harewood and cols performed a prospective, blinded study of patients with rectal cancer was to assess the impact of preoperative staging on treatment decisions and compare the tumor (T), nodal (N) staging performance characteristics of pelvic computed tomography (CT), rectal endoscopic ultrasonography (EUS), and EUS FNA. Eighty consecutive patients with newly diagnosed rectal cancer were prospectively evaluated. They concluded that EUS is more accurate than CT for determining T stage of rectal carcinoma and its use resulted in more frequent use of preoperative neoadjuvant therapy than if staging was performed with CT alone. The addition of FNA only changed the management of one patient, whereas FNA did not significantly improve N staging accuracy over EUS alone.

Steele and cols studied whether flexible probes for endorectal ultrasound (ERUS) could attain equivalent accuracy for bowel wall penetration. Forty-five patients were prospectively evaluated with flexible devices and results were compared with 20 rigid and 10 flexible probe studies. The learning curves of for each examination were also assessed. They found that the level of invasion was correct in 49% and nodal examinations were correct in 78%. Learning curves leveled out at 100 examinations with 87% accuracy for the rigid probe ($R = 0.46$) and 77% for the flexible devices ($R = 0.31$). They concluded that the coefficient of correlation for each method portends a more reliable learning curve for the rigid devices and that flexible devices were less accurate for level of invasion than the literature reported for rigid devices.

Mo and cols conducted a prospective study using a new technique and instrument (balloon sheath with miniprobe) in colon cancer staging and compared it with the conventionally used endosonography. One hundred and thirty-four patients underwent preoperative staging using the conventional (n=73) or balloon sheath miniprobe (n=61) endosonography. The overall accuracy rate was 85% for miniprobes and 89% for the conventional method. Lymph node metastasis was correctly determined in 67% with miniprobe and 77% with conventional method. The authors concluded that the balloon sheath miniprobe is a good alternative for evaluating lesions over the proximal colon and is superior to other modalities in obtaining a cross-sectional image even in tight, stenotic lesions. One limitation is its difficulty in assessing deeper structures such as lymph node groups and contiguous organ involvement.

3. Surgical treatment

Functional results after total mesorectal excision

Anorectal function is greatly disturbed after rectal surgery with or without radiotherapy (RT). To clarify the underlying mechanisms, van Duijvendijk and cols designed a prospective study to evaluate the effect of RT and surgery on anorectal function and clinical outcome in 34 patients with a rectal carcinoma who whose anorectal function was evaluated before surgery, 4 and 12 months postoperatively. Thirteen patients were lost to follow-up, 14 underwent surgery alone (total mesorectal excision [TME]), and seven also received RT (RT + TME). The functional outcome was disappointing in both groups, with at 4 months a significantly higher defecation frequency after RT + TME as compared with TME. They concluded that anorectal function after rectal surgery with or without RT is greatly hampered because of a decreased rectal compliance. After 12 months, partial improvement is shown, especially in the absence of RT.

Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer was undertaken by Kim and cols. They performed urine flowmetry and a standard questionnaire score before and after surgery in 68 males with rectal cancer. They observed significant differences in mean maximal urinary flow rate and voided volume before and after surgery (< 0.05), but no differences in residual volume before and after surgery were apparent. Five International Index of Erectile Function domain scores were significantly decreased after surgery (< 0.05). Sexual desire and overall satisfaction were greatly decreased in 39 patients (57.4%) and 43 patients (63.2 percent). Multiple regression analysis of factors showed that age older than 60 years was significant factor adversely affecting sexual function. They concluded that total mesorectal excision with pelvic autonomic nerve preservation showed relative safety in preserving sexual and voiding function.

The surgeon as a prognostic factor

Read and cols performed this study to determine the effect of surgeon specialty on disease-free survival and local control in patients with adenocarcinoma of the rectum. The records of 384 consecutive patients treated by colorectal surgeons (n = 251) and noncolorectal surgeons (n = 133) were reviewed independently. Actuarial disease-free survival and local control rates at five years were 77% and 93% for colorectal surgeons vs. 68% and 84% for noncolorectal surgeons ($P < 0.005$). Multivariate analysis revealed that pathologic stage and background of the surgeon were the only independent predictors of disease-free survival (both $P < 0.006$) and that pathologic stage, background of the surgeon, and proximal location of the tumor were independent predictors of local control (all $P < 0.02$). Radiation dose and use of chemotherapy were not significant factors. Sphincter preservation was more common by colorectal surgeons (52%) than noncolorectal surgeons (30% ;$p = 0.00004$). They

concluded that good outcome for patients with adenocarcinoma of the rectum who undergo neoadjuvant external beam radiotherapy and proctectomy is associated with subspecialty training in colon and rectal surgery.

