SEVENTH FRAMEWORK PROGRAMME OF THE EUROPEAN UNION

Support for training and career development of researchers
(Marie Curie)
Networks for Initial Training (ITN)

FP7- PEOPLE-2011-ITN

Clinical Applications

Work-package: 1
Deliverable: D1.1
Output of task: T1.1
Date: 04-06-2013

Delivered by**:**
ICR (Partner 6)

Project Number 290148

Software for the Use of Multi-Modality images in External Radiotherapy

Copyright

1. Introduction

The SUMMER project brings together research groups with expertise in many different areas relevant to the radiotherapy workflow. In order to focus the directions of research and provide maximum utility in the final results, a study was performed into the clinical requirements of the medical physicists and radiation oncologists who are the target end users. This brought up many interesting perspectives on the problems confronting radiotherapy in everyday practice. These can be combined with the more cutting-edge research questions in each group to create an end result which is both practical and innovative.

1.1. Candidate Treatment Localisations

The treatment of cancers is very dependent upon the location of the tumour. In order to restrict the problem domain to a manageable size, SUMMER will, at least initially, focus on treating only brain and lung cancers, and therefore the clinical requirements of the project will focus on the specific challenges involved with treating these sites. Potential additional localisations are the prostate, breast and head-and-neck.

1.1.1 Brain

Cranial tumours are an important localisation for SUMMER to focus on for several reasons:

1. the prognosis for cranial tumours, particularly high grade ones, continues to be comparatively poor,
2. radiation therapy is a major component in the treatment of most high grade cranial tumours and many low grade tumours,
3. the brain is one region in which the use of several multi-modal images is particularly important.

CT scans of the brain tend to have very poor contrast, so in order to clearly resolve soft tissue features MRI images are typically used. The MRI allows the contouring of organs at risk (often automatically), but there are still issues with delineating the tumour volume. Generally MRI images are still used, but the precise modality may be different between tumour classifications and grades. The grade of the tumour is first determined by biopsy, and low grade tumours will usually be contoured using FLAIR (Fluid Attenuation by Inversion Recovery) T2-weighted images, while high-grade tumours will instead mainly use T1-weighted images acquired after the injection of gadolinium contrast agent.

The fact that most cranial contouring is performed on the MRI means that an excellent registration between the CT and MRI scans is essential in order to have confidence in the position of the contours during dose calculation. In general the skull provides a good reference point which prevents too much deformation of the cranium, allowing good results to be achieved using rigid registration techniques. However, because of the long acquisition times of MRI scans, the patient couch is typically designed with greater comfort in mind than the RT treatment couch, and this can mean there is some deformation in the neck area, which can make an overall good fit hard to achieve, instead the oncologist must choose which region to prioritise in the fitting.

Unfortunately high grade cranial tumours tend to be highly infiltrative, small numbers of tumour cells can be found up to 2cm outside of the region which is visible on MRI. If these microscopic tumour cell colonies are not eradicated then a relapse becomes very likely, which leads to large uniform margins of between 1cm and 2cm generally being used in defining the CTV. However, this greatly increases the volume of the patient's head receiving high dose and makes it more difficult to maintain a low dose to vital organs at risk, such as the optical chiasm or brainstem. Instead, the current clinical focus is on using functional imaging modalities to discern the regions with microscopic tumour infiltration and hence define a non-uniform margin around the GTV, treating only those areas which are actually tumour.

There is also considerable current interest in mapping tumour heterogeneities. Brain tumours tend to be relatively heterogeneous tumours, with radio-resistant hypoxic areas and spatially varying growth activity. Although standard clinical practice is currently to deliver a flat dose to the complete tumour volume, clinical trials are currently investigating the potential for "dose painting", raising the dose to certain areas of the tumour to achieve a better control probability, while maintaining the healthy organ dose constraints.

