Original Article

Investigation on Performance Accuracy of Different Surrogates in Real Time Tumor Tracking at External Beam Radiotherapy

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A B S T R A C T

Purpose- In external beam radiotherapy of dynamic tumors, several errors raise due to inter- and intra-fractional motions. In order to compensate these errors, signals obtained from different surrogates are used to infer with tumor motion as real time. Therefore, a comparative assessment may be worthwhile on the effect of different surrogates in tumor motion tracking.

Methods- The performance accuracy of three internal-external surrogates entitled: external markers, diaphragm movement and lung volume was done using 4 Dimensional Extended Cardiac-Torso (4D-XCAT) phantoms. Adaptive Neuro Fuzzy Inference System (ANFIS) model was implemented to correlate the motion of surrogates with several tumors located in liver and lung, separately. Finally, the Root Mean Square Error (RMSE) of ANFIS model outputs in tumor motion prediction of different surrogates was compared as metric tool.

Results- The average value of RMSE of lung and liver tumors were 0.4 mm, 0.6 mm and 0.8 mm for external markers, lung volume and diaphragm motion, respectively.

Conclusion- Among three investigated surrogates, the best performance belonged to external markers strategy, while optimum location of these markers determined using an input selection algorithm in this method.

1. Introduction

In radiotherapy with external beam, the main challenging issue is delivering 3D uniform dose into tumor volume while minimizing high dose received by healthy surrounding tissues at the same time. The treatment quality of radiotherapy strongly depends on the accuracy of tumor localization during treatment planning process. However, in thorax region semi-regular motions of Heartbeat, gastrointestinal and especially breathing phenomena known as intra-fraction organs motion are problematic during treatment planning. These errors cause a significant positional uncertainty of target localization and can therefore reduce radiation treatment quality [1-4]. Several strategies have been proposed in order to minimize the tumor motion error. These strategies which are used clinically or are under developing include: breath holding, respiratory gating and real-time tumor tracking techniques [5-11]. In two latter cases, the patient can breathe freely during irradiation while the breathing motion is being monitored continuously to extract tumor position information. For this purpose, additional monitoring hardware such as fluoroscopy and optical tracking system (OTS) in combination with stereotactic X-ray imaging is required to track tumor motion in real time. Some of these motion monitoring devices include: continuous X-ray imaging (i.e. fluoroscopy) [12], electromagnetic [13], ultrasound [14], live

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MRI [15] and external surrogates [16-18]. Among them, the latter case is now clinically applied due to its feasibility and reliability in tumor motion estimation with less side effects and expenses. Several surrogates are currently available to be inferred with tumor motion such as: spirometer [18,19], strain gauge [18], Time-of-Flight Cameras [20] and external markers [16]. In radiotherapy with external markers, the tumor motion is predicted by means of motion data of external markers located on chest and abdomen surface of patient body. Moreover, an external signal can also be achieved from diaphragm motion as an alternative. A third suggestion, external motion signal may be obtained by measuring air volume released during inhalation-exhalation phenomena. In all given methods using external markers, lung volume and diaphragm based motions, a consistent correlation model is required to predict the tumor motion by means of extracted external signals. This correlation model must be firstly configured using training dataset at pre-treatment step. While the model was built, it was ready to infer tumor motion only by means of eternal signals. Comprehensive studies were done taking into account different aspects of available correlation models in our previous reports [21-23]. The aim of the present study is to investigate the accuracy of three different breathing surrogates entitled external markers, lung volume and diaphragm motion in tumor motion tracking taking into account the robustness and weakness of each method.

