Medical Factors of Brain Tumor Delineation in Radiotherapy for Software Design

Aselmaa, Anet; Goossens, Richard; Rowland, Ben; Laprie, Anne; Song, Yu; Freudenthal, Adinda

Publication date
2014

Document Version
Final published version

Published in
Proceedings of the 5th International Conference on Applied Human Factors and Ergonomics AHFE 2014

Citation (APA)
Aselmaa, A., Goossens, R., Rowland, B., Laprie, A., Song, Y., & Freudenthal, A. (2014). Medical Factors of Brain Tumor Delineation in Radiotherapy for Software Design. In T. Ahram, W. Karwowski, & T. Marek (Eds.), *Proceedings of the 5th International Conference on Applied Human Factors and Ergonomics AHFE 2014* (pp. 4865-4875)

Proceedings of the 5th International Conference on Applied Human Factors and Ergonomics AHFE 2014, Kraków, Poland 19-23 July 2014
Edited by T. Ahram, W. Karwowski and T. Marek

Medical Factors of Brain Tumor Delineation in Radiotherapy for Software Design

Anet Aselmaa[1], Richard H.M. Goossens[1], Ben Rowland[2], Anne Laprie[2] , Yu Song[1], Adinda Freudenthal[1]

[1] Faculty of Industrial Design Engineering
Delft University of Technology
2628 CE, Delft, The Netherlands

[2] Institut Claudius Regaud,
Toulouse, F-31052 France

ABSTRACT

In radiotherapy, the delineations of the volume of the macroscopic spread of the tumor as the Gross Tumor Volume (GTV), and the surrounding volume of the microscopic spread of the disease as the Clinical Target Volume (CTV), are key tasks for a high quality treatment plan. In order to design a software that also supports cognition, software designers need a deeper understanding of the physicians' cognitive processes and medical context. This paper presents a research about identifying main medical factors relevant for the delineation in the radiotherapy context as a first step in deepening the understanding for software design. Using two discussion formats with six radiation oncologists, we identified 29 medical factors regarding the delineations of tumorous volumes, categorized into: treatment context, tumor context and tumorous areas. In addition, the role of multimodal images, dose planning, and future wishes have been elaborated. These findings could support the software designers in using Evidence Based Software Engineering approach. It is expected that software designed based on the results presented here, is tailored towards the medical context and cognitive needs of radiation oncologists in the delineations of brain tumor, and therefore will improve the effectiveness and efficiency of their work.

Keywords: Cognition, Radiotherapy treatment planning, Brain tumors

1. INTRODUCTION

Human and non-technology issues are not trivial in the designing of biomedical information systems since both the complexity of tasks and the pressure on users are high (Pantazi, Kushniruk, and Moehr, 2006) . However, in many healthcare software systems, the interface and interaction design is not always optimal for the intended usage. For instance, in an evaluation of IPLAN® radiotherapy software (Ramkumar et al., 2014), more than 20 usability issues were discovered. Usability problems hamper the effective and efficient usages of the systems, thus further lowering the quality of the service (Teixeira, Ferreira, and Santos, 2012).

Acquiring the clinicians (users)' wishes by asking them is a general practice for improving usability while designing (and developing) a software. By *software design* one is referring here to the early phase of software engineering process where conceptual interface and interaction design is created, e.g. in the form of prototypes or use cases. However, only asking is not always sufficient since: 1) The perception of the clinicians does not necessarily correlate with the optimal performance (Andre and Wickens, 1995); 2) The clinicians' wishes may be limited by their own understanding of the complexity of their work and their design vocabulary. "Give clinicians what they want" without understanding their cognition and actions is insufficient (Karsh, Weinger, Abbott, and Wears, 2010). Therefore, to design a better software solution, it is important to study clinicians and their contexts for a better understanding of the complexities of their work - the tasks, processes, contexts, contingencies, and constraints (Karsh et al., 2010).

To understand clinicians and their daily tasks, the Human-centered design (HCD) is often used. HCD was developed for designing interactive systems. It aims at making systems usable and useful by focusing on the users, their needs and requirements by applying human factors/ergonomics, and usability knowledge and techniques (DIS, 2009). For instance, one of the four main HCD activities named "understand and specify context of use" aims to gather information regarding the users, tasks and organization, technical and environmental characteristics. In the usage of the HCD approach, K. Vicente (2010) encourages taking a systems approach in order to solve human factors problems across five different levels in the design: physical, psychological, team, organizational and political level.

In order to design a software solution fitting in the clinical context, a deeper understanding about the medical factors influencing delineation decisions is required. This paper presents a research approach for getting a deeper understanding of the psychological (cognitive) level of clinicians regarding the specific task of tumorous volumes delineation. The rest of the paper is arranged as follows: In sections 2, the details of the task, identifying the precise location and shapes of tumorous volumes in brain, are described; Section 3 presents the approach used in the research where two methods are introduced; In Section 4, the outcomes of the research are presented as a list of medical factors, elaboration of usage of different imaging modalities, impact of dose planning, and future wishes; Section 5 presents a discussion of the findings and the potential contributions of those outcomes to software design. Section 6 gives a short conclusion of this paper.

