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Towards fast human-centred contouring workflows for adaptive external beam radiotherapy

Nicolas F. Chaves-de-Plaza^{1,4}, Prerak Mody^{2,4}, Klaus Hildebrandt¹,
Marius Staring², Eleftheria Astreinidou², Mischa de Ridder³,
Huib de Ridder¹, & René van Egmond¹
Delft University of Technology, ²Leiden University Medical Center, ³University
Medical Center Utrecht, ⁴HollandPTC Delft, The Netherlands

Abstract

Delineation of tumours and organs-at-risk permits detecting and correcting changes in the patients' anatomy throughout the treatment, making it a core step of adaptive external beam radiotherapy. Although auto-contouring technologies have sped up this process, the time needed to perform the quality assessment of the generated contours remains a bottleneck, taking clinicians between several minutes and an hour to complete. The authors of this article conducted several interviews and an observational study at two treatment centres in the Netherlands to identify challenges and opportunities for speeding up the delineation process in adaptive therapies. The study revealed three contextual variables that influence contouring performance: usable additional information, applicable domain-specific knowledge, and available editing capabilities in contouring software. In practice, clinicians leverage these variables to accelerate contouring in two ways. First, they use domain-specific knowledge and relevant clinical features such as the proximity of the organs-at-risk to the tumour to enable targeted inspection of the delineation. Second, clinicians modulate editing precision depending on the effect they anticipate the edit will have on the patient outcome. By implementing these acceleration strategies in guidelines and contouring tools, developers and workflow builders could increase contouring efficiency and consistency without affecting the patient outcome.

Introduction

External Beam Radiotherapy (EBRT) is the most common form of RT and has become one of humanity's main tools against cancer, together with surgery and systemic treatment. In EBRT, ionizing radiation is directed at the patient's tumour to destroy the malignant cells. Over the last decades, significant technological improvements have been made in treatment planning and delivery, which increased the precision of EBRT. For instance, proton beam therapy (PT) can harness the ability of protons to deposit all their energy at a specific spot (Newhauser & Zhang, 2015; Wilson, 1946). This capability permits PT more precisely shape the radiation dose to the tumor, minimizing the dose to the surrounding healthy tissue and reducing side

In D. de Waard, S.H. Fairclough, K.A. Brookhuis, D. Manzey, L. Onnasch, A. Naumann, R. Wiczorek, F. Di Nocera, S. Röttger, and A. Toffetti (Eds.) (2022). Proceedings of the Human Factors and Ergonomics Society Europe Chapter 2022 Annual Conference. ISSN 2333-4959 (online). Available from http://hfeseurope.org

effects (Langendijk et al., 2013; Lundkvist et al., 2005; Simone et al., 2011; Thomas & Timmermann, 2020).

Harnessing the precision increase of dose delivery technology requires adapting the patient's treatment plan to the anatomy of the day. Figure 1 presents the general workflow of this treatment paradigm known as adaptive EBRT. Adaptive EBRT imposes severe time constraints on online treatment planning processes (orange boxes in Figure 1) because longer within fraction times can lead to new anatomical changes, offsetting the value of the adaptation. Also, an increase in the footprint of treatment planning processes would reduce patient throughput, compromising the viability of adaptive EBRT.

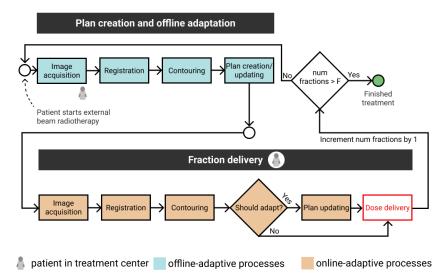


Figure 1. Schematic of external beam radiotherapy (EBRT) dose delivery pipeline. Each box corresponds to one process, and the diamonds to decisions in the workflow. The goal is to deliver the prescribed dose to the patient (red box) in F fractions spread over several days. Adaptive strategies help mitigate dose deviations due to changes in the patient's anatomy during the treatment. Adaptation can be online within a fraction (orange boxes) or offline between fractions (blue boxes).

The present study investigates the challenges that the contouring process poses to the implementation of adaptive EBRT. Despite the availability of auto-contouring technologies, contouring remains human-centred because clinicians need to perform an extensive quality assessment of the generated delineations to ensure that they do not contain inaccuracies (Cardenas et al., 2019; Nikolov et al., 2020; van Dijk et al., 2020; Vandewinckele et al., 2020). Therefore, to reduce the footprint of the contouring process, it is necessary to understand human factors that impact its duration.

This study extends prior works in two ways. First, it focuses on the time dimension of contouring performance, uncovering factors that influence it. Traditionally, researchers have directed their attention to analysing the effect of different image modalities, guidelines, contouring software, and experience on output-based performance metrics like accuracy and inter-observer contouring variability

(Bekelman et al., 2009; Brouwer et al., 2014; Steenbakkers et al., 2005, 2006; Vinod et al., 2016). This focus makes sense considering the influence that these metrics have on patient safety (Karsh et al., 2006; Njeh, 2008). Nevertheless, factors that affect time can also impact accuracy, motivating the need to study them. On the one hand, other things equal, accuracy degrades in time-constrained scenarios (Chignell et al., 2014; Pew, 1969). On the other, if clinicians perform demanding tasks for extended periods, they can become fatigued and lose situation awareness, which will also impact accuracy (Endsley, 2021; Evans et al., 2019).

Second, this work studies the contouring process in its clinical context. Prior works have investigated the effect of input devices and user interfaces on contouring time using experiments in highly controlled environments (Multi-Institutional Target Delineation in Oncology Group, 2011; Ramkumar, 2017; Steenbakkers et al., 2005). These studies' findings hold for the general contouring case. Nevertheless, this needs not to be the case in the time-constrained phase of adaptive EBRT (orange boxes in Figure 1). This study follows a qualitative context-driven approach to uncover factors that affect contouring performance in adaptive EBRT and discusses potential context-aware strategies to mitigate them. Adopting an ecological approach to researching human factors that affect contouring performance can help designing representative experiments and evaluations for contouring in time-critical scenarios (Flach et al., 2018). Furthermore, the findings from this study represent the initial step of methodologies like Ecological Interface Design, which aims to develop systems that promote adaptive performance (Vicente, 2002).

To summarize, the present study investigates factors that affect the duration of the contouring process and discusses potential mitigation strategies. It complements and extends prior studies that analysed human factors of contouring performance (Aselmaa et al., 2014; Ramkumar et al., 2017), providing an updated account of the process workflow in the time-critical context of adaptive EBRT. Finally, the present study contributes to the state-of-the-art of clinical contouring workflows in adaptive EBRT in two ways:

- 1. It reports the results of an observational study in two cancer treatment centres in the Netherlands. The study of the Contouring Workflow provided a situated account of the current contouring workflows in the context of adaptive EBRT, together with factors that can affect its performance.
- 2. It discusses acceleration strategies based on the context of adaptive EBRT that tool developers and clinicians can leverage to adapt the contouring workflow to time-constrained scenarios.

