being tested in clinical trials. Their perspectives will be discussed as well as the targeting of antibodies to minimal residual cancer cells in order to preempt metastasis formation.

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Clinical epidemiology

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A useful new concept is if clinical epidemiology would be recognised as the basic methodological tool for clinical cancer studies. The reasons are several:

1) Clinical epidemiology can be defined as the methodological arsenal for study of illness related outcomes in persons who have sought advice in the health care system. Epidemiology investigating causes of cancer has long grappled with problems in design and biostatistical analyses of studies done under difficult circumstances. The field has benefited methodologically and we can import these improvements to clinical studies as many of the basic problems (e.g. estimating risks, rates, relative and absolute effects of interventions etc) are the same. 2) Only in randomised clinical trials (RCT) and meta-analyses (MA) have we so far taken up the challenge, but both RCTs and MAs can improve even more. 3) Not everything can be studied by RCTs and methodologically sound designs are needed in such settings. Examples are studies of unintended effects of treatment and of prognostic markers. Today, many non-randomised cancer clinical studies do not make full use of their data due to unsuitable design and limited analytical scope. 4) In non-randomised clinical studies of intended effects of treatment, problems with bias are even larger than in other observational studies. All methodological lessons learnt from epidemiology are needed. 5) For some cancer diagnoses there exist large clinical databases, which however are little utilised. Well designed studies within those can be valuable for several purposes. 6) Research in diagnostic strategies need methodological improvement, correct diagnosis and early detection being key issues in cancer. 7) Studies in cancer forms with long survival entail problems such as effect modification from comorbidity and competing causes of death, which need to be analysed properly.

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Epidemiology in health policy

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Ideally, all of a society's activities should be assessed and particularly those carried out at the cost of the general public. Cancer prevention and control are not exceptions to this rule. Good, routine statistical back-up is very useful and can be supplemented by special studies. Experience from other countries is not necessarily always applicable or cannot always be repeated. Each country should thus make its own efforts for planning and evaluation.

The basic measure for health policy in cancer is the evaluation of the occurrence of cancer. The indicators incidence, prevalence and mortality can be used for various purposes in policy making. For planning and evaluation of health policy actions, predictions play a central role. Making reliable predictions for the occurrence of cancer is particularly challenging as the risk factors and their distributions and effects in a population are not precisely known for most cancers. Population-based survival rates provide a rough quality control of cancer care in a population. Unexpected differences have lead to studies elucidating the background of the findings.

A population-based cancer registry is an important instrument in this activity. It does not only provide the necessary numerical background but can also provide material for a variety of epidemiological studies of cancer aetiology and evaluation of interventions, provided that an adequate legal basis and sufficient resources exist. Under these conditions important economic savings may be achieved, both in the assessment and in the targets of assessment.

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Low penetrance susceptibility genes for breast cancer

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Mutations in BRCA1 and 2 account for about 15–20% of familial clustering of breast cancer. The number and type of genes that account for the remainder, is not clear. It is however plausible that at least some of this genetic predisposition is attributable to the effects of multiple, common, but individually weak genes.

The prospect of a polygenic approach to common disease, in which genotypic profiles are used to stratify individuals at different levels of risk, has raised much enthusiasm for its potential in targetting screening and prevention. Others are more sceptical, believing the size of genetic effects, compared with chance and environment, to be too small to be of practical use.

We have used a large population-based series of breast cancer cases to model the distribution of genetic risk in the population. The most plausible model gives a log-normal multiplicativity. The difference in risk between the lowest and highest quintiles is 40-fold. We conclude that genotype profiles are likely to be of use, and to provide more information than 'established' clinical risk factors.

To build a profile, one must identify the genes. Using association studies with snps in a large series of breast cancer cases and controls, we have identified 6 tentative positive associations in 29 candidate genes. The interpretation of these results will be discussed.

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Food consumption patterns, energy balance and cancer risk

Abstract not received.

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Impact of advanced technology in cancer of the head and neck

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Introduction: This paper discusses the merits of advanced technology; 3 clinical examples are taken from our own department. First, the evolution in intraoperative brachytherapy (IOBT). Secondly, Stereotactic Radiation Therapy (SRT) with modified frames, and thirdly the sparing potential of external beam Intensity Modulated Radiotherapy (IMRT) techniques.