2. RADIOTHERAPY

Primary brain tumors are less common (<1.5% of all cancers) in comparison with tumors of other organs (e.g., lung, breast, or colon). However, they are important cases to consider due to the extremely poor prognosis of patients, as well as the histopathologic complexity and biologic behavior of the tumor (Karkavelas and Tascos, 2011). Brain tumors are often treated with external radiotherapy in combination with surgery and/or chemotherapy. Radiotherapy damages the DNA of cancer cells. Sufficient doses may prevent the cell from reproducing, or even trigger apoptosis. Although this effect is more pronounced for rapidly reproducing tumor cells, the radiation also damages healthy tissue. Thus it is important to sculpt the dose distribution by targeting the tumor region with maximum dose while sparing the healthy tissue around it as much as possible.

Radiotherapy treatment planning for brain tumors is a complex process involving many participants and tasks. The complexity arises from the fact that radiotherapy must be personalized for each patient. The treatment planning starts with acquiring brain images using a variety of imaging modalities. This is followed by co-registering (fusing) the images to the same coordinate system. A physician then defines the tumorous volumes and organs at risk on those medical images (MRI, CT and/or PET). Once the volumes are defined, the actual dose delivery can be planned. Among different tasks within this workflow, the task identifying the tumor "correctly" would benefit most from an improved understanding of the cognitive processes that are involved in the process (Aselmaa, Goossens, Laprie, et al., 2013).

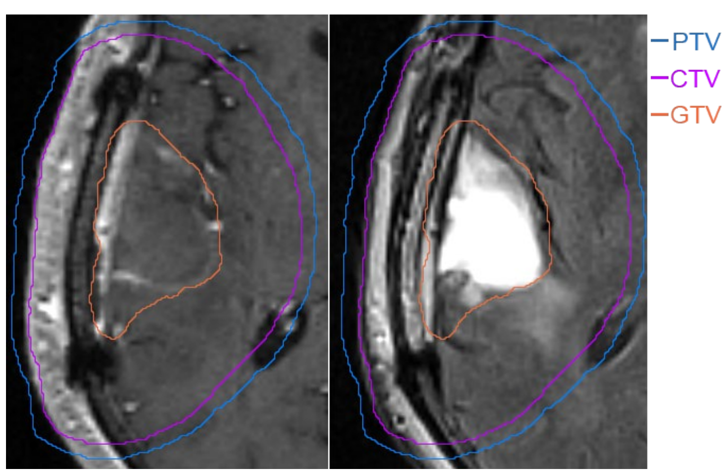

Figure 1 Example of "classical" target volumes GTV, CTV, PTV on one axial MR slice of the brain; left) T1-weighted image with gadolinium enhancement; right) FLAIR sequence

Figure 1 illustrates different volumes identifying brain tumor. They are: 1) Gross Tumor Volume (GTV) - the macroscopic spread of the tumor; 2) Clinical Target Volume (CTV) – the surrounding estimated microscopic spread of the disease; and 3) Planning Target Volume (PTV), the volume taking into consideration possible positioning errors during treatment delivery. The GTV is delineated on the available imaging modalities based on guidelines, treatment protocols, and the physician's experience. The CTV is then created by adding a margin around the GTV (e.g. for glioblastoma multiforme 2–3 cm (Mason et al., 2007)) and making needed adjustments. Finally, the PTV is created by adding a margin around CTV (for a typical brain treatment it is 3mm).

In the past decades, advances in medical imaging have made it possible to have additional information about the tumor biology and thus know better where additional dose might be needed. For instance hypoxic tumor areas are shown to be more radioresistant (Moeller and Dewhirst, 2006). In another example, metabolically active regions detectable with magnetic resonance spectroscopic imaging (MRSI) are predictive for the site of post-RT relapse (Laprie et al., 2008). In those cases, additional volume(s) might be created (as shown on Figure 2) based on which the dose boost area can be defined.

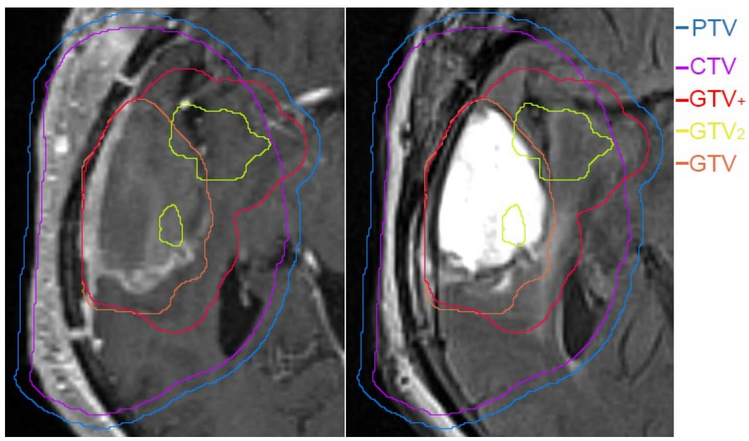

Figure 2 Example target volumes for dose boost on one axial slice, GTV2 = metabolic abnormalities, GTV+ = GTV+GTV2+enlargement; left) MRI T1 post gadolinium injection; right) MRI FLAIR

Previous research indicates that the GTV and the CTV are prone to inter- and intra-user variation (Weltens et al., 2001). This is especially critical since the systematic error introduced in the delineation step, will be carried on through the whole treatment planning (Weltens et al., 2001). These differences can be mainly explained by the subjective interpretation of the medical images. In addition, knowledge about tumors is still limited (though growing), resulting in medical uncertainty. Furthermore, users need to deal with a continuously growing number of medical images which makes the task cognitively challenging. All these factors result in variations of defined tumorous volumes.

