generated based on the not-edited auto-contours. These plans were not evaluated on the edited auto-contours by two different observers.

Results: Atlases used for auto-segmentation should carefully be selected, and validated in great detail to reach the most accurate segmentations. Compared to the use of a single-subject atlas, application of a multi-subject atlas improved the accuracy of the auto-contours. In the clinical validation study, an expert panel scored all auto-contours as 'minor deviation, editabile' or better. Compared to manual contouring, editing auto-contours reduced the hands-on time from 180 to 66 minutes. The dosimetric study showed that editing of auto-contoured neck CTV was inevitable to avoid (large) underdosages in the target, even when differences between the auto-contoured and edited structures were small. For salivary glands, the necessity of editing the auto-contours was less pronounced.

Currently we are using ABAS for auto-segmentation for most treatment sites (head-and-neck, neurology, lung, prostate, breast). ABAS is also used for adaptive treatments, when a patient needs a new CT due to anatomical changes. By using the initially segmented CT set as atlas, a high-quality structure set can automatically be generated for the new CT in very short time, hardly needing any manual editing of the contours. To realize a high throughput of ABAS, and to minimize human errors in its use, we developed an interface to run ABAS in a semi-automated way.

Conclusions: Multi-atlas based auto-contouring of CTV images proved to be a very useful tool for rapid delineation of target volumes and normal tissues. Although editing of auto-contours is inevitable, especially for the target, a substantial time reduction is achieved when editing auto-contours, instead of manually contouring from scratch.


**SYMPOSIUM: FIBROSIS**

**SP-0216**

Successful clinical trials in radiation-induced sequelae

S. Delanian

1Hôpital Saint-Louis, Department of Radiation Oncology, Paris, France

If the radiation-induced fibrotic (RIF) process involves irradiated tissues and organs, it is only highly symptomatic in some sparse delayed and irreversible local sequelae. Severity often depends on treatment-related factors, as radiotherapy dose-volume, combined chemotherapy, or combined major surgery (hematoma-lymphedema-infection), and/or patient’s co-morbidities. There is a histopathological heterogeneous patchwork comprising concomitant active cellular areas and sclerotic matrical areas, describing a delayed, healing with overwhelmed defenses mechanisms [1].

Therapeutic clinical experience is dependent on the severity of radiation-induced fibrosis at baseline, the quality of clinical assessment (best scoring), the availability of effective drugs, and sufficient treatment duration (minimum 6 months) for a chronic disease (quality of life, mental design). Management of radiation-induced sequelae should include: reduction of co-morbidity factors, plus control of any acute inflammation (infection, traumatism...) that worsens the underlying injury, plus use of antifibrotic agents [2], and promotion of tissue regeneration.

For moderate cases, medical management is based on an initial anti-inflammatory treatment with steroids ± antibiotics (repeated for any acute phase) that promotes further drug penetration in the irradiated volume, followed by a pentoxifylline-tocopherol combination [3,4] (or statins) to reduce fibroproliferative “heart” sequelae, boosted by an organ-targeted drugs (antiptic for enteritis, physiotherapy and gabapentin for neuromuscular disease,...) to control specific symptoms (microbial proliferation, neuromuscular irritation,...).

For severe injury including fibrosis and necrosis, management is again based on a first anti-inflammatory treatment; followed by vascular therapy (pentoxifylline, HBO, heparin, ACE inhibitors); or antifibrotic treatments especially PENTOCLO (combined pentoxifylline-tocopherol-clonidine) best described in osteoradionecrosis [5]; or antitumor necrosis (TGF/Tr or TNF); and regenerative option (dead tissue removal, stem cell mobilization, graft).

Controlled trials are necessary to identify useful drugs and their optimal combination (best strategy). However, to help patients with severe injury (pain, handicap, compression), we should always reduce radiation-induced fibrosis and also seek to compensate for tissue depletions by graft or cell regeneration, while taking into account organ specificities.

