antigen, staphylococcal enterotoxin A. This agent is capable of inducing exceedingly potent superantigen-dependent cellular cytotoxicity mediated by T-cells. Phase I trials designed to define the optimal dose and schedule of administration are in progress; multiple variables contribute to the identification of the proper dose for each patient. These new strategies are examples of contemporary approaches to antibody-promoted induction of cellular immunity.

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Targeted cytokine delivery with recombinant antibody fusion proteins for therapeutic intervention

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Purpose: A major goal of tumor immunotherapy is a cell-mediated antitumor response effective in eradicating disseminated metastasis followed by a persistent tumor protective immunity. We tested the hypothesis that this can be achieved by targeted cytokine therapy with genetically engineered antibody fusion proteins.

Methods: Syngeneic animal models of murine melanoma, neuroblastoma and colon carcinoma were established and treated with tumor specific recombinant antibody cytokine fusion proteins compared to mixtures of antibody and cytokine at equivalent dose levels.

Results: We demonstrate that the fusion proteins can eradicate experimental and spontaneous metastases and prolong the animals' life span in contrast to equivalent mixtures of antibody and cytokine. Effector mechanisms involved included natural killer cell mediated tumor cell eradication and CD8+ T-cell responses. This was demonstrated in vivo with immunodeficient animals and by depletions of CD8+ T cells or NK cells, followed by anti tumor cytotoxicity assays in vitro with purified T or NK cells.

Conclusion: These data demonstrate that targeted delivery of cytokines to the tumor microenvironement offers a new strategy to elicit an effective cellular immune response against metastasized tumors.

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Radiation induced anomalies in control of signal transduction in Ataxia telangiectasia and Fanconi anemia

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Ataxia telagiectasia (AT) and Fanconi anemia (FA) are recessive genetic diseases featuring increased predisposition to cancer, chromosomal instability and hypersensitivity to DNA damaging agents. In both syndromes, altered induction of the tumor suppressor protein p53 as well as that of p53-target genes (bax, gadd45 and wafl) after gamma-irradiation is observed. Moreover cells from AT and Fa display a deregulation of the apoptotic process spontaneously, after a gamma-rays exposure or following Fas activation. The recently observed alteration of Poly ADP ribose polymerase (PARP) and of DNA-PK cleavage might explain the altered response to ionizing radiations and suggests a deregulation of the ICE-like proteases. Our current investigation of the Bcl-2-like proteins and of the ICE-like proteases should give insights about the functions of the proteins altered in AT and FA. Our results support the contention that a) the AT and FA genes play a major role in regulating apoptosis; b) the hypersensitivity to genetoxic agents is related in both syndromes to necrosis rather than apoptosis.

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Molecular radiation biology at the clinical interface

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The last decade has been characterized by the development of an increased understanding of the role of signal transduction in carcinogenesis. We will review signal transduction models of tumor development with particular emphasis on the role of the ras oncogene in carcinogenesis and its role in signal transduction. We will also discuss the control of the cell cycle and the impact of oncogenes and tumor suppressor genes on the control of the cell cycle. Finally we will review the control of apoptosis and its integration with cell cycle control. This lecture will review the clinical evidence that radiosensitivity is a determinant of outcome in the radiotherapy of cancer and will also examine some of the methods that have been used to try to determine the impact of this factor on cancer management. We will also review the current data on the molecular mechanisms which underlie radioresistance to attempt to define targets for manipulation of radiosensitivity in the clinic. In particular we will show that the ras oncogene can be directly targeted with prenyl transferase inhibitors to sensitize human cell lines carrying naturally occurring ras mutations to the killing effects of ionizing radiation.

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Genetic determinants of radiosensitivity: Potential for therapeutic modulation

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Elucidation of the key components of the signal transduction pathways involved in the cellular response to DNA damage is fundamental to understanding mechanisms of therapeutic resistance. It is also critical to the development of novel strategies for modulation of radiosensitivity, p53 is an inducible regulator of the response to DNA damage; it is activated by DNA strand breaks, inducing G1 arrest via transcriptional regulation of the cyclin kinase inhibitor, p21. We have evaluated the role of p53 in the processing of DNA damage induced by ionising radiation in murine and human cells of defiend p53 status (wild type; knockout p53 −/−, mutant p53 expression systems) using endpoints of clonogenic survival, DNA repair, and mutability at the hprt locus.

