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Iterative Active Deformational Methodology for Tumor Delineation: Evaluation across Radiation Treatment Stage and Volume

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Abstract

Purpose—To introduce, implement, and assess an iterative modification to the active deformational image segmentation method as applied to cervical cancer tumors.

Materials and Methods—A comparison by Jaccard similarity (J_S) between this active deformational method and manual segmentation was performed on tumors of various sizes across pre-radiation, three weeks post-radiation, and six weeks post-radiation using a General Linear Mixed Model across 121 studies from 52 patients with stage IIB-IV cervical cancers.

Results—The deformable segmentation method produced promising levels of agreement including J_S factors of 0.71 ± 0.11 in the pre-radiation studies. The analysis illustrated a rate of improvement in J_S with increasing tumor volume that differed between the pre-radiation and six-weeks post-radiation stage ($p=0.0474$). In the large pre-radiated tumors each additional cm^3 of volume was associated with an increase or improvement in J_S of 0.0008 (95% CI: 0.0003, 0.0014). In the smaller post-radiation tumors, each additional cm^3 of volume was associated with a more robust improvement in J_S of 0.0046 (95% CI: 0.0009, 0.0082).

Conclusions—Agreement was strongly affected by tumor volume, and its performance was most impacted across volume in the later stages of radiation therapy. The deformation based segmentation method appears to demonstrate utility for delineating cervical cancer tumors, particularly in the earliest stages of radiation treatment where agreement is greatest.

Keywords

Active Deformational Model; Volumetric Changes; Cervical Cancer; Radiation Therapy; Image Segmentation; Magnetic Resonance Imaging (MRI)

INTRODUCTION

Magnetic resonance imaging (MRI) is increasingly used in oncology for cancer staging, response assessment, and radiation treatment planning. Improved tumor delineation can enhance objectivity and efficiency in clinical procedures. Delineation depends heavily on the expertise and experience of the rater regardless of subspecialty (1,2). The ability to perform high quality tumor delineation by automated image processing methods has generated considerable clinical interest (3). While automation is desirable, techniques that rely solely on automated methods have not definitively provided high quality tumor delineation, and therefore have not achieved significant clinical utility. There remains considerable motivation to improve semi-automated segmentation for delineation, including active deformable model segmentation methods.

In this study, we evaluate a new iterative semi-automated tumor segmentation method. Cervical cancer tumors were delineated using a completely manual segmentation method as well as the semi-automated approach. It was previously reported that challenges in the delineation of cervical cancer tumors include parametrial fat proximity, frequent tumor invasion to adjacent organs, edematous changes, and artifacts from organ motion (2). To determine the efficacy of the new segmentation method in the face of these confounding elements, we compare active deformational methods to manual delineation methods on a slice-by-slice basis using agreement metrics; we also assess the association of these metrics with tumor volumes and with the specific radiation treatment stage. Our goal is to evaluate agreement based on factors of radiation therapy stage and tumor volumetric size as well as their combined interaction. In this work, we employ Jaccard similarity (J_s) metrics to describe the ‘agreement’ between the manual and the newly introduced semi-automated segmentation method. Jaccard introduced this metric in 1901 (4,5). More recently, this metric was reported to be useful in the assessment of active contour methodology as applied to MR images to segment the cerebellum in pediatric patients with medulloblastomas (6).

Deformable models, which are evaluated in this work, were modified to provide an iterative process for tumor delineation. Deformable models also have shown advantages for medical images as these methods can operate on a large variety of shapes, on structures disturbed by noise, and on objects with partial occlusion on the edge (7). Additionally, these methods provide some advantages in that they employ a model-based approach. In this way, deformable models can be tailored to take a parametric form, making them intuitive to use, control, and understand. Alternatively, they can be made parameter-free permitting the algorithm to adjust to a wider set of topologies (8). Active deformation segmentation also provides a relatively fast method to identify structures as compared to other segmentation methods. For example, with active contours, curves are propagated to the boundaries of structures based on constraints using variational principles. However, active deformation methods can suffer when structures have large bending concavities or when the method is to be used in higher dimensional spaces, both conditions which may require additional tuning and adjustment.

Historically, the active deformation models known as ‘snakes’ were popularized by Kass, Witkin, and Terzopoulos (9). Nearly all deformable models have fundamental similarities to the classic snake model (10). Snakes and deformable models have been applied to many medical imaging problems for vascular, cardiac, lung, and brain structures (6,11-13), but to date their use is relatively new to tumor segmentation. Improvements now can be further described under three classes of development: parametric deformable models, geodesic snake models, and implicit snake models.