The Contouring Activity

An exploratory literature review was performed to establish baseline knowledge about the contouring activity and its role in adaptive therapies. The query used for the search (Scopus, PubMed, and Google Scholar) included the keywords: adaptive, adaptation, proton therapy, radiotherapy, contouring, automatic, semi-automatic, workflow, and head-and-neck. The latter term was relevant since the study's participants (next section) were specialists in this region. The search yielded around 50 articles with publishing years ranging between 2008 and 2021.

As Figure 2 depicts, the main inputs of the contouring activity are 3D images (stacks of hundreds of 2D images) that describe the patient anatomy. Among these, there is an image to contour, usually a Computerized Tomography (CT), and supporting information such as previous contours of the patient and other image modalities such as Magnetic Resonance Imaging (MRI) and Positron Emission Technology CT (PET-CT). Using available information, contouring consists of drawing the boundaries of anatomical structures relevant to the patient's cancer in the image to contour. The two main anatomical groups are the target volumes (TVs), which correspond to areas affected by tumoral cells, and the organs at risk (OARs), which correspond to healthy tissue.

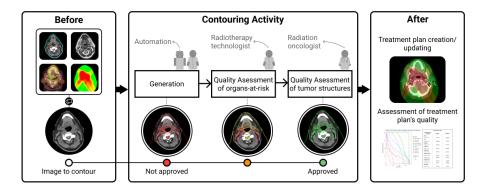


Figure 2. Components of the contouring activity. The inputs (left) are the image to contour and, optionally, other three-dimensional datasets like MRI and PET-CT scans and dose distribution volumes. The contouring activity has two main processes that several actors perform: generation of contours and its quality assessment. After approving the contours, clinicians can use them to create/update the patient's treatment plan and assess its quality.

As the right panel of Figure 2 indicates, the goal of the contouring activity is to produce contours suitable for creating or updating the patient treatment plan and assessing its quality. Several actors participate in this workflow in the clinic, distributing contouring tasks based on the anatomical structures' groups. In general, radiotherapy technologists (RTTs) start by delineating the OARs. After this, the radiation oncologists (ROs), who are directly responsible for the patient's outcome, assess the quality of the OARs contours and draw the boundaries of the TVs, the structures with the highest priority. The study described in the next section was designed based on this understanding of the contouring activity.

Study of the Contouring Workflow

A study of the contouring workflow was conducted to identify characteristics of adaptive EBRT affecting contouring performance and to identify context-dependent strategies that tool developers can leverage to improve it. The following subsections detail the study's design and describe the methodology used for analysing the resulting data.

Study design

Participants

Two radiation oncologists (RO) and two radiotherapy technologists (RTT) from two cancer treatment centres in the Netherlands specializing in the head-and-neck area joined the study. Table 1 summarizes the participants' information. One of the institutes, the Leiden University Medical Center (LUMC), offers photon-based volumetric modulated arc therapy (VMAT) treatments. The second, the Holland Proton Therapy Centre (HollandPTC), offers proton therapy (PT). Despite the differences in dose delivery technology, both institutions have a similar workflow, performing offline adaptations. The latter means that the patient's treatment plan is updated sparsely during treatment (entails re-executing blue boxes in Figure 1). The Institutional Review Board at the Delft University of Technology approved this research. Each participant provided informed consent to be part of the study.

Procedure

The study had three sessions. The first one, a one-hour-long semi structured interview, permitted establishing rapport with the participants and validated the initial understanding of the EBRT workflow. In the second and third sessions, the participants performed their contouring duties while being recorded. As Table 1 shows, these meetings lasted between one and two hours, depending on the participants' time. In the second session, clinicians performed initial contouring. The third focused on adaptive contouring, where clinicians perform a quality assessment of automatically generated contours. Given the limited clinicians' time to participate, they contoured a subset of anatomical including the tumours and organs close to them that could affect the patient outcome.

Table 1. Participants of the qualitative sessions. Two radiation oncologists (RO) and two radiotherapy technologists (RTT) from two institutions in the Netherlands participated. In some cases, due to their tight schedules, they could not attend all the sessions.

ID	Institution	Role	Session	Time (hours)
P1	LUMC	RO	1, 2, 3	5
P2	LUMC	RTT	2, 3	2
P3	HollandPTC	RO	1, 2	3
P4	HollandPTC	RTT	1, 2, 3	5

Materials

For the observational sessions, clinicians at each centre had access to the data of two previously treated head and neck patients. Each patient file included initial treatment planning data such as CT, PET-CT, and MRI scans and daily images such as CBCT and CT, relevant for sessions 2 and 3, respectively. For session 3, starting delineations could have been generated by another clinician or automated methods like deformable or rigid registration and deep learning-based contouring. For inspecting and editing the contours, clinicians used their routine software.

Data Analysis

Table 2. The first column presents the themes that emerged during the Thematic Analysis of the transcripts of the semi-structured interviews and observational sessions of the Study of the Contouring Workflow. The second column presents the coarser codes obtained after several grouping iterations finer ones. Lastly, the third column displays, for each theme, a representative example from the transcribed data.

Theme	Codes	Example
Adaptive contouring context	Clinical workflow, standardization, physical and clinical artifacts, training, institution specific considerations, EBRT technology	"Now it takes one day to do the whole plan. So, we have to make a new calculation and it has to go into the the LINAC so it has to get another check." [P2]
Structure priority and effect of inaccuracies on patient's treatment	Anatomical knowledge, downstream effects, characteristics of different anatomical structures, clinical priorities, tumour- related considerations	"I guess if it's an inner region where for instance the cheek region here. Those are minor [edits], but if we see this region where you have the parotid gland. There it could influence dose to the OARs quite significantly. So there. Then I would say it's a major [edit]." [P1]
Dealing with uncertain regions in the image-to- contour	Anatomical knowledge, image modalities, papers and guidelines, information required for certainty	"With the nasopharyngeal cancers, then I will take an MRI and then I will draw on the MRI. So, then I know exactly where the brainstem is." [P4]
Editing capabilities of contouring software	Characteristics of contouring software, experience with the tools, use of automation	"It seems to me that it's a model based one [automatically generated contour] because the model based one always has trouble here at the head of the mandible at the joint." [P3]
Distribution of labour and clinicians experience	Experience with the contouring task, collaboration, task distribution, protocols	"When an RTT does it [a contour]? Sometimes it's very nice and when a not so experienced RTT does it it's not a very good delineation and then it costs me either a lot of time to adjust every slice or I just start again and that's most of the time." [P3]

The recordings of the three sessions were transcribed and analysed using Thematic Analysis (Braun & Clarke, 2006). The coding process was bottom-up, first labelling patterns in the transcripts and then grouping the resulting fine-grained codes into coarser ones based on their similarity. Table 2 displays the underlying coarser codes, the resulting themes, and sample data excerpts. The screen recordings of sessions 2 and 3 were also relevant as they showcased the way clinicians interact with the user

interface during the contouring process. The interactions were mapped onto a timeline like the one that Figure 4 depicts. For the y-axis, the authors drew inspiration from the literature on contouring tasks (Aselmaa et al., 2017) but grouped them into four categories to simplify the coding process and the analysis. These are direct and indirect manipulation, navigation, and non-contouring interactions.