GTV represents the "visible" tumor. This offers the possibility of automatically detecting GTV by intelligent computational algorithms. This approach may reduce the inter-observer variability (and also the human effort). Research efforts toward this direction can be observed in numerous literatures and conferences. For instance, at the conference Medical Image Computing and Computer Assisted Intervention (MICCAI), there were challenges in 2012[1] and 2013[2] on Multimodal Brain Tumor Segmentation where multiple algorithms were presented. It can be expected that those automated algorithms will create sound GTV for a subset of cases soon. However, for general clinical use, current algorithms did not reach the satisfactory level. Thus, current radiotherapy software solutions often integrate the technological advancements and the physicians' cognition together as a semi-automated process, and a deeper understanding about the physicians' cognition and medical factors influencing delineation decisions is required in the development of those solutions.

3. RESEARCH APPROACH

In order to gain deep insights into the physicians' cognition, qualitative approach was taken where two parallel approaches: case and list discussion (both consisting of a preparatory task followed by a discussion), were used in

[1] http://www2.imm.dtu.dk/projects/BRATS2012/
[2] http://martinos.org/qtim/miccai2013/

order to get a global overview of physicians and their daily tasks. One of the aims while choosing the research approach was not to be limited to physical distances, and to be able to collect information from physicians in several different countries. Due to the busy work rhythm of physicians the aims was to keep the discussions as short as possible (between 10 and 15 minutes per discussion). Another aim was to give preparatory tasks to the participants prior to the discussion in order to trigger reflection on their work and to get them mentally prepared for the discussion. In total, six (female) radiation oncologists with varying levels of experience (3-21 years, starting from residency) from France, Germany and Netherlands participated in the study. Table 1 lists each participant and the types of research they joined.

Table 1 Overview of participants

	Case discussion	List discussion
Participant 1	Yes	No
Participant 2	Yes	Yes
Participant 3	Yes*	No
Participant 4	No	Yes
Participant 5	No	Yes**
Participant 6	Yes	No

** the discussion was more general than one case discussion*
*** no follow-up discussion due to time and language limitations*

For the first approach - case discussion, a preparatory worksheet with open-ended questions was sent to the four participants at least one week prior to the discussion. The participants were encouraged to print out the worksheets and take notes on it. The aim of the case discussion was to discuss in detail one difficult case of a brain tumor they had. The discussions were held over telephone call (three participants) or in person (one participant), and all discussions were audio recorded.

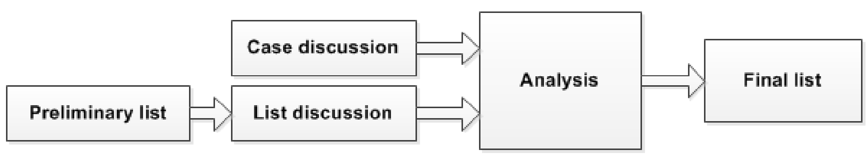

Figure 3 Approaches used in the presented research

For the second approach – list discussion, a preliminary list consisting of 31 medical factors was created. 19 medical factors were derived from the VASARI MR feature list (version 3.0[3]). VASARI project aimed to develop reproducible methods to classify MRIs of glioma tumors based on the observations familiar to neuroradiologists, in order to describe the morphology of brain tumors on routine contrast-enhanced MRI ("VASARI Research Project," 2013). In addition, 12 factors were identified based on prior ethnographic studies (Aselmaa, Goossens, and Freudenthal, 2013), workflow analysis (Aselmaa, Goossens, Laprie, et al., 2013), lectures given within the SUMMER consortium[4] and other medical literatures. The preliminary list consisting of 31 medical factors was then formatted into a worksheet, and was sent to the three participants at least one week prior to the discussion. After the participants had filled in the worksheet, a telephone call (audio recorded) was held to elaborate on their responses. With participant #5 there was no follow-up discussion due to a language barrier; however the translated worksheet is included in the analysis.

4. RESULTS

In this section, we present the identified medical factors (Table 2) based on the returned worksheets and the transcribed interviews. The factors are categorized as follows: treatment context (8 factors), tumor context (10 factors) and tumorous areas (11). The last column in the table indicates the number or participants mentioning the factor. It is important to highlight that if a factor was mentioned by only few participants, it does not imply that other participants did not find it relevant – it only means that it was not mentioned by other participants.