Parametric deformable models consist of curves that are dynamically conformed to internal (elastic) and external (image and constraint) forces (8,10). In geodesic snake formulations, the principal idea is to construct the evolution of a contour as a geodesic computation. A special metric is proposed (based on the gradient of the image) to let the state of minimal energy correspond to the desired boundary. Implicit snakes are defined by the geometric image structure in which the image itself is modified. Active deformable models using level set formulations can fall into the class of implicit snakes (8).

In an MR Cardiac imaging application Gupta et. al. (14) have performed other notable research using multi-step active deformation methods to describe ventricular wall segmentation. After identifying the outside heart wall, they improved the interior wall segmentation by using the information on the extraluminal boundary which is applied to the variational integration that is used to better control convergence of the interior wall.

All of the previously mentioned techniques are similar to the classic snake (9), in that a polygonal model where the vertices fall on $v(s)=[x(s) \ y(s)]^T$, and s is parameterized on the interval between 0 and 1 and x and y are 2D coordinates. The equation that describes energy minimization is as follows (9,15):

$$E_{Deform} = \int_0^1 E_{Internal}(v(s)) ds + \int_0^1 E_{External}(v(s)) ds \quad [1]$$

where $E_{internal}$ represents the energy of the curve due to bending, $E_{external}$ gives rise to image-derived forces that attract the spline to the object from bright-to-dark or from dark-to-bright. This choice is initialized by the user which is dependent on the image object.

$$E_{internal} = w_1(s) \left| \frac{dv}{ds} \right|^2 + w_2(s) \left| \frac{d^2v}{ds^2} \right|^2 \quad [2]$$

where w_1 and w_2 are weights of the snake spline that model elasticity and stiffness qualities, respectively,

$$E_{External} = \int_0^1 P(v(s)) ds \quad [3]$$

$$P(x, y) = -c |\nabla [G_\sigma \otimes I(x, y)]| \quad [4]$$

For the external energy expression, in two dimensions, $P(v(s))=P(x,y)$ represents the flow to the object based on gradient of gaussian smoothed image $I(x,y)$ where G_σ is a Gaussian function with a standard deviation of σ and c is a coefficient in which the user must provide initial estimates. The deformation spline converges to locations of strong edges in the image. After Euler Lagrange Formulation this becomes

$$-\frac{\partial}{\partial t} \left(w_1 \frac{\partial v}{\partial s} \right) + \frac{\partial^2}{\partial s^2} \left(w_2 \frac{\partial^2 v}{\partial s^2} \right) + \nabla P(v(s)) = 0 \quad [5]$$

Using the variational form above in which w_1 and w_2 shown in equation (2) are selectable parameters. This can be used to form the below equation:

$$v_i^{(s+\Delta s)} = v_i^{(t)} - \frac{\Delta s}{\gamma} (a\alpha_i^{(s)} + b\beta_i^{(s)} - \rho_i^{(s)} - f_i^{(s)}) \quad [6]$$

where α_i model tensile forces and β_i model flexural forces that originate from the internal energy terms reflecting the first and second terms of equation 6, respectively. The f_i terms represent the external forces from the third term in equation 6 and reflect contributions from external energy term as shown in equation 3 with equation 4 substitution. The final term of equation 6, f_i , models an inflationary force that is intended to improve performance of the algorithm in the presence of local minima. It is also used to set the preferred direction bright-to-dark or dark-to-bright locally along the deformable model path as described elsewhere (16). The origin of the inflationary term is attributed to Cohen (17).

MATERIALS AND METHODS

Patient Selection

To evaluate the model's performance, we assessed 121 cases from 52 patients with stage II-IVb cervical cancer whose tumors were delineated at different stages of radiation therapy. Mean age of patients in this study was 50.5 ± 15.6 years. All images were acquired after obtaining informed consent following protocol approval in accordance with our local institutional review board (IRB). For each patient, three stages were evaluated including the pre-radiation and two post-radiation phases. The protocol for the first post-radiation evaluation had a minimum interval of evaluation at two weeks, and an average the interval to treatment was 20.7 ± 5.2 days. The first post-radiation imaging stage is described in this work as 3 week post-radiation due to this mean time calculation. The second post-radiation treatment imaging evaluation was targeted for 6 weeks after the beginning of radiation treatment, occurred on average at 39.0 ± 5.0 days. For the pre-radiation image evaluation, 52 patient sets were available. The number of patient participants decreased to 39 at the first post-radiation imaging assessment and to 32 in the second (6-week) post-radiation evaluation. The decrease in patient participation was mostly due to health status and was not anticipated to impact the analysis for testing of agreement between manual delineation and semi-automated study based on the analysis techniques as described below.