2. Methods

2.1. 4DXCAT Phantom

A simulation study was done using NURBS based 4D XCAT anthropomorphic computational phantom developed by W. P. Segars. This phantom is commercially available to simulate dynamic organ motion mainly caused by breathing phenomena [24]. As XCAT phantom is a hybrid between the realism of pixel-based and the flexibility of geometry-based phantoms, it can model dynamic process better than other available cases [25]. In this study, for simulating a real breathing pattern, six different respiratory cycles were considered with reasonable breathing amplitude and frequency using motion dataset of real patients (Table 1). In order to do this, a maximum Anterior-Posterior expansion of chest wall and the time of respiratory period were determined based on respiratory motion parameters of real patients treated with Cyberknife Synchrony System at Georgetown University medical center (Washington DC).

It should be noted that in the simulation process, the time interval between two data acquisition steps was assumed to be 25 ms.

We defined nine tumors in lung and liver using XCAT phantom. 3 tumors in the right lung and 3 tumors in the left lung were considered in upper, middle and lower lobes of lungs. Moreover, 3 tumors assumed to be located at lower, middle and upper lobes of liver (Figure 1, right side). Three internal-external surrogates consist of: 1) diaphragm, 2) lung volume, and 3) external markers were investigated in tumor motion prediction using available motion dataset. Diaphragm motion and lung volume values were extracted from XCAT phantom directly. However, for external markers strategy, 49 points were assumed to be uniformly distributed onto the surface of the chest and abdominal regions while each point represents an external marker. The distribution of assumed points started from abdominal region with 5 cm distance in vertical and horizontal directions (Figure 1, left side).

Table 1. Characteristics of six different respiratory cycles created by XCAT Phantom.

Breathing cycle number	Time of respiratory period (sec.)	Maximum diaphragm motion (cm)	Maximum Anterior-Posterior expansion of chest wall (cm)
1	5	2	1.2
2	5	1.7	0.7
3	4	1.2	0.5
4	6	2.2	1.3
5	5.5	1.8	1
6	3.5	1	0.5

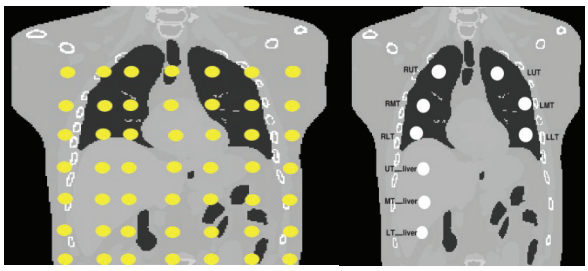

Figure 1. Left panel) external markers simulation. Right panel) internal tumors in lung as: RUT = Right Upper Tumor, LUT = Left Upper Tumor, RMT = Right Middle Tumor, LMT = Left Middle Tumor, RLT = Right Lower Tumor, LLT = Left Lower Tumor, and in liver as UT_liver = Upper.

2.2. Input Selection Algorithms

In radiotherapy with external markers as surrogates, the main challenging issue is using the external markers data points that have the most effective role at correlation with internal tumor motion. Therefore, it is worthwhile to mention a strategy to select the best signals form given external markers appropriate for tumor motion tracking. For this purpose, we proposed input selection algorithm.

This algorithm was first introduced by Zhang *et al*. as a strategy based on dimensionality reduction in data mining procedure [26]. Implementing this technique, the number of inputs, is reduced by removing irrelevant, redundant, or noisy data at external markers strategy. Therefore, most effective and remarkable makers data extracted from the whole dataset can improve predictive accuracy. In order to find the best location of the external markers, an input selection algorithm was employed using Weka software package [27]. Input selection algorithms are composed of two parts: 1) feature evaluation method and 2) searching method. In this work, Relief feature evaluation method [28] was used in combination with Ranker search procedure. Relief Attribute Evaluation evaluates the worth of an input by repeatedly sampling an instance and considering the value of the given input for the nearest instance of the same and different class [29]. Ranker search method Ranks features by their individual evaluations. It should be noted that because Relief Attribute Evaluation method is a single attribute evaluator, which evaluates the attributes individually, it should be used with the Ranker search method to generate a ranked list from which Ranker discards a given number [30].