**SP-0217**

New ideas from other discipline: Successful clinical trials in IPF (idiopathic pulmonary fibrosis)

B. Crestani

1Hôpital Bichat, Service de pneumologie, Paris, France

Idiopathic pulmonary fibrosis (IPF) is the most frequent idiopathic interstitial lung disease. IPF is a rare and severe disease. Estimated annual incidence is 5/100 000 and median survival is 3 years. Diagnosis depends on clinical data (absence of a cause) a possible or typical UIP (interstitial Pneumona, UIP) pattern on chest High Resolution CTscan, and a UIP pattern on lung biopsy, if performed (Raghv, Am J Respir Crit Care Med 2011; 183:788-824). In Europe a combination of prednisone, azathioprine and N-acetyl cysteine was the standard of care in IPF patients requiring a treatment. In the USA, the guidelines of the IDSA (International IDSA Expert Panel) recommend the use of nintedanib (BIBF 1120) for patients with IPF, with a mean survival duration of 6-12 months (D’Amonte and Caporali 2011). Nintedanib (also known as BIBF 1120) is currently being evaluated in IPF. This drug is available in Japan since 2008, and in some European countries since 2011. The approval of pirfenidone by the European Medicines Agency was based upon three phase III trials, one in Japan (Taniguchi, Eur Respir J 2010;35:821-9), and two in Europe-North American countries (the CAPACITY trials) (Noble, Lancet 2011; 377:1760-9). Both studies showed that pirfenidone reduced the decline of lung function as evaluated by forced vital capacity. In the CAPACITY trials, there was also a reduction in the decline of the 6 minutes walking distance, and a trend for an improved survival in the treated group. Tolerance of pirfenidone is acceptable with gastrointestinal (nausea, dyspepsia) and skin (photosensitivity, rash) side effects. The mode of action of pirfenidone is unknown. However pirfenidone has consistently demonstrated anti fibrocatation in different experimental models of lung (e.g. bleomycin-induced lung injury), heart, vessels and kidney fibrosis.

Many other molecules are being evaluated in therapeutic trials in IPF. Nintedanib (also known as BIBF 1120) is currently being evaluated in two phase III trials, after a successful phase II study (Richeldi, New Engl J Med 2011; 365:1079-87). In that study, treatment with nintedanib (150mg twice daily) reduced lung function decline and decreased the incidence of acute exacerbation of IPF. Gastrointestinal side-effects requiring the cessation of the drug were observed in about 16% of the patients. Nintedanib is a tyrosine kinase inhibitor targeting VEGFR, PDGFR, FGFR, and other kinases.

Many more molecules are being evaluated in phase I and phase II studies (see www.clinicaltrials.gov). Most of these molecules are targeting one specific pathway among many pathways which have been shown to be activated in IPF and in experimental models of pulmonary fibrosis. In the past, many molecules have failed (e.g. endothelin receptor antagonists, PDGFR antagonist, anti-TNF, warfarin,...). We hope that the new molecules being tested will finally allow for the improvement of IPF survival in the next future.

**SP-0218**

Modulation of irradiation-induced inflammation and fibrotic signalling: Lessons from mouse models

M. Scharpfenecker1, B. Floot1, K. de Cortie1, R.P. Coppes2, N.S. Russell1, F.A. Stewart1

1The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Department of Biological Stress Response, Amsterdam, The Netherlands
2University Medical Centre Groningen University of Groningen, Department of Radiation Oncology, Groningen, The Netherlands

