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Treatment response assessment for bladder cancer on CT based on computerized volume analysis, WHO and RECIST Criteria

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Abstract

Purpose—To evaluate the accuracy of our Auto-Initialized Cascaded Level Set (AI-CALS) 3D segmentation system, the World Health Organization (WHO), and the Response Evaluation Criteria In Solid Tumors (RECIST) criteria for estimation of treatment response of bladder cancer in CT urography.

Materials and Methods—Pre- and post- neoadjuvant chemotherapy treatment CT of 18 patients with muscle invasive localized or locally advanced bladder cancers were collected. The disease pathological stage determined by cystectomy after chemotherapy was available as reference standard of treatment response. Two radiologists measured the longest diameter and its perpendicular on the pre- and post-treatment scans. Full 3D contours for all tumors were manually outlined by one radiologist. AI-CALS was used to automatically extract 3D tumor boundary. The prediction accuracy of pT0 stage (complete response) at cystectomy by the manual, AI-CALS, WHO, and RECIST methods was estimated by the area under the receiver operating characteristic curve (AUC).

Results—The AUC for prediction of pT0 disease at cystectomy was 0.78 ± 0.11 for AI-CALS compared to 0.82 ± 0.10 for manual segmentation. The difference did not reach statistical significance ($p=0.67$). The prediction using RECIST criteria by radiologists with AUCs of 0.62 ± 0.16 and 0.71 ± 0.12 , respectively, was lower than those of the two 3D methods. The prediction using WHO criteria by radiologists with AUCs of 0.56 ± 0.15 and 0.60 ± 0.13 , respectively, was lower than all other methods.

Conclusions—The 3D pre- and post-treatment volume change estimates obtained by radiologist's manual segmentation and AI-CALS are more accurate for the irregular-shaped 3D tumors compared to the RECIST and WHO estimates.

Keywords

Bladder cancer; Response to treatment therapy; CT scans; Computer 3D segmentation; Level sets

1. INTRODUCTION

Bladder cancer can cause substantial morbidity and mortality among both men and women. It is estimated that 74,690 new bladder cancer cases will be diagnosed in 2014 [1]. Bladder cancer causes over 15,580 deaths per year in the United States [1]. Early diagnosis and treatment of bladder cancer is important to reduce the morbidity, mortality and their attendant costs compared to diagnosis at a later, more advanced stage that might involve deep invasion and/or metastasis.

Radical cystectomy is considered the gold standard for treatment of patients with localized muscle-invasive bladder cancer. However, about 50% of patients undergoing cystectomy for bladder cancer known to be only locally invasive at the time of surgery develop metastases within 2 years after cystectomy and subsequently die of the disease [2]. This is likely due to the presence of undetected microscopic local perivesical spread of tumor and/or microscopic regional or distant metastatic disease at the time of surgery. Neoadjuvant chemotherapeutic treatment of muscle-invasive operable bladder cancer has been shown to be beneficial for treatment of micrometastases and to improve resectability of larger neoplasms prior to radical cystectomy [3–5]. Chemotherapy involving methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy increases the probability of finding no residual cancer at surgery in comparison to radical cystectomy alone, and improves survival among patients with locally advanced bladder cancer [6, 7]. In clinical trials, down-staging with drugs before surgery was shown to have significant survival benefits [7, 8]. Current standard of care utilizes the neoadjuvant protocol, consisting of 12 weeks of chemotherapy preceding radical cystectomy.

Although patients with advanced disease can benefit from cisplatin based neoadjuvant chemotherapy, there are drawbacks. Chemotherapy has substantial toxicity and side effects [9]. Significant toxicities, primarily neutropenic fever, sepsis, and mucositis are associated with combination chemotherapy. Side effects such as nausea, vomiting, malaise, and alopecia are also common. In addition, because no reliable method yet exists for predicting the response of an individual patient to neoadjuvant chemotherapy, some patients may suffer from toxicities associated with the drugs without achieving beneficial effects, often also missing the opportunity for promptly instituted alternative therapy when their physical condition deteriorates. Chemotherapy is also expensive.

Early assessment of therapeutic efficacy and prediction of failure of the treatment would help clinicians decide whether to discontinue chemotherapy at an early phase and proceed to surgery and thus reduce unnecessary morbidity and improve the quality of life of the patient, and reduce costs. The ultimate goal is to improve survival for those with a high risk of recurrence while minimizing toxicity to those who will have minimal benefit. Therefore, development of an accurate predictive model for the effectiveness of a specific therapy is of critical importance for patients with bladder cancer.

Pathologic evaluation performed at the time of radical cystectomy is considered a “gold standard” for estimation of treatment response. However, this method cannot be used during the course of chemotherapy.