The question of which precise functional modalities are most appropriate is still the subject of intense debate. Although the most common PET tracer, FDG, is largely useless in cranial imaging because of the already very high take-up of glucose to the brain, there are several other newer molecules which are being proposed for use in brain imaging, including f-MISO for hypoxia imaging, amino-acid PET including 11C-methyl-L-methionine (MET) and 18F-fluoro-ethyl-L-tyrosine (FET) . MR spectroscopy has been used

for diagnostic purposes in the brain for many years, and now the spatial resolution offered by MRSI offers the potential to image various types of cellular activity in the brain. This is now being investigated in several clinical trials. The principal metabolites of interest in the brain are N-Acetyl Aspartate (NAA), Choline, Creatine and Lactate.
The lack of a clear current favourite amongst the functional imaging modalities makes it important for SUMMER to maintain considerable flexibility for multi-modality image fusion in cranial tumours. It is likely that for some time at least, different clinical centres will use different modalities and different tracers or metabolites for their functional imaging, so all of these must be supported in SUMMER, while also maintaining the possibility to add additional components in the future.
The other possible form of brain tumour is a distant metastasis due to a tumour elsewhere in the body. In this case the tumour is typically far less infiltrative than most brain tumours and the standard treatment uses stereotactic beams, delivering very high dose in just a few fractions. In this case the margins are much tighter against the tumour volume to reduce healthy tissue irradiation, and patient movement is restricted far more than even for conventional RT. This accuracy in the delivery of the dose makes the registration between imaging modalities even more important in order to guarantee the tumour volume is genuinely irradiated.

1.1.2. Lung

The principal reasons that lung tumours are an important area for SUMMER to be involved in are:

1. There can be a high degree of intra-fractional motion of both tumour and organs at risk due to patient respiration,
2. The location of the lung means that many critical organs at risk are in close proximity.
3. There are issue on both the lung tumour definition and motion and the mediastinum involvement

In contrast to the cranial situation, MRI is not a very useful imaging modality for lung tumours, due to the difficulties arising from the air-tissue boundaries. Instead the CT scan is the primary modality used for contouring, which reduces the importance of highly accurate image registration.
Radiotherapy can sometimes be the exclusive treatment of isolated tumours in case of surgery contraindication. Therefore high curative doses are needed. This may take the form of conformal RT, IMRT or stereotactic radio-surgery. The biggest challenge is to deal with the patient respiration, which can in some cases cause the tumour to move by several cm. This can be dealt with by using a 4D CT to model the motion of the tumour and to create a GTV which covers the complete cycle of tumour positions, but this in turn means an unnecessarily large GTV and higher healthy tissue dose. Often instead gating is used: here the patient's respiration is detected by some secondary equipment, either a spirometer or a camera tracked external marker, and the beam is only turned on at the correct part of the cycle. In many cases the patient will be asked to hold their breath to increase the length of time they are in the treatment position.
One of the challenges in treating lung cancer is that it is prone to metastases throughout the lymphatic system in the mediastinal region. The detection of metastatic lymph nodes is generally easiest on FDG PET, where the increased glucose update characteristic of tumour growth marks them out clearly, and such a PET scan forms a core component of all lung cancer treatments. The registration between CT and PET images is not so important in this case, as the lymph nodes can typically be seen on the CT, the PET scan only indicates which are infected by tumour. However, the quality of the images is still very important.
FDG PET can be used for both tumour and mediastinum delineation. Clinical trials are ongoing to define the role of FDG PET in dose prescription and dose painting.
Of great significance for lung tumours is the registration of CT images over time. Because of the comparatively elastic nature of the torso, combined with respiratory motion and common side effects such as weight loss over the course of the treatment, it is much more of a challenge to maintain the patient's position between fractions. Thus having a good elastic registration method is the first step towards adaptive re-planning of fractions, or at least to monitor the adjustments to the dose delivered to organs and tumour due to patient motion.
It has been well established clinically that the survival probability of lung cancer patients is directly correlated with the applied dose. For this reason it is obviously desirable to continue to escalate dose for these tumours. Unfortunately the location of the lungs close to the pulmonary system and other radiation sensitive organs, combined with the complexities of patient motion mean that the desire to escalate dose to tumour must be balanced against the limits for the healthy organs. This means that accurate segmentation, with the help of several imaging modalities, of organs at risk is essential to allow the best possible treatment plan.

