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

advancement of individual scientists, where the pharmaceutical industry is focused on financial reward. Doctors play a part in both aspects of this research and development (R&D) but there is currently an acknowledged threat to academic medicine with a recognised need to increase the number of practising cancer specialists throughout the world, and a recognition that academic medicine is more time consuming than routine practice. These factors can act as a disincentive both during training and in subsequent career advancement. The bureaucracy of conducting clinical trials gets evermore burdensome and this is a further disincentive to trainee doctors to pursue careers in academic medicine. The purpose of academic medicine is to produce an evidence base to inform the choice of specific management plans for individual patients, but the knowledge base on which so called "evidence based medicine" can be practiced is far from complete (eg. The variability in cancer registries throughout Europe).

Developments in both scientific discovery and their application are of course totally dependant on funding, but whereas the public understand the need for R&D funding it is frequently less clear where and how the monies for implementing such funds are being applied.

Implementation of research varies considerably and is critical to the relative availability of different treatments in different countries. A major influence on the relative availability of new treatments are the ageing population together with the increased incidence of cancer constantly requiring therefore greater resources, but at a time when advances in other areas of medicine are occurring to challenge the proportion of funding and resource available for cancer treatments. It is therefore clear that not only choices for individual patients have to be made but also the choices of treatment programmes in general for given populations. This requires serious debate.

Licensing authorities serve to protect the public from the application of ineffective or toxic treatments, but the choice of which treatments to make available is a debate where everyone has a role, scientists, doctors, politicians and the public at large. The key factor in addressing such choices is true knowledge of the potential benefits, risks and costs of introducing new cancer managements. Much work is needed to improve an understanding of this evidence-based medicine and to increase awareness of the choices available. Organisations such as FECS can play a major part in informing this discussion most particularly through encouraging the public (including patients) to participate in this major modern dilemma.

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The European approach to approving new anticancer medicines

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Assessment of new anticancer medicines is most often done through the Centralized Procedures where two member states act as rapporteur for the clinical part of the dossier.

While assessment of the preclinical part is well defined, the Note for Guidance for evaluation of anticancer medicinal products in man (NFG) addresses mostly cytotoxic agents and may not provide sufficient guidance for rare cancers or situations.

Ample possibilities for support by external experts are provided 1) during the assessment by each member state where national experts or Experts from the European list can be consulted; 2) before CPMP meetings by addressing specific questions to the Therapeutic Area Group Oncology: this group is still recent so that its exact contribution is not known yet.

The applicant can get guidance from the CPMP before submission of the Marketting Application through Sector Scientific Advice and Orphan Drugs. However this approach is less systematic than at the FDA level.

Some questions are raised:

1) Lack of homogeneity of the member-states concerning preferred endpoints: while the NFG clearly indicates Progression- or Disease-free survival as valid endpoints some rapporteur put more emphasis on Survival or Quality of Life.

2) Lack of common definition for "Outstanding Activity" when application is not supported by phase III data (rare disease or situations, pediatrics).

3) Lack of in depth reflexion on the use of surrogate endpoints.

4) Duration of the Evaluation Phase in particular for innovating agents

5) Lack of homogeneity in the evaluation of similar situations and agents of similar mechanism of action are concerned.

Altogether 2/3 of the submitted applications ultimately receive a positive assessment. It is to be noted that when dossiers are simultaneously submitted to FDA and CPMP, European assessment is generally longer.

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Setting priorities in health budgeting in Finland

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The need for setting priorities is due to aging population, expensive new technology, patient expectations, a tendency for medicalisation, and health care financial problems. According to the Finnish Act on the Status and Rights of Patients, "every patient is without discrimination entitled to health and medical care required by his state of health within the limits of those resources which are available to health care at the time in question." All possible care cannot be arranged because of limited resources, and this is recognized also in the law. This leads to the necessity of setting priorities. Finland is not creating an "Oregon list" according to which some diseases and treatments would strictly be left unfunded. However, it is essential to get the best possible value for the available resources. If several treatment alternatives are available, the most cost-effective therapy must be chosen. Health technology is assessed on national level and specialist groups are creating national treatment guide lines.

Priorities are set on different levels of health care. State budget is divided to different sectors of the society, municipalities allocate their budget to different sectors, hospitals prioritise between departments and activities, and an individual health care provider decides individual treatments and in what order they are arranged.

The state duty is to ascertain that all citizens have access to basic health and social services. Priorities are set by legislation, development programs, and via budgets. Legislation gives the terms of reference for priorities: municipalities have, e.g., a duty to provide primary health care and specialised care. Some of their duties have been clearly spelled out, e.g., maternity clinics and vaccination programs. Legislation is, however, rather general.

The state steered health care activities rather closely in the 1970s and 1980s. Since 1993 state has been dividing a monetary subsidy to each municipality for its health and social services. Municipalities have become very autonomous in allocating this money to different activities. The big amount of municipalities and their variable financial situations have led to big differences between variety, sufficiency, and quality of services. Some of the priorities may not be set well, e.g., specialised care may be financed on the expense of primary health care.

To even out the exceptionally high costs municipalities incur in care for an individual patient, the hospital districts have worked out a system for equalising expensive care costs. The state has now also started to guide municipalities more specifically than before. There are specific decrees on how to provide certain services, e.g., substitution treatment for opiate addicts. State has also started to grant special ear-marked state money to certain areas. Child psychiatry and treatment of drug addicts have been targeted in this manner. The state is paying for a number of health care development projects and monetary support is given to shortening queues to certain operations. Finland is planning on quaranteeing access to treatment within set time and, to prepare for this, a group of experts is setting concrete treatment indications.

Pharmaceuticals are financed via social insurance institution instead of state and municipality taxes. Due to rising drug expenditure there is a need to control drug use and expenditure. Life saving and very beneficial drugs are reimbursed by a higher percentage that other drugs. Those drugs that are too expensive compared with their usefulness are not reimbursed at all.

How to prioritise via budget? Competition may increase efficiency in certain areas, e.g., cleaning and nutrition and laboratory services. Budget cuts save money but unless savings are planned carefully beneficial treatments will also be endangered. If there is only a certain amount of money for a certain purpose, patient may be left without these treatments by the end of the year. By increasing user charges it is possible to redirect demand for services. However, lower socioeconomic groups are affected more than others and use of both important and less important treatments may decrease.

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Setting the agenda - in cooperation with doctors

Abstract not received.