[3] https://docs.google.com/spreadsheet/viewform?formkey=dHIxSC1vOXZQUGZfV19KUkhNbmVYRHc6MA
[4] http://summer-project.eu

Table 2 Medical factor influencing delineation

	Medical factor	Influence on delineation	BY
TREATMENT CONTEXT	Institute	Radiotherapy is different in each institute. Direct impact on the delineation practices, such as which regions are included in the GTV/CTV or what margins are used for different tumors.	#4 #6
	RT treatment type	The geometrical complexity of contours is limited by technical capabilities of the treatment machine. For IMRT more complex contours are possible. Impact on PTV margins. Stereotactic treatment requires more precision in delineation.	#2 #4 #6
	Re-irradiation	Delineation for re-irradiation is more challenging since it is difficult to separate between residual tumor and the radiation induced changes. The first treatment plan is used for better understanding of the area treated before.	#1 #2 #3 #6
	Curative or palliative	For curative setting there is more effort in trying to take the volume as small as possible. For palliative setting there is less concern for long-term side-effects.	#1 #2 #6
	Strong clinical symptoms	Either increases cautiousness (not to do more damage), or in case of permanent damage would allow including the damaged area.	#2 #4 #5
	Patient had/has chemotherapy	Probability for side effects is greater for combined therapy which means that it can encourage smaller (more cautious) contours. Images prior to chemotherapy might be needed.	#2 #5
	Surgery	More challenging. Tumor bed is to be included in target volumes.	#1..#6
	Imaging modalities	In different cases, different imaging modalities are acquired and available for use. The delineation process is directly influences by the available data.	#1..#6
TUMOR CONTEXT	Type of primary tumor	Defines which imaging modalities to pay more attention to, the expected tumor behavior, which areas to pay more attention to.	#2 #4 #6
	Changes in tumor	The tumor changes between different image acquisitions are taken into account. All sequences should be examined.	#1 #2 #4
	Tumor histology	CTV margin depends on the histology	#4 #5
	Tumor grade	Low grade tumors are less aggressive, thus the CTV margin is smaller. Tumor grade defined which imaging modality is more useful for macroscopic tumor.	#2 #4 #5
	Tumor growth direction	Knowledge about the expected tumor growth direction helps in deciding whether abnormality is tumorous or might be something else	#2
	Close tumor proximity to organ at risk	Extra information (e.g. thin layer MRI or FET-PET) is needed to be able to better differentiate between the tumor and the proximal organ at risk. Adjustments (CTV and PTV) might be made according to the proximal organ at risk.	#2 #3 #5
	Anatomic barriers	Anatomic barriers (e.g. bone) can act as natural border for the tumor.	#6
	Size of the tumor	Very big sized tumors require more attention to reduce the total volume where possible since the harm to the patient cannot be greater than the possible benefit.	#2 #4 #5 #6
	Multifocal or multicentric tumor	Additional locations need to be checked, like spine, for metastasis. Satellite lesions are included in GTV	#2 #4 #5
	Mid-line crossing of the tumor	Midlines crossing contrast enhance tumor is generally included in the GTV.	#2 #4
TUMOROUS AREAS	Tumor bed/surgical cavity	In case the tumor was completely resected, the surgical bed represents the CTV. In the case of partial tumor resection, the surgical bed is included in GTV together with residual macroscopic tumor.	#1 #4 #6
	Macroscopic tumor	The visible tumor; in case of post-surgery referred to as residual tumor	#1.. #6
	Contrast enhancing area	Contrast enhancement on post-gadolinium injected MRI T1 represents the macroscopic tumor. Lack of expected contrast enhancement requires using different imaging modalities.	#2 #4 #5
	Edema	Edema is often included in the target volume. In case the edema crosses midline and is very far from the macroscopic tumor, it might be left out since the whole brain cannot be treated.	#2 #4 #5 #6
	Necrotic tumor	Located within the macroscopic tumor and part of the GTV.	#2
	Calcification	Included in GTV	#2 #5
	Infiltration	Additional modalities might be needed to understand the extent of infiltration (e.g. CT scan for bone). Infiltrative part of the tumor is included in the GTV. Additional modalities might be needed to understand the extent of the infiltration.	#2 #4 #5
	Satellites	Additional locations need to be checked, like spine, for metastasis. Satellite lesions are included in GTV	#2 #4
	Metabolic abnormalities	Metabolic abnormalities are generally assumed to be tumor and thus included in the GTV. However, the correlations are still being investigated with clinical trials.	#2 #4 #5
	Hypoxia	Hypoxia, one of the metabolic abnormalities, is included in the GTV. However the dose delivered to hypoxic volume might be increased.	#2 #5
	Cyst(s)	Cysts are included in the GTV or CTV, though they are not too common	#2 #4 #5

The presented 29 factors all influence to the delineation process to a bigger or smaller extent. However, few of them are either more frequent or have greater impact.

Different institutes have different treatment protocols and approaches to the delineation. It is most evident in the practice of choosing which tumorous area is included in which target volume. Also the margins that are used to generate CTV from GTV vary. However, this is not a new finding. As participant #6 said *"the way people delineate gliomas is different in different hospital"*, and participant #2 *"Radiotherapy is very different according to the center"*. Even though there are guidelines, each institute often adapts them to their practice (Chang et al., 2007).

Radiotherapy treatment plan is an outcome of a collaborative teamwork. When there are difficult decisions to make, other colleagues are asked for input. For example, participant #2 mentioned during the case discussion, that *"I have asked more experienced oncologist"*. It was also mentioned by participant #3 *"and we also discuss cases"*. Additionally, collaboration was identified as one of the important factors also during prior ethnographic studies (Aselmaa, Goossens, and Freudenthal, 2013). Munoz, Mollo, Barcellini, and Nascimento (2011) investigated the collaboration within the whole radiotherapy workflow and identified that informal communications are the most used strategies to collaborating.

