resistant to short term FUra exposure retain full sensitivity to the continuous exposure to the same agent. These data suggest that biochemical modulation of FUra should take into account the schedule of fluoropyrimidine administration. Based on this rationale, we completed a phase 2 trial of schedule-oriented biochemical modulation of FUra in advanced colorectal cancer patients, based upon a hybrid regimen of 2 biweekly cycles of FUra bolus (600 mg/sqm), preceeded by (24 h interval) MTX, 200 mg/sqm (in order to maximize the RNA effect of the drug) alternating with FUra continuous infusion, 200 mg/sqm daily for 3 weeks, modulated by leucovorin, 20 mg/sqm weekly bolus (in order to maximize the DNA effect). Among the 33 consecutive patients accrued there were 3 CR and 13 PR (RR = 48%, 95% CL, 31–66%). Eleven patients had a minor response and 4 of them showed tumor shrinkage ranging between 46% and 49%. After a median follow-up time of 26 months, 10 patients are still alive. The median PFS and overall S were 9.6 and 20.2 months, respectively. The low toxicity of the bolus part of our regimen prompted us to pursue its intensification by adding a further modulator to MTX. Our recent finding of a strong synergism between bolus FUra and IFN, obtained *in vitro* on the same tumor model, generated a phase 2 trial employing the same regimen plus IFN (3,000,000 U im q12h × 4, starting at the time of FUra bolus administration). Among 42 patients 4 CR, 15 PR (RR = 45%), 6 MR and 10 SD were obtained. Since the results of the two trials are similar showing twice as much activity and less toxicity than bolus FUra +LV or MTX → FUra, a randomized comparison is now ongoing between our original hybrid regimen without IFN and MTX → FUra.

306

COMPARISON OF CANCER PATIENTS SURVIVAL ACROSS EUROPE

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The EUROCARE study group was funded by the European Union to assess the survival of cancer patients throughout Europe. The first data analyzed and published in collaboration with the International Agency for Research on Cancer show variations between countries in survival probability for colo-rectal, stomach and breast cancer for which stage at diagnosis is an important determinant of survival. In contrast, little difference is seen for cancers which respond well to cytotoxic therapy such as Hodgkin's disease or testicular cancer. It is suggested that variations in the speed of access to the most adequate care system may explain part of the observed differences.

The steering committee of the group consists of F. Berrino, J.W. Coebergh, M. Coleman, J. Estève, J. Faivre, T. Hakulinen, C. Martinez, M. Sant, A. Verdecchia, S. Welson.

307

IMPACT OF QUALITY CONTROL ON TREATMENT OUTCOME

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Quality control in radiotherapy reinforces the quality established within the framework of general programs of quality assurance.

The control applies to the most critical aspects of treatment, thus enabling the elimination of systematic and sometimes random errors.

Can quality control have an impact on treatment outcome?

In radiotherapy, the result is dependent on several factors, starting with the exactitude of the initial diagnosis and ending with the therapeutic follow-up. In the literature, data show that some loco-regional failure and, in certain cases, the decrease in survival can be attributed to treatment error. Quality control in radiotherapy enables the analysis of various typical errors and their consequence, particularly with regard to target volumes, irradiation fields, dose, or errors in calculation. This knowledge can limit errors to a minimum. Various systems, more or less sophisticated, should be able to limit errors before or during the treatment. Quality control leads to the improvement of treatment outcome; some examples will be given. However, these results are not always obvious. Quality control has a role to play in certain clinical circumstances which are difficult to analyze without precise and objective information on patient outcome. It can be an important component in the treatment of localizations that have had mediocre results.

Besides its contribution to the improvement of local control and survival, quality control can also be an essential means of improving and decreasing post-therapeutic complications.

308

THE IMPACT OF CANCER NURSING ON TREATMENT OUTCOMES

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The care of patients with cancer, from diagnosis to terminal care, demands the support of a multidisciplinary team in both hospital and community settings. Nurses spend more time caring for this group of patients than do any of their clinical colleagues. Therefore nurses are ideally placed to play a pivotal role in the co-ordination of the diversity of care which is required for the patient with cancer. It has been demonstrated that intervention by clinical nurse specialists enhances patient care and results in cost reduction in a number of areas and that nurses are critical to the success of clinical trials. Currently treatment outcomes are measured both in terms of survival and quality of life of the individuals concerned. In each of these areas nurses have a significant role to play through clinical practice, education and research. Advances in these areas will ensure the continued improvement in the provision of nursing care and hence the efficacy of treatment for patients with cancer.