Material & Methods: We routinely implant cancers of the base of tongue; the dosimetry of this volume implant is time consuming, due to the need for catheter identification on X-ray films. For that reason our protocol does not permit IOBT in volume implants. A solution was presented by CT-based automatic catheter recognition. An additional innovation is the introduction of inverse planning, making BT now a real 3DCRT/IMRT treatment option. The 2nd clinical example is SRT for boosting the primary. Recently the TLC/GTC-frame (Radionics), was modified in our institute to eliminate the problem of not being able to use SRT frames because of severe mucositis. Thirdly, the sparing potential of IMRT using dMLC or step and shoot techniques, will be illustrated (large fields and boost combined). For 3DCRT/IMRT in general, we developed a 3-D target definition of the neck. We are now working on similar guidelines for various primary sites.

Results and Discussion: All 3 clinical examples demonstrate advancement in technology being beneficial to the treatment of H & N cancer patients. However, a price is to be paid. First we will show cost computations for an exemplified tumor (T2bN2 Nasopharynx), treated in our center as of 1996 by neoadjuvant chemotherapy (CHT) in combination with conventional external RT (70 Gy), and brachytherapy (11 Gy). As of 2001, this patient will be treated by neoadjuvant CHT, IMRT 70 Gy and SRT (11.2 Gy), however, with a significant increase in total costs. Secondly, the departments of Radiation-Oncology in The Netherlands have on average a waiting time (WT) of 4–6 wks. The increasing effort in implementing advanced technology in the clinic, given also the shortage of highly skilled personnel, can lead to an increase in the WT and therefore to a less favourable situation. In fact,

the increase in WT might cause a bigger loss in tumor control and/or higher morbidity, with again a rise of health care costs.

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Intensity Modulated Radiation Therapy (IMRT) in lung cancer

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For patients with limited disease (LD) small cell lung cancer (SCLC), accelerated radiation therapy (40–54 Gy/3–3.5 weeks) applied simultaneously with the first or second cycle of full dose chemotherapy has lead to significant improvements in long-term survival in randomized trials[9, 5, 8]. However, a local relapse rate of 42–55% is an argument for radiation dose or dose-intensity escalation. In the randomized trials, an incidence of grade 3–4 acute esophageal toxicity of about 30% suggests that the maximum tolerated dose-intensity (MTDI) was reached for radiation. This was confirmed by Choi et al., who found that the MTDI was limited by acute esophageal toxicity at 45 Gy in 30 fractions over 19 days[2] in a phase I dose escalation trial of radiation simultaneously with chemotherapy in LD-SCLC. IMRT offers a window for dose(-intensity) escalation by its ability to generate intentionally inhomogeneous dose distributions from which i) the low-dose volume coincides with the location of the esophagus and ii) the dose intensity is consistent with the MTDI. The high-dose volume conforms to the tumour up to a dose-gradient zone at close distance from the esophagus. In locally advanced (LA) non-small cell lung cancer (NSCLC), dose escalation is limited at about 70 Gy by pulmonary toxicity when radiation only is used[7, 6, 11, 1]. Local control was less than 50% in these studies. With hyperfractionated accelerated radiotherapy or simultaneous radiochemotherapy, acute esophageal toxicity may become a second dose limiting factor[10, 12]. In planning studies, we have demonstrated that an assembly of parasagittal intensity modulated beams allowed 20–30% dose escalation (when compared to non-IMRT 3D-plans) at equitoxic levels for lung and spinal cord[3, 4]. With such promising news, why isn't IMRT investigated in dose escalation studies for LD-SCLC and LA-NSCLC? The answer lays in radiation-dose uncertainties in and around lung tissue, caused by inaccuracies of all conventional computation algorithms which are further aggravated by i) intensity variations in the beams and ii) narrow photon beam collimation. Inaccurate dose computation misguides the dose distribution optimization processes which are typical for IMRT. Monte carlo based dose computations are accurate and will allow safe introduction of IMRT for lung cancer as soon as more computer performance is widely available and the work-in-progress regarding the linear accelerator head modelling is finished

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Conformal radiotherapy of prostate cancer in clinical practice