Initial Contouring

Results

Initial contouring (IC) occurs when executing the plan creation and offline adaptation process in Figure 1 for the first time. At LUMC and HollandPTC, initial contouring (IC) takes two to six hours for head-and-neck (HN) cancers, requiring delineating more than twenty structures. The following paragraphs group the observations about the IC workflow into three characteristics, finishing with a discussion on how these can affect contouring performance.

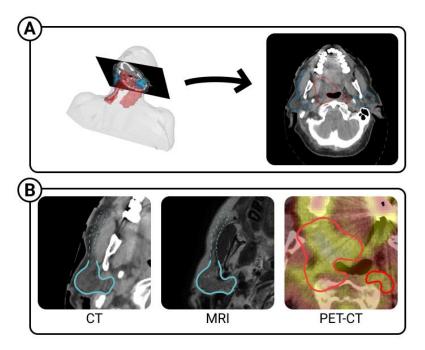


Figure 3. Available information available at contouring. The central input is the image to contour which, as panel A depicts, is a three-dimensional image made from several 2D slices. Other three-dimensional images available at the surveyed centres are magnetic resonance imaging (MRI) and positron imaging technology CT (PET-CT) scans. As panel B shows, MRI helps differentiate soft tissue, and PET-CT aids in detecting and delineating tumours.

Usable Additional Information

At IC, no pre-existing contours of the patients exist, given that this process occurs after they have started treatment. Instead, clinicians use information from multiple image modalities acquired beforehand. The main image modality in radiotherapy, CT,

usually does not provide enough boundary information when the contrast between adjacent tissues is not enough or when there is noise or artifacts in the image acquisition process. In these cases, clinicians rely on Magnetic Resonance Imaging (MRI) and Positron Emission Technology-CT (PET-CT) scans, acquired for most patients at HollandPTC and LUMC. As Figure 3 shows, MRI helps differentiate soft tissue structures: "MRI makes it easier for us to delineate the parotid glands because you can see them very good at an MRI.". For PET-CT, this modality permits clinicians to locate tumours and estimate their boundaries with higher precision: "We actually scan all of our head and neck patients [with PET-CT] because it makes our delineations so much accurate, so that is now standard." [P1].

In practice, clinicians align additional images to the CT before using them for contouring. This process, known as image registration, can take several minutes per image pair and requires the clinician's intervention to verify the alignment's quality. Registering the images allows clinicians to scroll through them in parallel using the contouring software, enabling direct comparison of the structures in both scans.

Applicable Domain-Specific Knowledge

In some cases, the information in the images is not enough. At IC, this happens when MRI and PET-CT scans are not available and moreover there are no pre-existing contours of the patients (they just started the treatment). In these cases, clinicians rely on domain-specific knowledge they access in two ways. First, they leverage guidelines (Brouwer et al., 2015) and atlases that describe and indicate what the contours should look like, respectively. Second, they draw on their experience. Experienced clinicians know what areas can be challenging to delineate given the available data. They use this domain-specific anatomical knowledge to direct their attention and estimate contours over unclear image boundaries. An example of this dynamic occurs when the radiation oncologists (ROs) review the delineations created by the radiotherapy technologists (RTTs): "We [ROs] think that it [delineating the swallowing muscles] is too hard for RTTs, need quite a bit of anatomical knowledge to know where they are exactly. And in this case, this patient doesn't have a very big tumour in the throat, but most of the time patients have quite a big tumour here. And you can't see the swallowing muscles that good. So, then you need to know exactly where they run from to delineate them." [P1].

Editing Capabilities of Contouring Software

In practice, at IC, clinicians create the contours from scratch. As the timeline on the top section of Figure 4 depicts, this entails starting with an empty delineation and gradually building the contours through a series of interactions. At the surveyed institutions, clinicians favoured a semi-automatic workflow, which consisted of two phases. First, they generated initial contours using the between-slice interpolation tool. This tool requires clinicians to manually delineate a subset of the slices spanning the structure, after which the rest of the structure's contours will be interpolated (this autocompletion corresponds to the indirect editing interaction around the second eighty in Figure 4). Finally, revert to the manual brush tool to correct inaccuracies. As the timeline shows, the generation of contours takes more time than the refinement, and clinicians spend most of the time directly editing the delineations with the brush.

Initial contouring (~142 seconds with manual brush + slice interpolation)

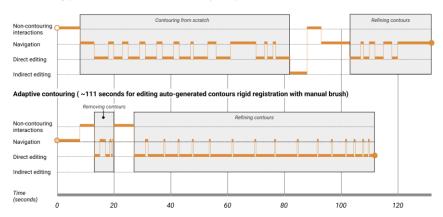


Figure 4. Interaction timelines for initial and adaptive contouring. In both cases, a radiotherapy technologist from LUMC (P2 in Table 1), delineated the right submandibular gland of a head and neck cancer patient. The x-axis encodes time, and the y-axis differentiates the principal interaction categories. Non-contouring interactions correspond to changes in the interface that do not affect the contours, like changing the layout or visualization parameters. Navigation refers to changing the current slice of the image to contour. Finally, direct and indirect manipulations entail altering the delineations in the 2D slice or through a button in the menu, respectively. Note how initial contouring starts from scratch (empty circle) while adaptive contouring starts with pre-generated delineations (partially filled circle).

Discussion

Clinicians use contours produced at IC to create the patient's treatment plan. Therefore, they seek maximal accuracy, often at the expense of longer task durations. The three characteristics of the IC context described before affect contouring time in several ways. First, extra image modalities reduce the task difficulty, which can result in reduced dwelling times to determine where the contour should go. Nevertheless, additional images need to be registered to the main one, a time-consuming process that could offset the performance benefits gains that the process offers. Second, domain-specific knowledge can reduce the extent of the contouring task by letting clinicians direct their attention to where it is needed. Yet, following the accuracy directive, they still must go through the whole volume to ensure no inaccuracy remains. Finally, the semi-automatic between slice interpolation tool spares clinicians from needing to edit several slices but still requires significant manual effort to initialize the method.

Adaptive Contouring

Results

LUMC and HollandPTC implement an offline-adaptive dose delivery pipeline, which entails updating the treatment plan several times during treatment by repeating the plan creation and offline adaptation process between fractions. Adaptive contouring (AC) occurs in this setting and differs from initial contouring (IC) in that the time is

more critical and the resources scarcer. At the surveyed institutions, AC takes one to two hours for head and neck cancer patients. Like the previous section, the following paragraphs detail the AC context and discuss how it affects the process' performance.