MR Imaging

Cervical cancer tumors were delineated from Fast Spin Echo (T2-FSE) sets with the following parameters from a General Electric (GE) 1.5T MRI system: TE=125 ms, TR=5 s, FOV=25×40 cm at matrix=192×256, slice thickness/gap=4mm/1.0mm over 48 slices.

Image Processing and Segmentation Method

For the iterative active deformation model we have selected as the basis of our segmentation method, from among the many potential variants of the deformable model, a variant of the classic polygonal model. Iterative active deformation was performed using in-house software implemented in Matlab™ (Natick, Ma) with 'C' based dynamically linked libraries. An example of the overall iterative deformational scheme is shown in figure 1. The procedure for iterative active deformation (contour) was performed on a slice by slice basis as follows: 1) The user initializes points on the outside of the tumor. 2) Active deformation is applied starting from user-initialized points until terminated by the user for each 2D slice. 3) A morphological filter, erosion $A \ominus B$ if moving from outside to inside of the structure or dilation $A \oplus B$ if iterating from the inside to the outside of the structure, shrinks the overall enclosed curve demarcated by the vertices slightly smaller than the original patch. The structuring element for this filter was chosen to be a 3×3 circle. 4) Vertices used in the

polygonal snake were moved to the point closest to the new filtered patch via identification of the minimum projected distance to the curve. 5) From that point, the operation is applied in the opposite direction to grow from the inside to outside by resetting the inflation term in equation 6 to reflect the change in direction as well as to alternate for each iteration between bright-to-dark (growing inward) and from dark-to-bright (growing outward). 6) The user has an option at each iteration step to force node locations. 7) To control the growing number of points with each iteration, the numbers of points are reduced by a thinning algorithm based on Euclidean distance and priority score. 8) The user decides whether to terminate the process or continue by iterating back to step 3 or saving the contour points.

Data Evaluation—We compared the newly developed iterative active deformational segmentation method with manual delineation using the Jaccard Similarity Factor (J_s). The original delineations were performed by a radiation oncologist who has more than decade of experience in delineation of cervical cancer tumors. The J_s , which is more stringent than a standard method based on volume agreement, is defined as

$$J_s = \frac{\text{pixels}(a \cap m)}{\text{pixels}(a \cup m)} \quad [7]$$

where ‘a’ represents the set of pixels identified by the semi-automated delineation and ‘m’ is the set of pixels identified in manual delineation. The J_s is a ratio of number of pixels in the intersection of these sets over the union of these sets. With poorer spatial co-localization of sets ‘a’ and ‘m’ the J_s value is driven to smaller values. This is due to the numerator which is the intersection of the sets being reduced suggesting poorer and poorer agreement. However, when the sets are perfectly in the same spatial position it is possible to approach a maximal value of 1 in the case when the numerator and denominator become more equal suggesting high agreement in spatial position and size of the sets. The results of a comparison of automatic delineation to manual segmentation were conjectured to depend on tumor volume and radiation treatment stage. Each observed tumor was categorized according to the radiation stage when it was evaluated (pre-radiation, three weeks post-radiation, or more than six weeks post-radiation). Tumor volume (in cm^3) was evaluated as a continuous variable. To account for correlation among observations of tumors within individual patients and for attrition in sample size over time, J_s was analyzed in a general linear mixed model (GLMM) (18). The GLMM analysis, performed using SASTM (Cary, NC) *PROC MIXED*, assessed the performance of J_s while accounting for the influences of tumor volume, radiation treatment stage, and their interaction (table 1) in the following statistical model:

$$J_s = \beta_0 + \beta_1 \text{VOL}^{\text{TUMOR}} + \beta_2 \text{RAD}^{\text{STAGE}} + \beta_3 (\text{VOL}^{\text{TUMOR}} * \text{RAD}^{\text{STAGE}}) \quad [8]$$

$\text{VOL}_{\text{TUMOR}}$ (tumor volumetric size) and the $\text{RAD}_{\text{STAGE}}$ (radiation treatment stage) are modeled along with their interaction to evaluate associations with J_s .