The transforming growth factor beta (TGF-β) signalling pathway plays a central role in the development of normal tissue fibrosis after irradiation. TGF-β is a key regulator of cell growth and differentiation; it affects the immune system and controls the homeostasis of extracellular matrix. Accordingly, mice lacking the TGF-β signalling intermediate Smad3 are protected from irradiation-induced fibrosis. Moreover, knockdown of the TGF-β/Smad3 downstream target Pai-1 protects mice from fibrosis after intestinal irradiation. Although radiation fibrosis has been extensively
studied, the mechanisms of its initiation and chronic extension still remain to be resolved. Yet, it is clear that development of fibrosis after radiation cannot simply be explained by the function of one mediator, but requires the interplay of several cytokines and growth factors and multiple cell types. Our studies have identified the TGFB-receptor endoglin as new player in radiation-induced fibrosis development in the kidney. Mice expressing halved levels of endoglin (Eng+/-) mice displayed reduced fibrosis, but also less vascular damage after a single dose of kidney irradiation compared to irradiated Eng+/- mice. This was accompanied by decreased mRNA expression of Tgfβ1 and pro-fibrotic downstream targets such as p-31, Ctgf or Col3a1. We also noticed that development of fibrosis in the kidney was accompanied by infiltration of inflammatory cells, mainly macrophages. Macrophages are crucial for tissue repair, but may also promote kidney fibrosis by secreting pro-fibrotic growth factors and cytokines as shown in several models of disease. Macrophage numbers were significantly upregulated in both irradiated Eng+/- and Eng+/- kidneys; however, the upregulation was less pronounced in Eng+/- mice. In addition, expression of macrophage-expressed pro-inflammatory, pro-fibrotic and anti-angiogenic cytokines interleukin 1-beta (Il1b) and interleukin 6 (Il6) was strongly reduced in the irradiated kidneys of Eng+/- compared to Eng+/- mice.

As endoglin is not only expressed on endothelial cells, but also on monocytes/macrophages, we are currently investigating whether changes in endoglin cell function or phenotype contributes to differential fibrosis formation in Eng+/- and Eng+/- mice. We are also analysing whether macrophage depletion prevents fibrosis formation after kidney irradiation. Furthermore, we are testing whether the anti-inflammatory, immunomodulatory and anti-fibrotic drug Thalidomide impedes the development of radiation-induced kidney fibrosis.

In summary, we suggest that endoglin mediates the inflammatory response in irradiated tissues by regulating macrophage infiltration and cytokine production thereby contributing to the development of irradiation-induced kidney fibrosis.

SYMPOSIUM: IMAGING FOR BRACHYTHERAPY

SP-0219
Imaging for brachytherapy: Head and neck, and prostate
B. Carey
St James Institute of Oncology, Radiology, Leeds, United Kingdom

Brachytherapy has benefited considerably from advances in imaging techniques in recent times. Tumour volumetric-based radiation planning based on excellent delineation of tumour anatomy has much improved our ability to target malignant tissue whilst sparing non-malignant tissues. The highly conformal nature of Brachytherapy has further benefited from newer functional imaging techniques based on recognition of the altered biological and molecular processes occurring within tumour tissue. New paradigms for treatment planning and radiation delivery are now becoming possible based on the potential to define areas of varying functional activity within the anatomical tumour mass. Established 3D tumour volume generation platforms and morphological imaging techniques can now be modified by new information provided by functional imaging such as PET and MRI. Brachytherapy for prostate and Head & Neck cancers can benefit from data that quantifies areas of cellular and molecular disruptions within the tumour mass and thus offers the potential to individualise the Brachytherapy radiotherapy plan for each patient. Prostate Brachytherapy includes both High Dose Rate and Low Dose Rate techniques and has become widely adopted as a valid treatment for prostate tumours. Historically, imaging has played a relatively small role in the management of clinically localized prostate cancer but in more recent years, medical imaging techniques, such as TRUS, CTV and MRI have improved the clinical management of patients with prostate cancer. Brachytherapy offers the possibility of better local treatment with less morbidity and improved outcomes; more accurate imaging has contributed to better staging and patient selection as well as more accurately image-guided treatment delivery.

