necessary for oncological reasons. Reconstruction of the sphincter function is achieved using a seromuscular cuff. This procedure avoid an abdominal colostomy. The neosphincter can also be formed secondarily, after a prior abdominoperineal excision with transabdominal colostomy. Quality of life will be improved, especially if an artificial anus can be avoid.

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Radiotherapy of early localised rectal cancer

J.P. Gérard, P. Romestaing, F. Mornex, J.M. Ardiet. *Service de radiothérapie, C. H. Lyon-Sud, France*

Purpose: To evaluate the role of radiotherapy alone for cure in the treatment of "early" rectal cancers with 2 different approaches.

Patients and treatment: Between 1980–96, 149 patients divided in 2 groups. *Group A:* 106 pts with T1 and early T2N0 treated with endocavitary irradiation alone. Median dose of contact x -ray 95 Gy (4–5 fractions) and iridium 192 implant as a boost in 29 pts (25 Gy/1 day). *Group B:* 43 pts with T2-3 NO-1 in inoperable patients treated with contact x-ray (70 Gy/3 F) followed by external beam radiation therapy: 39 Gy/13 F/17 days + 4 Gy concomitant boost and iridium 192 implant (20 Gy/1 day).

Results: *Group A:* overall and specific 5-year survival was 83% and 94%. LOCO-regional failure were seen in 15 pts (12 were salvaged). *Group B:* overall and specific 5-year survival was 68% and 74%. Loco-regional failure were seen in 32 pts (72%). no grade 3 complication was observed.

Discussion: Surgery remains the basic treatment of rectal cancer. In highly selected cases irradiation alone can cure early T1-2 NO tumors and in inoperable patients some larger T2-3 tumors.

[1] Ref. J.P. GERARD Int. J. Rad. Oncol. BP (1996) 34: 775–83
[2] Rad. Oncol. 1996-38: 131–37

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The surgeon and surgical procedure as a prognostic factor

John Northover. *ICRF Colorectal Cancer Unit, St Mark's Hospital, Harrow, Middlesex HA1 3UJ, UK*

The outcome of surgery for colorectal cancer varies between surgeons. Although there may well be selection bias in the cohort studies which indicate this effect, some single institution data exist to support this contention. The range of difference between surgeons in post operative complications, local recurrence and survival is larger than any likely effect of presently available adjuvant therapy.

Assuming no selection bias, surgeon variation must be due to differences in surgical technique sufficient to translate into different outcomes. Despite the likely size of this effect there have been almost no prospective randomised studies in this field. At present the two areas of technique which may be important variables are extended pelvic lymphadenectomy, as promulgated mainly by Japanese surgeons, and Heald's technique of total mesorectal excision. It is likely that both these approaches contain all the elements of best surgical practice; it is also likely that they are more radical than is necessary to produce optimum oncological outcome, with functional side effects that might be avoidable by lesser procedures It should be a matter of high priority for surgeons to design and perform prospective comparative trials to answer some of these important questions.

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Camptothecins

Axel-R. Hanauske, III. *Department of Medicine, Klinikum rechts der Isar der Technischen Universität München, FRG*

Camptothecins (C) are a new class of antitumor compounds which act through inhibition of topoisomerase I, an enzyme crucial for changes in the topology of DNA during replication. The initial step for the induction of cell death by these agents is the formation of a stable DNA-drug-topoisomerase I complex (DDTC) during S-Phase. A fork-collision model has been developed to explain cell cycle phase specificity and implies the irreversible arrest of moving replication forks by the DDTC. Although the parent compound camptothecin showed promising activity in preclinical models, subsequent clinical trials yielded unacceptable toxicities Subsequently, analogues [irinotecan (CPT-11), topotecan, GI 147211, 9-amino-camptothecin, 9-nitro-camptothecin] have been developed and are now in various stages of clinical evaluation. Oral formulations of C are also under investigation. CTP-11 is clinically active against colorectal cancer and is currently evaluated in combination regimens. Topotecan and GI 147211 are active in ovarian and small-cell lung cancer. 9-amino-camptothecin and 9-nitro-camptothecin are currently being evaluated in Phase I trials. Other analogues are in preclinical evaluation. C are promising new agents with a unique mechanism of action, peculiar clinical pharmacology, and widespread clinical activity which will become part of the standard armamentarium of the practicing oncologist in the future.

