of life improvement. New therapies with molecular targets have been developed and gaining ground in the treatment of NSCLC.

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Secondary cancer as a side-effect to treatment of malignancies

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The success of cancer treatments carries with it the possibility of developing a new cancer later in life. Data compiled by the NCI Surveillance, Epidemiology and End Results Program indicate that second cancers, taken together, now appear as the fourth or fifth most common tumors. While lifestyle, other environmental, and genetic factors contribute to the second cancer burden, so do the therapies used to prolong life. Thus, it is of clinical and public health importance to evaluate carefully the occurrence of second cancers as they relate to curative treatments, and where possible, to develop preventive strategies. The study of cancer following radiotherapy (RT) provides data on both high dose (e.g., direct exposure to organs in the radiation field) and low dose (e.g., scatter radiation to organs outside the primary beam) effects; interactions with other therapies (e.g., platinum and other chemotherapy may enhance leukemia development), genetic conditions (e.g., the tumor suppressor gene, retinoblastoma, influences RT-induced sarcoma), or environmental factors (e.g., smoking may potentiate RT-related lung cancer); as well as temporal and age patterns of radiation-induced cancer. The study of cancer following chemotherapy has primarily focused on secondary leukemia but data are emerging that other sites may occur in excess, including the bone and lung. The knowledge gained from patient studies has influence the choice of therapies with cranial and spinal irradiation for childhood leukemia becoming less common, as has adjuvant radiotherapy for breast cancer; and alkylating agents with less leukemogenic potential have replaced more leukemogenic combinations such as MOPP. Important large studies will be summarized, including patients treated for Hodgkin's disease, cervical cancer, and breast cancer and children treated for retinoblastoma, leukemia and other cancers.

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Late effects of paediatric bone marrow transplantation. Results of a single institution.

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Many children are surviving bone marrow transplantation (BMT) and require long-term follow-up care. The number of late BMT survivors is expected to increase as new indications for transplant emerge and as supportive care improves. Long-term survivors bear special risks and need particular types of screening, prevention, and treatments. Risks for long-term survivors relate to the high-dose chemotherapy used as conditioning for BMT but also to conventional chemotherapy received before BMT. The quality of survival and the total burden of late morbidity were evaluated in 91/120 patients with minimum survival of 5 years (median 9; 5-19) after BMT for solid tumor in our Institution since 1980. Conditioning regimens were various, according to diagnosis and periods, but contained busulfan 56% (median dose 600 mg/m2) of the patients (pts) %. None of the patients received radiation therapy (RT) as part of the regimen but 45 pts (50%) had received previous radiation.

Median age at evaluation was 9 years. Growth and endocrine function, cardiovascular, pulmonary, hepatic and renal status, other organ toxicities, neuropsychological outcome and second malignant neoplasms (SMN) were recorded.

GH deficiency was observed in 9 pts, of whom 5 did not have cranial irradiation. The difference between the weight and the height-SD value at BMT and at evaluation was +0.11SD and –0.6DS respectively. 64% of the female population have an ovarian damage: 100% after busulfan and 29% after busulfan free regimens. Only 1/16 of the non irradiated boys have normal testicular function after busulfan, whereas 20% of the males treated with other regimens.

Eleven pts had lung abnormalities, symptomatic in 8 (4 had previous mediastinal RT, 2 had restrictive sd before BMT and 1 a neurological pathology). Nine pts had cardiotoxicity with SF<30%, symptomatic in 2 (of whom one underwent cardiac transplantation). All of them had been treated by anthracyclines before BMT.

One pt had grade 2 and 6 had grade 1 glomerular toxicity. 26% of the evaluated pts had a minor tubular function failure. Among pts treated with a busulfan containing regimen, 17% developed a focal nodular hyperplasia of the liver without any clinical or biological dysfunction.

All of pts with severe ototoxicity (grade 3 and 4) had previously received platinum-coumpounds treatment.

The majority of the pts tested had normal IQ (above 85). The incidence of IQ scores below 75 was 17% for the FSIQ, 17% for the VIQ and only 6% for the PIQ. The educational and professional outcomes of most pts were within the normal range.

Four pts developed an SMN (1 AML, 1 sarcoma, 1 melanoma, 1 basocellular carcinoma)

In conclusions: Gonadal dysfunction was common in pubertal survivors of both genders. The observed cardiotoxicity is likely realted to anthracyclines given before BMT. These results suggest also that the cognitive and social function of children is not detrimentally affected 5 years post BMT.