Although recent studies have reported that high-volume surgeons and hospitals have better outcomes for colon cancer resections, it remains unclear whether there are other factors that are more important than volume. Ko and cols undertook this study to evaluate the importance of the volume variables relative to other factors. A full-model logistic regression was performed on 22,408 patients undergoing colon cancer resection. More than 30 different independent variables were included. Overall mortality was 2.8%. The significant predictors for mortality included age, gender, comorbid disease, operation severity and volume (both hospital and surgeon). The baseline probability analysis shows that the mortality for a baseline case is 12/1000. If this baseline case goes to a high-volume hospital or surgeon, the mortality will decrease to 11/1000 and 10/1000, respectively. Overall, the volume variables, although statistically significant, have a relatively smaller effect on outcome compared with other factors.

Martling and cols published the experience with 652 patients who had an abdominal resection for rectal cancer in Stockholm after the 'TME project', which was a collaborative project that included surgical workshops, and demonstrated also the role of surgeon as an independent prognostic factor. The aim of this study was to assess the impact of the project on the practice of rectal cancer surgery in Stockholm and to analyse whether surgeon case volume and participation in the workshops influenced patient outcome. Outcome was compared in patients operated on by teams that included high-volume surgeons (more than 12 operations per year) with teams that included low-volume surgeons (12 operations or fewer per year), as well as between teams that including workshop participants and non-participants. They found that outcome was significantly better in patients treated by high-volume surgeons (local recurrence: 4% x 10% - p=0.02; rectal cancer death 11% x18% - p =0.007). Radiotherapy, TME and sphincter-preserving surgery were more common among patients treated by workshop participants. They concluded that the TME project has had an impact on rectal cancer surgical practice in Stockholm. Variability in patient outcome was mainly related to case volume, with better results obtained in patients treated by high-volume surgeons.

Dowdall and cols reviewed the results of 82 consecutive TME procedures for rectal cancer in a surgical practice in which patients with rectal cancer were less than 15 each year. Anastomotic leak occurred in two (3 per cent) of 68 patients, both of whom recovered without additional surgery. There were two local recurrences (3 per cent) among 69 patients who underwent 'curative' surgery. At a median follow-up of 190 weeks, the survival rate for Dukes' stage A, B, C and 'D' was 100, 83, 68 and 18 per cent respectively. They concluded that outcome achieved in a surgical practice with a broad case mix and relatively low annual case volume was comparable to that from larger centres. Appropriate surgical training and attention to technical detail may be as important as case volume in determining outcome after surgery for rectal cancer.

Protective stoma in low anterior resections

Marusch and cols have assessed the value of a protective stoma in low anterior resections for rectal cancer by a prospective multicenter study involving 75 German hospitals comparing postoperative results of procedures performed with and without a protective stoma. Among 482 low anterior resections, no protective stoma was constructed in 334 patients (69.3 percent), whereas 148 (30.7 percent) received such protection. In the group receiving a protective stoma, however, neoadjuvant radiochemotherapy was more common, the tumors were lower, the total mesorectal excision rate higher, the intraoperative complication rate was higher, and the duration of the operation was longer. The differences were all significant. The overall anastomotic leakage rate was identical in the two groups, but reoperation rate was significantly lower in patients receiving a protective stoma (p = 0.02). They concluded that particular benefit of a covering stoma is the reduction in the rate of leaks requiring surgery and thus in the severe consequences of an anastomotic leakage.

Machado and cols compared the surgical outcome of 161 patients with rectal carcinomas operated with a total mesorectal excision and a colonic J-pouch. Eighty patients were operated on in a surgical unit using routine defunctioning stomas (96 percent), whereas 81 were operated on in a department in which diversion was rarely used (5 percent). No difference between the two centers was found in postoperative mortality, pelvic sepsis (anastomotic leaks; 9 vs. 12 percent) or reoperations. They concluded that the routine use of diversion does not protect the patient from anastomotic complications or pelvic sepsis.