309

WHY IS CANCER OUTCOME DIFFERENT?

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The first evidence that patients treated in a research protocol fared better than the rest came from Stiller's analysis of children with cancer. He compared the outcome of those treated in Medical Research Council (U.K.) trials with those treated in peripheral non-academic paediatric units, and showed such devastating differences that referral patterns changed dramatically. Now almost 100% of children with cancer in the U.K. are treated in specialist centres.

Similar large (and unacceptable) differences were seen in a study of five centres in one U.K. city in the treatment of teratoma. The centre which saw most patients and randomized in EORTC trials had a 10% better patient survival than any of the others and for ovarian cancer, the same holds true and so on and so on. The message is unpopular with doctors who believe they know all about treatment and thus have no need for trials, and with doctors who work in district hospitals and stubbornly hold on to patients who should be referred to specialist centres. But the audience which matters consists of cancer patients, and they, armed with this information, can demand more specialists and more access to clinical trials.

310

PREVENTION OF LOCOREGIONAL RECURRENCE OF RECTAL CANCER: INTERSURGERY VARIABILITY

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In a German prospective multicentre study (1101 unselected patients operated for solitary rectum carcinoma from 7 institutions), following anterior resection or abdomino-perineal excision for cure (R0, M0) loco-regional recurrence was observed in 21.6% with an interdepartment variability between 10% and 37% and an intersurgeon variability between 4% and 55%. The frequency of loco-regional recurrences was not influenced by adjuvant treatment (used in only 15% of the patients), but was in the control of the surgeon. It was reduced by avoidance of intra-operative local tumor spillage and local radicality, in particular total mesorectum excision in each carcinoma of the middle and lower third. The best method to prevent loco-regional recurrences is good surgery.

311

QUALITY OF SURGERY

C. McArdle

Local recurrence is a major cause of morbidity and mortality following apparently curative resection for colorectal cancer. The overall local recurrence rate is approximately 20%; there is however considerable variation amongst individual surgeons. After correction for stage of the disease at the time of the presentation these differences persist.

Pathological studies have shown that the presence of lateral resection margin involvement is associated with the subsequent development of local recurrence. It is therefore tempting to believe that surgeons with a high turn over may achieve better results. Analysis of over 4,000 patients undergoing colorectal cancer surgery suggests that this is not necessarily

Further studies are required to identify those factors which contribute to high local recurrence rates and are amenable to treatment.

312
PRE- AND POSTOPERATIVE RADIOTHERAPY IN THE PREVENTION OF LOCAL REGIONAL RECURRENCE OF RECTAL CANCER

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In patients with rectal carcinoma, pre- and postoperative radiotherapy has been used in addition to surgery in order to decrease the local recurrence rates and possibly improve survival. The conclusions that can be reached after results achieved in 18 randomized trials including more than 7000 patients are that using preoperative radiotherapy, a clear dose-response relationship is present. At comparable doses, preoperative radiotherapy is more efficient than postoperative in reducing local failures. This has also been confirmed in the only trial comparing preoperative with postoperative radiotherapy. In order to reach similar efficacy, 15 Gy higher dose is required postoperatively. Neither approach alone has had any significant influence on survival in individual trials, although it is likely that a survival benefit will be seen after moderate dose preoperative radiotherapy. Toxicity profiles, both acute and late also favour a preoperative approach, although inappropriate techniques will result in unacceptably high toxicity levels. Further research should focus on timing the most optimal chemotherapy in addition to preoperative radiotherapy.

313
COMBINED RADIO-CHEMOTHERAPY AS ADJUVANT TREATMENT OF RECTAL CANCER. RATIONAL RESULTS AND POSSIBLE FUTURE DIRECTIONS

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After curative surgery, the prognosis and the patterns of failure of colon and rectal cancers are quite different. The overall 5 year survivals are respectively 55% and 45% with a median time to the diagnosis of recurrence of 18 and 13 months. Liver and peritoneal metastases account for 60% of the recurrences of colon cancer whereas local failures (LF) represent about 10%. On the contrary, LF, liver and lung metastases are equally distributed and account each for 30% of rectal cancer failures. These figures explain why adjuvant treatment should be adapted to the site of the primary. The aims of adjuvant treatment in rectal cancer are both survival and local control, keeping acute and late toxicity to an acceptable level.

The postoperative approach permits to select patients on the basis of the pathological findings. None of the four randomised published trials demonstrated that a 50 Gy postoperative dose is able to decrease significantly the LF rate in Dukes B and C patients. Increasing the dose seems inappropriate for multicentric trials and will certainly conduct to an increased acute and late toxicity.