All participants mentioned surgery as a factor. All physicians considered the post-operative (especially with partial resection) setting challenging. For example, when they were asked about what was the most difficult part of the case discussed, physician #1 said *"how things have moved because there is a surgery"* while keeping in mind that "*still you don't want to miss the surgical cavity"*. It was also confirmed by participant #3 that it is challenging to understand what is what: *"Well, it's always post-operative setting where it's difficult. […] you have to differentiate between residual tumor after resection and post-operative changes".* In addition, movements of tissue also make it difficult to use image fusion as there is loss of information on the fused images. *"And the co-registration [fusion] is difficult because you co-register [fuse] and then it's not there anymore"*(#1). This is due to the fact that *"the anatomy of the brain can be changed after surgery"* (#2).

When the patient has had surgery, the tumor bed (also called surgical cavity or operative bed) is included in the delineated target volumes. Tumor bed typically has contrast enhancement around it. However, whether it should be included in GTV or CTV varies. In the case of a complete tumor resection, the tumor bed is considered CTV as mentioned by participant #4*"when there isn't no tumor anymore that's CTV directly"*. However, if the tumor was only partially resected, normally it means that there is macroscopic tumor - *"There is a GTV, yes. When it's partial surgery. Because there is macroscopic tumor"*(#4). However, there seem to be differences between institutes and physicians in whether tumor bed is GTV or CTV. As participant #4 mentioned *"some radiation oncologists talk about GTV after surgery [complete resection], I think that's false"*.

One of the common changes in the brain due to the tumor is edema – excess fluid collecting in the intercellular space. Participant #3 mentioned *"it is sometimes difficult to differentiate between edema and tumor"*. Most of the times, edema is considered to be due to the tumor infiltration and thus included in the CTV. However, inclusion of edema in target volumes depends on the type of the tumor. For instance, participant #6 gave an example of benign meningioma where the edema is not included. In most cases when edema is present, it encompasses the surgical cavity. Additionally, as participant #2 mentioned, edema in the images may a result of the prior surgery. In case of such uncertainty, additional medications might be given to the patient to see if the edema will go away, if not then it is assumed to be tumor.

In the current way of defining target volumes (as was shown in Figure 1), where the dose is delivered to the PTV, there is no difference to the patient outcomes whether an area is part of the GTV or the CTV since it will be within the irradiation field anyway. However, one of the future visions is to have more complex treatment plans where the heterogeneity of the tumor is matched with complex dose plans. For such treatment approaches, however, it is important to define well all the different areas. This approach is based on the use of theragnostic imaging. Theragnostic imaging refers to the use of information from medical images to determine how to treat individual patients while taking into account scientific progress in molecular and functional imaging, in radiotherapy planning and delivery, and in clinical radiation (Bentzen, 2005). Participant #2 mentioned as a future wish that she would like to know *"what are the most important places in the tumor anatomy we have to irradiate with larger dose or something like this"*.

4.1 Imaging modalities in delineation process

Delineating tumorous volumes is done on various imaging modalities and image sets, and as such they inevitable influence the process.

4.1.1 Choosing the right data for the right action

Depending on the institute and the situation, there are different imaging modalities used for different tasks. GTV and CTV are typically delineated on one or more MRI sequences. The common MRI sequences used are T1 (before and after gadolinium injection), T2 and FLAIR. There is always a CT scan for radiotherapy treatment planning due to technical limitations of dose plan calculation. When asked from one of the participants which modalities were used, she said *"with mainly T1 gadolinium… and CT scan for planning"* (#1).

The variation of whether the newer imaging modalities are acquired depends on the institution and the treatment type (e.g. routine treatment or clinical trial). New MRI imaging techniques evaluate tissue blood flow (perfusion imaging), water motion (diffusion imaging) and brain metabolites (proton magnetic resonance spectroscopy) (Drevelegas and Papanikolaou, 2011). *"On the diffusion you see the pathways of the tumor growing. And the extent of abnormalities [..] you want to see how bad it is and diffusion helps you. Same with perfusion. And same with spectroscopy"* (#1). Additionally PET imaging modality could be used with a suitable tracer (e.g. FET-PET) in order to reduce uncertainties, *"FET-PET CT is a possibility to differentiate between active tumor and pseudo-regression [disappearance of contrast uptake] on MRI"* (#2).

Based on the knowledge about the tumor (type, histopathology), physicians know which MR sequence is most suitable for identifying the macroscopic spread. High-grade tumors are expected to have contrast uptake on post-gadolinium injection MRI T1. The contrast uptake then indicates the macroscopic spread of the tumor. Low-grade tumors, however, do not have contrast uptake, but they do have enhancement on MRI T2 or FLAIR sequences and thus these sequences give a better understanding of the macroscopic spread (#2).

With the advances of radiotherapy, the number of re-irradiations is increasing. However, at the time being there are limited possibilities to differentiate between radiation induced changes and tumor recurrence on the available images. Until now though, there is no one imaging modality which can assist physicians. In one study, 11C-Choline PET/CT was shown to provides an effective mean to distinguish brain tumor recurrence from radiation injury; however 11C-Choline PET/CT also indicated false negatives (Tan, Chen, Guan, and Lin, 2011).