RESULTS

The iterative active deformational method produced promising levels of agreement, including J_s factors of 0.71 ± 0.11 in the pre-radiation studies. The total number of pixels recorded by manual delineation was 88% of the number produced by the semi-automated segmentation, indicating a potential for overestimation in the active deformation methods. Figure 3 illustrates the scatter plot that was used to screen for evidence of systematic over- or under-estimates of the tumor volumes determined by semi-automated segmentation as

opposed to manual delineation. The iterative active deformational delineation method for each slice converged within several seconds, so there was little concern over the method's general efficiency compared to that of manual delineation. When applying the GLMM model in equation 8 to evaluate Jaccard similarity, we retained the interaction term because its marginal level of significance ($p=0.0992$) was of interest in this exploratory study of semi-automatic delineation methods. The analysis illustrated a rate of improvement in J_S with increasing tumor volume that differed between radiation treatment stages 1 and 3 ($p=0.0474$), but not between stages 2 and 3 ($p=0.1189$), nor between stages 1 and 2 ($p=0.1965$). In the relatively large tumors assessed at the pre-radiation stage, each additional cm^3 of volume was associated with an increase or improvement in J_S of 0.0008 (95% CI: 0.0003, 0.0014). In the smaller stage 3 tumors, each additional cm^3 of volume was associated with a more robust improvement in J_S of 0.0046 (95% CI: 0.0009, 0.0082). The improved agreement, based on tumor volume, differed significantly between pre-radiation and six weeks post-radiation stage tumors (difference=0.0038; 95% CI: 0.00005, 0.0075). All results are summarized in table 1 and illustrated in figures 2A and 2B.

While the scatter plot in figure 3 suggested overestimation by the deformable models, we further quantified 95% confidence intervals for the ratio of IADP over manual delineation volumes. For the purpose of evaluating these ratios, a bootstrapping technique was used to calculate confidence intervals (CI). We used the bootstrapping procedure because even when a ratio is formed from two normally distributed random variables, the result may not be itself normally distributed. A bootstrapping technique calculates confidence intervals without making assumptions concerning normality (19).

Table 2 summarizes mean ratios and bootstrap CIs for the three stages of radiation treatment (pre-treatment, three weeks after, and six weeks after initiation of treatment). Semi-automated segmentation estimated the volume of 52 pre-radiation tumors to contain, on average, 1.10 times the number of pixels counted through manual delineation. The ratio's bootstrap 95% confidence interval of 0.80 to 2.23 suggested that overestimation of tumor volume was not significant. Similarly, the ratio (and bootstrap 95% CI) for volume estimates on the 39 tumors measured three weeks after radiation was 1.56 (95% CI: 0.56, 3.23), and for the 30 tumors measured six weeks after radiation 1.83 (95% CI: 0.45, 4.00).

DISCUSSION

GLMM analysis showed the associations between tumor volume, treatment stage, and Jaccard similarity (J_S) to be similar (see table 1). Better agreement occurred with larger tumors within all three stages of radiation treatment. Additionally, by modeling agreement as having distinct regression slopes (with respect to tumor volume) for each treatment stage, we established that regardless of treatment stage, smaller tumors produce lower J_S . Moreover, the difference in regression slopes (the association between J_S and volume is stronger among tumors in the latest stage of radiation treatment) suggests that decreased tumor volume interferes more with J_S in the third radiation treatment stage than in the pre-radiation stage. This finding is explainable through radiation effects. Inflammatory processes that progress after radiation treatment can dramatically reduce the imaging edge definition. This reduced definition may in turn adversely impact convergence of the active deformational method. Additionally, smaller tumors (which are more prevalent in the post-radiation stage) are also associated with worse performance than larger tumors in this method. We observed that smaller irradiated tumors present shorter and less distinct boundaries, making it more challenging to achieve a desirable convergence in some cases.

Our method utilized a polygonal model for each active contouring step. This iterative structure may be integrated with other variations of the snake thus permitting numerous

enhancements to the deformational method (8,12). However, even with the deployed polygonal iterative active deformational models, the technique achieved reasonable accuracy, particularly in the pre-radiation stage ($J_S=0.71$; see table 1).

We have shown potential utility in applying iterative active deformational models to the semi-automatic delineation of tumors. The iterative process permitted the ability to readjust and correct in the delineation process. However, some challenges still exist with these methods. Blur in edges produced by partial volume artifacts and radiation treatment seems to be the most dominant factor in the performance of the active contour method over other complications such as size or location. Invaginating structures still challenge the method, though the iterative process seems to provide some additional opportunity for correction. Semi-automated applications such as these may become particularly useful in the future as rapidly advancing scanner technology becomes increasingly capable of generating larger number of images per patient. T2-weighted images were used for delineation as part of our protocol without direct viewing of post-contrast T1. Pre-contrast images are less dependent on timing of the contrast injection and sequence choices, particularly in cases where dynamic contrast enhancement (DCE-MRI) protocols may be employed. Relying on both T1 and T2-weighted images (two potential targets for delineation) would create multi-spectral information that would likely enhance segmentation. Accounting for the multi-spectral information generated by T1 and T2 image sets would require robust image registration algorithms and reformulation of the internal energy equation. This study aimed to demonstrate the feasibility of using the active contour segmentation for the delineation of cervical cancer tumors based on a single target.