Usable Additional Information

In contrast with IC, at AC, no extra images of the patient are acquired. Therefore, clinicians have access to the image to contour, a CT at LUMC and HollandPTC, the images acquired for IC, and the approved IC contours. In practice, clinicians only use the latter and do so in two ways. First, because IC contours document all the clinical decisions made for the current patient, they use them as a patient-specific atlas to resolve complex contouring tasks. Regarding having an atlas for contouring, P4 mentioned that "it's always nice to have it [the atlas] like a verification. Because the brainstem isn't that difficult, but like if you have the swallowing muscles or something, that's really something. If you have the atlas side by side, it really can come in handy." [P4] Second, clinicians use approved IC contours to create an initial segmentation. For this, they align, or register, the IC and AC images and then "propagate" the contours from the former to the latter.

Applicable Domain-Specific Knowledge

In addition to general anatomical knowledge, at AC, clinicians use knowledge about dosimetry and the patient tumour to structure and guide the contouring process. On the one hand, it can help them direct their attention to critical areas. On the other, it lets them modulate the contouring based on the structure's relevance to the patient's treatment plan. For instance, P2 mentioned that while some contours require maximal attention and precision: "... with this type of organs, as with all the nervical organs, as in optical nerves and brain stem and spinal cord, when it's critical, so when the PTV is nearby, then it's very important that we draw this very precise." Others accept rougher contours as they will not significantly impact the patient's outcome: "this submandibular gland, it gets too much dose, so it won't work. After irradiation, this one is gone. So, at that point, we can decide to delineate, but it isn't, it's OK if it isn't quite perfect."

Editing Capabilities of Contouring Software

As mentioned before, clinicians do not start delineating from scratch at AC. Instead, they generate a starting point by propagating the contours from the initial scan to the current one. Therefore, the goal at AC is to perform a quality assessment (QA) of these delineations. The timeline in the bottom section of Figure 4 exemplifies the series of interactions that clinicians usually perform during the QA process. In the timeline, it is possible to see how starting from partial delineations, they reach the final ones after a series of relatively long direct editing interactions interleaved with brief navigation operation ones. Between slice interpolation, the tool clinicians use for contouring from scratch does not work for contour refinement. Therefore, for extensive errors across multiple slices like the one Figure 5 depicts, clinicians face two options. Either manually fix the contour on every slide or delete the delineation and re-do it from scratch using between-slice interpolation.

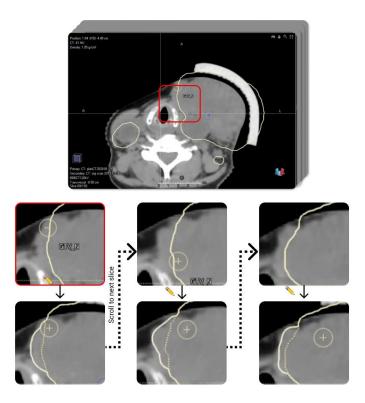


Figure 2. Editing faulty delineations often entails redundant interactions. The top image presents an inaccurate auto-generated contour of a tumoral structure. As can be observed, the internal side of the contour fails to include the whole structure, which causes an error that spans three slices. The images below present the sequence of steps that P1 followed to amend the inaccuracy.

Discussion

While clinicians use IC contours for creating the treatment plan, they use AC contours to update the plan. For this reason, at this stage, their primary concern therefore seemed to be to faithfully translate IC contours to the current patient anatomy. The identified contextual characteristics affect AC performance in several ways. First, having information about the role that each structure plays in the patient's treatment helps direct clinicians' attention to delineations that can affect the patient outcome. A potential pitfall of the current prioritization approach is that it is purely heuristic and based on clinicians' experience instead of available information such as the planned dose. Second, by using IC-approved contours, clinicians can reduce the time for analysing and editing complex or large regions by propagating them via registration. Nevertheless, same as with other image modalities at IC, the time it takes to perform the registration might offset the time gains. Finally, although contouring is overall faster at AC due to the contours being pre-generated, there is no tool to efficiently perform QA, requiring clinicians to invest significant manual effort.

Discussion

The Study of the Contouring Workflow provided an understanding of several characteristics that affect contouring duration in adaptive EBRT. This section takes these observations as input and lays down several ways of accelerating the adaptive contouring activity, which is increasingly time-pressured due to clinics implementing more responsive adaptative workflows. The discussion differentiates between the inspection, navigation, and editing tasks, which account for most of the delineation time. Figure 6 summarizes the study's findings and the resulting context-dependent acceleration strategies.

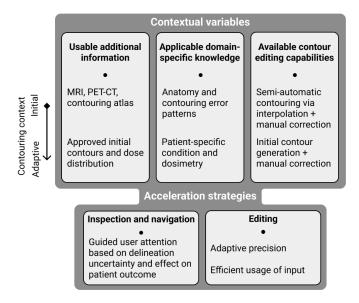


Figure 3. Schematic of the approach that the present study followed. First, it identified three variables that influence contouring performance and described their roles in the initial and adaptive contouring contexts. These variables were then mapped to strategies for accelerating the inspection, navigation, and editing tasks.

Inspection and Navigation

In adaptive contouring, clinicians prioritized inspection of tumour contours because an error could result in overexposure of surrounding organs to radiation or, worse, in underexposure of the cancerous tissue (Aliotta et al., 2019). This observation suggests that patient-specific treatment-level information provides a valuable signal to define the contouring priority of anatomical structures. Heuristics based on dose information allow clinicians to decide faster (Marewski & Gigerenzer, 2012). Nevertheless, problems like cognitive bias, loss of situation awareness, or varying levels of experience can introduce inconsistencies in a heuristic-based contouring process, which could risk patient safety (Graber et al., 2002; Tversky & Kahneman, 1974). Protocols and checklists could be implemented to enable effective heuristics usage while mitigating their pitfalls (Chan et al., 2012; Chera et al., 2012; Marks et al., 2011). These could be based on metrics like Normal Tissue Complication Probability

(NTCP) that have been shown to affect the patient outcome (Brouwer et al., 2014). Figure 7 presents an example of prioritization based on the local characteristics of the dose distribution. As can be observed, while a potential inaccuracy in the tumour delineation has a high priority, errors in the parotid glands are less urgent due to their lower impact on the patient's treatment.