4.1.2 Combining information from multiple modalities

One of the challenges with using multiple images is that different images show different information as mentioned by participant #2, *"There are a lot of cases where MRI and PET-CT are not the same. They show different volumes"*. In such situations physicians need to decide how the overcome the discrepancies. As it was elaborated further *"The tumor in the contrast enhancement [in FET-PET] was smaller so I decided to use the PET for delineation [..] as the first imaging. [..] I have done GTV by thresholding for the PET-CT as orientation [..] and then I've looked over the MRI and also take in some parts – there was enhancement in [MRI] T2"*. The main reason for using multiple modalities is that by combining the information from each of them, the identified volumes are less likely to miss the tumorous cells. This was also brought up during one of the case discussion, *"there are parts in the MRI there is no contrast enhancement, but there was uptake in the PET" (#2).*

The delineation process consists of continuous checking and adjustment. *"When the tumor has not been operated, so there is a GTV [macroscopic tumor]. [Then] I do a margin of 17mm around. Automatically. And then I look on the FLAIR or T2 sequence if all the edema is in the margin. [..] If edema is out the margin I change [..] I enlarge my contour. I consider all the edema is disease" (#4).* This was mentioned by all participants that they do a contour (on the modality suitable for the task in hand) and then check on other modalities. In the case of a surgery there is a need of comparison of pre-surgical and post-surgical images. And after a patient had a surgery, there are more images needed to be able to better understand what is what.

T2 or FLAIR is used for delineating edema. *"The [MRI] T2 is great to see the edema because we take it in our contour"* and *"And then I look on the FLAIR or T2 sequence if all the edema is in the margin [..].if edema is out [of] the margin [..] I change my contour"* (#4). Additionally PET imaging, if available, could be used as mentioned by participant #3 *"In the example of astrocytoma grade II it is very helpful to have good quality MRI but also to have aminoacid PET to differentiate between edema and tumor"*.

4.1.1 Temporal view of images

Typically there are multiple sets of images of a patient, e.g. diagnostic and treatment planning images. However, in case of a surgery there are additional images have been acquired both before and after surgery (depending on the organizational set-up). The practice of using pre-operative images varies between physicians. For instance, participant #6 takes pre-operative images (in the case of glioblastoma) into account only if they have very big difference compared to the planning images. However, different practice is to create GTV by combining what is seen on all the sequences acquired at different moments in time. As participant #2 said *"I would try to include all images [in the delineation] of GTV if it is logical and possible"*.

One important aspect for delineation is to compare the created contours on the images acquired in different moments of time. *"The gadolinium enhancing lesion before surgery and the residual enhancing lesion after surgery" #1*. As one physician (#1) was describing *"I wanted to take all the place where there was relapse"* which is seen in the pre-operative images; *"and then all the relapse that was operated and then the little region [of the residual enhancing lesion after surgery]"* which are seen in the post-operative images. Another example, mentioned by participant #4 *"I contour in the post-operative and I verify on the pre-operative"*. This was later elaborated, *"If I contour the tumoral bed, [to verify] I look to the preoperative images. Because we have to.. just look if the tumoral bed is, how to say that, logical."*.

Physicians have extensive knowledge about anatomy and tumor biology. As such, they are able to reason the changes seen by comparing temporal images and make a decision on what to include and what not based on the synthesis of the information. *"Sometimes you [..] know how the tumor behaves [..] if I see in this direction [tumor growth direction] something strange I will say it's tumor, but if it's apart from the prior GTV for example then it's maybe another reason"* (#2).

4.2 Dose planning

During delineation, the physicians are estimating the feasibility of covering the target volumes they are creating with the dose they want. As physician #2 mentioned *"If I know that I have the possibility to use IMRT, I probably would tend to draw geometrically complex contours."* This was then further explained, that physicians know about the technical limitations of the geometrical shapes of dose that different types of machines can deliver. Since the aim is to have good dose coverage to the defined target volumes, physicians need to decide already during the delineation what areas to include or exclude in order to reach a geometrical shape that can be sufficiently covered with radiation.

Medical research has shown that tumor is not a homogeneous tissue, but is heterogeneous. Dose-painting represents the idea to visualize tumor sub-volumes with a potential resistance problem and to paint some additional dose onto that volume (boost) (Ling et al., 2000).. For delineation, however, this means that additional volumes need to be created (as shown in Figure 2). For example participant #3 mentioned that *"would discuss to give a boost on the hypoxic area."* Another situation, where volumes need to be clearly defined, is when there is a dose boost to the macroscopic spread of the tumor, as participant #3 mentioned *"If you give a boost, you would like to boost the tumor, the macroscopic tumor itself, and not the edema"*.

4.3 Wishes for the future

One of the aims of radiotherapy is to treat the tumorous volume and avoid future relapse in that area. Predicting the tumor relapse area is an ongoing research area. As a future wish, participant #2 said *"if we [could] know the future. In which direction the tumor will grow."* There is constant wish for medical advancement, as participant #3 mentioned *"of course development of new imaging modalities would be great. [..]In the cases when you are not sure of the infiltration and it's the microscopic spread of gliomas would be helpful to have better imaging modalities"*. From technological advancement point of view *"it would be nice to have higher resolution of course."* (#3).

