# Teaching Lectures

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## Screening methodology

E. Lynge. *University of Copenhagen, Institute of Public health, Copenhagen, Denmark*

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

J.F. Bosset. *Besançon University Hospital, Radiation Therapy Department, Besançon, France*

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

E. Van Cutsem. *U.Z. Gasthuisberg, Internal Medicine, Leuven, Belgium*

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

J.M. Pontes. *Instituto Portugues Oncologia, Oncologia Cirúrgica, Porto, Portugal*

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,

skin, limbs, gynaecology and digestive surgery area, in which reconstruction was essential in obtaining a better oncological control and a better quality of life.

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## How to do the sentinel node?

E.J.T. Rutgers. *The Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands*

It has been shown sufficiently that the sentinel node procedure (SNP) is -at least- equal to axillary lymph node dissection (ALND) or axillary nodal sampling to show or exclude axillary lymph node metastasis in the great majority of patients. Many experienced "teams" are able to identify the SN in the axilla in almost 100% (> 95%) of patients, and after backup axillary clearance the false-negative rate (missing the positive node) varies between 1-5%. In general, 30-40% of SN are tumour positive, and a further 40% of non-SN in the axilla contain metastases. Till date, it is not possible to predict a less then 10% chance of non-SN positivity if the SN is positive, even if primary cancers are small or SN contains only micrometastases. Therefore, if the SN is tumour positive, treatment of the axilla, either by ALND or by radiotherapy, is advised.

The SN-procedure may serve two aims:

Omitting axillary treatment (clearance) in patients who's axillary SN are tumour negative. If this is the main goal, different injection techniques (intratumoural, peritumoural, subareolar, intracutaneous, low versus high volumes) appear not to matter: all techniques will result in the identification of the SN in the axilla in the great majority of patients.

Lymphatic mapping. The identification of all tumour positive SN around the breast: in the axilla, intramammary, periclavicular and/or in the internal mammary chain nodes (IMC). If this purpose is aimed at, only parenchymal injection techniques (intratumoural, peritumoural) will drain the tracers to these sites. Some groups showed a 30% drainage to extra-axillary nodes (20% IMC), 80-85% retrieval rate and about 20% are tumour positive (5% the only positive node). Albeit that with this technique staging of the primary cancer is improved, it is unclear whether this will lead to important changes in treatment and consequently more or less toxicity and a better outcome.

What are to steps to be taken to achieve a high identification rate and a low false negative rate?

1. Start with a proper training course.
2. Go through a learning curve of at least 20 patients.
3. Work within a proper team (breast surgeon, nuclear medicine and pathologist).
4. Indication: unifocal invasive breast cancer, < 3-4 cm, clinically node negative.
5. Use preoperative ultrasound of the axilla and FNA-cytology.
6. Use the triple identification technique: lymphoscintigraphy, patent blue dye, intraoperative probe and palpation of the axillary content.
7. Use IHC with cytokeratins in the SN to reduce your false negative rate.
8. Maintain your experience by performing at least 5-6 cases a month.

Be careful in the following clinical situations (these indications are considered experimental):

- Multifocal invasive cancer.
- After large excisional biopsies.
- After upfront or neoadjuvant chemotherapy.
- In DCIS.

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## Signal transduction therapy

A. Levitzki. *Hebrew University of Jerusalem Alexander Institute of Life Scien, Department of Biological Chemistry, Jerusalem, Israel*

Over the past 20 years the molecular bases of numerous diseases have been discovered. The pathophysiologies of many of these diseases are frequently derived from aberrations in either **intra** cellular or **inter** cellular signaling pathways. This is particularly true of proliferative diseases such as cancers, leukemias, atherosclerosis, restenosis and psoriasis and of inflammatory diseases such as sepsis, rheumatoid arthritis, autoimmune diseases and tissue rejection. These findings have refocused medical research on seeking out new modalities for disease management. The new paradigm shift focuses on designing therapeutic modalities aimed at restoring normal signaling or bringing about the demise of the diseased cells without harming their normal neighboring cells. In the lecture we shall discuss this paradigm shift and cite the emerging therapies based on the new molecular understanding of signal transduction pathways.

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## New directions in the treatment of mesothelioma

R. Stahel. *Universitatsspital Zurich, Department of Oncology, Zurich, Switzerland*

The causative association between occupational exposure to asbestos and malignant mesothelioma has been identified in 1960.Taken into account a latency period of 20-50 years and a decline on workplace exposure in Europe after the 70ies it has been estimated that the incidence of mesothelima in Europe will double each year until about 2020. Over 80% of mesothelioma arise from the pleura, the reminder from the peritoneum, the pericardium, and the tunica vaginalis. Histologically, malignant mesothelioma is commonly classified into epithelial (60%), sarcomatoid or mixed type. For staging of pleural mesothelioma the TNM system is commonly used. Up to now, there has been no uniformly accepted standard therapy for pleural mesothelioma. The best-documented potentially curative approach to mesothelioma has been pleuropneumonectomy, followed by chemotherapy and radiotherapy (trimodality approach) in selected patinas with earlier stages of disease. The absence of mediastinal lymph node metastasis and the presence of the epithelial subtype are associated with a better prognisis. Several chemotherapeutic agents demonstrated activity against mesothelioma in phase II studies; these include doxorubicine, platinum compounds, vinorelbine, and the antimetabolites. Several recent studies phase II studies have documented good activity combining cisplatin/gemcitabine and oxaliplatin/raltirexed. A major step forward has been the only prospective randomized study in pleural mesothelioma comparing single agent cisplatin with the combination of cisplatin and premetrexed, which demonstrated superior survival for the combination therapy. In vitro, several signal transduction pathways have been identified to be of importance in mesothelioma, including EGF, TGF$\alpha$, VEGF, PDGF$\beta$, bcl-2/bcl-xL, survivin and trail. Promising preclinical results have been obtained with the EGFR tyrosine kinase inhibitor gefitinib, but the result of a recent phase II study have been disappointing. Full adjuvant chemotherapy after pleuropneumonectomy is not feasible in many patients. Based on the promising results of neoadjuvant chemotherapy in non-small cell lung cancer and the availability of combination chemotherapy with reasonable clinical activity such as cisplatin/gemcitabine, we initiated a multicenter study of three cycles of neoadjuvant chemotherapy followed by pleuropneumonectomy with or without radiotherapy to problem regions. Intermediate results will be presented.