29 INVITED

Cervix cancer screening in low-resource settings

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Countries in South and Central America, Sub-Saharan Africa and South and South-East Asia account for more than 80% of the world-wide burden of cervical cancer. The risk of disease and death from cervical cancer has remained largely uncontrolled in high-risk developing countries due to lack of or inefficient screening programmes. Consequently, precancerous lesions are rarely diagnosed and treated and invasive cancers generally present at advanced stages of disease with poor survival. Cytology screening programmes in developed countries have resulted in dramatic reduction in the burden of cervical cancer. However, cytology testing requires complex inputs in sample collection, processing, reading and reporting of smears. Cytology-based screening programs have been introduced in some developing countries, particularly in South and Central America, over the last three decades. Generally, they have achieved very limited success in preventing incidence of and mortality from cervical cancer in those regions. The findings from studies addressing the comparative performance of conventional cytology and its potential alternatives such as visual inspection with acetic acid (VIA), magnified VIA (VIAM), visual inspection with Lugol's iodine (VILI) and HPV DNA testing in detecting cervical cancer and its precursors will be discussed in the context of evolving public health policy on introducing new and effective programs in low-resource settings and in re-organizing existing programmes. The accuracy of VIA and VILI seem to be similar to that of good quality cytology in most recent studies in developing countries Early findings from randomized trials evaluating these tests for their effectiveness in reducing incidence of and mortality from cervical cancer will also be described. Further information from on-going studies on the cost-effectiveness of different screening approaches in preventing cervical cancer will be useful in formulating public health policies to guide the organization of population-based screening programmes in developing countries. The large body of research findings and managerial guidelines should be taken into account while reorganizing existing inefficient screening programmes and when considering new initiatives in low- and medium-resource settings.

Scientific Symposium
Molecular targeting in radiotherapy

30 INVITED

Epidermal growth factor receptor (EGFR) inhibitors and radiotherapy

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Background: Inhibition of the EGFR in combination with radiation is a rapidly evolving field of preclinical and clinical cancer research.
Materials and Methods: Overview of experiments and clinical studies
Results: Overexpression of the EGFR correlates with increased risk of local failure after radiotherapy. Inhibition of the EGFR by tyrosine kinase inhibitors (TKI) or monoclononal antibodies (mAb) decreases the proliferation rate of tumor cells in vitro and, in some tumor cell lines, increases cellular radiosensitivity. In tumor models in vivo regression and growth delay is generally improved by combined treatment compared to irradiation alone. In some experiments (using mAb) this translates into increased local tumor control. It could be shown that decreased repopulation of clonogenic cells and improved reoxygenation during fractionated radiotherapy contribute importantly to this effect. Several phase I and II clinical studies and one large randomised trial in head and neck cancer indicate clinical effectiveness of the combined approach.
Conclusions: Molecular targeting of the EGFR combined with radiotherapy has demonstrated effectiveness on all steps of the translational research chain. Considerable heterogeneity exists between different tumors and between different substances available calling for further mechanistic studies and development of predictive tests.

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Farnesyltransferase inhibitors as radiation sensitizers

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Alterations in expression or activation of signal transduction pathways are hallmarks of cancer. Additionally some of these changes are associated with alterations in drug or radiation sensitivity. Ras was the first signal transduction component shown to increase radiation resistance. Upstream and downstream pathways from Ras could thus be targets for manipulation of radiosensitivity. EGFR expression and Akt phosphorylation have also been associated with the response to radiation. Retrospective studies evaluating EGFR and Akt in patients treated with multimodality therapy found a significant association between EGFR expression or phosphorylation of Akt and treatment failure. Moreover, these data are strengthened by in vitro and in vivo studies from a large number of labs showing that inhibition of EGFR, Ras, PI3K, and Akt radiosensitized cancer cell lines.
A number of early clinical trials have now looked at signal transduction inhibitors in cancer treatment, either as single agents or in combination with chemotherapy, radiation or combined modality. Results from several of these trials will be discussed to suggest that EGFR, Ras and PI3K may mediate resistance through a common pathway. In addition to EGFR and Ras, PTEN can also regulate the PI3K pathway. Identifying a common signal for EGFR, Ras, or PTEN that results in radiation resistance may uncover targets for developing molecular based radiosensitization protocols for tumors resistant to radiation and thus improve local control.

32 INVITED

Cyclooxygenase-2 inhibitors in radiation therapy

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Dysregulation of many signaling pathways are involved in tumor development and confer resitance to standard cancer treatment. Cyclooxygenase (COX) enzymes are involved in the transformation of arachidonic acid into prostaglangines. Two isoforms of COX exist: COX-1 is thought to be the constituent isoform involved in homeostasis of normal cell functioning and COX-2 can be induced by cytokines, growth factors, and tumor promoters. Cyclooxygenase 2 (COX-2) is often overexpressed in premalignant and malignant states and overexpression is often asociated with poor clinical outcome. COX-2 derived prostaglandin participate in carcinogenesis, inflammation, apoptosis inhibition, metastasis, invasion and angiogenesis. COX-2-derived PGs have been shown to protect cells from radiation damage. There is a growing interest in the potential use of select COX-2 inhibitors in combination with chemotherapy or radiation therapy. Selective COX-2 inhibition enhances tumor response to ionizing radiation in preclinical studies both *in vivo* and *in vitro*. This increase in tumor radiation response occurs through a direct increase in tumor intrinsic radiosensitivity. The likely mechanisms involve accumulation of cells in the radiosensitive G2-M phase of the cell cycle and inhibition of repair from sublethal radiation damage. Irradiation can elevate intratumoral levels of COX-2 protein and its products, particularly prostaglandin E(2) [PGE(2)]. The increase in tumor COX-2 levels post irradiation occurs at the mRNA level, this phenomenon is blocked by COX-2 inhibitors. Inhibition of COX-2 activity or neutralization of PGE(2) activity enhances radiation response even in tumors where COX-2 expression is restricted to the tumor neovasculature. Selective COX-2 inhibitors enhance the effect of radiation on tumors that express COX-2 but not on COX-2-lacking tumors. Thus, selective COX-2 inhibitors may have potential as radiosensitizers for treatment of human cancers. Early phase I trials with radiation therapy showed that the toxicity profile is acceptable and randomized trials are required to assess the efficacy of such combinations.

33 INVITED

Molecular modulation of normal tissue radiation responses

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Increased understanding of molecular signaling pathways that control cell proliferation, apoptosis, differentiation and angiogenesis has opened new avenues for specific targeting of cancer therapeutic drugs. Many of these pathways are activated in tumors or inflammatory tissue but not in healthy normal tissues. The majority of research to date has been directed at increasing tumor responsiveness to therapy, *e.g.* by switching off activated cell proliferation signals or targeting specific oncogenes that confer radio-resistance or drug resistance. However, successful cancer treatments depend on avoiding serious normal tissue complications as well as increasing tumor response. There is now increasing awareness of the growing number of long-term survivors of cancer and the impact that late normal tissue radiation damage has, both on their quality of life and survival. This has stimulated efforts to investigate mechanisms and potential targets for intervention in the development of normal tissue damage.
Intervention strategies can broadly be categorized as aiming to increase the acute tolerance of mucosal tissues to radiotherapy or to inhibit the progressive development of late damage in irradiated tissues. The first approach generally employs specific growth factors, either to stimulate