1.1.3. Head and Neck

Head and neck tumours are a suitable candidate for SUMMER because:

1. 95% of head and neck tumours are treated with radiation either post-operatively or in an exclusive setting with or without chemotherapy,
2. just as with cranial tumours, a large number of imaging modalities are typically used in designing the treatment plan.

The majority of contouring is performed on the planning CT as this is the most closely linked to the dose map, no registration errors can occur. However studies have shown that adding in additional imaging modalities can reduce the inevitable inter-observer variation in defining tumour volumes [Metwally2011]. Just as in the case of lung tumours, PET is often used for screening lymph nodes for metastases (although not in every case as in lung treatments) without registering on to the CT. It is still unclear whether such a registration is useful for contouring; currently the ICR use registered PET scans for about 10% of patients. Magnetic Resonance techniques are slightly more commonly applied, being used in about 25% of cases. Perfusion and diffusion are currently the most useful MR modalities for head and neck cases. However, research continues into the most suitable combination of modalities to give the necessary information. This combination will change with the tumour location, grade and site, and will probably also change over time, so it is important that SUMMER is as flexible as possible in the modalities it supports.

1.1.4. Breast

Breast cancer is an important localisation to investigate because:

1. it is the most common form of cancer among women, affecting 1 in every 8 women,
2. treatment in most cases can be highly curative
3. 95% of breast cancer patients receive postoperative RT.

At the ICR 26% of patients treated with RT are treated for breast cancer. The majority will be young or in early middle age, but with appropriate treatment most should make a full recovery and have a good quality of life after treatment. This means that although the treatment is not as challenging or complex as for many others, having an efficient and effective approach to treating breast cancer will have a major impact for many patients and avoid organs at risk.

Historically breast tumours have been treated with an irradiation of the whole breast, but it is becoming increasingly common to instead perform a selective irradiation around the visible tumour volume. MRI is the standard imaging modality used to get good contrast of the tumour region, and must be accurately registered to the planning CT. MRSI has also been shown to provide very accurate results in imaging tumour tissue [Belkic2006], with the principle metabolites of interest being Alanine, Choline, Lactate and Taurine.

Because it is comparatively easy to deliver dose to the breast without any major risk to sensitive organs, at least along certain paths, it is becoming more popular to perform either stereotactic or hypo-fractionated treatments, with a small number of fractions and a high dose per fraction. This has the advantage of reducing treatment time but makes it even more important that the contours are accurately positioned and a good registration is achieved between imaging modalities.

1.1.5. Prostate

Prostate cancer is an important localisation to investigate because:

1. it is the most common form of cancer among men,
2. traditional surgical treatment is falling out of favour.

Often considered as the male equivalent of breast cancer, there are also some important differences between the two: prostate cancer tends to affect much older people than typical breast cancer patients, and in general more men will die with a prostate tumour, but from another cause, than will die due directly to the prostate cancer. The standard treatment for prostate cancer is either surgery or radiation therapy, but it is becoming increasingly unclear if surgery is either necessary or beneficial in many cases, as it has many severe side effects such as urinary and sexual dysfunction.

On the radiotherapy side, there is a choice between external beam therapy and brachytherapy where the dose is produced by an implanted radioactive source. Both of these require excellent imaging as the prostate is surrounded by radiation sensitive organs such as the bladder and rectum. The process is further complicated by the elastic deformation which is caused by the rectum filling over time. T2-weighted MRI is the standard imaging modality used to delineate the prostate and organs at risk as it offers the best contrast, however for brachytherapy the patient's treatment position is necessarily not that used to acquire the MRI images, which means further elastic registration is required to manage this deformation. MRSI is also being considered as a potential tool for tumour delineation, focusing on the

metabolites Choline, Creatine and Citrate, Diffusion and Perfusion MRI are also investigated for target volume definition and dose-painting either with external RT or brachytherapy.
During brachytherapy treatment ultrasound is generally used to image the insertion of the radioactive sources and this ultrasound image has to be registered with the MRI and the CT for interactive dose calculation as the sources are being inserted, performing a correct image fusion of US and MRI is a very interesting area of research as the patient is not in the same position: prone for MRI and dorsal lithotomy for ultrasound before implantation.