Civelli and cols evaluated radiologically with water-soluble radio-opaque contrast enema 152 patients who underwent colo-anal anastomosis and J pouch reconstruction with a protective colostomy. A total of 54 fistulas were seen (35.5%). Fifty-seven patients were treated with surgery alone (group A) and 95 patients received adjuvant treatment (group B). Respective incidence of fistulas between these groups was 28.9% and 38.9%. They concluded that two factors appear to contribute to the high prevalence of fistulas in this series: extension of radiological screening to all operated patients and adjuvant radiotherapy. All fistulas resolved with medical treatment alone. Postoperative monitoring with water-soluble contrast enema appears to be the diagnostic procedure of choice because it is well tolerated, non-invasive and a reliable aid in planning the proctective colostomy closure.

Laparoscopic surgery

Lacy and cols reported the results of a a randomised trial to compare efficacy of laparoscopy-assisted colectomy (LAC) and open colectomy (OC) for treatment of non-metastatic colon cancer in terms of tumour recurrence and survival. Probability of cancer-related survival was higher in the LAC group (p=0.02). LAC was independently associated with reduced risk of tumour relapse (hazard ratio 0.39, 95% CI 0.19-0.82), death from any cause (0.48, 0.23-1.01), and death from a cancer-related cause (0.38, 0.16-0.91) compared with OC. This study, involving 219 patients, was

possibly the first one to report a superiority of LAC for treatment of colon cancer in terms of cancer-related survival and tumour recurrence, since advantages in morbidity and hospital stay had been previously described. This cancer related advantage was due to differences in patients with stage III tumours.

Feliciotti and cols undertook a study was to compare long-term outcome in unselected patients undergoing either laparoscopic (LH) or open hemicolectomy (OH) for colonic cancer. A subset of 149 patients from a total of 197 elective patients were included in this prospective nonrandomized study and the allocation to each group, being laparoscopic (n=74) or open (n=75) was done on the basis of the patient's choice. Follow-up for both groups ranged from 36 to 96 months (mean, 48.9). No significant difference was found regarding local recurrence, metachronous metastases or cumulative survival probability. Sixty-four LH patients (86.5%) and 65 OH patients (86.7%) are disease-free.

Lumley and cols reported the results obtained in a series of 154 patients who underwent a potentially curative laparoscopic-assisted resections for colorectal surgery with a median follow up of 71 (range, 7-108) months. The overall recurrence rate in this group was 6 percent (21 recurrences). There was one port site recurrence after a potentially curative procedure (0.6 percent). Perioperative mortality was 1 percent (2 patients). Unadjusted five-year median survival data for Australian Clinico-pathological Staging A was 91% (3.5% recurrence); Staging B, 83% (15% recurrence) and for Staging C, 74% (26% recurrence). They concluded that in selected patients a laparoscopic resection for colorectal cancer produces acceptable intermediate to long-term oncologic outcomes and a low long-term complication rate.

Silecchia and cols reported an incidence of 0.9% (16 cases) of abdominal wall recurrence rate after laparoscopic resection undertook in 1,753 cases for colorectal cancer. In this study, smooth plastic and metal ports were introduced through the shaved abdominal wall of a cadaveric sheep and suspended in a water-bath containing radiolabelled LIM 1215 human colonic cancer cells for 30 min.

In a experimental study, Brundell and cols compared the role of material composition of laparoscopic ports on tumour cell adherence. Radioactivity on both ports and port sites was measured and the number of cells adherent to each structure was calculated. They found that increased numbers of cells were detected on metal ports ($P < 0.001$) when compared with plastic ports. Significantly greater numbers of cells were also detected on the sites through which metal ports had passed than on sites through which plastic ports had passed ($P = 0.03$). They concluded that in this model, the use of metal ports as opposed to plastic ports resulted in increased deposition of tumour cells on both ports and port sites.

Other topics in surgery

Sentinel lymph node in colon cancer: Nastro and cols

Emergency one-stage surgery for obstructing left-sided colorectal carcinomas:
Huang and cols

Major colorectal cancer resection should not be denied to the elderly.
Smith and cols

Pelvic exenteration and sacral resection for locally advanced primary and recurrent rectal cancer
Yamada and cols

4. Adjuvant therapy

Role of reirradiation

Mohiuddin and cols reviewed 103 patients with recurrent adenocarcinoma of the rectum who underwent reirradiation with concurrent 5-fluorouracil-based chemotherapy. The initial radiation median dose was 5040 cG. After the reirradiation, 34 patients also underwent surgical resection for residual disease. The median interval and 5-year survival rate of patients undergoing surgical resection after reirradiation was 44 months and 22% compared with 14 months and 15% for patients treated with reirradiation only (P = 0.001). Treatment was generally well tolerated. Fifteen patients required a treatment break and early termination of treatment for Grade 3 and higher diarrhea, moist desquamation, or mucositis. Late complications were seen in 22 patients, including persistent severe diarrhea in 18 patients with 10 patients requiring long-term parental support, small bowel obstruction was seen in 15 patients, fistula formation in 4 patients, and coloanal stricture in 2 patients. They concluded that in patients with recurrent rectal carcinoma, high doses of reirradiation can be delivered with acceptable risks without prohibitive long-term side effects. Surgical salvage and long-term survival of patients are possible.