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Long-term risk of cardiovascular disease following treatment for cancer

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Radiation-induced heart disease includes a wide spectrum of cardiac pathologies, such as pericardial disease, myocardial dysfunction, valvular heart disease, electrical conduction abnormalities and coronary artery disease. In recent years, there has been increasing evidence that, with long-term follow-up, radiation-induced coronary artery disease will probably pose the most serious health hazard of irradiation (RT) of the heart. Chemotherapy (CT) with anthracyclines has long been known to induce cardiomyopathy, with a cumulative dose-response effect. The risk of treatment-induced heart disease has been studied most extensively in survivors of Hodgkin's disease (HD), breast cancer and childhood cancer.

Mortality from CVD has been extensively examined in several large series of *HD* patients. In the largest study (n=4665; treatment period: 1940-1985), the risk of death from myocardial infarction (MI) following mediastinal irradiation was 2.6 fold increased as compared with the general population. The relative risk (RR) was substantially lower for patients irradiated after 1967. The cardiac mortality risk in a cohort of 2232 HD patients treated at Stanford University between 1960 and 1991 was 3.1 times increased as compared to the general population. RRs of acute MI death and death from all other cardiac diseases were 3.2 and 2.9, respectively. The routine blocking of the left ventricular and subcarinal regions introduced in 1972 did not affect the risk of acute MI death, but significantly lowered the RR of death from all other heart diseases (5.3 before 1972 vs 1.4 thereafter). At 20 or more years after HD treatment, the RRs of acute MI death and death from all other cardiac diseases were 5.6 and 8.8, respectively. Age at irradiation turned out to be a major determinant of mortality from heart disease, with by far the highest RR observed for patients irradiated before age 20, and little excess risk associated with RT after age 50. Recently, we also demonstrated a 6-fold increased RR of death from cardiac diseases in 1261 HD patients treated in the Netherlands between 1965 and 1987 (median follow-up time, 17.8 years) before the age of 40. The RRs for dying of CVD were increased especially for patients treated at the age of 20 years or less (RR=13.6). When these patients attained older ages, we observed trends of decrease for the elevated mortality from CVD. For all patients the increased RRs of death from CVD seemed to level off after 20 years, albeit based on small numbers.

Mortality from CVD in patients irradiated for *breast cancer* has been extensively studied, with inconsistent results. Since excess risk has been rather consistently observed for survivors treated before 1970, the controversy concerns in particular breast cancer patients irradiated with modern techniques. In the Netherlands we recently examined CVD mortality in a series of 3900 breast cancer survivors treated between 1970-1981 (median follow-up, 12.6 years). Compared to the general female population, the number of cardiovascular deaths in the study population was within the

range of normal expectancy (standardized mortality rate (SMR) = 1.1; 95% CI: 1.0-1.3). However, when analyzed by treatment modality, we found a 2.2 fold increase for irradiated patients (95% CI: 1.4-3.6) compared to non-irradiated patients. Thus for non-irradiated patients, cardiovascular mortality was significantly decreased in comparison to the general population, indicating that the risk profile for breast cancer may be protective against CVD. A healthier lifestyle after breast cancer may also play a role. The radiation-related risk was especially increased after more than 10 years follow-up, and even more for patients treated before age 45 (SMR = 2.6; 95% CI: 1.4-4.5). Analysis by laterality showed for the internal mammary chain field similarly increased CVD mortality for left and right side (SMR = 2.1; 95% CI: 1.2-3.7) against no RT; for the chest wall field, irradiation on the left side revealed a significantly increased CVD mortality against no radiation (SMR = 2.5; 95% CI: 1.1-6.4); compared to radiation to the right chest wall the risk was 1.6 fold increased, though not significantly.

The above studies did not find an association between CT and risk of cardiac death, but doxorubicin-containing CT had not been used much in these series. Others have shown that irradiation of the heart may contribute to the risk of doxorubicin-induced cardiomyopathy. It is not clear whether the combined effects of anthracyclines and cardiac irradiation are additive or more than additive. Although a few studies reported on nonfatal cardiac events, incidence of CVD was not compared with that in the general population. The reason for the lack of valid risk estimates for cardiovascular morbidity probably is that most countries do not have national statistics on the incidence of CVD in the population.

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Understanding of treatment related late effects using radiation induced fibrosis as an example

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The risk of normal tissue is frequently the limiting factor when deciding the dose of radiotherapy. Especially the late and often progressive morbidity constitute a problem, and the risk of such morbidity must be balanced with the potential benefit of the cancer treatment. It is estimated that approx. 3-4% of all irradiated patients will suffer from severe morbidity and even morbidity. The increasing knowledge on late effects have consequently given attention to modern techniques of precision radiotherapy (e.g. IMRT) which due to better focused physical dose distribution may reduce the problem. Late radiation morbidity is organ and tissue related, but in general is it considered to be dependent of the volume and total dose and the number of fractions, in such a way that larger doses per fraction causes a relative increase in morbidity when compared with the probability of tumor control. So far have the attempt to modify the therapeutic ratio thus been to reduce the physical dose of radiation to the organs at risk, and optimize the fractionation schedule by hyperfractionation.