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Marine organisms – Are they a worthwhile source?

S.B. Kaye. *CRC Department of Medical Oncology, University of Glasgow, UK*

Forty years ago, Pettit and colleagues began a search for novel antineoplastic agents in marine organisms, which represent a life form of extraordinary longevity (over 3 billion years). Cancer is unknown in these animals, and the hypothesis is that their survival results from the evolutionary development of complex chemical protective agents with potent antiproliferative activity. More recently this search has been extended by specialist companies such as Pharma Mar SA. A large number of peptides have been isolated from a range of organisms, including the tunicates, sponges, bryozoans and algae, and shown to possess a high degree of antitumour activity in preclinical screens, including those involving human tumour xenografts. Several compounds have already reached clinical trial. These include the protein kinase C modulating agent bryostatin I, which was found in Phase I trials to have activity in melanoma, non-Hodgkins lymphoma, ovarian and cervical cancer, the protein synthesis inhibitor, didemnin B, with activity in glioma, and the antimicrotubule agents LU 103793 (a synthetic analogue of dolastatin) and ecteinascidin-743. Toxicities seen include myalgia (bryostatin), vomiting (didemnin B) and myelosuppression (LU 103793). Bryostatin-I is the most advanced in clinical assessment, and Phase II trials are proceeding. The preliminary signs of clinical efficacy, together with the wealth of novel structures in the development pipeline, gives rise to optimism that the sea will indeed prove to be a worthwhile source of anticancer agents.

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Matrix metalloproteinase inhibitors

J. Verweij. *Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands*

Matrix metallo proteinases (MMPs) function in the degradation of extracellular matrix proteins that constitute connective tissue. In cancer there appears to be a local and temporal imbalance between the levels of activated enzymes and their inhibitors. This imbalance results in a break-down of the extracellular matrix. Degradation of the extracellular matrix is necessary when invasive tumor cells penetrate tissues, gain access to blood vessels, exit blood vessels and colonize distant sites. Thus, inhibition of the process might result in prevention of cancer progression. For this purpose synthetic matrix metallo-proteinase inhibitors (MMPIs) have been developed. In preclinical studies they were shown to inhibit organ colonization by tumor cells as well as lymphatic spread. The resultant was increased survival. In addition, there are data that MPIs are additive to the effect of cytotoxic drugs. Clinical studies up to now have been limited. Local intraperitoneal or intrapleural administration of batimastat resulted in postponement of necessary drainage procedures, but especially the intraperitoneal application was limited by to local side effects. For this reason, the present focus is on MPIs with appropriate oral bioavailability. Marimastat is the first example of an orally available MPI that was extensively studied, CGS 27023A recently also entered clinical studies. Efficacy data on MMPIs will be reviewed.

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Compounds inhibiting angiogenesis

L.Y. Dirix. *University Antwerp, Department of Medical Oncology, Belgium*

The dependency of tumour growth on a vascular supply is established. Shutting off the supply route would lead to tumour necrosis, preventing its development would lead to growth inhibition, both at primary and secondary sites. Accessibility of vessels for systemically administered compounds, the small (or absent?) chance of resistance development and the projected limited toxicity of agents directed at a quiescent cell population, are highly promising. These two types of anti-vascular treatment need to be distinguished. The first aims at selective tumour vessel destruction and

