Giving "neoadjuvant" chemotherapy has made it possible to show that the response of the primary tumor to preoperative treatment predicts whether therapy will be efficacious against micrometastatic disease and hence to predict prognosis. Local control of the primary tumor remains the domain of surgery. Marginal or intralesional operations are associated with high rates of local recurrence. Wide surgical margins as defined by the Musculoskeletal Tumor Society, however, are sufficient. Removal of the whole involved compartment is generally not necessary. As is the case with systemic recurrence, tumor response to preoperative chemotherapy influences the risk of local recurrence. With improved imaging techniques, particularly Mill, the past decade has seen a major shift away from amputation towards limb-salvage. In experienced hands, the latter can be performed without unacceptably high local failure rates, but this implies not only high technical skills, but also exquisite care in defining whether limb-salvage will be safe for a particular patient or not. Around the knee, the rotation plasty offers an alternative for those for whom limb-salvage is not feasible. Large scale studies on the long-term functional and psychosocial outcomes following various types of surgery are currently under way.

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Genes predisposing to colon cancer

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Most colorectal cancers are sporadic. When one or more members of the proband's family also have cancer, this is referred to as familial occurrence. It occurs in some 20 per cent of all cases. Among the familial colorectal cancers, two conditions displaying Mendelian inheritance of susceptibility are recognized. Hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as Lynch syndrome, accounts for 3–5% of all colorectal cancer, and is caused by inherited mutations in the mismatch repair genes. Familial adenomatous polyposis (FAP) accounts for less than 1 per cent of all colorectal cancers and is caused by mutations in the APC gene. Other high-penetrance susceptibility genes are very rare or not yet known. Thus most of the familial colorectal cancers are still molecularly unexplained. Recent findings suggest that a variety of low-penetrance gene mutations and polymorphisms may explain familial occurrence. Moreover, epigenetic phenomena, such as gene silencing by promoter methylation, and loss of imprinting, may be important predisposing factors, but their heritability is not yet proven. The molecular basis of familial colorectal cancer is highly heterogeneous.

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BRCA1 and BRCA2 in cell response to genotoxic lesions

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Germline mutations in either the *BRCA1* or the *BRCA2* gene are responsible for the majority of hereditary breast cancers. The proposition that BRCA1 might a role as a caretaker of the genome was first put forward by the demonstration that, in mitotic and meiotic cells, BRCA1 can interact with Rad51, which plays a major role in repair and/or recombination processes. From there, multiple observations have converged to support the concept that BRCA1 and BRCA2 play a role in monitoring and/or repairing DNA lesions. The relaxation of this monitoring caused by mutations of either of these two genes leaves unrepaired events leads to the accumulation of mutations and ultimately to cancer. Radiation-induced death pathways of human cells with various BRCA1 and BRCA2 genotypes has been studied. Upon irradiation, the lack of functional BRCA1 and BRCA2 leads consistently to defective DNA double-strand breaks repair. This impairment manifests itself by production of micronuclei and loss of proliferative capacity. Heterozygous BRCA1 and BRCA2 mutation leads also to an exaggerated radiosensitivity with a radiation-induced loss of proliferative capacity. The existence of a phenotype related to radiosensitivity in $BRCA1^{+/-}$ and $BRCA2^{+/-}$ cells raises question relative to the response of heterozygous women to radiation exposure.

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The role of ATM gene in cancer predisposition

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Ataxia-telangiectasia (A-T), resulting from mutations in both copies of the ATM gene, is a rare multiorgan recessive disorder characterised by an exceptionally high risk of cancer and acute sensitivity to ionising radiation. Heterozygotes, comprising 0.2–1% of the population have been found to have an increased risk of cancer, in particular breast cancer. This has been supported by some studies but not confirmed by others. In view of this discrepancy, we have performed a Scandinavian study on cancer risk in 1328 relatives of 55 AT patients using the population based cancer registries and civil registration systems available in these countries. The SIR for all cancers was 1.19 (1.01–1.4). For breast cancer the SIR was 1.53 (1.0–2.3) for the total cohort, with the highest SIRs in Finland and Norway (1.9 and 1.7) and lowest in Denmark and Sweden (1.3 and 1.0). When breast cancer risk by type of relative was studied, a significant elevated risk for mothers was found SIR 7.5 (2.4–17.5). In grandmothers the SIR was 1.52 (0.5–3.6) and in great grandmothers 1.56 (0.5–3.6). The SIR for breast cancer at young age (50. Forty-four families have been available for blood sampling, and mutation analyses in these families are ongoing. So far 62 out of the 88 alleles (70%) have been found mutated of which 50 are sequence verified. Genotyping of the relatives are in progress to more accurately estimate the risk of cancer, particular breast cancer in ATM mutation carriers in the Scandinavian cohort. In the Norwegian cohort 27 of the 28 mutated alleles have been identified. Ten different mutations have been found of which one is found in 16/28 (54%) of the mutated alleles and another in 2/26 (8%). For six of the mutations a multiplex PCR assay has been developed and screening of 500 breast cancer patients form consecutive series as well as 500 controls are ongoing. So far we have screened 302 cases and no mutation carrier has been found. However, two other rare variants (not sequence verified yet) were seen in this cohort. In a previous study of the founder mutation in a cohort of breast cancer patients from a region including the valley where this founder mutation originate from, we found 1/145 ATM carriers. All mutations found in the Norwegian AT patients will be screened for in the breast cancer cases and controls.

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Genetic abnormalities in thyroid tumours

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Thyroid tumours comprise medullary thyroid carcinoma (MTC), developing from neural crest-derived C cells and tumours originating from the epithelial follicular cells. Although originating from the same follicular cell, papillary and follicular carcinomas are regarded as different biological entities. The thyroid, therefore, appears to provide a good model for studying the cytogenetic features and the molecular basis of tumorigenesis of different neoplasias with common origin.

In papillary thyroid carcinomas, (PTC) our studies have indicated that, overall, about 50% of the tumors show the activation of an oncogene with tyrosine-kinase activity, derived from either one of two membrane receptor genes called proto-TRK (Nerve Growth Factor receptor), and proto-RET (Glial cell Derived Neurotrophic Factor family receptor). We then defined a total of 6 oncogenes which are part of this superfamily of oncogenic tyrosine-kinases and we determined their activation mechanisms. An interesting problem regards the correlation between ionizing radiations and the development of PTCs. This aspect of scientific research has gained particular importance after the dramatic increase of papillary carcinomas of the thyroid in children exposed to radiations after the nuclear accident in Chernobyl. Our first important contribution to this problem was the demonstration that, in a series of these tumors, a high frequency of RET oncogenic activation was found. In follicular thyroid carcinomas, we and others have defined a role of mutated RAS oncogenes. Moreover, we were among the first to report the specificity and frequency of p53 mutations in thyroid tumors (about 75% of cases) and its association with undifferentiated carcinomas. Finally, experimental data will be presented on the role of proto-RET mutations associated with inherited (MEN2) or sporadic medullary thyroid carcinoma (MTC).

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