Before prioritizing errors, clinicians need to detect them. Several methods have been proposed in the literature for assisting this task. They vary in the information and the mechanism used to perform the search. As for the former, it is possible to compute shape (Heimann & Meinzer, 2009; Hermann & Klein, 2015) and image or appearancerelated (Gao et al., 2010) characteristics of the contours, e.g. the surface area or the intensity histogram, respectively. Another possible indicator of the contours' quality is their uncertainty or variability, which can come from historical patient data (Chu et al., 2013), the auto-contouring algorithm (LaBonte et al., 2020; Mody et al., 2021), or directly from the image-to-contour (Top et al., 2011). After gathering all these sources of information, available techniques identify potential errors in two ways. Firstly, by letting a classifier automatically find data-based rules for separating inaccurate from the accurate regions (Altman et al., 2015; Chen et al., 2015; Hui et al., 2018; Kalpathy-Cramer & Fuller, 2010; McIntosh et al., 2013; Rhee et al., 2019; Sandfort et al., 2021). Secondly, they delegate the search task to the users, presenting them with the traditional two-dimensional image and contour slices together with informative overlays such as uncertainty iso-lines (Al-Taie et al., 2014; Prassni et al., 2010) and contour box plots (Whitaker et al., 2013). These two-dimensional visualizations have been augmented by adding three-dimensional views (Lundström et al., 2007; Raidou et al., 2016) and letting the user interact with the data by filtering and sorting mechanisms (Furmanová et al., 2021; Saad et al., 2010).

Two challenges that existing error detection tools face are maintaining users' trust in the system and lowering the cognitive load they impose. As to the former, a system failing to spot inaccuracies that affect the patient's treatment (false negatives) would erode the users' trust (Asan et al., 2020; White et al., 2011). This might explain the limited adoption of automatic error detection systems in clinical practice. Regarding cognitive load, abrupt context changes when guiding clinicians' attention to different parts of the 3D image can build up fatigue, potentially leading to errors like classifying a true positive the system suggested as a false positive (Allnutt, 1987; Persson et al., 2019). Visualization methods like 3D views complementing attention guidance mechanisms could help mitigate this issue.

Editing

Currently, clinicians use mostly manual tools when fixing an inaccuracy. For errors that occupy a large portion of the volume, like the example in Figure 5, this often means that the user will perform similar edits across slices. Existing semi-automatic interactive contouring techniques mitigate this issue by extrapolating rough feedback provided by the clinician. Their general workflow consists of two steps. First, the clinician provides a rough indication of the change to be made or the area to update via coarse inputs such as scribbles, points, or a bounding box. Based on this input, the algorithm proceeds to update the segmentation. Traditionally Markov Random Fieldbased algorithms are being used (Kato & Zerubia, 2012; Rother et al., 2004). Recently,

deep learning-based implementations have appeared that offer more sophisticated suggestions based on the clinician's input (Dai et al., 2015; Lin et al., 2016; Maninis et al., 2018).

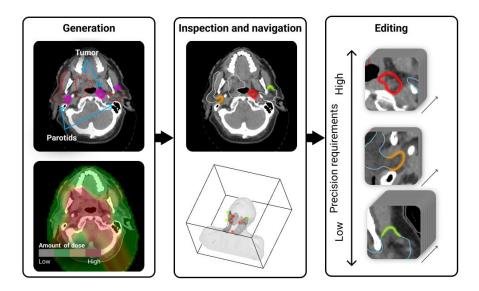


Figure 4. Components for accelerating the inspection, navigation, and editing tasks. The first step (leftmost column) is to generate the contours and gather extra information like delineation variability and the dose distribution. Based on these sources, potential errors can be flagged and categorized depending on their effect on the patient outcome. In the example, an error in the tumour's delineations was flagged as high priority (red) because it can significantly change the treatment plan. As for the parotid glands, the orange inaccuracy is in a region where the dose distribution varies more quickly than in the case of the green one. Therefore, subsequent processes (like treatment plan updating) that rely on the orange contours could be more sensitive to changes in these contours.

The adoption of these semi-automatic interactive editing tools in the clinic remains challenging. Based on discussions with clinicians, the reason for their resistance to these interactive editing tools seems to be that they perceive scribbles as a blunt tool for communicating to the algorithm what they want. Therefore, more research is needed to determine which type of input mechanism the clinicians prefer and how the algorithm should respond (Amrehn et al., 2016; Hebbalaguppe et al., 2013). For instance, do they prefer coarse inputs like scribbles? Or would they be more comfortable with high precision inputs such as selecting a contour from an ensemble of candidates (Ferstl et al., 2016)? With editing being the most time-consuming QA operation, obtaining a synergy between humans and AI is paramount.

Limitations and Future Work

A limitation of this work is the reduced number of treatment centres and clinicians surveyed in the study, which might have led to weighting heavily on custom institutional practices and personal preferences. As a promising solution, questionnaires like the one reported in (Bertholet et al., 2020) could be prepared to

validate the conclusions with a larger pool of participants. Another limitation is the qualitative nature of the timelines used to illustrate the dynamics between the clinicians and the contouring software. In further studies, we plan to use keystroke logging software to include more fine-grained actions and more accurate timings. The latter would be especially valuable for comparing different segmentation tools.

In terms of future work, we will translate the findings of this study into a practical human-centred contouring protocol that clinicians can adapt to their institution-specific adaptive EBRT capabilities and constraints. In addition to the clinician-level considerations that the present article considered, such protocol will also account for team dynamics, which also emerged as a performance factor in the surveyed institutions.

Conclusion

This study characterized the contouring workflows in adaptive EBRT. An observational study at two treatment centres in the Netherlands revealed several context-dependent characteristics that influence delineation performance. Based on these observations, strategies for accelerating inspection, navigation, and editing tasks were discussed. By applying these when developing and commissioning tools, tool builders and clinicians can decrease the delineation time and thus increase the suitability of this process for time-critical therapies like online-adaptive EBRT.

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References

- Aliotta, E., Nourzadeh, H., & Siebers, J. (2019). Quantifying the dosimetric impact of organ-at-risk delineation variability in head and neck radiation therapy in the context of patient setup uncertainty. *Physics in Medicine & Biology*, 64(13), 135020. https://doi.org/10.1088/1361-6560/ab205c
- Allnutt, M. F. (1987). Human factors in accidents. *British Journal of Anaesthesia*, *59*, 856–864. https://doi.org/10.1093/bja/59.7.856
- Al-Taie, A., Hahn, H. K., & Linsen, L. (2014). Uncertainty estimation and visualization in probabilistic segmentation. *Computers & Graphics*, *39*, 48–59. https://doi.org/10.1016/j.cag.2013.10.012
- Altman, M. B., Kavanaugh, J. A., Wooten, H. O., Green, O. L., DeWees, T. A., Gay, H., Thorstad, W. L., Li, H., & Mutic, S. (2015). A framework for automated contour quality assurance in radiation therapy including adaptive techniques. *Physics in Medicine and Biology*, 60, 5199–5209. https://doi.org/10.1088/0031-9155/60/13/5199