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Pathways and time effect of radiation-induced apoptosis

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The dominant cause of radiation-induced cell death is loss of clonogenic capacity due to unrepaired DNA damage. The recent (re)emergence of apoptosis may provide an alternative to this conventional cell kill model. One of the signalling mechanisms initiated by radiation that transduces cell membrane-derived death signals to the nucleus, and does not require DNA damage as a triggering mechanism, is the sphingomyelin (SM) pathway. This pathway is initiated by hydrolysis of the plasma membrane lipid SM, generating ceramide, a potent inducer of apoptosis. We have recently shown that ceramide activates a cascade of kinases that leads to stimulation of *stress-activated protein kinase (SAPK),* a critical event in radiation-induced apoptosis. In bovine aortic endothelial cells (BAEC) radiation induced a biphasic pattern of ceramide generation and SAPK activation. The first, immediate phase of SAPK activation occurred independently of *de novo* protein synthesis, while the second, starting around 4 h, was abolished by cycloheximide. Which of both radiation-induced signals is essential to cause apoptosis, remains to be established. Recent studies have implicated an important role of the interleukin-1β-converting enzyme (ICE)-like proteases in TNF- and Fas-mediated apoptosis. CPP32 has been identified as the protease that cleaves poly (ADP-ribose) polymerase (PARP) during apoptotic DNA degradation. In BAEC, radiation-induced CPP32 cleavage products were identified around 10 h after exposure, but inhibition of this protease by the tetrapeptide DEVD did not affect radiation-induced apoptosis. Currently, studies are conducted to further evaluate the role of the ICE-like protease cascade in radiation-induced apoptosis, and to establish its relation with the ceramide-SAPK signalling pathway.

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Induced radioresistance: Possible mechanisms and impact in the clinic

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Stress responses are upregulated following exposure to radiation and other DNA-damaging agents. Therefore response may be dose-dependent so that small acute radiation exposures, or exposures at very low dose rates, are more effective per unit dose than larger exposures above a threshold where induced radioprotection is triggered. This is termed low-dose hypersensitivity (HRS) and induced radioresistance (IRR) as the dose increases. HRS/IRR has been recorded in studies with yeast, bacteria, protozoa, algae, higher plant cells, insect cells, mammalian and human cells *in vitro*, and in studies on animal models *in vivo*. There is indirect evidence that HRS/IRR in response to single doses is a manifestation of the same underlying mech-

anism that determines the well-known adaptive response in the two-dose case and that it can be triggered by high and low LET radiations as well as a variety of other stress-inducing agents such as hydrogen peroxide and chemotherapeutic agents. Little is currently known about the precise nature of this underlying mechanism, but there is evidence that it operates by increasing the amount and rate of DNA repair, rather than by indirect mechanisms such as modulation of cell-cycle progression or apoptosis. Changed expression of some genes, only in response to low and not high doses, may occur within a few hours of irradiation and this would be rapid enough to explain the phenomenon of induced radioresistance although its specific molecular components have yet to be identified. There may be a benefit in treating intrinsically radioresistant tumours with very small doses per fraction, to take advantage of HRS clinically.

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The surgeon as a prognostic factor in decision making in breast cancer

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The basic treatment of breast cancer is surgery. The surgical procedure aims at three objectives: 1) the intention to cure, 2) staging, and 3) provide variables for a prognostic index. The surgeon is the prime figure in achieving those goals.

For all three purposes axillary dissection is required. If the surgeon fails in performing a meticulous axillary dissection, the decision making regarding adjuvant therapy is badly influenced. In Denmark, low risk patients are treated by loco-regional therapy alone and only high risk patients receive systemic therapy. The decision making is mainly based on knowledge of axillary nodal status. Thus, inaccurate staging puts the patient at jeopardy of undertreatment.

In Danish DBCG nationwide protocols axillary dissection is compulsory as a staging procedure for accurate selection of patients for adjuvant trials. Further, the method is used for prognostic information as well as for regional control of the disease. No subset of patients with invasive cancer has been selected for no axillary surgery.

In this presentation the frequency of node positivity by tumour size is reported. Further, the calculated probability of false negative nodal staging and its consequence for survival is analysed. Moreover, in DBCG protocols the correlation between the number of examined lymph nodes and the rate of axillary recurrence has been investigated in subset of patients with or without radiotherapy to the axilla.

Conclusion: Meticulous surgery is necessary for proper decision making in breast cancer treatment.

