sensitivities reopened the discussion with a new strategy: induction CT followed, in good responders, by XRT or, in poor responders, by S. To date, 3 randomised trials have been published with such a design. The VA trial on larynx and the EORTC 24891, for hypopharynx had similar conclusions. In both trials there was no difference in survival between this experimental approach and the standard treatment (S + postop XRT) but 50% to 66% of survivors could retain their larynx. In the French trial (GETTEC) only T3 larynx SCC were eligible. The survival was poorer in the experimental arm. A meta-analysis (MACH-NC) of the 3 trials concluded in a non significant trend for a better survival in the surgical arm but 58% of larynx could be preserved in the experimental arm.

Conversely, subtotal surgery may avoid performing, in selective cases, a total laryngectomy. Finally, notable advances have improved XRT results: new fractionation, acceleration, both or concurrent administration of XRT and CT.

Clearly, there are different ways to preserve the larynx function which are still to be compared. As a result, this approach still remains in the field of clinical research.

1207

Chemoradiotherapy as treatment of choice in oesophageal cancer

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In a prospective randomized controlled trial of neoadjuvent chemoradiotherapy versus surgery alone for patients with Carcinoma of the oesophagus we have observed that multimodal therapy can downstage tumour size, node stage, lymphovascular invasion and radial margin involvement. A complete response was obtained in 25% of adenocarcinomas and 32% of squamous carcinomas.[1]

Surgery may not have been necessary in some of these patients. One patient who did not proceed to surgery because of a severe myocardial infarct was tumour free for 4 yrs before developing a recurrence. Of 2 patients in whom surgery were omitted because of deteriorating performance status, 1 survived $2\frac{1}{2}$ yrs before developing a recurrence and 1 was tumour free at last review at 2 yrs. One patient survived 30 mths despite having an incomplete response. Nine further patients survived for short periods or are still being followed up.

[1] Walsh T., Noonan N., Hollywood D., Kelly A., Keeling N., Hennessy T., *A comparison of multimodal therapy & surgery for esophageal adenocarcinoma.* N. Eng. J. Med. 1996, 335/462-7.

1208

Chemo-radiotherapy reduces the need for a permanent colostomy

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A permanent stoma can rarely be avoided during radical surgery for *squamous carcinoma (SCC) of the anus or for adenocarcinomas (adenas) of lower third of the rectum.* Since primary radiotherapy (XRT) yields colostomy-free survival rates of 60–80% for SCC, it should be considered primary treatment, with surgery for failures. However, for *adenos* the cure rate is below 50% for tumours over 5 cms diameter. After XRT for adenos, planned *local execision* is safe but for tumours >5 cms radical surgery with *pouch procedures* are prefferred. Concomitant cytotoxic chemotherapy (chemo) appears to enhance the XRT-sensitivity of both tumours. In SCC three large phase III clinical trials have been demonstrated an improvement in local control when XRT is combined with 5-fluouracil (5-FU) with no major increase in toxicity. Similar improvements appear in non-randomised studies in adenos, but randomised studies have shown increased postoperative complications following chemo-XRT. Since the optimal chemo-XRT schedule has yet to be decided, phase I/II studies should be conducted on patients with advanced inoperable/reccurrent adenos using drugs with known activity like raltitrexed, oxaliplatin or irinotecan.

1209

Multimodality approaches in breast cancer: What have we learned?

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There is now an increasing need for a multidisciplinary approach to the treatment of early breast cancer to obtain a high local control rate and survival. With this multidisciplinary approach, there is a high probability of preserving the breast.

An increasing number of patients with DCIS are being discovered due to screening programs. The preliminary results of clinical trials in DCIS demonstrate that radiotherapy can reduce the local excision after microscopically complete excision of tumors up to 5 cm. On the other hand, a longer follow up is still necessary to define which subgroup will benefit most from radiotherapy.

For stage I and II invasive breast cancer, breast conserving therapy (BCT) has been shown to result in equivalent survival rates to mastectomy. With the introduction of the sentinel node biopsy, the treatment morbidity is reduced considerably for a large number of patients. Patients younger than 35 years old have a higher 1ocoregional recurrence rate after breast conserving therapy. The increased use of adjuvant chemotherapy has reduced the amount of local recurrences; it is uncertain what the contribution is to the results of BCT in younger patients.

The difference in treatment outcome, which varies per institute, has led to an intensive quality assurance program This has proved most effective as the results of a major EORTC trial (>5500 patients) showed much less variation in locoregional recurrence rate between participating institutes.

1210

Limb salvage for soft tissue sarcoma: Multimodal procedures or improved surgery?

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It is common observation that amputations for soft tissue sarcoma (STS) progressively decreased in the recent decades. In the same span of time different multimodal treatment policies were experienced to improve local and systemic control with an impact on survival: perioperative radiation therapy, adjuvant chemotherapy, isolated limb perfusion, and combinations. These adjuvant procedures are usually conceived to be responsible for improving limb salvage surgery, but their role was never proved. In the last 20 years the survival rate of patients with STS had a minimal improvement, if compared with the number of amputations which significantly dropped from 40/50% to 10/20%. We reviewed 1319 patients with extremity STS operated in our Institute in the period 1965-1998. The amputation rate stratified by years was respectively: 1965-, 75 = 71% (37/52 pts), 1976-Œ85 = 16% (46/287), 1986-Œ95 = 8% (61/764), 1996-Œ98 = 3% (6/216). By their own any single procedure helped local control and conservative operations but in details: RT is the main adjuvant tool for local control, but its rationale, even if more standardized in the recent period, did not change grossly by years. Moreover the indication to RT, as for adjuvant CT, is usually decided postoperatively and has no role on the surgical choice between conservative versus ablative operation. Preoperative CT was employed in 143 cases (111 with intra-arterial delivery of Adriamycin): shrinkage of the lesion was documented in about 40% of cases, but the split from amputation versus conservative operation was estimated around 4%. More recently hyperthermic isolated limb perfusion chemotherapy seems to improve these conservative possibilities: we perfused 70 cases, mainly in the last five years and their final role in local control is still under evaluation, however not responsible of the important improvement reported between the Œ70ties and the Œ80ties. Surgical reconstructive methodologies and vascular prosthesis were employed in less than 10% (128/1319) of our operations and changed the surgical indication in favour of limb sparing surgery in less than 3%. In conclusion all adjuvant or sophisticated procedures are effective on local control but do not give reason for the dramatic drop of amputations that is mainly due to improved anatomo-surgical knowledge and practice.

1211

Combination therapy for osteosarcoma

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Osteosarcoma, the most common primary bone cancer, usually afflicts adolescents and young adults. The primary is often located in an extremity, and micrometastases to lung or bone are almost ubiquitously present. In order to be successful, treatment must eradicate both the primary and all metastases. Today, this goal can frequently be achieved by combining surgery with systemic chemotherapy. The main aim of chemotherapy in this setting is the eradication of micrometastases. Most successful protocols include two to four of the drugs methotrexate, doxorubicin, cisplatin, and ifosfamide.

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.

1212

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.

1213

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.

1214

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.

1215

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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