surgical oncologist should be equally aware of today's new science of molecular biology and the opportunities it presents in the diagnosis and managment of the cancer patient.

Understanding the molecular aetiology of cancer offers an opportunity of earlier intervention by applying screening to high risk groups, for example, in subjects of genetic risk of breast or colon cancer or using molecular markers to screen for cells exfoliated from cancer, as in bladder or colon cancer. It also enables different interventions such as cyclo-oxygenase inhibitors to prevent the progress of colonic polyps.

In established cancer the genetic alterations can be utilised to not only predict outcome but also to predict outcome for theory and ultimately to devise new therapies. In breast cancer the over-expression of hormone receptors have long been established as a target for therapy but this is now extended to the use of anti-HER2 treatments.

This talk will discuss the potential utility for the surgical oncologist.

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The Kaposi's sarcoma associated human herpesvirus 8 - epidemiology and pathogenicity

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The epidemiology of Kaposi's sarcoma (KS) amongst North American and Northern European patients with AIDS suggests that an infectious agent other than HIV is involved in its pathogenesis. Epidemiological data indicate that human herpesvirus 8 (HHV-8), also termed Kaposi's sarcoma associated herpesvirus, is the sought-after agent. DNA of HHV-8 is invariably found in all forms of KS where the virus is present in the KS spindle cell. In contrast, HHV-8 DNA is not regularly detected in most other malignancies. Although current serology does not allow to assess the HHV-8 prevalence in the general population with certainty, high titers of HHV-8 antibodies are almost exclusively found in KS risk groups. In addition, HHV-8 seroconversion has been shown to precede KS development. The mechanisms and genes involved in HHV-8 pathogenesis are less clear. HHV-8 belongs to a family of transforming viruses, and several candidate oncogenes have been identified by using rodent fibroblast transformation assays. In addition, the virus encodes and induces several cytokines and angiogenic factors. This is of particular interest as models of KS pathogenesis developed before the discovery of HHV-8 emphasized the importance of inflammatory cytokines. However, expression of most of these genes could not be shown in latently infected tumor cells. Only the virus encoded cyclin D homolog, a nuclear antigen encoded by open reading frame 73, and the viral FLICE inhibitory protein have been shown consistently to be transcribed in the majority of latently infected cells. In addition, a novel HHV-8 encoded transcription factor with homology to the family of interferon response factors is expressed in latently infected B-cells. Although the expression pattern of viral genes in KS is not certain yet, it appears likely that the pathogenetic role of HHV-8 in KS may be rather complex and differs from other virus-induced malignancies.

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Thyroid cancer after irradiation

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External irradiation to the neck during childhood increases the risk of papillary thyroid carcinoma (PTC). The latency period is at least 5 years. The risk is maximal at 20 years. The risk is increased after a dose to the thyroid as low as 10 cGy. Above this dose there is a linear relationship between the dose (up to 1500 cGy) and the risk of carcinoma. Risk factors include a young age at irradiation and above age 15 years the risk is not increased; female sex and familial susceptibility. In children exposed to 1 Gy to the thyroid, the excess risk is 7.7.

A tumorigenic effect on the thyroid of iodine isotopes in children has been suggested by the increased incidence of PTC in the Marshall Islands after atomic bomb testing, and more recently in Belarus and Ukraine, as a consequence of the Chernobyl accident. However, there is no evidence that the risk of PTC is increased in adults given 131 I; the increased incidence of thyroid carcinomas observed in western countries since 25 years is not related to the Chernobyl fall-out, but rather to more extensive thyroid examination in the general population.

RET/PTC rearrangements are found in 60–80% of radiation induced PTC and in only 5–15% of PTC occurring in the absence of radiation exposure.

Subjects exposed to radiation during childhood should be submitted to follow-up. Any thyroid nodule warrants a complete work-up including a fine needle aspiration biopsy. The initial treatment, follow-up and long term prognosis are similar to those of PTC patients with no history of neck irradiation.

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The colorizing of cancer cytogenetics

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Karyotype analysis has depended on chromosome banding techniques since their introduction around 1970. The information thus obtained is relevant for diagnosis, prognosis, and disease monitoring in patients with hematologic malignancies and increasingly also in solid tumors. Some technical developments in recent years have helped bridge the gap between chromosome-level and molecular-level investigations. Interphase or metaphase fluorescence in situ hybridization (FISH) with chromosome- or locus-specific DNA probes can identify rearrangements too subtle or too complex to be disclosed by chromosome banding alone. On the negative side, this type of investigation only reveals those aberrations one tests for and is therefore not suitable for the initial screening of tumors. Comparative genomic hybridization (CGH), on the other hand, which uses tumor genomic DNA and normal DNA as competing probes and normal metaphases as templates, is a genuine screening method that detects copy-number changes. CGH does not detect balanced rearrangements, however, nor does it detect differences among cells. Spectral karyotyping (SKY) and Multiplex-fluorescence in situ hybridization (M-FISH) use a pool of painting probes that label each chromosome with a different fluorochrome combination, and are particularly promising to characterize complex interchromosomal rearrangements. It does not detect intrachromosomal changes, however, and breakpoint assignment is unreliable. The last addition to the field is Cross-species color banding (RxFISH), which uses probes originating from flow-sorted, differentially labeled gibbon chromosomes. Because of the extensive sequence homology between gibbon and human DNA (98%) and the many chromosomal rearrangements that have occurred during evolution, the hybridization of these probes onto human metaphases results in a specific color banding pattern for each human chromosome. The combination of these new FISH technologies with standard chromosome analysis will ensure that the future of cancer cytogenetics is bright and colorful.

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Cure of chronic myeloid leukeaemia

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Chronic myeloid leukaemia (CML) is thought to be due acquisition of a BCR-ABL fusion gene in conjunction with Ph chromosome in a single multipotential haemopoietic stem cell whose progeny gain a proliferative advantage and eventually replace all normal haemopoietic tissue. Conventional cytotoxic drugs alone or in combination are effective in reducing the size of the leukaemia cell mass but do not adequately differentiate between leukaemic and normal cells; moreover some Ph-positive stem cells may be 'deeply' quiescent and thereby escape the action of anti-leukaemic drugs. Experience with allogeneic stem cell transplantation (allo-SCT) over the last 20 years suggests that the majority of those who survive 5 years are probably cured because (a) the incidence of relapse thereafter is very low, and (b) most remain persistently negative for BCR-ABL transcripts when studied by the most sensitive RT-PCR. The mechanism of cure is uncertain but much evidence suggests that it is due to a combination of the drugs and radiotherapy used as conditioning and a graft-versus-leukaemia (GVL) effect mediated by donor lymphocytes. The possibility that cure can be mediated by a GVL effect alone or in association with reduced-intensity conditioning is now being tested in many specialist units but conclusive results are not yet available. The biological basis of GVL remains unknown but candidate target antigens include: BCR-ABL oligopeptides, proteinase-3, WT1, minor histocompatibility antigens. A variety of immunisation strategies are now being designed for patients not eligible for allo-SCT and some have entered the clinic. Meanwhile the ABL kinase inhibitor STI571 has proved remarkably effective at reducing the leucocyte count and restoring Ph-negative haemopoiesis in previously untreated patients; currently it seems unlikely that this agent alone will cure more than a small proportion of patients but combinations of STI with IFN, cytarabine or other agents may do so; moreover the possibility of using STI in conjunction with an autograft procedure is attractive. The issue of whether a GVL effect is a necessary prerequisite for cure of CML may be answered within the next ten years.