in the context of maternal breast cancer'. Generating a theory from the children themselves, who are experiencing their mother's cancer diagnosis and treatment, was central to this study. To date most studies relevant to this area have investigated parents perceptives of children's experiences or examined children's own experiences many years following their mother's breast cancer diagnosis.
The aim of this particular grounded theory study was to generate a theory about the experiences of 7−11 year old children whose mothers' had been diagnosed with and receiving treatment for early-stage breast cancer with a view to contributing to knowledge development. Analysis of the data revealed that the main concerns of the participants were the processes involved in navigating their lives through a period of disrupted mothering. The substantive theory of 'protecting' was conceptualised from the data to describe children's experiences in the context of maternal breast cancer. This theory had three sub-core categories of Shifting Normality, Shielding and Transitioning, with numerous properties and sub-properties. The central argument in this study is that the children were trying to protect their own lives and well as that of their mothers. The findings provide a mechanism for understanding how the perceived loss of the 'well' mother raised concerns for the children and resulted in adaptations of roles and responsibilities.
It is suggested that there is a gap in services where the needs of children, whose mother had cancer, are not adequately met in that the children had little, if any, opportunity to meet with healthcare professsionals. In addition, parents may need assistance with how they can talk with their children about the diagnosis and the changes in family life. Children's experiences of parental chronic illness is a healthcare issues for the present and the future and the healthcare system needs to identify future services and developments if society is to truly value children and listen to children's voices.

Scientific Symposium (Sat, 24 Sep, 11:15−13:15)
Improving the Therapeutic Ratio of Radiotherapy: New Concepts to Protect Normal Tissues

5 INVITED

Molecular Targeting to Protect Normal Tissues

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Strategies for 'molecular-based' modification of normal tissue responses to irradiation must be designed for the underlying pathobiology in the individual tissues and organs, and the biology of the contributing cell populations as well as their interactions. Interventions in the processing of radiation damage can be directed against any step of the pathogenetic cascade in cells, including early production of free radicals (e.g. hypoxia, radical scavenging), activation of transcription facors (such as NFkB or AP-1), modulation of intracellular and juxta-/parakrine signaling cascades (activation/deactivation of growth factor signaling pathways, inflammatory signaling and others), or modulation of the immune response. Moreover, 'tissular' reactions may be modified, such as proliferation/differentiation in early responding tissues, the chronic oxidative stress response, the vascular response, or the fibrotic tissue remodeling in late responding tissues. Examples will be presented. However, the mechanisms of action underlying the protective or ameliorative effects must be clarified in order to design optimum clinical protocols. Therefore, before clinical investigation, modification approaches should be thoroughly tested in animal models, with relevant (fractionated) irradiation protocols and relevant endpoints. Results from single-dose and fractionation studies can be divergent, as has been demonstrated in a number of preclinical investigations. In order to prove selectivity and to guarantee a therapeutic gain, any strategy, if applied during or shortly after the oncological treatment, must also be tested for potential tumour effects.
Today, most of the normal tissue targeting strategies must be considered experimental. Most promising, with first clinical studies, are the interaction with (some) growth factor signaling cascades, the interruption of chronic oxidative stress (in late tissue reactions), and the treatment (mobilization and transplantation) with stem cells, haematopoietic, mesenchymal and tissue-specific. It must, however, be assumed that strategies targeting single molecules or cascades will only result in a delayed tissue response, because of the activation of backup pathways in the cells and tissues. Hence, 'modification cocktails' may be required, but the efficacy of their individual components must first be tested under the premises outlined above.

6 INVITED

Stem Cells − Role for Radiation Response and Therapeutic Approaches

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Inevitably normal tissues are also exposed to ionizing radiation during the treatment of cancer with radiotherapy. Many factors play a role in the response of tissues to irradiation, but ultimately the ability of stem cells to reconstitute functional cells determines the onset and the severity of the radiation effects. The maintenance and repair of the tissue integrity are the primary roles of the tissue stem cell. Stem cells are undifferentiated reside between differentiated cells and are able to self-renew to prevent aging. In contrast, progenitor cells although capable of producing specialized cell types have a limited life-span as they are incapable of self-renewal. Stem cell therapy provides a potential prevention or treatment of radiation-induced normal tissue damage. Several stem cell types are being investigated for their potential use in stem/progenitor cell therapy: embryonic stem cells, induced pluripotent stem cells, tissue adult stem cells (ASC), mesenchymal stem cells (MSC) and epithelial progenitor cells (EPC). Of these the last three are used as or are close to clinical application and will be discussed in the current presentation.
Mobilisation or injection of bone marrow derived MSCs have been shown to ameliorate radiation-induced side-effects in gut, skin, oral mucosa and salivary gland, potentially through modulation of immunogenicity, apoptosis and the secretion of cytokines/growth factors that stimulate regeneration, but not through transdifferentiation. Indeed, stimulation of surviving stem/progenitor cells using growth factors has been shown to be promising in e.g. gut and salivary glands albeit only when sufficient stem/progenitor cell remain after irradiation. For tissue in which vascular damage is the main cause of organ dysfunction after irradiation, transplantation or mobilisation of bone marrow derived EPCs and vascular progenitor cells may result in inhibition of normal tissue damage, although also for such therapies survival of local stem/progenitor cells seems to be a prerequisite. Independent from the number of surviving stem/progenitor cells ASC transplantation seems to be a promising therapy. For mouse salivary gland the potential of such therapies has been shown and are currently being translated to clinical application. Recent developments will be discussed. The application of stem/progenitor cell therapy in all its forms to reduce normal tissue effects will have a tremendous impact on radiation oncology in the near future.

7 INVITED

Possible Intervention Strategies to Reduce Radiation-induced Heart Disease

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Radiotherapy is a common treatment for breast cancer and Hodgkin's lymphoma and it is associated with good long-term survival prognosis. Unfortunately, increased risk of cardiovascular disease is now recognized as a late complication when significant volumes of the heart and coronary arteries are included in the radiation field. We showed previously in mice that radiotherapy induces dose- and time-dependent changes in the heart, starting with an acute epicardial inflammation and microvascular damage and progressing to vascular leakage, myocardial fibrosis and amyloid depositions. Intervention to inhibit the progressive inflammatory changes or stimulate vascular recovery could help to prevent cardiac failure at later times after irradiation. This presentation will review the limited published data available and describe novel approaches to inhibit radiation-induced heart damage.
Pre-clinical studies in rats have investigated amifostine, pentoxifylline/tocopherol I (Vit. E) or the ACE inhibitor captopril in heart radiation models. Amifostine is able to prevent radiation-induced reduction in coronary flow and aortic flow and decreased the histopathological changes seen at 6 months post-irradiation. Pentoxifylline/Vit. E reduced TGF-β1 mRNA levels and subsequently reduced fibrosis. Captopril did not prevent cardiac dysfunction, but did reduce myocardial fibrosis and prevented left ventricular capillary density loss after local heart irradiation. In myocardial infarct models, thalidomide has been shown to attenuate the development of fibrosis and promote vessel maturation. Other experimental studies have shown that bone-marrow-derived endothelial progenitor cells (BM-EPC) can stimulate vascular recovery and improve cardiac function after myocardial infarction. We are currently setting up experiments to evaluate the potential of thalidomide or BM-EPC to stimulate vascular recovery after cardiac irradiation in mice.