2.3. ANFIS Correlation Model

As mentioned above, at radiotherapy with external surrogates, correlation model is a main component that infers tumor motion using motion data of external surrogates obtained from external markers, lung volume and diaphragm. Selecting a proper correlation model yields an accurate tumor tracking with less uncertainty error.

2.3.1. ANFIS Structure

In this work, we developed an adaptive neuro-fuzzy correlation model by implementing embedded fuzzy logic and neural network toolbox of MATLAB (The Math Works Inc., Natick, MA) [31]. ANFIS combines fuzzy rules set with the numeric power of neural network systems. Moreover, since the utilized motion dataset is highly variable with large uncertainty, ANFIS may be optimal to trace tumor motion as well in comparison with other available models based on our former studies [21-23]. Fuzzy inference system of ANFIS is based on Sugeno type and membership functions are generated by FCM data clustering algorithm. This clustering strategy has been proven to be proper among current available data clustering algorithms [31-33] and the membership functions derived by this strategy are in Gaussian shape. “If-then” rules are connected with AND operator representing minimum selection criteria in antecedent and consequent parts of fuzzy inference system.

2.3.2. Model Configuration and Performance

Firstly, the proposed ANFIS correlation model must be configured using synchronized external-internal motion data in training step before treatment. After model configuration, it is able to infer tumor motion as a function of time using only external motion data as input. In this work, the model was configured by the motion information of first five cycles and the last breathing phase was used as model test (Table 1). Nine tumors located in lung and liver were predicted using each of the three internal-external surrogates, separately and RMSE between benchmarked and a model output was calculated according to the following metric tool:

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(A_i - P_i)^2} \quad (1)$$

Where, N is the number of predicted samples, A_i is *i*th output in the dataset as real position information

and P_i is the *i*th predicted output by the model.

As the next step, the results of ANFIS model for each surrogate were compared with each other to find the best one.

3. Results

Figure 2 shows the prediction RMSE of all tumors in lung and liver using ANFIS correlation model fed by each of the proposed surrogates.

In order to measure the difference between the accuracy of different surrogates, F-test was also applied as statistical test. Furthermore, Duncan test was implemented to evaluate the mean error of these algorithms. The results of two statistical tests were shown in Figure 3.

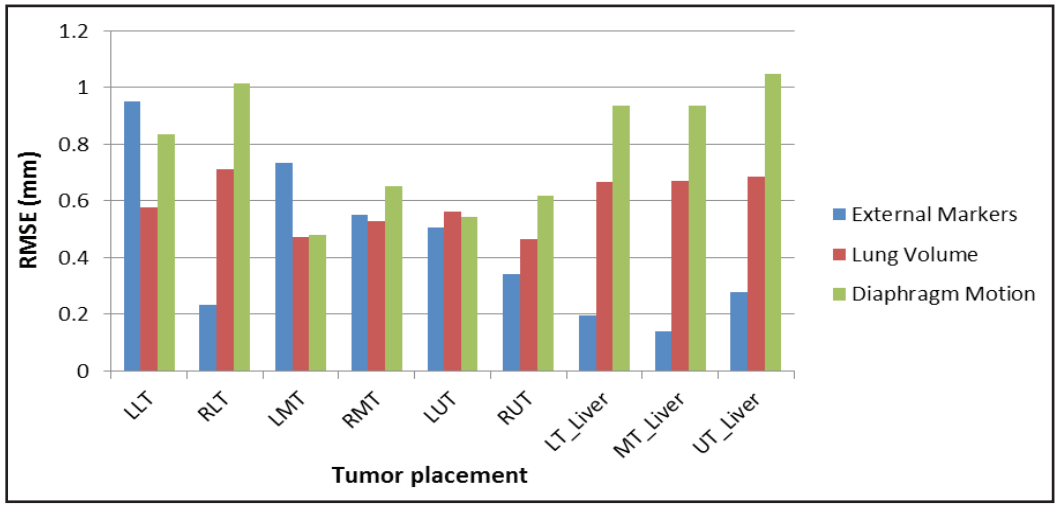

Figure 2. Prediction error of each of the tumors shown in Figure 1 right panel, using each of the surrogates.