Radiotherapy alone for rectal cancer ?

Gerard and cols analyzed the long-term result of 63 patients treated with curative intent by radiotherapy (RT) alone, using a combination of contact RT, external beam RT, and brachytherapy with an iridium implant. Patients were considered unsuitable for surgery because of the presence of severe comorbidity or because they did not consent to surgery and the possibility of a permanent stoma. With a median follow-up time of 54 months, the primary local tumor control rate was 63%; after salvage surgery, the ultimate pelvic control was 73% (46 of 63). The 5-year overall survival rate was 64.4%. No severe Grade 3-4 toxicity was seen. Good anorectal function was maintained in 92% of living patients. The T stage was a strong prognostic factor, with a 5-year overall survival rate of 84% and 53% for T2 and T3 lesions, respectively, in

patients <80 years old. They concluded that high-dose irradiation to a small volume can provide a high therapeutic ratio for rectal cancer.

Nakagawa and cols reviewed 52 patients with mid or low rectal tumors underwent CRT (external beam radiation plus 5-fluorouracil plus folinic acid). Patients who had low rectal tumors with complete response (CR) were not submitted to surgical treatment. In a mean follow-up of 32.1 months, clinical evaluation after CRT showed complete response in 10 cases (19.2%), all low tumors. Among these, 8 (80%) presented with local recurrence within 3.7 to 8.8 months. All other patients were submitted to surgery, independently of the response. Seven had local recurrences after CRT plus surgery (17.9%). The authors concuded that exclusive CRT approach is not safe to treat patients with low infiltrative rectal carcinoma.

The impact of preoperative chemoradiotherapy

Valentini and cols evaluated the impact of tumor response, tumor and nodal downstaging and pTNM classifications on long-term outcome in 165 patients with rectal cancer treated with preoperative 5-FU-based concurrent chemoradiation. The median follow-up was 67 months. After preoperative chemoradiation, clinical response and tumor/nodal pathologic downstaging showed a close correlation with improved outcomes. The better 5-year survival and local control in pT0-2 patients regardless of their initial stage seems to confirm a heterogeneity in rectal cancer patients. The responder population showed a behavior similar to rectal cancer diagnosed at Stage cT1-2 and treated with conservative surgery alone.

Similar results were found by Theodoropoulos and cols, retrospectively evaluated the impact of response to preoperative chemoradiation therapy on 88 patients with ultrasound Stage T3/T4 rectal cancers. All patients were operated in six weeks or longer. T-level downstaging was demonstrated in 36 (41%) and complete pathologic response was observed in 16 (18%). At a median follow-up of 33 months, 86.4% were alive. The overall recurrence rate was 10.2 percent. Patients with T-level downstaging and complete pathologic response were characterized by significantly better disease-free survival ($P = 0.03$, $P = 0.04$) and better overall survival ($P = 0.07$, $P = 0.08$). None of the patients with complete pathologic response developed recurrence or died during the follow-up period. They concluded that advanced rectal cancers that undergo T-level downstaging and complete pathologic response after chemoradiation therapy may represent subgroups that are characterized by better biologic behavior.

Delaney and cols published the experience from the Cleveland Clinic with 259 patients who underwent curative anterior or abdominoperineal resection with TME for T3 lesions within 8 cm of the anal verge. Patients were grouped by receiving preoperative radiotherapy (PRT) ($n = 92$) or not ($n = 167$). Patients who received RTP had an increased overall survival (63% x 52%) and increased overall survival for node-negative patients from (82% x 58%), with no benefit for node-positive patients. There was no significant difference in local recurrence rates. They concluded that PRT should be advocated for all patients with T3 rectal cancers less than 8 cm from the anal verge, even if the surgery includes a properly performed TME.