- Amrehn, M., Glasbrenner, J., Steidl, S., & Maier, A. (2016). Comparative Evaluation of Interactive Segmentation Approaches. In T. Tolxdorff, T. M. Deserno, H. Handels, & H.-P. Meinzer (Eds.), *Bildverarbeitung für die Medizin 2016* (pp. 68–73). Springer. https://doi.org/10.1007/978-3-662-49465-3_14
- Asan, O., Bayrak, A. E., & Choudhury, A. (2020). Artificial Intelligence and Human Trust in Healthcare: Focus on Clinicians. *Journal of Medical Internet Research*, 22(6), e15154. https://doi.org/10.2196/15154
- Aselmaa, A., Goossens, R., Rowland, B., Laprie, A., Song, W., & Freudenthal, A. (2014, July 19). Medical Factors of Brain Tumor Delineation in Radiotherapy for Software Design. Proceedings of the 5th International Conference on Applied Human Factors and Ergonomics.
- Aselmaa, A., van Herk, M., Laprie, A., Nestle, U., Götz, I., Wiedenmann, N., Schimek-Jasch, T., Picaud, F., Syrykh, C., Cagetti, L. V., Jolnerovski, M., Song, Y., & Goossens, R. H. M. (2017). Using a contextualized sensemaking model for interaction design: A case study of tumor contouring. *Journal of Biomedical Informatics*, 65, 145–158. https://doi.org/10.1016/j.jbi.2016.12.001
- Bekelman, J. E., Wolden, S., & Lee, N. (2009). Head-and-Neck Target Delineation Among Radiation Oncology Residents After a Teaching Intervention: A Prospective, Blinded Pilot Study. *International Journal of Radiation Oncology*Biology*Physics*, 73, 416–423. https://doi.org/10.1016/j.ijrobp.2008.04.028
- Bertholet, J., Anastasi, G., Noble, D., Bel, A., van Leeuwen, R., Roggen, T., Duchateau, M., Pilskog, S., Garibaldi, C., Tilly, N., García-Mollá, R., Bonaque, J., Oelfke, U., Aznar, M. C., & Heijmen, B. (2020). Patterns of practice for adaptive and real-time radiation therapy (POP-ART RT) part II: Offline and online plan adaption for interfractional changes. *Radiotherapy and Oncology*, 153, 88–96. https://doi.org/10.1016/j.radonc.2020.06.017
- Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology*, *3*, 77–101. https://doi.org/10.1191/1478088706qp063oa
- Brouwer, C.L., Steenbakkers, R.J.H.M., Bourhis, J., Budach, W., Grau, C., Grégoire, V., van Herk, M., Lee, A., Maingon, P., Nutting, C., O'Sullivan, B., Porceddu, S.V., Rosenthal, D.I., Sijtsema, N.M., & Langendijk, J.A. (2015). CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, 117, 83–90. https://doi.org/10.1016/j.radonc.2015.07.041
- Brouwer, C.L., Steenbakkers, R.J.H.M., Gort, E., Kamphuis, M.E., van der Laan, H.P., van't Veld, A.A., Sijtsema, N.M., & Langendijk, J.A. (2014). Differences in delineation guidelines for head and neck cancer result in inconsistent reported dose and corresponding NTCP. *Radiotherapy and Oncology*, 111, 148–152. https://doi.org/10.1016/j.radonc.2014.01.019
- Cardenas, C.E., Yang, J., Anderson, B.M., Court, L.E., & Brock, K.B. (2019). Advances in Auto-Segmentation. *Seminars in Radiation Oncology*, 29, 185–197. https://doi.org/10.1016/j.semradonc.2019.02.001

- Chan, A.J., Islam, M.K., Rosewall, T., Jaffray, D.A., Easty, A.C., & Cafazzo, J.A. (2012). Applying usability heuristics to radiotherapy systems. *Radiotherapy and Oncology*, 102, 142–147. https://doi.org/10.1016/j.radonc.2011.05.077
- Chen, H., Zhang, S., Chen, W., Mei, H., Zhang, J., Mercer, A., Liang, R., & Qu, H. (2015). Uncertainty-Aware Multidimensional Ensemble Data Visualization and Exploration. *IEEE Transactions on Visualization and Computer Graphics*, 21, 1072–1086. https://doi.org/10.1109/TVCG.2015.2410278
- Chera, B.S., Jackson, M., Mazur, L. M., Adams, R., Chang, S., Deschesne, K., Cullip, T., & Marks, L.B. (2012). Improving Quality of Patient Care by Improving Daily Practice in Radiation Oncology. *Seminars in Radiation Oncology*, 22, 77–85. https://doi.org/10.1016/j.semradonc.2011.09.002
- Chignell, M., Tong, T., Mizobuchi, S., & Walmsley, W. (2014). Combining Speed and Accuracy into a Global Measure of Performance. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 58, 1442–1446. https://doi.org/10.1177/1541931214581301
- Chu, C., Oda, M., Kitasaka, T., Misawa, K., Fujiwara, M., Hayashi, Y., Nimura, Y., Rueckert, D., & Mori, K. (2013). Multi-organ segmentation based on spatially-divided probabilistic atlas from 3D abdominal CT images. *Medical Image Computing and Computer-Assisted Intervention: MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention*, 16(Pt 2), 165–172. https://doi.org/10.1007/978-3-642-40763-5_21
- Dai, J., He, K., & Sun, J. (2015). *BoxSup: Exploiting Bounding Boxes to Supervise Convolutional Networks for Semantic Segmentation*. 1635–1643. https://openaccess.thecvf.com/content_iccv_2015/html/Dai_BoxSup_Exploiting_Bounding_ICCV_2015_paper.html
- Endsley, M.R. (2021). Situation Awareness. In *Handbook of Human Factors and Ergonomics* (pp. 434–455). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781119636113.ch17
- Evans, S.B., Cain, D., Kapur, A., Brown, D., & Pawlicki, T. (2019). Why Smart Oncology Clinicians do Dumb Things: A Review of Cognitive Bias in Radiation Oncology. *Practical Radiation Oncology*, *9*, e347–e355. https://doi.org/10.1016/j.prro.2019.03.001
- Ferstl, F., Kanzler, M., Rautenhaus, M., & Westermann, R. (2016). Visual Analysis of Spatial Variability and Global Correlations in Ensembles of Iso-Contours. *Computer Graphics Forum*, *35*(3), 221–230. https://doi.org/10.1111/cgf.12898
- Flach, J.M., Hancock, P.A., Caird, J., & Vicente, K.J. (2018). *Global Perspectives on the Ecology of Human-Machine Systems*. CRC Press.
- Furmanová, K., Muren, L. P., Casares-Magaz, O., Moiseenko, V., Einck, J. P., Pilskog, S., & Raidou, R. G. (2021). PREVIS: Predictive visual analytics of anatomical variability for radiotherapy decision support. *Computers & Graphics*, 97, 126–138. https://doi.org/10.1016/j.cag.2021.04.010
- Gao, X., Su, Y., Li, X., & Tao, D. (2010). A Review of Active Appearance Models. *IEEE Transactions on Systems, Man, and Cybernetics, Part C (Applications and Reviews)*, 40(2), 145–158. https://doi.org/10.1109/TSMCC.2009.2035631
- Graber, M., Gordon, R., & Franklin, N. (2002). Reducing Diagnostic Errors in Medicine: What's the Goal? *Academic Medicine*, 77, 981–992.