2. Oncological focus within SUMMER

This section aims to discuss the specific clinical issues of relevance to each group working on the SUMMER project.

2.1. MR spectroscopy (ICR)

Magnetic Resonance Spectroscopy Imaging (MRSI) is a non-invasive imaging technique which has the potential to map metabolic activity in the human body, particularly in the brain. A 1H MR frequency spectrum contains resonances corresponding to several metabolite compounds associated with either healthy or abnormal activity. Using Chemical Shift Imaging (CSI) techniques, a sequence of spectra may be acquired corresponding to different voxels across the patient's brain, providing spatial information about the distribution of metabolic abnormalities. At least one metabolite concentration metric (CNR>2) has already been shown to be indicative of relapse in glioblastoma patients, and there are many ongoing studies into identifying further similar metrics for other metabolites. Furthermore, there is at least one phase III clinical trial, Spectro-Glio, which is currently investigating radiotherapy dose escalation based on the CNR>2 metric.
However, there is currently no standard solution for integrating this MRSI data into the contouring process. Although it is acquired using a standard MRI scanner, data from machines from different manufacturers are currently only available in manufacturer-specific, primitive formats. The raw data requires considerable processing in order to transform it into usable spectra, and again this is largely a closed, manufacturer-specific step in the process. In some cases it is impossible to export the data once processed, making it extremely difficult to incorporate MRSI into any other application.

2.1.1. Data Processing

The first and most important component that must be developed to integrate spectroscopy into radiotherapy planning is a universal processing pipeline. This must be capable of importing data from all the major manufacturer formats and processing them all in a common way to extract the metabolite concentrations. It must work with any pulse sequence and any set of metabolites.
As with other medical data, MRSI processing requires some user validation, checking error bounds and reviewing artefacts. This process should be made as streamlined as possible to reduce the time spent by the user on this step. This can be achieved by automating the simpler validation tasks, and carefully designing the interface for the spectroscopy component.

2.1.2. Data Analysis

MRSI brings a great deal of novel data to the functional evaluation of the tumour environment and tools to evaluate this data are still in their infancy. It is important that SUMMER can support the standard methods for visualising metabolic data, such as metabolite ratio maps, in the most flexible way possible, but further investigation is also required to identify innovative perspectives on the spectroscopic data and incorporate the most relevant ones into the SUMMER interface.

2.2. fMRI (FSL)

Functional Magnetic Resonance Imaging, like MRSI is a non-invasive and non-ionising functional imaging modality used in the brain and spinal cord for imaging cerebral activity. By measuring the changes in blood oxygenation over time, fMRI can identify which regions of the brain are active or inactive. Resting-state fMRI identifies networks of linked regions throughout the brain, while task-based fMRI tracks the specific areas which are activated by the patient performing tasks or responding to stimuli.