conceptually tumours shrink due to the metabolic consequences. This is categorised as vascular targeting; the effect of isolated limb perfusion might be due to selective tumour vessel toxicity. An agent such as CM101 binds to tumour endothelium, activates complement and causes selective endothelial damage. Targeting tissue factor to tumour endothelium results in selective and rapid necrosis. The second approach interferes with the processes ECs undergo during neoangiogenesis: basal membrane degradation and matrix invasion, migration, proliferation and tube formation. Different agents are given anti-angiogenic properties because they inhibit EC proliferation in vitro. This might result in tumour growth inhibition. This class harbours compounds such as TNP-470, PF-4, metalloproteinase inhibitors, and endostatin. Our current cytotoxic drugs have also anti-angiogenic activity in vitro. This should lead to the distinction between EC-selective and non-selective compounds. Different agents as diverse as growth factor antagonists, antiintegrins and endostatin, however do result in tumour regression. This suggests an ongoing remodelling of tumour vasculature with induction of drug induced EC apoptosis and/or a critical role of activated EC for tumour growth. The difficulties in the clinical development of these compounds will be discussed.

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Antisense oligonucleotides in cancerology

J.R. Bertrand, V. Hélin, E. Fattal[1], P. Couvreur[1], C. Malvy. *URA 147 CNRS, Institut G. Roussy PR2, rue Camille Desmoulins 94800 Villejuif; [1]URA 1218 CNRS, Faculte de Pharmacie, 92290 Chatenay Malabry, France*

The concept of antisense oligonucleotides in cancerology is a direct consequence of the results of molecular biology. These small synthetic DNAs (often with chemical modifications) are used in tumor cells to target genes which are active to support the cell proliferation. These genes can be proto-oncogenes, growth factors, transcription factors, factors involved in the signal transmission from the cell membrane to the nucleus... The aim is to prevent specifically the protein synthesis of one gene through a Watson Crick interaction between the oligonucleotide and the RNA transcript. Therefore with molecular weights comparable to the ones of some classical anticancer agents, oligonucleotides are expected to be much more specific and less toxic. Many oligonucleotides have been described in the last 10 years as efficient against transformed cells in culture. In the last 4 years they have also been shown to inhibit, with efficiency, the growth of human tumors grafted to mice after local or systemic administration. These results already demonstrate that in various instances it is possible to greatly reduce the tumor growth by targeting one single genetic event. However we have still to learn a lot at the basic level about how oligonucleotides work and how to improve their efficiency. Among other questions a major one is how are they delivered to their site of action in the cell? Vectorization and/or serum deprivation are required in cell culture to obtain gene inhibition. However oligonucleotides already display activity in animal as free injected molecules. Actually 4 clinical trials are taking place in phase 1 with oligonucleotides targeting specific genes involved in cancers (PKC, p53, c-myb, c-raf).

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Identifying tumour hypoxia

M. Nordsmark. *Danish Cancer Society, Department of Experimental, Clinical Oncology, Aarhus University Hospital, Denmark*

There is experimental and clinical evidence that hypoxic tumour cells create resistance to several cancer therapies. The definition of tumour "hypoxia" is dependent on the assay used.

Recently, direct identification of hypoxia in human tumours has become feasible using either polarographic oxygen sensitive electrodes or by the use of hypoxia marker assays, such as detection of nitroimidazole labelling by the use of antibody techniques, ^{18}F PET, or ^{123}I SPECT. Also indirect estimates of tumour hypoxia, such as tumour blood perfusion by laser Doppler, vascular staining techniques and functional MRI or ^{31}P MRS energy measurements, have been reported.

It is now becoming clear, from a large number of clinical studies using different assays, that hypoxia exist in most tumours but not in all. The level of hypoxia is heterogeneous both within and between tumours, and data obtained with oxygen electrodes indicate that the variability between tumours is larger than the variability within a tumour. Moreover, the oxygenation status is independent of histopathological tumour type and tumour size.