In the non-surgical treatment of head and neck tumours, Brachytherapy offers an excellent treatment for organ-preservation with local tumour control. Image guidance is central to the optimization of this treatment with careful dose escalation facilitated by accurate delineation of tumour and structures at risk. Adaptive image-guided Head & Neck Brachytherapy can complement newer surgical techniques and better understanding of tumour biology in this area will incorporate newer boost techniques also.

The inherent goal of Brachytherapy is to safely deliver adequate radiation to those areas of tumour tissue that are considered necessary based on our current understanding of tumour biology and radiation response. Imaging is central to the success of this treatment.

SP-0220
Interstitial breast brachytherapy: the role of multimodality imaging
M. Jolicoeur
Hôpital Charles Lemoine, Radiation Oncology, Montréal, Canada

Before the era of breast conservation therapy using external beam radiotherapy (EBRT) and before the invention of linear accelerators and its widespread use in breast cancer treatment, brachytherapy using radium needles was the first method of breast irradiation. Interstitial breast implants started at the beginning of the XXth century either as mono-therapy or associated to surgery. Over the years, breast brachytherapy was less and less used but it remained an option as a boost to EBRT. Nowadays with the increase use of partial breast irradiation, breast brachytherapy is gaining more importance. Unlike prostate, breast brachytherapy is not widely practiced because it was always considered by many to be too operator and skill dependent, partly because of the lack of easy and precise imaging. It is evident that for more accuracy, imaging is necessary in breast brachytherapy as it is in EBRT, to plan and optimize the treatment. The need of accuracy is even more important in brachytherapy because it provides the most conformal coverage of tumor and normal tissue sparing radiotherapy technique.

So in this era of highly targeted radiotherapy, breast brachytherapy faces the same challenges of volume delineation at each step of the process: in pre-planning, during implant and at dosimetry. The first step is the identification of the surgical bed to be implanted. This is not an easy task as reflected by the numerous papers in the literature. At the time of brachytherapy the cavity is often collapsed and difficult to find. We conducted a phase II study Using MRI imaging to help in the delineation of the surgical bed and therefore help to plan precisely where to place the implant. The second step is the precise placement of the interstitial needles into the breast around the target. This is of great importance since it will, in a way, determine the dosimetry. Ultrasound can be used as a step-by-step procedure. As in prostate brachytherapy a real-time imaging during the procedure would be ideal. The ultimate step, the dosimetry, is to maximize the dose to the target volumes and to minimize the dose to the adjacent organs at risk. At this step the quality of imaging is important for the delineation of the volumes and for reconstruction of the material implanted. CT scan allows implant reconstruction very easily but MRI allows accurate surgical bed delineation. Therefore a robust image fusion capacity has to be available. Ultimately, the goal would be to find a 3D imaging modality that could serve both purposes and could be integrated in the treatment planning system.

This presentation is aimed to determine the role of modern imaging modalities in all the steps of interstitial breast brachytherapy. It is our opinion that more accurate imaging will help the wide application of interstitial brachytherapy for breast cavity boost, partial breast irradiation and second conservative treatment for in-breast recurrences.

SP-0221
Gynaecology
J. Dimopoulos
Metropolitan Hospital, Athens, Greece

Abstract not received

SYMPOSIUM: EU PROJECTS 2

SP-0222
First clinical experience with head and neck and lung cancer patients within the ARTFORCE project
H. Bartelink1, J.J. Sonke2
1The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Department of Radiation Oncology, Amsterdam, The Netherlands
2First clinical experience with head and neck and lung cancer patients within the ARTFORCE project

The ARTFORCE project (Adaptive and innovative Radiation Treatment FOR improving Cancer patients treatment outcome) now runs for more than a year, consisting of two clinical trials combined with fundamental research in molecular biology, i.e. predicting tumour response and physics; image guidance and dosimetry performed in a multi-institutional environment.

The small-cell lung cancer study aims to improve local control and test the hypothesis of iso-toxic dose redistribution. Patients are