Iranian Journal of Medical Physics

ijmp.mums.ac.ir

Clinical Accuracy Analysis and Error Modeling in the CyberKnife System; A Comparative Study

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ARTICLE INFO

Article type:
Original Paper

Article history:
Received: June 12, 2024
Accepted: Nov 17, 2024

Keywords:
Respiratory Tracking System
CyberKnife
Radiotherapy Setup Errors
Stereotactic Body Radiation Therapy

ABSTRACT

Introduction: This study conducted a clinical accuracy analysis of Synchrony Respiratory Tracking System across different CyberKnife generations (G3, G4, VSI, and M6) to provide comprehensive comparing across different generations. Additionally, appropriate regression models were developed to explain the behavior of standard deviation (SD) of the errors (correlation and prediction) and tumor motion in each region.

Material and Methods: The clinical log data was analyzed to assess the correlation and prediction errors. A retrospective analysis was conducted on 46 patients with thoracic or abdominal cancers treated using the CyberKnife G3. Furthermore, the F-test, P-value, and R^2 analysis were applied to model the SD of correlation and prediction errors as a function of tumor displacements across five lung regions and two abdomen regions.

Results: Using a systematic approach, linear, quadratic, cubic, or piecewise regression models were proposed for SD of the errors across tumor displacement. The estimated radial Synchrony error (mean±SD) for the CyberKnife G3, G4, VSI, and M6 was 2.60±0.93 mm, 2.00±0.60 mm, 1.79±1.16 mm, and 0.66±0.23 mm, respectively.

Conclusion: The results indicate that correlation error remains predominant in both lung and abdominal regions across all CyberKnife generations. However, prediction error has been significantly reduced in the G4, VSI, and M6 systems. This improvement is attributed to the newer generations incorporating a combination of historical pattern-matching filters and least-mean-square filters. Error modeling based on tumor motion in different regions reveals a linear relationship between errors and target amplitude in the lung region, while the liver and pancreas regions exhibit non-linear relationships.

► *Please cite this article as:*
Samadi Miandoab P, Setayeshi S, Saramad Sh. Clinical Accuracy Analysis and Error Modeling in the CyberKnife System; A Comparative Study. Iran J Med Phys 2025; 22: 36-43. 10.22038/ijmp.2024.80469.2411.

Introduction

A suitable alternative approach for patients who suffer from thoracic or abdominal cancers is stereotactic body radiation therapy (SBRT). SBRT is a technique that delivers highly precise and intense doses of radiation to tumor cells while minimizing damage to surrounding healthy tissues [1-4]. In this regard, one of the main challenges is to ensure that the 3-dimensional (3D) radiation dose is received properly to the dynamic tumors moved with the patient's breathing. Several commonly used strategies for motion management have been proposed, such as motion-encompassing, breath-holding, shallow breathing, respiratory gating, and real-time tumor tracking [5-9]. One promising method for motion compensation in SBRT is real-time tumor tracking, integrated into the CyberKnife system (Accuray Inc., Sunnyvale, CA). The CyberKnife system is an image-guided radiosurgery platform with a compact 6 MV Linear Accelerator (Linac) mounted to a robotic manipulator [10, 11].

The Synchrony Respiratory Tracking System (SRTS) in the CyberKnife system performs real-time tracking and delivery by using the correlation and prediction models [11-13]. The basic concept of the SRTS is to synchronize respiratory patterns with tumor motion, allowing a correlation model to estimate tumor motion based on the patient's breathing [7, 11]. Using periodic X-ray images, the correlation model is also updated every 60- or 120-seconds during treatment. Currently, the CyberKnife system employs three types of correlation models: linear, quadratic, or constrained fourth-order polynomials [14]. Note that the accuracy of radiation dose delivery is strongly impacted by the system latency due to data acquisition and robotic response. To mitigate this, the SRTS incorporates a prediction model to compensate for these delays [15, 16].

Error assessment is essential in the SRTS for investigating sources of uncertainties. According to previous studies, the uncertainties have three principal components [15-24]. 1) Targeting errors in radiation dose delivery, known as end-to-end (E2E) targeting errors, which arise from uncertainties in the robot's position within the 3D workspace, external

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optical tracking, and X-ray imaging systems. 2) Correlation errors, which are caused by uncertainties in the model types and internal-external dataset relationships. 3) Prediction errors, stemming from the strategy used to predict the tumor location ahead of time to compensate for the system latency. Although some reports have investigated uncertainties and errors in the SRTS of the CyberKnife system [15-24], the following concerns remain unresolved:

1. There are no comprehensive studies comparing the different generations of CyberKnife systems.
2. Limited research has been conducted to compare the accuracy of the SRTS in the lung and abdominal regions.
3. Error modeling for both the correlation and prediction models, specifically in relation to tumor motion across different regions and directions, remains insufficiently explored.