Noninvasive evaluation of the bladder cancer treatment response can be performed during the course of chemotherapy (after one or two cycles) with CT or MRI by measuring tumor size, providing accurate anatomical images of the tumor. CT is an effective modality for measuring primary site gross tumor volume (GTV) that has been used as a biomarker for predicting tumor treatment outcome in the bladder [10].

Accurate measurement of GTV on a 3D modality, such as CT or MRI, requires delineation of tumor boundary slice-by-slice. However, the time and costs required for the clinicians to outline cancer margins on a large number of CT urograms (CTU) slices for each case precludes such labor-intensive method to obtain GTV estimation of every pre- and post-treatment tumor evaluation in daily practice.

Currently, clinical estimation of the tumor size is based on the World Health Organization (WHO) criteria [11] as well as the Response Evaluation Criteria In Solid Tumors (RECIST) criteria [12]. In the WHO criteria [11] the longest tumor diameter and its perpendicular are measured. The response to treatment is estimated as percent reduction in the product of the longest tumor diameter and its perpendicular between post- and pre-treatment measurements. In the RECIST criteria [12] only one diameter (longest tumor diameter) is measured. The response to treatment is estimated as percent reduction in the longest tumor diameter between post- and pre-treatment measurements. Both methods, however, can be inaccurate and can produce large inter- and intraobserver variations especially for tumors with irregular shape. The volumetric information available in CTU scans is vastly under-utilized [13].

With the increasing number of bladder cancer patients treated with neoadjuvant therapy and the radiologists' increasing workload, the role of automatic and semi-automatic segmentation tools in the evaluation of tumor response to treatment on cross-sectional imaging studies becomes increasingly important. Previously we have demonstrated that the tumor size change in response to treatment can be accurately estimated by the computerized segmentation system for different types of head and neck tumors.[14, 15]

The purpose of this preliminary study is to evaluate the potential usefulness of a computerized system developed in our laboratory for segmenting bladder cancers imaged in CTU and estimating the GTV to assist radiologists in monitoring the GTV change in response to neoadjuvant chemotherapy, and to compare the automatic estimation to results based on the WHO and RECIST criteria.

2. MATERIALS AND METHODS

2.1 Data set

The data collection protocol had been approved by our Institutional Review Board (IRB) and is Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient informed consent was waived for this retrospective study. Our data set contained temporal

CTU volume pairs from 18 patients with muscle invasive localized or locally advanced bladder cancer who underwent neoadjuvant chemotherapy treatment. Fifteen patients were male and three were female. The patients' ages ranged from 37 to 73 years (mean = 60.1 years). The primary tumors were stages T1 to T4. Twelve of the tumors were flat and six of the bladder tumors were papillary.

For the estimation of the change in tumor extent, a CTU scan from a pre-treatment exam and a CTU scan obtained following three-cycles of chemotherapy were used for each case, resulting in 36 CTU scans collected for the 18 patients. The CT studies were acquired in our clinic with a variety of GE scanners (GE, Waukesha, WI), including the GE LightSpeed series scanner models Ultra, Pro 16, and LightSpeed16. The pixel size ranged from 0.586 to 0.977 mm. The slice interval was 0.625, 1.25, 2.5 and 5.0 mm.

For all cases, cystectomy was performed after the course of neoadjuvant chemotherapy was completed and the disease outcome was available as reference standard of treatment response. Thirty three percent of patients (N=6) had pT0 disease (complete response) at cystectomy.

To obtain a reference standard for comparison with the computer segmentation, one radiologist (E.C.) with 15 years of experience reading CTU using an in-house developed graphical user interface (GUI) identified and marked 18 temporal pairs of primary site cancers on the CTU scans with bounding boxes. The sizes of the bounding boxes were varied to enclose the tumors of different sizes. In addition, for all 18 cancers, following WHO and RECIST criteria, the radiologist measured the longest diameter and its perpendicular on the pre- and post-treatment scans by using an electronic caliper provided by the GUI. These estimations are referred to as Readings Rad 1. The size measurements for every lesion were performed on the 2D slice where the lesion is best represented (with its maximum size) defined as the "best slice". The average size (the longest diameter) for the 18 primary cancers was 43.1 mm (range: 11.2 – 77.7 mm) on the pre-treatment CT scan and 19.1 mm (range: 2.6 – 59.9 mm) on the post-treatment CT scan. For all 18 cancers, the radiologist also manually outlined the full 3D contours on both the pre- and post-treatment scans using the GUI.