Another difficulty in current work that was mentioned by the participants (#2, #6), is to have the post-surgical images acquired with 48 hours to avoid post-surgical effects, which hamper the readability of the images. However, the radiotherapy department is separate from surgical department or imaging department. Solving this problem would require inter-departmental(institutional) workflow improvements. The participants also mentioned more practical needs for their daily work. Participant #1 mentioned *"I would like to have easy access to diffusion, perfusion and MR spectroscopy data"* and generalized it to *"I would like to have an easy switch from one imaging modality to another"*. Another participant, while emphasizing differences between institutes, mentioned *"It is very helpful if the software is good responding, well responding and fast enough to respond to every kind of input"* (#3).

5. DISCUSSION

Using the proposed two methods, we identified main medical factors influencing the delineation of tumorous volumes. In addition, we also elaborated on the usage of imaging modalities and described the impact of dose planning. Based on these, a deeper understanding of the medical context and the cognitive work of physicians is given. Using the Evidence Based Software Engineering (EBSE) (Kasoju, Petersen, and Mäntylä, 2013), it is possible to translate those medical factors and the deeper insights regarding the delineation process in to evidences that guides the design and development of software solutions for radiotherapy physicians.

In software (design and) development, requirements play an important role. Using the identified factors as guidelines, we could ensure that also cognitive and environmental aspects are embedded in the software. For instance, the factor “institute” would require the designer to identify institute dependent practices and to ensure that the designed solution and the accompanying requirements are flexible across institutes. Another factor “imaging modalities” combined with “institute” forces the designer to acknowledge that there are differences in practice on what type of data will be available and as such the designed solution (and requirements) should be able to adapt to the context.

Many of the evidences can be used in the interface design with the ecological interface design (EID) method. EID is a theoretical framework for designing human-computer interfaces for complex sociotechnical systems; its primary aim is to support knowledge workers in adapting to change and novelty (K. J. Vicente, 2002). As it was seen from the discussion with the physicians, delineating tumorous volumes is a very personalized process. Even though the process might seem to be the same on a higher level, every patient is different and as such the decisions to be made are different.

It became evident from the discussions, that there are two dominant interactions that physicians’ are engaged in: 1) checking the contour on different views; 2) adjusting of the contour, if new information was seen on the different view. As such, during software design (and development) special focus is needed in order to reach an ergonomic solution for these interactions.

6. CONCLUSIONS

The aim of the proposed research is to identify medical factors that are influencing the delineation of macroscopic speard of the tumor and surrounding microscopic spread of the tumor in radiotherapy context. Two discussion approaches -preliminary list based discussion and case discussions - were used for exploring the cognitiveprocess. The found factors were concluded in three categories: treatment context (8 factors), tumor context (10 factors) and tumorous areas (11).. More thorough explanations have been given about the impact of surgery and presence of edema. In addition, the role of multimodal images, the relations to dose planning and other interesting findings have been elaborated. These findings can be used as evidences which cansupport the development of radiotherapy software solutions.

The presented research is the first attempt to bridge the gap between physician’s cognition and software designers. By providing an overview of different medical factors covering various aspects, we expect to support software designers in creating solutions that cognitively fits the task of delineating tumorous volumes. In addition, these medical factors could support software designers in linking clinical reasoning with automatic delineation algorithms.

ACKNOWLEDGEMENTS

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7-PEOPLE-2011-ITN) under grant agreement PITN-GA-2011-290148. It is part of European Union project called Software for the Use of Multi-Modality images in External Radiotherapy (SUMMER) project.

REFERENCES

Andre, A. D., & Wickens, C. D. (1995). When Users Want What's not Best for Them. *Ergonomics in Design: The Quarterly of Human Factors Applications, 3*(4), 10-14. doi: 10.1177/106480469500300403

Aselmaa, A., Goossens, R. H., Laprie, A., Ken, S., Fechter, T., Ramkumar, A., & Freudenthal, A. (2013). Workflow Analysis Report. http://summer-project.eu/work/deliverables/.

Aselmaa, A., Goossens, R. H. M., & Freudenthal, A. (2013). *What is sensemaking in the context of external radiotherapy treatment planning?* Paper presented at the Design of Medical Devices 2013 – Europe (DMD'13), Delft, Netherlands. http://designofmedicaldevices.eu/public/documenten/Design_of_Medical_Devices_Europe_2013_Abstracts.pdf

Bentzen, S. M. (2005). Theragnostic imaging for radiation oncology: dose-painting by numbers. *The Lancet Oncology, 6*(2), 112-117. doi: 10.1016/S1470-2045(05)01737-7

Chang, E. L., Akyurek, S., Avalos, T., Rebueno, N., Spicer, C., Garcia, J., . . . Maor, M. H. (2007). Evaluation of Peritumoral Edema in the Delineation of Radiotherapy Clinical Target Volumes for Glioblastoma. *International Journal of Radiation Oncology*Biology*Physics, 68*(1), 144-150. doi: http://dx.doi.org/10.1016/j.ijrobp.2006.12.009

DIS, I. (2009). 9241-210: 2010. Ergonomics of human system interaction-Part 210: Human-centred design for interactive systems *International Standardization Organization (ISO). Switzerland*.

Drevelegas, A., & Papanikolaou, N. (2011). Imaging Modalities in Brain Tumors. 13-33. doi: 10.1007/978-3-540-87650-2_2

Karkavelas, G., & Tascos, N. (2011). Epidemiology, Histologic Classification, and Clinical Course of Brain Tumors. In A. Drevelegas (Ed.), *Imaging of Brain Tumors with Histological Correlations* (pp. 1-12): Springer Berlin Heidelberg.