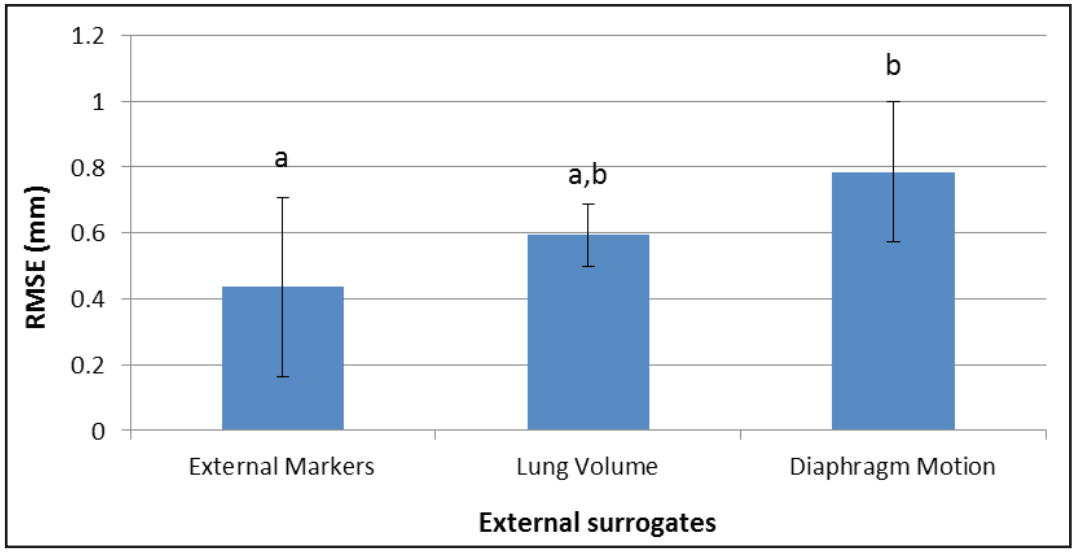

Figure 3. Result of Duncan statistical test for lung and liver tumors prediction using internal-external surrogates. Each of the "a" and "b" words shows a separate group for average value of prediction error of each internal-external surrogate for all nine tumors. Each group has a significant difference with others in average value of prediction error.

In Figure 3, each of a and b words shows a separate group which has a significant difference with others in an average value of prediction error. This means that if two surrogates are placed in a same group, there is no significant difference between them. Based on Duncan test as seen in this Figure, diaphragm

motion has the worst performance between 3 proposed surrogates for tumor motion tracking in lung and liver. Furthermore, the best performance is resulted by external markers based method. The ratios of RMSE of tumor motion prediction by external markers to that of lung volume and diaphragm motion were 0.7 and 0.5, respectively.

The effect of using different surrogates on the run-time of the ANFIS prediction model is shown in Figure 4. The graph indicates that the run times of models fed by diaphragm motion and lung volume signals are almost the same, but this value is higher for model fed by external markers signal. This is due to existing a large amount of external data achieved by markers and also further computational complexity considering input selection algorithm. However, all of these run times are low enough to predict the tumor motion in real time mode.