Concerning these subjects, a comprehensive analysis was conducted on 33 patients with thoracic cancers and 13 patients with abdominal cancers (160 treatment fractions) treated with CyberKnife G3 system. The obtained results were compared with different CyberKnife generations, including CyberKnife G4, VSI, and M6 systems, to provide a deeper understanding of the accuracy, errors, and uncertainties across the evolution of the CyberKnife. Furthermore, an analysis was performed to explain the behavior of model errors [standard deviations (SD) in both correlation and prediction models] in relation to tumor motion in different regions and directions, with the goal of identifying suitable models.

Materials and Methods

Data Source and Properties

Treatment log files from 46 patients with thoracic and abdominal cancers, treated using the CyberKnife G3 system, have been evaluated. The treatment characteristics, including the tumor sites, treatment fractions, peak-to-trough distance (cm), peak-to-peak time (sec), and treatment time (min), are shown in Table 1. It should be noted that the use of this data has been approved by the Georgetown Institutional Review Board for research purposes (IRB-2005-309) [25]. Furthermore, the technical accuracy of the SRTS in the CyberKnife G3 system has already been described in detail [23].

Logfile Analysis in CyberKnife Synchrony System

The CyberKnife system generates five log files; Markers.log file, ModelPoint.log file, Modeler.log file, Predictor.log file, and ERSIdata log file [15, 23]. In this study, the ModelPoint.log file is used to quantify correlation errors. The correlation error is obtained by comparing the locations of tumors determined in X-ray images to the tumor's location estimated by the correlation model. The difference between the corresponding modeling points and the prediction algorithm is computed using the prediction model. In this context, the Predictor.log file is used to analyze prediction errors. For correlation and predictor errors, the overall mean value and SD per fraction were computed in three directions (superior-inferior (SI), left-right (LR), and anteroposterior (AP) directions).

Table 1. Treatment characteristics for 46 patients (160 treatment fractions)

Area	Treatment Fractions	Peak-to-trough distance (cm)					Peak-to-peak time (sec)					Duration Time (min)
		Mean	Max	Min	SD	RMS	Mean	Max	Min	SD	RMS	
Lung Apex Left	3	0.03	0.09	0.00	0.01	0.04	3.81	8.04	1.09	0.67	3.87	30.56
Lung Bronchus Right	1	0.43	0.71	0.08	0.12	0.45	4.26	8.21	1.47	0.77	4.33	68.33
Lung Hilum	4	0.47	1.47	0.11	0.16	0.50	3.92	8.55	1.95	0.83	4.03	32.30
Lung Hilum Left	3	0.39	0.62	0.16	0.09	0.40	4.49	10.19	2.63	0.89	4.58	22.95
Lung Hilum Right	8	0.48	1.23	0.14	0.14	0.50	3.72	7.96	1.81	0.73	3.80	30.62
Lung LAP	1	0.81	1.69	0.22	0.23	0.84	5.13	9.52	2.85	1.02	5.23	33.33
Lung LLL	10	0.50	1.86	0.13	0.20	0.55	3.56	8.46	1.79	0.80	3.67	24.64
Lung LUL	33	0.45	1.21	0.13	0.14	0.48	3.75	8.04	1.82	0.75	3.83	30.24
Lung RLL	15	0.46	1.18	0.13	0.13	0.48	3.76	8.20	1.78	0.77	3.84	30.99
Lung RML	13	0.43	1.19	0.09	0.13	0.45	3.72	7.78	1.69	0.72	3.80	36.71
Lung RUL	15	0.45	1.31	0.13	0.14	0.48	3.71	8.25	1.83	0.78	3.81	29.67
Liver	6	0.48	2.13	0.10	0.18	0.52	3.59	8.73	1.67	0.87	3.71	39.34
Pancreas	28	0.48	1.45	0.11	0.15	0.50	4.12	8.51	2.10	0.80	4.21	36.96
Retro-peritoneum	10	0.38	1.08	0.07	0.14	0.41	4.09	8.35	2.17	0.81	4.18	32.84
Chest Wall	6	0.43	1.08	0.12	0.13	0.45	3.76	8.12	1.85	0.75	3.84	30.40
Internal mammary nodes	5	0.15	0.40	0.05	0.05	0.16	3.74	8.39	1.99	0.80	3.82	27.33

LLL, LUL, RLL, RML, RUL, indicate Left Lower Lung, Left Upper Lung, Right Lower Lung, Right Middle Lung, and Right Upper Lung, correspondingly.
SD = Standard Deviation, RMS = Root-Mean-Square.