When it comes to individual risk factors, may these be related to certain co-morbidities, but otherwise has it been the assumption that almost all patients in principle have the same risk and sensitivity for developing late morbidity. Earlier attempt to estimate in vitro radiosensitivity have indicated some potential individual variation, but the methods used have been too crude for predictive clinical use, except for patients with rare genetic disorders (e.g. ataxia telangiectasia).

The use of new biological genomic techniques together with an increased understanding of variations in genetic function and expressions have, however, opened a new dimension in our understanding of the pathogenesis of late effects. Results from cDNA gene expression have identified radiation induced expression profiles with distinct patterns related to sensitivity, but unfortunately this will require in vitro radiation of living cells. More importantly are there strong indications that polymorphisms in specific candidate genes may be related to both general radiosensitivity as well as tissue related morbidity (e.g. fibrosis).

The presentation will give an overview and update of the biological basis of radiation related morbidity using the genetic based variations in radiation related fibrosis as an example.

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FECS EUROCARE Pilot study on late outcomes of colorectal cancer treatment

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Background: Survival of cancer patients is well documented through cancer registries (CR). Late toxicity and quality of life results are known mainly from hospital based reports with selection bias. To have a more objective view of late outcomes in colorectal, the Federation of European Cancer Societies (FECS) and the EUROCARE project, carried out a pilot study to assess if contact through general practitioner (GP) is a reliable way to analyse late outcome of therapy.

Material and methods: From the EUROCARE high resolution study, a representative sample of all incident cases of invasive histogically verified colon and rectum cancers (ICD9 1530-1548) occurring in the years 1990 (300 cases) and 1997 (300 cases) were included. Three CR were involved (Varese in Italy, Côte d'Or in France and Mersey in UK). After written informed consent the data on late outcomes were collected through two questionnaires. The first one filled by GP and the second one (EORTC. QLQ-CR38 modified) by the patient contacted by GP. The late effects to study included: permanent stoma, bowel function and anorectal continence, urinary and sexual dysfunction and second malignant tumors.

Results: Up to now, a little more than 50% of the Italian Cancer Patients filled in the questionnaire which was consistent with the expectation of this trial. For logistic reasons data from the french and british registries were not fully available at the time of writing. The preliminary results for the italian patients are summarised in table.

	Colon		Rectum		All patients
Year of diagnosis	*1990*	*1997*	*1990*	*1997*	*1990-1997*
GPs traced	56	70	33	38	197 (98%)
GPs filling in the questionnaire	33	39	24	29	125 (62%)
Patients filling in the questionnaire	30	38	19	23	110 (55%)
Permanent stoma	3 (9%)	2 (5%)	12 (50%)	8 (28%)	25 (20%)
immediate	3	–	7	5	15
delayed	–	2	5	3	10
Bowel dysfunction					
GP	2 (6%)	2 (5%)	2 (8%)	2 (7%)	8 (7%)
Patients	26 (96%)	30 (79%)	9 (47%)	14 (61%)	79 (72%)
Sexual dysfunction:	10 (33%)	7 (18%)	5 (26%)	9 (39%)	31 (28%)
Difficulty in erection	7	4	4	9	24 (42%)
Pain during intercourse	3	3	1	–	7 (13%)
Second tumour (any sites)	2	10	3	2	14% (17)

Conclusions: From this preliminary data it is possible to validate the method of using GP (may be using also the patient consultant) to trace and receive questionnaire on late outcomes from patients sampled in CR. The present data also indicate a trend toward stoma reduction with time, underestimation of bowel dysfunctions by GP and the need to follow the patient for second cancers.

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An overview of decision making - who has a right to decide?

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The treatment that an individual patient receives is ultimately dependant on the knowledge of the doctor and the patient's choice. However this specific decision is the end result of a complex series of decisions involving choice. Assuming appropriate knowledge of these choices the problem can be addressed in two ways. Firstly what *absolute* choice is available (scientific progress) and secondly, what *relative* choices are available as a consequence of political and financial decisions relevant to the part of the world in which the patient is needing treatment. For the former there may be few choices but for the latter there are many.

The development of new treatments for cancer (not just drugs) is fundamentally dependant on scientific discovery and its application. There are obvious tensions between academic research and industrial support. Academia is concerned with development of true knowledge and the career