2.3. PET (UKF)

Positron-Emission Tomography (PET) used with a FDG tracer shows the glucose metabolism that is increased in most solid and lymphatic malignancies, such a metabolism is not visible on a CT. Magnetic Resonance Spectroscopy (MRS) can provide metabolic map of a lesion and is able to distinguish recurrent tumor from radiation necrosis or radiation injury. Finally, fMRI (functional MRI) is mainly used in brain affection, to monitor growth and function of any remaining brain tumor following the treatment.
Positron Emission Tomography (PET) is a flexible functional imaging technology which works by injecting positron emitting radioactive isotopes in the patient. The corresponding 512 keV electron pairs produced when each positron annihilates are then detected and a map of activity is calculated. The flexibility arises because the positron emitters can be attached to many different chemicals, leading to uptake by different processes in the body and therefore imaging of different functional behaviours. The most common clinically used PET compounds are fluorodeoxyglucose (FDG) which is a glucose analogue indicating sites of high metabolic activity, but many more are either under development or are applicable in specialist cases. Other used isotopes are carbon-11, nitrogen-13, oxygen-15 and rubidium-82.
PET Scanners are able to produce 2D, 3D and 4D datasets. The usage of 2D and 3D datasets is similar to the usage of 2D and 3D datasets of anatomical imaging methods. To capture movement of organs and tumors 4D PET can be used. The main field of application of 4D image acquisitions is in imaging of the thorax to capture the inner body movements due to respiration. To acquire the images the respiration phase of the patient is segmented into time bins. To detect the time bins during respiration the expansion of the thorax is measured by a gating system (e.g. an elastic belt around the thorax). The photons observed by the detector are assigned to one of these time bins depending on the alignment to the signal of the gating system.

2.3.1. Co-registration

To combine the functional information of PET images with the anatomical information of CT or MR images the images are overlaid in a way that pixels that belong to the same structure overlap. Modern combined scanners like PET/CT do this step during the image acquisition.

2.3.2. Tumour segmentation

The problems of PET image segmentation are low spatial resolution, high noise and low contrast. Several PET image segmentation methods have been proposed. These methods make use of a variety of image segmentation methods like:

- edge detection
- thresholding
- region growing
- clustering
- stochastic models
- deformable models
- learning methods

The most common methods in clinical use belong to the thresholding group. Threshold based methods provide good results, are very easy to implement and fast to compute.
One factor that needs to be taken into account during PET image processing is the partial volume effect. This error occurs when a small object or a part of an object is only covered partly by the spatial resolution either in x-, y- or z-direction of the scanner. The signal of the object is then influenced by the signal of surrounding structures. There exist several attempts to correct the partial volume effect. Some of them try to use information from other image modalities like MRI and CT others try to assess the problem in the image reconstruction phase.

2.4. Registration (MUW)

Each image used during a radiotherapy treatment will typically be taken at a different time or using a different modality from every other image. In order to relate the structures visible on one image with those on the others, it is vital to identify the necessary transformations to convert between the co-ordinates of each image. In the case of brain tumours, this can largely be achieved with rigid rotation and translation, whereas for lung tumours this is not an accurate method, and elastic deformation between images may be preferable to achieve good results and will be addressed in the SUMMER project.

2.4.1. Interactive Registration

Automated registration algorithms have demonstrated the ability to match two images much more accurately than the human eye can. However as they typically search for local rather than global optima it is not uncommon for an automated registration to become stuck relatively far from the obvious (to a human user) position. Allowing the registration algorithm to take a rough registration as its initial guess will typically allow the registration time to be greatly reduced.

2.4.2. Partial Registration

In some situations, images may be registered which have very good agreement in some areas and poor agreement in others. This can occur for example in head cases where the shaped MRI couch and the flat planning CT couch cause the patient's spine to be in different alignments in each modality. A simple registration of the spinal region is clearly impossible in this case, however the upper skull and brain areas are not subject to the same deformation and can still be registered with a high degree of accuracy. It is therefore important for the user to be able to specify sub volumes of each image which should be either included or excluded from the registration algorithm's search, to prevent the distorted areas negatively influencing the search.

2.5. Automatic OAR segmentation (AQUILAB)

Delineating contours on a patient's planning CT is a skilled job which must be carefully supervised by the oncologist in charge of treatment. In order to alleviate some of the time-burden placed on the oncologist by this role, automatic segmentation can be used to calculate the majority of the contours, which then need only be checked and validated by the oncologist.
This automatic process is also very useful in dealing with inter-user variability. It is a widely observed phenomenon that two oncologists asked to delineate the same contour on an image will inevitably disagree. For some cases with high contrast this can be only on the order of 1-2mm, but in more difficult cases a separation of 2cm or more is not uncommon. Using automatic segmentation will provide a more repeatable base contour, and while the user will always be able to make modifications based on the unique features of the case, this initial contour should reduce the uncertainty associated with purely manual contouring.