In order to study the effect of the interobserver variability of the tumor measurements, a second radiologist (R.C.) with 25 years of experience reading urinary tract cases, independently measured the longest diameter and its perpendicular for the 18 bladder cancers on the pre- and post-treatment scans on the "best slice" following the WHO and the RECIST criteria by using the same electronic caliper. The estimations by this radiologist are referred to as Readings Rad 2.

2.2 Segmentation of bladder lesions on CTU

We have developed an auto-initialized cascaded level set (AI-CALS) method for bladder lesion segmentation. A pilot study of the feasibility of AI-CALS segmentation of bladder lesions on CTU scans was reported previously [16]. The system consists of three stages: preprocessing, initial segmentation, and 3D level set segmentation. The system uses as input an approximate bounding box for the lesion of interest. The bounding box is defined by the

user with the help of a Graphic User Interface (GUI) developed in our laboratory. The GUI is designed for efficient navigation through the images of a 3D volume, efficient definition of the box, i.e., the volume of interest (VOI) enclosing the lesion in the 3D CTU volume, and the display of the automatically or manually segmented lesion outlines. The box is defined by placing a resizable rectangle at the image slice where the lesion is seen the best and by marking the top and the bottom image slices that enclose the lesion. The user can edit the location and the size of the rectangle by dragging with different mouse buttons, and select or change the top and the bottom slices by a single click at the slice. It is not required that the box encloses the lesion tightly. After the bounding box is defined, the user can launch the AI-CALS segmentation within the GUI, which will automatically segment the lesion and then display the obtained 3D contours overlaid on the images of the CTU slices on the GUI for review. This process can be performed by a radiologist or by an assistant trained by the radiologist on how to identify the lesions in the bladder.

The AI-CALS level set segmentation is automatically performed in the user-defined VOI, described above. It consists of three stages: the first and second stages of AI-CALS generate an initial 3D contour, and the third stage refines the initial contour. In the first stage, preprocessing techniques including smoothing, anisotropic diffusion, gradient filters and the rank transform of the gradient magnitude are used to obtain a set of smoothed images, a set of gradient magnitude images, and a set of gradient vector images, which are used in the second and third AI-CALS stages.

In the second stage, the AI-CALS system automatically labels a subset of voxels in the VOI for analysis of lesion statistics based on the attenuation, gradient, and location of the voxels. A subset of voxels that belong to smooth areas and are relatively close to the center of the lesion is identified and used as a statistical sample of the full population of voxels in the object of interest. The mean and standard deviation of this subset of voxel are computed. The preliminary lesion contour is obtained after applying a threshold and selecting the set of voxels falling within 3.0 standard deviations of the mean and with values above -400 HU. A set of 3D image processing techniques (morphological dilation filter, 3D flood fill algorithm, and morphological erosion filter) subsequently applied to the contour will connect nearby components and extract an initial segmentation surface [16].

In the third stage, the initial segmentation surface is propagated towards the lesion boundary through a bank of cascading level sets. The first 3D level set slightly expands and smoothens the initial contour. The second 3D level set pulls the contour towards the sharp edges, but at the same time it expands slightly in regions of low gradient. The third 3D level set further draws the contour towards sharp edges. Finally, a 2D level set is applied to every slice of the segmented object to refine the 3D contours. To maintain inter-slice cohesion, the 2D level set is propagated only for a small number of time steps.

In summary, from the user prospective there are two steps: (1) define the VOI to initiate the AI-CALS segmentation, and (2) review the 3D contours, if preferred, after the AI-CALS segmentation is finished. The user is not involved during the three stages of AI-CALS process.

2.3. Evaluation methods

Receiver operating characteristic (ROC) analysis was performed and the area under the ROC curve (AUC) was calculated to estimate the accuracy for prediction of pT0 stage (complete response) at cystectomy by the manual (3D), AI-CALS (3D), WHO (2D), and RECIST (1D) methods. The statistical significance of the difference between the different methods was evaluated using the ROCKIT software package (University of Chicago, IL [17]).

4. RESULTS

An example of the computerized 3D level set segmentation of a bladder tumor on pre- and post-treatment CT scans is shown in Figure 1. The pre- and post- treatment volumes for the 18 primary bladder tumors calculated from the radiologists' outlined contours are plotted in Figure 2. For the 18 primary bladder tumors, the average pre- and post-treatment volumes were 31.4 cm³ (range: 5.1 – 138.5) and 11.4 cm³ (range: 0.2 – 54.7) respectively.