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Tumour hypoxia and treatment outcome

E. Lartigau. *Department of Radiotherapy, Institut Gustave Roussy, 94800, Villejuif, France*

Tumour oxygenation is a factor influencing the response of human solid tumours to radiotherapy or to certain cytotoxic drugs. Despite technical limitations, needle pO_2 probes were first used to assess the oxygenation status of human tumours in the 1950's.

This invasive technique was improved in the late 1980's with the appearance of new polarographic equipment's, using fast responding electrodes movements programmed to minimise the effects of tissue compression. The pO_2 values recorded in normal tissues were in general lower than in tumours. Most of tumours had low pO_2 values (defined as values below 1.33 kPa, 10 mmHg): these values were found in 83% (29/35) of the patients with an ENT tumour and 46% (6/13) of the patients with melanoma.

The differences observed between tumours have long suggested that pO_2 measured by polarography could be a discriminant factor for treatment response. From the end of the 60's, data have been published showing that pre-radiotherapy measured pO_2 was of predictive value for treatment outcome. However, different parameters have been used to define tumour hypoxia (median, hypoxic fraction, % <2.5 mmHg), making comparisons difficult. The results of the more recent studies will be presented together with proposals on oxygen manipulation to sensitise solid human tumours to treatment.

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The influence of the tumor microenvironment on malignant progression

A.J. Giaccia[1], R.M. Alarcon[1], M. Brody[2], J. Calaoagan[2], N. Mazure[1], R.M. Sutherland[3], K.R. Laderoute[4]. *[1]Dept. of Radiation Oncology, Stanford University School of Medicine; [2,4]The Pharmaceutical Discovery Division, SRI International; [3]Varian Biosynergy Inc., USA*

Angiogenesis, the development of new blood vessels, is a highly regulated process that is genetically controlled by alterations in tumor suppressor gene function and physiologically controlled by oxygen tension (hypoxia). In this study, we investigated how low oxygen conditions influenced the expression of the anti-angiogenic gene, thrombospondin I (TSP-1) and the pro-angiogenic gene, vascular endothelial growth factor (VEGF) in cells that differ in their expression of the p53 tumor suppressor gene or the bcl-2 anti-apoptotic gene. We found that hypoxia increased the transient induction of TSP-1 in cells containing a wild-type p53 genotype and that the basal and inducible expression of TSP-1 was undetectable in cells lacking p53. In contrast, VEGF was induced under hypoxic conditions, regardless of the cellular p53 genotype. In cells expressing a conditionally inducible myc proto-oncogene, hypoxia also transiently induced the expression of the TSP-1 which was undetectable by 12 h post-treated. Although hypoxia also increased the expression of VEGF, it only remained elevated in cells containing bcl-2, suggesting that decreasing the apoptotic responsiveness of cells to hypoxia permitted sustained expression of VEGF. Sections from tumors derived from these same cells indicated that VEGF and hypoxic regions co-localized, but that TSP-1 levels were low and did not co-localize with hypoxic regions These studies suggest that fluctuating oxygen tensions play an important role in driving tumor progression both by influencing cell death and stimulating angiogenesis. Supported by NCI grant PO1CA67166

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Hypoxic modification in radiotherapy

Jens Overgaard. *Danish Cancer Society, Department of Experimental, Clinical Oncology, Aarhus University Hospital, Denmark*

It is well established that solid tumors may contain oxygen deficient hypoxic areas and that cells in such areas will cause tumors to be resistant to ionizing radiation. Experimental clinical studies during the last 30 years have shown that this source of radiation resistance can be eliminated or modified by a variety of procedures that include high oxygen content gas breathing and use of nitroaromatic radiation sensitizers. By 1997 over 10,000 patients in 82 randomized trials had undergone treatment designed to modify tumor hypoxia prior to radiation therapy. Although a number of these trials showed no benefit, an overview analysis showed that modification of tumor hypoxia significantly improved the loco-regional tumor control after radiotherapy. The treatment benefit could mostly be related to an improved response in head and neck. Similarly to the local control benefit, the overall survival rate