The 3D radial error was also calculated as the square root of the sum of squares of errors in the SI, LR, and AP directions. In this study, inherent E2E for robotic tracking error, which was calculated through a test on a motion platform, was 0.50 ± 0.30 mm for all directions. Furthermore, the total tracking error (radial Synchrony error) is defined as the square root of the sum of squares of the correlation, prediction, and E2E tracking errors.

Error Modeling in CyberKnife Synchrony System

Hoogeman et al. [8] showed that there was a relationship between the SD of the errors (correlation and prediction errors) and motion amplitude. Therefore, in this study, the SD of the errors as a function of tumor amplitude motion in the lung and abdominal regions was investigated. The workflow of the proposed methodology is shown in Figure 1. The initial analysis tested the hypothesis of a significant statistical relationship between the SD of the correlation/prediction error and tumor amplitude. To evaluate this, an F-test was conducted on the input-output data. If the F factor is greater than a critical value Fc (F/Fc> 1), it means that the variation between the mean squares of SD the errors and the tumor amplitude is unlikely due to random chance. Additionally, if the P-value is also less than 0.05, the F-test is considered passed, indicating a statistically significant relationship between the input-output data. In summary, a large F factor points to a significant effect in the input-output data, while a small F factor (P-value less than 0.05) indicates that there is less than a 5% chance that the observed difference is due to randomness.

