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