The proposed semi-automated segmentation method may overestimate the identified tumor volume in certain cases. The volume ratios for each radiation stage have increasing means (albeit with large 95% confidence intervals) of 1.10, 1.56, and 1.83, respectively, for preradiation, three weeks post radiation, and six weeks post-radiation. The bootstrap confidence interval estimated at each stage covered the ratio equal to 1.0, implying that no firm statistical evidence exists for volume overestimation. However, the trend in mean ratios may suggest that volume overestimation, while unimportant in tumors measured before radiation, may become of greater concern as radiation treatment progresses.

Variation due to inter and intra-observer variability is a particular challenge to active deformational methods. For this study consistent education on procedural pitfalls were monitored in a manner similar to that described elsewhere (20). In such cases, there is greater motivation to apply active deformation methods as they can require a small number of “point clicks” to initiate delineation. Careful diagnostic procedures were used to examine model residuals, and the mixed model accounted for unequal sample sizes between the radiation therapy stages. Challenges to the active deformational method exist in sharply invaginated structures; however, it appears the iterative process provides opportunities to improve segmentation. In these cases, automatic techniques can reduce the hand fatigue that is common in manual tumor delineation, provided that they achieve acceptable agreement with manual methods, for example, by exceeding a specified J_S level.

Further improvements in automatic techniques may also have implications for advancing fields such as dynamic contrast enhanced-MRI (DCE-MRI) and molecular imaging and magnetic resonance spectroscopy (MRS), particularly when sensitivity to overall tumor delineation may influence results (1,2). It is also possible that, with additional improvements, these methods can record image processing parameters as performed by physician experts for use in a training setting for advancing techniques with neural nets. These recorded parameters can be further used to guide resident trainees and to provide greater oversight in the tumor delineation process when an expert is unavailable.

Understanding the behavior of segmentation techniques is particularly important, and accuracy may be impacted directly by volume changes over the course of radiation treatment.

In conclusion, we have introduced, implemented, and assessed an iterative technique to modify the active deformational image segmentation of cervical cancer tumors on MRI. This study demonstrates that smaller tumor volumes degrade agreement and that the efficacy of the iterative active deformational methodology becomes increasingly challenged in later radiation treatment stages.

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Fig. 1.

T2-weighted MR images of cervical cancer for delineation are shown. A) Outlined in blue illustrates a 4 point starting condition of the manual segmentation (control points are red '+' signs). B) Red dotted line illustrates an iteration step. C) Yellow arrows illustrate continued iteration of algorithm from step shown in B. D) Contains the morphological filter step to drive boundary inward (following the yellow dotted arrow direction). E) The active contour is reversed in direction and expands to the final segmentation result which is shown as a red solid line. F) The manual delineation is illustrated in green.

Figure 2.

B) Box-and-whiskers plot illustrating the distribution of agreement factors for each stage of radiation treatment, collapsed across volume within each treatment stage.

Figure 3.

The scatter plot used to screen for over- or underestimation of the tumor volumes as evaluated by the interactive active deformable segmentation (IADS) as compared to the manual delineation volumes. A line $Y=X$ is superimposed on the graph as a visual aid to demonstrate the location where perfect concordance between the volume measures would occur.

Table 1

The mean and standard deviation (SD) of the tumor volumes and Jaccard similarity (J_S) factors by radiation treatment stage (pre-treatment, post-three weeks, and post-six weeks).

<u>Radiation Stage</u>	N	Tumor Volume (cm ³)		J_S Agreement	
		Mean	SD	Mean	SD
Pre-Radiation	52	70.48	48.51	0.71	0.11
3 weeks Post-Radiation	39	33.88	28.29	0.54	0.15
6 weeks Post-Radiation	30	14.48	11.93	0.45	0.13

Table 2

Means of ratios of the volume between the Interactive Active Deformational Process (IADP) and the manual delineation measure with bootstrapped 95% confidence intervals (CI).

Volume ratio (IADP vs. manual delineation)				
			Bootstrapped 95% CI	
Radiation Stage	N	Mean	Lower limit	Upper limit
Pre-Radiation	52	1.10	0.79	2.27
3 weeks Post-Radiation	39	1.57	0.57	3.25
6 weeks Post-Radiation	30	1.83	0.45	4.01