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In three-dimensional conformal radiotherapy, the high-dose region is adapted in three dimensions to the shape of the tumor. The advantages are a reduction of acute and late side-effects. Furthermore, it is possible to raise the dose to the tumor, thereby potentially increasing tumor control rates. A prerequisite for conformal radiotherapy is a high geometrical accuracy. Geometrical uncertainties are mainly caused by deviations of the position of the tumor relative to the treatment portals. Three different sources of geometrical uncertainty can be distinguished: definition of the tumor volume, variations of the position of the tumor relative to the bony anatomy, and deviations of the set-up of the patient relative to the isocentre of the treatment.

Uncertainties in the definition of the prostate in MR and CT images were evaluated for 18 patients. The CT volumes were 40% larger than the MR volumes; the differences were mainly located at the apex and at the base of the seminal vesicles. This interscan variation was found to be larger than the interobserver variation.

The center of mass (CM) motion of prostate and seminal vesicles was studied, using repeat CT scans. The motion along the AP axis was larger than along the SI axis, while motion along the LR direction was small. The motion of the CM of the seminal vesicles was larger than the motion of the prostate. The systematic component (variation between patients) was larger than the random component (due to daily variations).

Patient setup deviations were studied using an electronic portal imaging device. Using the appropriate decision rules for setup corrections, the systematic component could be reduced substantially: the percentage of patients with a 3D systematic deviation larger than 5 mm was reduced from 30% to 1%.

The margin, necessary to account for these uncertainties amounts to 0.7 times the Standard Deviation (SD) of the total random component of the organ position variation. For the systematic component, the margin amounts to 2.0 - 2.5 times the SD of the total systematic component. Since tumor motion gives the largest contribution to the overall systematic deviation, reduction of margins can be obtained by reduction of the systematic component of tumor motion.

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Current status of Hadrontherapy with carbon ion beams

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Purpose: Heavy ions possess advantageous dose localization at depth and RBE increases with increasing LET in depth, which gives the improved ratio of the 'biologically equivalent dose' between the peak and plateau. In addition, heavy ions are specifically efficient against hypoxic cells or cells in a resistant phase, and exhibit little repair of cells irradiated in the peak. The NIRS has been evaluating the efficacy of carbon ions generated by Heavy Ion Medical Accelerator in Chiba(HIMAC) in Phase I/II trials ongoing since 1994.

Methods: As of April 2001, more than 1000 patients are enrolled in the study. Of them, 829 patients who have a minimum follow-up of 6 months are analyzed. In Phase I/II dose-escalation trials, doses were escalated by 5~10% increments to provide for patient safety and determine appropriate RBE values.

Results: In this study the patients with locally advanced tumors and those with medically inoperable tumors were mainly treated. As with the radiation related morbidity, there were 5 patients (0.6%) who developed Grade 3 late skin reactions. Two patients developed acute pneumonitis with severe dyspnea at rest. For them steroid treatment was required with significant improvement. Of the patients whose GI tract was partially or totally irradiated in the initial trials, 16 patients developed serious complications of the esophagus or bowels. Among them 2 patients died of recurrence but the remaining 14 patients are alive and free of tumor. Two year local control rates were 60~80% for head and neck tumor, 62~86% for Stage I NSCLC, 80% for liver cancer, 97% for prostate carcinoma, 50~75% for uterine cervix carcinoma, and 75% for bone/soft tissue sarcomas.

Conclusions: Carbon ion therapy has shown promise against a variety of tumors that are hard to cure with other modalities. Tumors that responded favorably to carbon ions include non-squamous cell tumors such as adenoca, adenoid cystic ca, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. Locally advanced tumors, slow-growing tumors, or medically inoperable tumors are also suited for carbon ion therapy. In treatment of parallel organ tumors the overall treatment schedule was successfully shortened to 1~3 weeks or even shorter, which minimized the proliferation of tumor cells during treatment.

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Surgical treatment of metastatic disease: are the number of metastases a limit for surgical resection of lung metastases

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Surgery is a standard procedure for the treatment of lung metastases in selected patients with malignant tumors. The main selection criteria for candidates to such approach include the primary tumor type, duration of free interval between the initial tumor treatment and the lung relapse,