- Hebbalaguppe, R., McGuinness, K., Kuklyte, J., Healy, G., O'Connor, N., & Smeaton, A. (2013). How interaction methods affect image segmentation: User experience in the task. 2013 1st IEEE Workshop on User-Centered Computer Vision (UCCV), 19–24. https://doi.org/10.1109/UCCV.2013.6530803
- Heimann, T., & Meinzer, H.-P. (2009). Statistical shape models for 3D medical image segmentation: A review. *Medical Image Analysis*, 13(4), 543–563. https://doi.org/10.1016/j.media.2009.05.004
- Hermann, M., & Klein, R. (2015). A visual analytics perspective on shape analysis: State of the art and future prospects. *Computers & Graphics*, *53*, 63–71. https://doi.org/10.1016/j.cag.2015.08.008
- Hui, C.B., Nourzadeh, H., Watkins, W.T., Trifiletti, D.M., Alonso, C.E., Dutta, S.W., & Siebers, J.V. (2018). Quality assurance tool for organ at risk delineation in radiation therapy using a parametric statistical approach. *Medical Physics*, 45, 2089–2096. https://doi.org/10.1002/mp.12835
- Kalpathy-Cramer, J., & Fuller, C.D. (2010). Target Contour Testing/Instructional Computer Software (TaCTICS): A Novel Training and Evaluation Platform for Radiotherapy Target Delineation. AMIA Annual Symposium Proceedings, 2010, 361–365.
- Karsh, B.-T., Holden, R.J., Alper, S.J., & Or, C.K.L. (2006). A human factors engineering paradigm for patient safety: Designing to support the performance of the healthcare professional. *BMJ Quality & Safety*, 15 (suppl 1), i59–i65. https://doi.org/10.1136/qshc.2005.015974
- Kato, Z., & Zerubia, J. (2012). Markov Random Fields in Image Segmentation. Foundations and Trends® in Signal Processing, 5(1–2), 1–155. https://doi.org/10.1561/2000000035
- LaBonte, T., Martinez, C., & Roberts, S. A. (2020). We Know Where We Don't Know: 3D Bayesian CNNs for Credible Geometric Uncertainty. ArXiv:1910.10793 [Cs, Eess]. http://arxiv.org/abs/1910.10793
- Langendijk, J. A., Lambin, P., De Ruysscher, D., Widder, J., Bos, M., & Verheij, M. (2013). Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach. *Radiotherapy and Oncology*, 107, 267–273. https://doi.org/10.1016/j.radonc.2013.05.007
- Lin, D., Dai, J., Jia, J., He, K., & Sun, J. (2016). ScribbleSup: Scribble-Supervised Convolutional Networks for Semantic Segmentation. 3159–3167. https://openaccess.thecvf.com/content_cvpr_2016/html/Lin_ScribbleSup_Scribble-Supervised_Convolutional_CVPR_2016_paper.html
- Lundkvist, J., Ekman, M., Ericsson, S.R., Jönsson, B., & Glimelius, B. (2005). Proton therapy of cancer: Potential clinical advantages and cost-effectiveness. *Acta Oncologica*, 44, 850–861. https://doi.org/10.1080/02841860500341157
- Lundström, C., Ljung, P., Persson, A., & Ynnerman, A. (2007). Uncertainty Visualization in Medical Volume Rendering Using Probabilistic Animation. *IEEE Transactions on Visualization and Computer Graphics*, *13*, 1648–1655. https://doi.org/10.1109/TVCG.2007.70518
- Maninis, K.-K., Caelles, S., Pont-Tuset, J., & Van Gool, L. (2018). *Deep Extreme Cut: From Extreme Points to Object Segmentation*. 616–625. https://openaccess.thecvf.com/content_cvpr_2018/html/Maninis_Deep_Extreme_Cut_CVPR_2018_paper.html

- Marewski, J.N., & Gigerenzer, G. (2012). Heuristic decision making in medicine. *Dialogues in Clinical Neuroscience*, *14*, 77–89. https://doi.org/10.31887/DCNS.2012.14.1/jmarewski
- Marks, L.B., Jackson, M., Xie, L., Chang, S.X., Burkhardt, K.D., Mazur, L., Jones, E. L., Saponaro, P., LaChapelle, D., Baynes, D.C., & Adams, R.D. (2011). The challenge of maximizing safety in radiation oncology. *Practical Radiation Oncology*, 1, 2–14. https://doi.org/10.1016/j.prro.2010.10.001
- McIntosh, C., Svistoun, I., & Purdie, T. G. (2013). Groupwise Conditional Random Forests for Automatic Shape Classification and Contour Quality Assessment in Radiotherapy Planning. *IEEE Transactions on Medical Imaging*, *32*, 1043–1057. https://doi.org/10.1109/TMI.2013.2251421
- Mody, P., Chaves-de-Plaza, N., Hildebrandt, K., van Egmond, R., de Ridder, H., & Staring, M. (2021). Comparing Bayesian Models for Organ Contouring in Head and Neck Radiotherapy. *ArXiv:2111.01134 [Cs, Eess]*. http://arxiv.org/abs/2111.01134
- Multi-Institutional Target Delineation in Oncology Group. (2011). Human-computer interaction in radiotherapy target volume delineation: A prospective, multi-institutional comparison of user input devices. *Journal of Digital Imaging*, 24, 794–803. https://doi.org/10.1007/s10278-010-9341-2
- Newhauser, W.D., & Zhang, R. (2015). The physics of proton therapy. *Physics in Medicine and Biology*, 60(8), R155–R209. https://doi.org/10.1088/0031-9155/60/8/R155
- Nikolov, S., Blackwell, S., Zverovitch, A., Mendes, R., Livne, M., De Fauw, J., Patel, Y., Meyer, C., Askham, H., Romera-Paredes, B., Kelly, C., Karthikesalingam, A., Chu, C., Carnell, D., Boon, C., D'Souza, D., Moinuddin, S.A., Consortium, D.R., Montgomery, H., ... Ronneberger, O. (2020). Deep learning to achieve clinically applicable segmentation of head and neck anatomy for radiotherapy. *ArXiv:1809.04430 [Physics, Stat]*. http://arxiv.org/abs/1809.04430
- Njeh, C.F. (2008). Tumor delineation: The weakest link in the search for accuracy in radiotherapy. *Journal of Medical Physics*, *33*(4), 136. https://doi.org/10.4103/0971-6203.44472
- Persson, E., Barrafrem, K., Meunier, A., & Tinghög, G. (2019). The effect of decision fatigue on surgeons' clinical decision making. *Health Economics*, 28, 1194–1203. https://doi.org/10.1002/hec.3933
- Pew, R.W. (1969). The speed-accuracy operating characteristic. *Acta Psychologica*, 30, 16–26. https://doi.org/10.1016/0001-6918(69)90035-3
- Prassni, J., Ropinski, T., & Hinrichs, K. (2010). Uncertainty-Aware Guided Volume Segmentation. *IEEE Transactions on Visualization and Computer Graphics*, *16*, 1358–1365. https://doi.org/10.1109/TVCG.2010.208
- Raidou, R.G., Marcelis, F.J.J., Breeuwer, M., Gröller, E., Vilanova, A., & van de Wetering, H.M.M. (2016). Visual Analytics for the Exploration and Assessment of Segmentation Errors. The Eurographics Association. https://doi.org/10.2312/vcbm.20161287
- Ramkumar, A. (2017). *HCI in interactive segmentation: Human-computer interaction in interactive segmentation of CT images for radiotherapy*. https://repository.tudelft.nl/islandora/object/uuid%3A0f0259f1-0c33-442f-b851-86a846e736fc