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The surgical procedure and the surgeon as a prognostic factor in gastric cancer

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Purpose: There is no consensus about the extent of surgical treatment of patients with operable gastric cancer: lymph node dissection limited tothe preigastric nodes (D1), the present Dutch standard, or extended to the regional nodes (D2). This issue is addressed in a Dutch multicenter (78 centers) randomised trial.

Methods: Design and short term results were reported previously (1); the present paper will focus on survival and relapse risk till 5 years (the present abstract restricted to RO cases). Mean number of dissected lymph nodes was 15 in D1 and 31 in D2. Also issues concerning the individual surgical performance are addressed.

Results: From August 1988 until July 1993, a total of 1078 patients were randomised preoperatively: 639 in each group. Of these, 82 patients were ineligible, 285 patients were non-curative (R2) and 78 microscopically non-curative (R1). The remaining 633 patients underwent a RO resection (339 D1 and 294 D2), Median age and male-female ratio were equal in both groups. Also the distribution of site of tumour, of T-stage and of node negative/positive tumours was similar in both groups. Median follow-up duration for the patients alive is 54 months (range 29–83). Overall rates and relapse risks (44 post operative deaths excluded) of RO patients are summarized in Table 1.

Table 1

	Overall survival						Relapse risk					
	1 yr		3 yrs		6 yrs		1 yr		3 yrs		6 yrs	
	N	%	N	%	N	%	N	%	N	%	N	%
D1	299	88	197	62	71	52	274	14	191	33	62	44
D2	237	81	164	59	66	62	228	12	158	31	62	38

Conclusion: A conventional comparison with a logrank test does not give rise to significant differences in survival and relapse risk D1 and D2 resections. However, the underlying assumption of a logrank analysis (proportional hazards) does not seem to fit very well. A clinically relevant benefit for D2 with respect to relapse risk eventually translated into survival benefit at future follow-up analyses cannot be excluded. On the basis of our present results we cannot substantiate the benefit of extended lymphadenectomy in general Dutch hospitals by general surgeons. There was no significant difference observed between volume related morbidity/mortality/survival however there was a substantial variation among reference surgeons.

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The surgeon and surgical procedure as prognostic factor

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At least since 1978, when Fielding was the first to publish datas on differences between various surgeons concerning complications after operations for colorectal cancer, it is well realized that the surgeon is a prognostic factor in the postoperative course. Later on, datas were available that surgeons also may influence longterm outcome after surgery for colorectal cancer. In the eightieth, in Germany a patient care study was performed with seven institutions participating. Primarily, the aim of this study was not to identify the influence of surgeons on outcome. However, together mainly with tumor related items postoperative complications, anonymously the surgeons and the institution were documentated, too. In addition, all patients were followed up at least for five years.

As a result, concerning logoregional recurrence, the institution was identified as an indepentend prognostic factor. Furthermore, in three institutions with more than 100 operations performed during the recruitment period, surgeons could be identified as a prognostic factor, too.

The question arises, what the reasons for these differences might be. The factors to be discussed are centralisation and specialization including the volume of surgery, but in addition, the influence of organisation, amongst these the impact of quality management.

From the datas available it can be concluded that centralisation and specialization and volume of surgery as well do not guarantee high quality by itself. However, a certain volume may be essential. It seems, however that the adherence to the steps of quality management are the most important factors. A special interest in as special field may be the basic prerequisite.

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The surgeon as crucial factor in reducing mortality and morbidity in pancreatic resection for cancer

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Purpose: Recent data shows a significant drop in mortality for major pancreatic resections for cancer. In a prospective study we evaluated possible causes for the reduced mortality in a specialist center.

Methods: 152 consecutive patients with pancreatic or periampullary cancer were included preoperatively in a prospective standardised protocol consisting of preoperative investigation, operative technique and postoperative care.

Results: 88 men and 64 women with a mean age of 67 years underwent pancreatic resection. 34 patients had significant preoperative risk factors. (ASA III or IV) Median operation time was 448 minutes and mean blood loss 1.6 units. Mortality was 0.6% (1/152) while postoperative complications occurred in 32 patients (21%). Major complications occurred in 8 patients (5%) of whom 4 patients (3%) needed relaparotomy.

Conclusion: In a specialist center, even patients with preoperative risk factors can undergo major pancreatic surgery with low mortality and morbidity. Standardised preoperative assessment and operative technique combined with experience may be responsible for the decrease in mortality and morbidity.