surgery versus RTX showed irrespective of the margin status a clear local control benfit for the addition of RTX in the range of 15−20%. Moreover, the improvement of post-RTX recurrence rates from 20−30% for total doses of <50 Gy to less than 10−20% for >50 Gy suggests an underlying dose-effect relationship. However, a recent study showed no benefit for dose escalation >56 Gy except for increased rates of late complications. An EORTC study addressing RTX for progressive disease closed in 2008, whose results are still pending. The oral paper will collect the current evidences for multimodal treatment including adjuvant, neoadjuvant or definitive radiation for desmoid tumours hitherto.

415 INVITED

Systemic Treatment for Aggressive Fibromatosis

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Aggressive fibromatosis (AF), or desmoid tumour is a rare, fibroblastic proliferative disease. AF may present sporadically or more rarely as a manifestation of the hereditary syndrome Familial Adenomatous Polyposis (FAP). In 85% of sporadic tumours mutations are found in the β-catenin gene *CTNNB1* leading to increased activity of β-catenin and the characteristic immunohistochemical nuclear staining for β-catenin [1]. There is a marked female predominance and some tumours arise in the anterior abdominal wall after pregnancy. Despite the absence of metastatic potential, AF may cause debilitating symptoms such as pain, deformity and in some cases life threatening organ damage because of their locally invasive nature. A proportion of patients with AF can simply be observed, because the disease may become quiescent [2,3]. Otherwise surgery is the mainstay of treatment, sometimes followed by radiotherapy. However, surgery is unpredictable since the disease may recur in spite of negative resection margins or alternatively fail to recur in spite of positive margins. Radiotherapy is also used for recurrent or primary disease, depending on the site. Systemic treatment is reserved for patients with unresectable recurrence or if surgery would be too morbid. The most commonly used drugs as first line agents are tamoxifen [4], usually with a non-steroidal anti-inflammatory drug (NSAID), or NSAIDs alone. There are reports of activity with COX-2 inhibitors, such as celecoxib. Active chemotherapy approaches include weekly administration of methotrexate with either vinblastine [5] or dacarbazine, and doxorubicin, with or without dacarbazine [4]. One of the most active reported chemotherapy agents is pegylated liposomal doxorubicin (Caelyx/Doxil), with a marked improvement in pain and high disease control rate of 92% reported in one small series [6]. Of the molecularly targeted agents imatinib has activity, with some responses and prolonged disease stabilisation[7,8]. However, a recent report indicates that sorafenib appears to be a much more active agent with 25% partial remissions, 70% improvement in symptoms and a 95% disease control rate [9]. Currently the molecular targets underlying the activity of agents such as imatinib and sorafenib are unclear and further research is required to clarify these.

References

[1] Domont J, Salas S, Lacroix L, et al. British journal of cancer 2010; 102: 1032−6.
[2] Bonvalot S, Eldweny H, Haddad V, et al. Eur J Surg Oncol 2008; 34: 462−8.
[3] Fiore M, Rimareix F, Mariani L, et al. Annals of surgical oncology 2009; 16: 2587−93.
[4] de Camargo VP, Keohan ML, D'Adamo DR, et al. Cancer 2010; 116: 2258−65.
[5] Azzarelli A, Gronchi A, Bertulli R, et al. Cancer 2001; 92: 1259−64.
[6] Constantinidou A, Jones RL, Scurr M, Al-Muderis O, Judson I. Eur J Cancer 2009; 45: 2930−4.
[7] Chugh R, Wathen JK, Patel SR, et al. Clin Cancer Res 2010; 16: 4884−91.
[8] Penel N, Le Cesne A, Bui BN, et al. Ann Oncol 2011; 22: 452−7.
[9] Gounder M, Lefkowitz RA, Keohan ML, et al. Clin Cancer Res 2011 (epub on line).

Special Session (Tue, 27 Sep, 11:30−12:30)
New Insights in Metastatic Processes

416 INVITED

Growth Control and Cancer Metastasis

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The process of cancer metastasis, described in simple terms, comprises multiple steps involving changes in cell-cell and cell-matrix adhesion, enhanced motility, invasion of surrounding matrices and vascular structures, dissemination through the blood and/or lymphatic circulation, extravasation and lodgement in lymph nodes or tissues and then progressive growth at the secondary site. At each stage, there are important autocrine and paracrine interactions between tumour and host cells, many of which are effected by what might loosely be called growth factors. Ligands bind to receptors on either the cell that produces them, or more often to neighbouring cells, stimulating a plethora of downstream signalling cascades and changes in cell behaviour. The term 'growth factor' is misleading as many of the pathways stimulate not only cell proliferation, but also cell motility and invasion. What is more, both primary and secondary tumours generally require a blood supply to develop progressively, and this too is generally stimulated by angiogenic growth factors produced by the tumour which act upon vascular (and in some cases also lymphatic) endothelial cells and pericytes. One important family of growth receptors are the receptor tyrosine kinases (RTK), including EGFR, HER2, c-MET (particularly important in motility), PDGFR, FGFR etc. These are often overexpressed or mutated in cancers and are the targets for many small molecule and antibody-based therapeutic agents such as erlotinib and trastuzumab. Common downstream signalling pathways activated by these cell surface receptors include the MAP kinase and PI3 kinase pathways, which themselves can be activated by mutation or overexpression. Other major cell surface receptors are G-protein coupled receptors for cytokines, many of which are implicated in inflammatory cell activity (which can promote angiogenesis and invasion) and/or the tropism shown by certain tumours for organs where the ligands are commonly expressed (eg CXCR4CXCL12). There are also many examples of growth factor receptors that induce an epithelial-mesenchymal transition (EMT) which favours enhanced motility and chemotaxis in response to gradients of their ligands − which again may localise tumour cells to a particular tissue. In addition, metastases may preferentially develop where there are high concentrations of RTK ligands: for example, EGFR-expressing colon carcinoma cells favour liver where there are high levels of TGFalpha. Also, HER2/3 expressing breast cancers may favour the brain as a site of metastasis as it expresses high levels of neuregulins which bind to and transactivate these receptors. So overall, 'growth factor' signalling has been shown to affect each and every stage of the metastatic process, from inducing cell proliferation, detachment, motility, tropism and survival at secondary sites.

417 INVITED

Matrix Metalloproteases and Remodelling of the Extracellular Matrix

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Matrix metalloproteinases (MMPs) have many functions in the cellular microenvironment through cleavage of proteins leading to their activation, inactivation or removal. As a result broad-spectrum inhibitors of these enzymes were unsuccessful in clinical trials in cancer patients. We have examined the nature of protumorigenic and antitumorigenic targets and functions of MMPs in both normal epithelium and neoplastic epithelium using transgenic mouse models. MMPs play an important role in the proliferation and morphogenesis of normal epithelium. Our data indicate that MMP9, MMP13 and MMP14-dependent remodelling of the collagen scaffold regulates cell invasion and migration and inflammatory cell infiltration. In addition in tumours they regulate the structure and permeability of the vasculature. MMPs increase VEGF bioavailability and also increase production of antiangiogenic extracellular matrix fragments. The microenvironment also contributes critically to drug response through the regulation of vascular permeability and innate immune cell infiltration. MMP9 null mice, which have increased vascular permeability, were more responsive to the chemotherapeutic drug doxorubicin. Thus remodeling of the extracellular microenvironment may have important actions on drug responses. As we gain insights into these mechanisms they will aid in refining protocols for treating cancer.