2.5.1. Uncertainty

As with registration, it is really important for the oncologist to understand the uncertainties associated with an automatic segmentation. These uncertainties will almost certainly vary around each contour depending on the contrast with neighbouring regions, but there is currently no ability to quantify or visualise this. If the software can visually identify both regions of high confidence and bands of uncertainty, this will reduce the degree of corrections which have to be made, and by visualising the range of uncertainty, even help to guide the modifications the oncologist makes, reducing inter-user variation.

2.5.2. Interaction with the algorithm

It is unfortunately common for automatically segmented contours to have some errors, spreading out too far over a low contrast boundary, or cutting off part of the region. At the current time, the only way to solve these kind of errors is by a completely independent manual contouring step, which increases the potential for user variation. If the oncologist could have an iterative interaction with the algorithm, able to give it hints about the way to contour certain challenging features, this would reduce the inter-user variation as different users' hints would still result in the same generated contour. It would also reduce the contouring time if errors on many slices could all be fixed with the addition of one or two hints.

2.6. Visualisation (VRVis)

Visualisation is an extremely important part of any radiotherapy software. It is the visualisation more than any other component which will guide the oncologist in their evaluation and validation of the registration and segmentation, so it is essential that it supports efficient and flexible use. The visualisation should make it easy for the oncologist to navigate through the datasets, keeping track of spatial position, window levels and image modalities.

2.6.1. Flexibility

The most important feature for the visualisation is intuitive flexibility: different oncologists will have different preferences about how they look at different images, and which modalities are most useful for

each task, so a single visualisation style cannot suit every user. It is also common that an individual user will want to rapidly switch between modalities to compare a particular feature. Afterwards the user will probably want to return to the original configuration they were using, without having to spend a long time readjusting parameters.

2.6.2. Brain Visualisation

The most important challenge in brain visualisation is supporting the large number of distinct modalities which are typically used: planning CT, T1, T2, FLAIR, diffusion, fMRI, spectroscopy etc. Fusions should be possible between as many modalities as possible without sacrificing clarity.

2.6.3. Lung Visualisation

The most important challenge in lung visualisation is managing patient motion. This means in part handling 4D datasets and delivering a smooth and intuitive way to navigate through space and time, but it is also important that the range of motion can be interpreted even while viewing a single time point.

2.7. User perception and interaction (TUD)

Although it is to be hoped that the automatic segmentation process will generate a high quality set of contours, the final decisions regarding the delineation of both organs at risk and tumour volumes must always be taken by the treating radiation oncologist. This means that the facility must exist within SUMMER to view image slices from the various modalities, evaluate the existing contours and make any necessary modifications to them.

2.7.1. Easy and precise contouring

Contouring is a significant portion of any radiation oncologist's daily routine, so it is important that the process not be too taxing, physically or mentally. It is also important that the contouring process is as time-efficient as possible to increase the patient throughput. This means that the oncologist must be able to draw the contour that they want first time, not have to make several corrections as this is both frustrating and time-consuming.
In creating SUMMER, different contouring mechanisms will be explored and compared such as mouse-, pen- and gesture-based. Furthermore the possibility of contouring on non-orthogonal slices or in 3D will also be considered. It will be important to evaluate the performance of these different approaches, both in terms of contour quality and speed of contouring.

2.7.2. Contouring assistance

As discussed above in Automatic Segmentation, manual contouring currently generates considerable inter-user variation. Even in cases where an automatically segmented contour has already been generated, it is usual for the oncologist to make some changes according to their personal experience. However it has been demonstrated that contours each drawn by a group of oncologists working as a team tend to converge much more.
While it is clearly impractical to have all contouring done by a team, the resulting contour reliability is highly desirable. By understanding the main issues which lead to uncertainty and variation in individual contours for each treatment localisation, SUMMER can provide visual cues or relevant additional information which will give the user insights into the contour without restricting their ability to make judgements for individual cases. This should reduce the variation in contours.