Table 1 shows the AUC results for all the experiments. The AUC for prediction of pT0 disease at cystectomy was 0.78±0.11 for the AI-CALS compared to 0.82±0.10 for the manual segmentation. The difference did not reach statistical significance (p=0.67). The prediction of pT0 disease using the RECIST criteria by the two radiologists with AUCs of 0.62±0.16 and 0.71±0.12, respectively, was lower than the two 3D methods. The prediction of pT0 disease using the WHO criteria by the two radiologists with AUCs of 0.56±0.15 and 0.60±0.13, respectively, was lower than all other methods. Figure 3 compares the ROC curves for the estimations by the volumetric and the RECIST criteria.

5. DISCUSSION

The results of our study suggest that the automated segmentation system showed promising performance by providing reasonable segmentation including lesions that radiologists found to be difficult to visualize. One such example is shown in Figure 1. Most of the boundaries between the lesion and the adjacent normal bladder tissue had very low contrast on both the pre- and post-treatment scans. However, AI-CALS was able to find reasonable boundaries in this case on both scans.

The 3D pre- and post-treatment volume estimates obtained by the manual segmentation and the computer segmentation provided the best estimations of the tumor treatment response (Table 1 and Figure 3). The comparisons between the percent pre-to-post-treatment volume change by manual segmentation and the percent volume change by (1) the automatic segmentation AI-CALS, (2) the estimate by the WHO criteria, and (3) the estimate by the RECIST criteria, revealed that the 3D AI-CALS was closest to the treatment response estimation based on the manual segmentation. The estimates by the RECIST criteria, although closer than the estimates by the WHO criteria, were still far from the estimate based on manual segmentation. One reason is that the bladder tumors have complicated shapes and the 1D and 2D measurement cannot represent adequately the 3D pre- and post-treatment tumor shapes. The estimates by the 2D WHO criteria were slightly lower than

those by the 1D RECIST criteria, which may be attributed to the relatively small data set size and the relatively large variability of the shapes of the bladder tumors.

There are limitations in this preliminary study. The data set is relatively small. Although the AI-CALS segmentation performance for the different types of primary tumors in this study and our previous validation study [16] using 28 cases of bladder lesions with single CTU examinations indicate that the automatic segmentation is relatively robust, a larger data set with different types of lesions and pre- and post-treatment CTU scans will be useful to further confirm its generalizability for quantification of tumor volume change. We will continue to enlarge the data set and evaluate the potential variability in performance in the future. In this preliminary study, we obtained the reference standards by having one radiologist provide manual outlines of the lesions. To study the inter- and intra-observer variabilities in manual segmentation of bladder tumors, it will be necessary to obtain independent segmentation by several radiologists and also repeated segmentation by individual radiologists. We will investigate the effects of these variabilities on the assessment of volume change and treatment response in future studies.

Despite the potential advantages that GTV can offer in estimation of the response to treatment, GTV is not routinely measured due to time and effort required to make these calculations. A reliable and efficient automated segmentation tool would enable the prognostic information of tumor volume measurements to be routinely integrated into the management of patients with bladder cancer.

In conclusion, our preliminary results indicate that the computerized AI-CALS segmentation system can produce reliable 3D segmentation for a variety of bladder tumors. The 3D pre- and post-treatment volume estimates obtained by radiologist's manual segmentation and AI-CALS provided more accurate volume change measurements of 3D tumors with irregular shapes compared to those from the 1D (RECIST) and 2D (WHO) estimates. This preliminary study suggests that the 3D automated segmentation tool has the potential to assist in assessment of tumor volume and response to treatment for bladder cancer.

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Figure 1.

A bladder carcinoma on pre- and post-treatment CTU scans. (a) An axial slice on the pre-treatment scan, (b) the automatic segmentation (solid contour) superimposed on the pre-treatment scan. (c) An axial slice on the post-treatment scan, (d) the automatic segmentation (solid contour) superimposed on the post-treatment scan. The lesion is segmented in 3D but only the best slice marked by radiologist for each scan is shown.

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Figure 2.

The pre- and post-treatment volumes for the 18 primary bladder tumors calculated from the manually outlined full 3D contours by an experienced radiologist (Rad 1).

Figure 3.

The ROC curves for prediction of pT0 disease at cystectomy for 18 primary site tumors: AI-CALS (AUC= 0.78±0.11), Manual Reference (AUC = 0.82±0.10), RECIST Radiologist 1 (AUC = 0.62±0.16), and RECIST Radiologist 2 (AUC = 0.71±0.12).

Table 1

The areas under the receiver operating characteristic curves (AUCs) for prediction of pT0 disease at cystectomy.

Estimation method	Type	AUC
AI-CALS	3D	0.78±0.11
Manual Reference	3D	0.82±0.10
WHO Rad1	2D	0.56±0.15
WHO Rad2	2D	0.60±0.13
RECIST Rad1	1D	0.62±0.16
RECIST Rad2	1D	0.71±0.12