The experience from the Memorial Sloan-Kettering Cancer Center, as published by Ruo and cols , also supported the benefits of preoperative radiotherapy. Sixty-nine patients with locally advanced (T(3-4) and/or N1) primary rectal cancer were prospectively followed after being treated with preoperative RT to the pelvis followed by resection in 4-7 weeks. With a median follow-up of 69 months, 5-year recurrence-free survival (RFS) was 79%. RFS was significantly worse for patients with aggressive pathologic features and positive nodal status identified in the postirradiated surgical specimen. In patients with greater than 95% rectal cancer response to preoperative RT +/- chemo, only one patient has died as a consequence of cancer, another has died of an unrelated cause, and the remainder were free of disease with a minimum follow-up of 47 months. They concluded that a marked response to preoperative RT +/- chemo may be associated with good long-term outcome but was not predictive of RFS.

5. Metastatic disease

Sequential resection of lung and liver metastasis: is it indicated ?

Labow and cols analyzed 21 patients who had pulmonary metastases after hepatic resection, of which 12 (57%) underwent pulmonary resection. Four patients who underwent pulmonary resection had multiple lung metastases and eight had isolated metastasis. There were no perioperative deaths in the pulmonary metastasectomy group. Contraindications to pulmonary resection included extensive pulmonary disease and concurrent extrapulmonary disease. A survival benefit was noted at 3 years for the resected versus the unresected group (60% vs 31%). Survival was no different between the resected pulmonary recurrence patients and the resected hepatic metastases only patients (60% vs 54%). They concluded that pulmonary metastasectomy can be performed safely and effectively in patients with recurrent disease after hepatic resection for colorectal metastases.

Ike and cols undertook a retrospective analysis of 15 patients who underwent lung resection for metastatic colorectal cancer after previous partial hepatectomy for the same reason. Five-year survival rates after resection of lung metastasis was 50%. There was no significant difference in survival after lung resection between patients who had sequential liver and lung resection versus those who had lung resection alone. They concluded that sequential lung resection after partial hepatectomy for metastatic colorectal cancer may lead to long-term survival.

Yamada and cols reviewed 10 of the 17 patients with pulmonary recurrence after hepatectomy for colorectal metastases who underwent surgical treatment. Operative mortality was 0%, and a postoperative complication was observed in 1 patient after pulmonary metastasectomy. The overall 5-year survival rate after pulmonary metastasectomy was 10.0%, and the median survival was 21.7 months. One patient underwent resection two times for remnant lung recurrence after first lung metastasectomy, and is alive with no evidence of recurrence 77.9 months after the first

pulmonary resection, and 50.7 months after the third pulmonary resection. They also concluded that pulmonary metastasectomy after hepatectomy for metastases from colorectal cancer is a safe treatment, and might offer prolonged survival for highly selected patients.

Simultaneous colorectal and hepatic resections: is it safe ?

de Santibanes and cols analyze the results of resection of colorectal cancer and liver metastases in one procedure in 71 cases. Median followup time was 29 months. The median hospital stay was 8 days, morbidity was 21% and operative mortality was 0%. Recurrence rate was 57.7% (41 or 71), and progression of disease was detected in 33.8%. Overall and disease-free survivals at 3/5 years were 45% / 38% and 17% / 9%, respectively. They concluded that simultaneous resection of colorectal cancer and liver metastases can be performed with low morbidity and mortality rates, avoiding a second surgical procedure.

Prognostic significance of intrahepatic lymphatic invasion

Sasaki and cols retrospectively analyzed data obtained from 67 consecutive patients who underwent hepatectomy for liver metastasis from colorectal carcinoma. Intrahepatic spread was classified into discreet categories that were evaluated separately. The presence of intrahepatic lymphatic invasion significantly and adversely affected the overall and disease free survival rates and was shown statistically to be an independent predictor of recurrence and death after hepatectomy in patients with liver metastases from primary colorectal carcinoma.

To improve the diagnosis of intrahepatic lymphatic invasion, Kane and cols examined the technique of intraoperative hepatic lymphatic mapping with isosulfan blue dye in humans. Intrahepatic dye injection was performed in patients undergoing surgical exploration for colorectal liver metastases. The location of all blue-stained lymphatics and lymph nodes was recorded. All stained and unstained lymph nodes were biopsied for pathologic examination. Thirteen intraoperative lymphatic mapping procedures were performed in 11 patients and a blue-stained lymphatic was visualized in 11 of 13 injections (85%). They concluded that intraoperative hepatic lymphatic mapping with isosulfan blue dye is a simple, rapid, and safe technique in humans. It may serve as an adjunct to random lymph node biopsy for the identification of periportal and celiac nodal metastases before liver resection in patients with metastatic colorectal carcinoma.