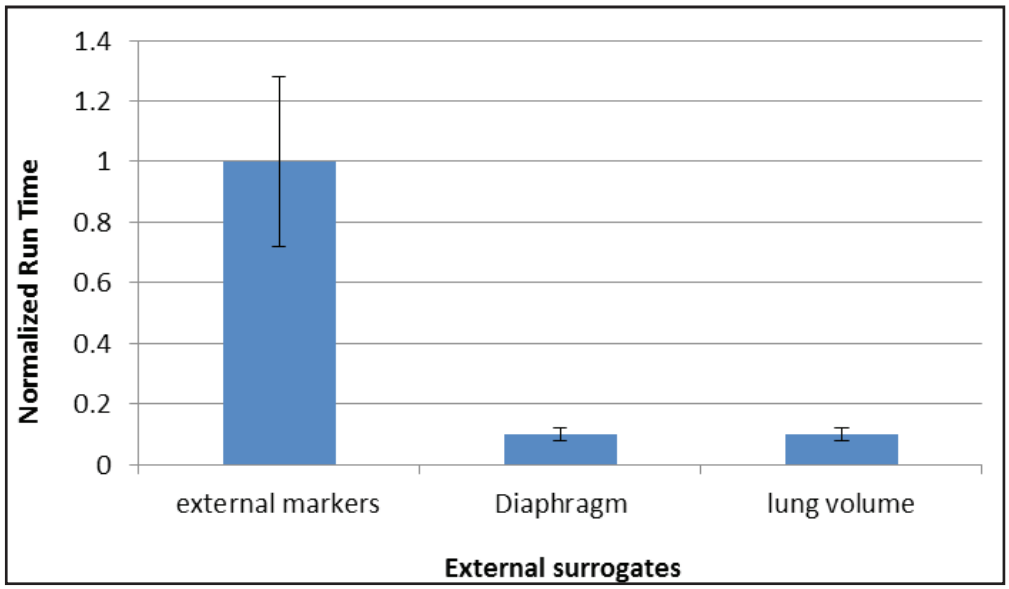

Figure 4. Comparison of run time of ANFIS model fed by different surrogates consisting: external markers, diaphragm and lung volume.

4. Discussion

Simulation is a powerful tool for studying different properties of human body. An important aspect of simulation is to have a realistic computerized phantom or model of the human like 4DXCAT phantom.

In the present study, three different surrogates including diaphragm motion, lung volume and external markers were comparatively investigated in real time tumor motion prediction. ANFIS correlation model was implemented as a correlation model to predict tumor motion using signals obtained from internal-external surrogates. Nine tumors in upper, middle and lower parts of lung and liver organs were taken into account to cover all possible dynamic tumors in these two organs. Based on the results between three investigated surrogates, the best performance accuracy was achieved using external markers. It should be noted that the optimum location of external markers were initially determined using an input selection algorithm. As illustrated from the result section, the location of external markers play an important role at success degree of a correlation model during tumor motion prediction [34-36]. In this study, 5 external markers were considered as the optimum number to have best correlation with tumors motion through trial method. It should be noted that the number of external markers located on thorax and abdomen regions of patients ranges from 3 to 5. These values are validated at different literatures since markers less than 3 cannot provide enough dataset for model configuring at pre-treatment and feeding during treatment. While markers more than 5 makes problems in practical during patient setup and also a large amount of dataset are not necessary and may causes over-parameterization issue in model performance.

It's worth mentioning that each proposed strategy has its unique robustness and drawback as feasibility, simplicity and accuracy of each method as most important issues. Using diaphragm motion as surrogate may be simple regarding with two other strategies. Since its motion may be traced fluoroscopically, additional imaging dose received by patients is much more than other techniques and this issue must be taken into account according to ALARA principal. Although motion information achieved by diaphragm as surrogate may not be perfect to increase targeting accuracy. In external surrogates technique both imaging dose and tumor motion inaccuracy is addressed as well. But the complexity of this method is more than the rest methods while using several external markers on patient surface. Concerning lung volume strategy, it should be noted that there is still lacking enough information to be inferred with tumor motion with high accuracy.

Finally based on our dataset and motion prediction model used here in this study diaphragm surrogate has highest RMSE regarding with lung volume and external markers.

In this study, we investigated three external-internal surrogates to predict tumor motion in external beam radiotherapy as comparative study. Final analyzed results showed that optimum located external markers have the most predictive power in comparison with lung volume and diaphragm motion. Though the study here focuses on finding optimum external-internal surrogates using XCAT phantom, the proposed idea can be implemented on real patient data as our future studies.

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