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

Results: Atlas-uses 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, editable’ 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) underdoses 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, 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 fast and effective 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 sequela**

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If the radiation-induced fibrotic (RF) 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 desmoplasia 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 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 anti-fibrotic 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 (anti-septic for enteritis, physiotherapy and gabapentin for neuromuscular disease,...) to control specific symptoms (microbial proliferation, neuromuscular irradiation,...).

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 anti-fibrotic treatments especially PENTOCLO (combined pentoxifylline-tocopherol-clonidine) best described in oesophageal fibrosis [3]; or anticytokine (TGF 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 depletion by graft or cell regeneration, while taking into account organ specificities.

1. Delanian, Radioter Oncol 2004;73: 119-31;
3. Delanian J Clin Oncol 2005; 23:8570-9;
4. Hamana, Radioter Oncol 2012, in press;

**SP-0217**

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

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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 (Intermediate Pulmonary Fibrosis) pattern on chest High Resolution CTscan, and a UIP pattern on lung biopsy, if performed (Raghu, 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, on the basis of the IFIGENIA study (Demedts, New Engl JMed 2005;353:2229-42). The IFIGENIA study compared the triple therapy with the combination of prednisone, azathioprine and placebo, and showed that the triple therapy reduced lung function decline. However, this triple therapy was recently shown to be less effective in preventing the placebo (IPF clinical research network, NewEngl J Med 2012;366:1968-77).

Currently pirfenidone is the only drug approved for the treatment of 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 European-North American countries (the CAPACITY trials) (Noble, Lancet 2011; 377:757-9). 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, dysphagia) and skin (photosensitivity, rash) side effects. The mode of action of pirfenidone is unknown. However pirfenidone has consistently demonstrated anti-fibroticaction 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 VEGF, 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**

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The transforming growth factor beta (TGF-B) 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-B signalling intermediate Smad3 are protected from irradiation-induced fibrosis, scar tissue and mortality. Moreover, knockdown of the TGF-B/Smad3 downstream target Paf-1 protects mice from fibrosis after intestinal irradiation. Although radiation fibrosis has been extensively