Combined postoperative radiotherapy and chemotherapy produced a benefit in some studies at the expense of a high rate of acute toxicity and treatment interruption in about 20–30% of the patients. Moreover, the treatments induced unacceptable high rate of late toxicity after sphincter sparing procedures.

On the other hand, moderate dose, in the 25–35 Gy range, preoperative irradiation significantly reduced LF in four large randomised trials totalling more than 3000 patients. This reduction in LF had the same magnitude for all Dukes' stages (50 to 65%). Furthermore in the latest report of the Stockholm 2 trial, a definite increase in overall survival was observed in patients treated by preoperative irradiation.

The comparison of the therapeutic ratio issued from the post or preoperative adjuvant therapeutic approach, definitely favours the preoperative irradiation.

The next step is to evaluate in selected patients (T3–T4 resectable stages), the optimal integration of chemotherapy with preoperative irradiation and whether post operative chemotherapy should be added. These two questions are addressed in the current EORTC 22921 protocol. Beside the main goal of this trial, increase in overall survival, the evaluation of sphincter function and quality of life have also been selected as a new end point in this trial.

314
NO ABSTRACT

315
PREDICTION OF RADIOSENSITIVITY: MOLECULAR AND CELLULAR ASSAYS

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Accurate prediction of response to conventional radiotherapy can guide the radiation oncologist to modify treatment for individual patients, or patient groups, to increase the chance of cure and limit morbidity. One of the most important parameters affecting radiotherapy outcome is intrinsic radiosensitivity. This presentation will assess the molecular and cellular assays available at present and those being developed. Molecular assays can be divided into those measuring some aspect of DNA damage and those measuring the presence, mutation or expression of genes suspected to be involved in radiosensitivity. The performance of some assays has been tested by comparing results with cell killing. Almost none of them has yet been tested in clinical trials of radiotherapy for predictive potential. Mixed results have been obtained with DSB induction and repair, some finding a good correlation with cell kill, but with many exceptions. Much progress has recently been made in discovering critical genes in DSB repair (e.g. ku70, ku80, scid). In addition, several oncogenes and supressor genes have been associated with radiosensitivity changes. However, the complexity of the cell's response to radiation hinders the choice of genes to screen for radiosensitivity prediction, although there is now clear hope for the future. The most trusted cellular assay is that of colony formation after *in vitro* radiation. Reports of positive correlations with radiotherapy outcome exist, although more studies and more rapid assays are needed. Alternatives are those for chromosome damage, apoptosis induction and cell cycle blocks. Results of their predictive potential can be expected in the next few years.

316
APOPTOSIS: RELEVANCE TO RADIOTHERAPY

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Apoptosis is a central part of normal development. Under some circumstances, however, apoptosis can also be seen in response to a number of abnormal stimuli which include hormonal or growth factor manipulations, aberrant gene expression, particularly of oncogenes or anti-oncogenes, and in response to a number of toxic agents including chemotherapeutic drugs and X-rays. It is for these latter reasons that apoptosis has generated great interest among oncologists and cancer biologists both because of the potential insights it may yield into carcinogenesis and in the hope of generating new strategies for cancer treatment. Control of apoptosis, like carcinogenesis, seems to be linked to some of the genes which also regulate cell cycle progression. Thus, the Rb, p53 and myc oncogenes which in the normal cell are involved in cell cycle regulation also are involved in the control of apoptosis. There is some evidence that the radiosensitivity of cells may be related to their rate of spontaneous apoptosis or to the extent of induction of apoptosis by X-rays. Our group has focussed on the relationship of cell cycle perturbations by radiation to the induction of apoptosis by X-rays. These studies suggest several new areas for the development of new therapeutic strategies which will be discussed.

317
THE IMPACT OF DNA REPAIR IN RADIOTHERAPY

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DNA repair has an impact on radiotherapy at two levels. 1: The prolongation of treatment, either by fractionation or decreasing dose-rate allows a greater time for repair during the treatment period resulting in a reduced cytotoxicity in both tumour and normal tissues. 2: DNA repair is an important determinant of variation in cellular sensitivity. Thus variation in normal tissue damage and tumour response may be determined to a significant degree by DNA repair capacity. There have been significant advances recently in the understanding of the mechanisms and genetics of DNA repair in mammalian cells. This includes the identification of the xrcc5 gene as being part of a DNA dependent protein kinase and its association with V(D)J recombination. Such progress