Karsh, B.-T., Weinger, M. B., Abbott, P. A., & Wears, R. L. (2010). Health information technology: fallacies and sober realities. *Journal of the American Medical Informatics Association, 17*(6), 617-623. doi: 10.1136/jamia.2010.005637

Kasoju, A., Petersen, K., & Mäntylä, M. V. (2013). Analyzing an automotive testing process with evidence-based software engineering. *Information and Software Technology, 55*(7), 1237-1259. doi: 10.1016/j.infsof.2013.01.005

Laprie, A., Catalaa, I., Cassol, E., McKnight, T. R., Berchery, D., Marre, D., . . . Moyal, E. C.-J. (2008). Proton Magnetic Resonance Spectroscopic Imaging in Newly Diagnosed Glioblastoma: Predictive Value for the Site of Postradiotherapy Relapse in a Prospective Longitudinal Study. *International Journal of Radiation Oncology*Biology*Physics, 70*(3), 773-781. doi: 10.1016/j.ijrobp.2007.10.039

Ling, C. C., Humm, J., Larson, S., Amols, H., Fuks, Z., Leibel, S., & Koutcher, J. A. (2000). Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *International Journal of Radiation Oncology* Biology* Physics, 47*(3), 551-560. doi: 10.1016/S0360-3016(00)00467-3

Mason, W., Del Maestro, R., Eisenstat, D., Forsyth, P., Fulton, D., Laperrière, N., . . . Thiessen, B. (2007). Canadian recommendations for the treatment of glioblastoma multiforme. *Current Oncology, 14*(3), 110.

Moeller, B. J., & Dewhirst, M. W. (2006). HIF-1 and tumour radiosensitivity. *Br J Cancer, 95*(1), 1-5. doi: 10.1038/sj.bjc.6603201

Munoz, M. I., Mollo, V., Barcellini, F., & Nascimento, A. (2011). *Design of a safe computer-supported cooperative environment in radiotherapy: exploratory identification of cooperation strategies.* Paper presented at the 29th Annual European Conference on Cognitive Ergonomics.

Pantazi, S. V., Kushniruk, A., & Moehr, J. R. (2006). The usability axiom of medical information systems. *International Journal of Medical Informatics, 75*(12), 829-839. doi: 10.1016/j.ijmedinf.2006.05.039

Ramkumar, A., Varga, E., Niessen, W. J., Laprie, A., Rowland, B., & Freudenthal, A. (2014). *Comparison of heuristic evaluation and think-aloud protocol: A study in radiotherapy contouring software*. Paper presented at the Human Factors and Ergonomics conference 2014, Chicago, Illinois, USA.

Tan, H., Chen, L., Guan, Y., & Lin, X. (2011). Comparison of MRI, F-18 FDG, and 11C-choline PET/CT for their potentials in differentiating brain tumor recurrence from brain tumor necrosis following radiotherapy. *Clinical nuclear medicine, 36*(11), 978-981. doi: 10.1097/RLU.0b013e31822f68a6

Teixeira, L., Ferreira, C., & Santos, B. S. (2012). User-centered requirements engineering in health information systems: A study in the hemophilia field. *Computer methods and programs in biomedicine, 106*(3), 160-174. doi: 10.1016/j.cmpb.2010.10.007

VASARI Research Project. (2013, 28 February 2013). from https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project

Vicente, K. (2010). *The human factor: revolutionizing the way we live with technology*: Random House LLC.

Vicente, K. J. (2002). Ecological Interface Design: Progress and Challenges. *Human Factors: The Journal of the*

Human Factors and Ergonomics Society, 44(1), 62-78. doi: 10.1518/0018720024494829

Weltens, C., Menten, J., Feron, M., Bellon, E., Demaerel, P., Maes, F., . . . van der Schueren, E. (2001). Interobserver variations in gross tumor volume delineation of brain tumors on computed tomography and impact of magnetic resonance imaging. *Radiotherapy and Oncology, 60*(1), 49-59. doi: 10.1016/S0167-8140(01)00371-1

IN MEMORIAM OF DR.IR. ADINDA FREUDENTHAL

Adinda was born in Utrecht on 29 April 1963. After completing her studies in the Faculty of Industrial Design Engineering at Technical University of Delft, Adinda spent three years working as a project manager for the architects firm Cie. In 1992, she returned to TU Delft to work as a PhD student. In 1999, Adinda was awarded her PhD on the subject of “The design of home appliances for young and old consumers”.

After being awarded her PhD, she continued working in the Faculty of Industrial Design Engineering as an assistant professor. Her research focused on increasing the user-friendliness of equipment used in healthcare. From 2011, Adinda worked as an associate professor and she had become specialized in the area of “Intelligent healthcare: Design of ICT-involved medical socio-technical systems”. During her career, she taught on numerous design courses, including: “Telematics products and service design”.

Her commitment to research enabled her to attract some major projects, including “ARIS*ER” (EU FP6), “The intervention cockpit” (STW) and “SUMMER” (EU FP7). She provided expert leadership to these projects, and successfully supported the research with the help of PhD students and postdocs.

Adinda was an extraordinarily committed and valued colleague who will be greatly missed.