- Ramkumar, A., Stappers, P. J., Niessen, W. J., Adebahr, S., Schimek-Jasch, T., Nestle, U., & Song, Y. (2017). Using GOMS and NASA-TLX to Evaluate Human–Computer Interaction Process in Interactive Segmentation. *International Journal of Human–Computer Interaction*, *33*, 123–134. https://doi.org/10.1080/10447318.2016.1220729
- Rhee, D. J., Cardenas, C.E., Elhalawani, H., McCarroll, R., Zhang, L., Yang, J., Garden, A S., Peterson, C.B., Beadle, B.M., & Court, L.E. (2019). Automatic detection of contouring errors using convolutional neural networks. *Medical Physics*, 46, 5086–5097. https://doi.org/10.1002/mp.13814
- Rother, C., Kolmogorov, V., & Blake, A. (2004). 'GrabCut': Interactive foreground extraction using iterated graph cuts. *ACM Transactions on Graphics*, *23*, 309–314. https://doi.org/10.1145/1015706.1015720
- Saad, A., Hamarneh, G., & Möller, T. (2010). Exploration and Visualization of Segmentation Uncertainty using Shape and Appearance Prior Information. *IEEE Transactions on Visualization and Computer Graphics*, *16*, 1366–1375. https://doi.org/10.1109/TVCG.2010.152
- Sandfort, V., Yan, K., Graffy, P.M., Pickhardt, P. J., & Summers, R.M. (2021). Use of Variational Autoencoders with Unsupervised Learning to Detect Incorrect Organ Segmentations at CT. *Radiology: Artificial Intelligence*, *3*(4), e200218. https://doi.org/10.1148/ryai.2021200218
- Simone, C.B., Ly, D., Dan, T. D., Ondos, J., Ning, H., Belard, A., O'Connell, J., Miller, R. W., & Simone, N. L. (2011). Comparison of intensity-modulated radiotherapy, adaptive radiotherapy, proton radiotherapy, and adaptive proton radiotherapy for treatment of locally advanced head and neck cancer. *Radiotherapy and Oncology*, 101, 376–382. https://doi.org/10.1016/j.radonc.2011.05.028
- Steenbakkers, R.J.H.M., Duppen, J.C., Fitton, I., Deurloo, K.E.I., Zijp, L.J., Comans, E.F.I., Uitterhoeve, A.L.J., Rodrigus, P.T.R., Kramer, G.W.P., Bussink, J., De Jaeger, K., Belderbos, J.S.A., Nowak, P.J.C.M., van Herk, M., & Rasch, C.R. N. (2006). Reduction of observer variation using matched CT-PET for lung cancer delineation: A three-dimensional analysis. *International Journal of Radiation Oncology*Biology*Physics*, *64*, 435–448. https://doi.org/10.1016/j.ijrobp.2005.06.034
- Steenbakkers, R.J.H.M., Duppen, J.C., Fitton, I., Deurloo, K.E.I., Zijp, L., Uitterhoeve, A.L.J., Rodrigus, P.T.R., Kramer, G.W.P., Bussink, J., Jaeger, K. D., Belderbos, J.S.A., Hart, A.A.M., Nowak, P.J.C.M., van Herk, M., & Rasch, C.R.N. (2005). Observer variation in target volume delineation of lung cancer related to radiation oncologist—computer interaction: A 'Big Brother' evaluation. *Radiotherapy and Oncology*, 77, 182–190. https://doi.org/10.1016/j.radonc.2005.09.017
- Thomas, H., & Timmermann, B. (2020). Paediatric proton therapy. *The British Journal of Radiology*, 93(1107), 20190601. https://doi.org/10.1259/bjr.20190601
- Top, A., Hamarneh, G., & Abugharbieh, R. (2011). Active Learning for Interactive 3D Image Segmentation. In G. Fichtinger, A. Martel, & T. Peters (Eds.), *Medical Image Computing and Computer-Assisted Intervention MICCAI 2011* (pp. 603–610). Springer. https://doi.org/10.1007/978-3-642-23626-6_74

- Tversky, A., & Kahneman, D. (1974). Judgment under Uncertainty: Heuristics and Biases. *Science*, *185*(4157), 1124–1131. https://doi.org/10.1126/science.185.4157.1124
- van Dijk, L.V., Van den Bosch, L., Aljabar, P., Peressutti, D., Both, S., Steenbakkers, R.J.H.M., Langendijk, J.A., Gooding, M.J., & Brouwer, C.L. (2020). Improving automatic delineation for head and neck organs at risk by Deep Learning Contouring. *Radiotherapy and Oncology*, *142*, 115–123. https://doi.org/10.1016/j.radonc.2019.09.022
- Vandewinckele, L., Claessens, M., Dinkla, A., Brouwer, C., Crijns, W., Verellen, D., & Elmpt, W. van. (2020). Overview of artificial intelligence-based applications in radiotherapy: Recommendations for implementation and quality assurance. *Radiotherapy and Oncology*, 153, 55–66. https://doi.org/10.1016/j.radonc.2020.09.008
- Vicente, K.J. (2002). Ecological Interface Design: Progress and Challenges. *Human Factors*, 44, 62–78. https://doi.org/10.1518/0018720024494829
- Vinod, S.K., Min, M., Jameson, M.G., & Holloway, L.C. (2016). A review of interventions to reduce inter-observer variability in volume delineation in radiation oncology. *Journal of Medical Imaging and Radiation Oncology*, 60, 393–406. https://doi.org/10.1111/1754-9485.12462
- Whitaker, R.T., Mirzargar, M., & Kirby, R.M. (2013). Contour Boxplots: A Method for Characterizing Uncertainty in Feature Sets from Simulation Ensembles. *IEEE Transactions on Visualization and Computer Graphics*, 19, 2713–2722. https://doi.org/10.1109/TVCG.2013.143
- White, M.P., Cohrs, J.C., & Göritz, A.S. (2011). Dynamics of Trust in Medical Decision Making: An Experimental Investigation into Underlying Processes. *Medical Decision Making*, *31*, 710–720. https://doi.org/10.1177/0272989X10394463
- Wilson, R.R. (1946). Radiological Use of Fast Protons. *Radiology*, *47*, 487–491. https://doi.org/10.1148/47.5.487