Teaching Lectures

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Screening methodology

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Cancer screening is intervention in the natural history of a cancer disease. Screening means testing of healthy people in order to diagnose so far asymptomatic cancers or precancerous lesions. The patients can then receive an earlier and potentially more efficient treatment. The purpose of screening is to decrease the mortality from the cancer disease. If precancerous lesions are also detected and treated a decrease is expected also in the incidence of the invasive disease. The effect of screening can be measured only by comparing the disease specific mortality (and sometime incidence) between a screened population and an unscreened control population. This can be done best in randomised controlled trials (RCT). So far only mammography screening for breast cancer and faecal occult blood test screening for colorectal cancer have been studied in RCTs. Studies are under way of screening with flexible sigmoidoscopy for colorectal cancer and adenomas, and of screening with prostate specific antigen for prostate cancer. Observational studies have to be used when data from RCT are missing. Observational studies are available on Pap smear screening for cervical dysplasia, and on screening with colonoscopy for colorectal cancer and adenomas.

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Interactions radio-chemotherapy

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The concept of combining chemotherapy to radiation for the treatment of solid tumours emerged empirically 50 years ago. Its value was demonstrated in patients with epithelial cancers especially when the two modalities were delivered concurrently. The mechanisms by which conventional chemotherapy enhances the local effect of ionizing radiations are complex and remain largely unknown. These include DNA repair inhibition, cell-cycle interference, alteration of cell-death regulation, cytokinetic cooperation at the cellular level and at the tissue level, reoxygenation, increased drug uptake, inhibition of repopulation or angiogenesis. The main objective of the combination is to increase local tumour control which may ultimately conduct to better overall survival. Other objectives are organ preservation and quality of life. Normal tissue tolerance is a critical issue. Chemo-radiation generally increases acute toxicity which can lead to a decreased compliance. It could also be responsible for an increase in late effects. Therefore each component of the combination and the sequence should be optimized to obtain the best therapeutic index. Chemo-radiation is now standard treatment for many locally advanced cancers as oesophagus, lung, head and neck, anus, pancreas, rectum. It could be used alone or in the preoperative or postoperative setting. Because the benefits observed in phase III clinical trials were obtained in carefully selected patients, this approach should be implemented carefully and evaluated in the daily practice. Teams should be specifically trained, patients be informed of possible toxicities and their management (including analgesics, nutritional aspects, hospitalisation if necessary). Recently, tissue micro-array technics and immuno-histochemistry developments make rapidly accessible the identification of molecular targets thought to influence the effect of radiation on tumours. New fields open for clinical research are (not limited): intervention on cytokines and growth factors (HER, TKs inhibitors); targeting hypoxia with new bioreductive drugs; or the tumour blood vessel with anti VEFG; or ras oncogene via farnesyltransferase inhibitors; or prostaglandins via cyclooxygenase-2 enzyme inhibitors. These targeting therapies will be used in combination with conventional chemo-radiation and some of these strategies will be used in adjuvant setting as well.

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Cox-2 inhibition in gastrointestinal cancer

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Over the past decade, a series of studies have suggested that the enzyme cyclo-oxygenase (COX) represents a therapeutic target for preventing cancer. Epidemiologic studies showed that the use of non-steroidal anti-inflammatory drugs (NSAIDs) was associated with a reduced risk of developing several malignant diseases including colorectal cancer. NSAIDs also protect against the formation of tumours in animals. The finding that NSAIDs inhibit COX suggested that prostaglandins, the products of COX activity, substantially contribute to carcinogenesis. For example, COX-derived prostaglandins have been implicated in angiogenesis. The recent development of selective inhibitors of the inducible form of COX, COX 2, represents another important advance.

There is extensive evidence, beyond the finding that COX 2 is commonly overexpressed in both premalignant tisssues and malignant tumours, to suggest that COX 2 is mechanistically linked to the development of cancer. The most specific data supporting a cause-effect relation between overexpression of COX 2 and carcinogenesis come from genetic studies with transgenic mice that overexpressed the COX 2 gene. Pharmacologic evidence also implicates COX 2 in tumorigenesis: selective COX 2 inhibitors such as celecoxib and rofecoxib reduce the formation of intestinal, breast, lung, bladder and tongue tumours in animals. In addition to preventing tumorigenesis, selective COX 2 inhibitors suppress the growth of established tumours.

COX 2 affects many processes that are important in carcinogenesis such as angiogenesis, apoptosis, inflammation, immunosuppression and invasiveness.

The emerging role in COX and of COX 2 inhibitors in Barret oesophagus is under extensive investigation.

In humans it has been shown that celecoxib can reduce the number and the size of adenomatous polyps in the colon in patients with the familial adenomatous polyposis syndrome (FAP). Studies with rofecoxib are ongoing in this indication. Studies with celecoxib and rofecoxib after endoscopic resection of sporadic adenomas to try to reduce the risk of recurrence of colonic adenomas are ongoing. In patients with colorectal cancer randomized clinical trials are ongoing of chemotherapy +/- celecoxib or rofecoxib after surgery with the aim to reduce the cancer relapse rate and to increase the survival. The EORTC GI group is performing a randomized trial in patients with metastatic colorectal cancer of chemotherapy +/- celecoxib (irinotecan + 5-FU/LV or capecitabine).

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Filling the gap - reconstructive surgery

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Oncological treatment is a therapy that is more and more based in multidisciplinarity.

The horizontal transmission of clinical essays results is the key element for the development of therapy in the various pathologies. Vertically, the development of new techniques, namely in surgery, has allowed the optimisation of treatment, having as a primary objective the improvement of quality in general and quality of life in particular.

Surgery still has the main role in the initial treatment of solid tumours. The objective of preserving the functional and the aesthetic aspects is becoming more inherent to surgery. This goal is only possible to achieve through an active merge of knowledge and skills of the oncological and reconstructive scope. At the level of an institution this scope may be reunited in one surgeon only or be the result of active co-operation of mixed teams. This presentation is an example of these two possibilities. Thus if in some areas, as head and neck, the model is one surgeon for all, in others as gynaecology or digestive surgery a team co-operation is required.

We present a series of clinical examples, in the head and neck, breast,