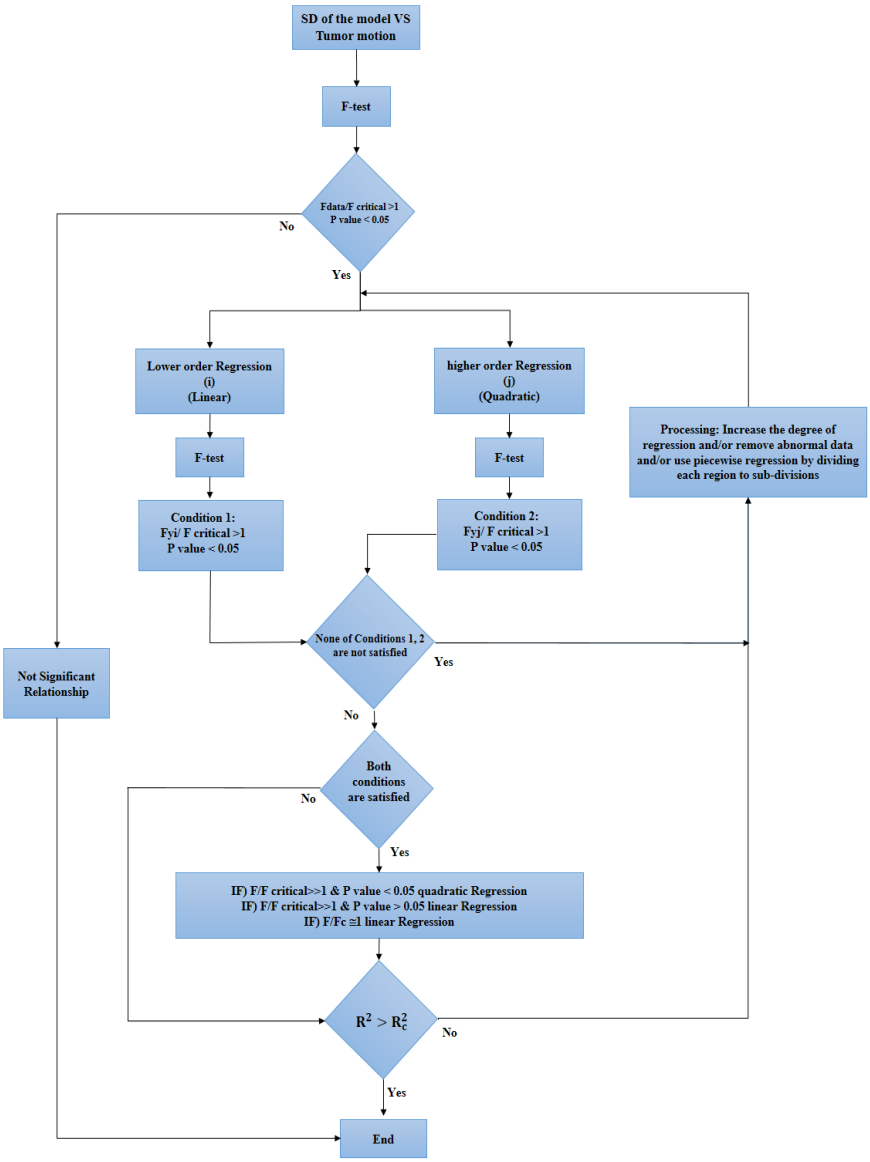

Figure 1. The workflow of analysis to investigate the standard deviation (SD) of the model error as a function of tumor motion

To develop an appropriate model for the SD of errors as a function of tumor amplitude, both lower-order (e.g., linear) and higher-order (e.g., quadratic) regression models were proposed. It is necessary to ensure that these models maintain the significant relationship between input-output data. Therefore, similar to the previous step, an F-test was performed on the data and the proposed regression models. If both models fail the F-test, modifications are required, such as applying higher-order or piecewise regression models, and/or processing the input-output data to remove outliers. If only one of the models passes the F-test, that model is selected as the primary regression model. However, if both models pass the F-test, an additional F-test is conducted to statistically compare the higher-order and lower-order models, where the highest coefficient of the higher-order model is set to zero for comparison. At this stage, different outcomes are possible:

1. If F/Fc is significantly greater than 1, and the P-value is less than 0.05, the higher-order regression model (e.g., quadratic) is selected.
2. If F/Fc is much greater than 1, and the P-value is greater than 0.05, the lower-order regression model (e.g., linear) is chosen.
3. If F/Fc is close to 1, the lower-order regression model (e.g., linear) is preferred.

Finally, to assess the strength of the relationship between the selected regression model and the data, the R^2 value is calculated. In this context, the F-test evaluates the goodness-of-fit, while the R^2 value indicates how well the model explains the variation in the data [26]. Noted, the R2 value alone does not determine the adequacy of a regression model. Instead, it indicates the percentage of the variation in the output variable (SD of the errors) explained by the input variable. Thus, an R^2 value of one means the model accounts for all variability in the response data around the mean. For example, if the R^2 value is 0.50, and the model passes both the F-test and the P-value test, it suggests that, with good statistics support, the model explains about half of the observed variation within the data. In this study, the model is considered valid if the R^2 value exceeds a predefined threshold (e.g., Rc^2=0.30); otherwise, the process is revisited to the processing section.

Results

Patient characteristics

In this study, 160 treatment fractions across 46 cancer patients were analyzed. Peak-to-trough distance (mean ± SD) in thoracic cancers (33 patients) and abdominal cancers (13 patients) was 0.47±0.15 (cm) with the ranges 0.00-5.12 (cm) and 0.48±0.15 (cm) with the ranges 0.00-4.62 (cm), respectively. The mean total tracking time per fraction was 29.30 min (range: 8.30-80.80 min) and 36.90 min (range: 5.00-106.30 min) for thoracic and abdominal cancers, respectively. In this regard, Table 1 provides detailed results on peak-to-trough distance and total tracking time across various tumor locations.

Systematic Review

The clinical log data from 160 treatment fractions were analyzed to assess the model errors. Histogram analysis of correlation and predictor errors for all treatment fractions are shown in Figure 2a and Figure 2b, respectively. The largest correlation and predictor errors were observed in the SI direction. The total absolute mean (range) of correlation errors across all patients was 0.98 mm (0.12-2.50 mm) in the SI direction, 0.92 mm (0.15-2.13 mm) in the LR direction, 0.47 mm (0.00-1.25 mm) in the AP direction, and 1.50 mm (0.50-3.00 mm) in the 3D radial. On the other hand, the total absolute mean (ranges) of the prediction errors was 1.21 mm (0.10- 4.00 mm) in the SI direction, 0.92 mm (0.10-3.90 mm) in the LR direction, 0.90 mm (0.00-5.00 mm) in the AP direction, and 1.85 mm (0.00-3.00 mm) in the 3D radial.

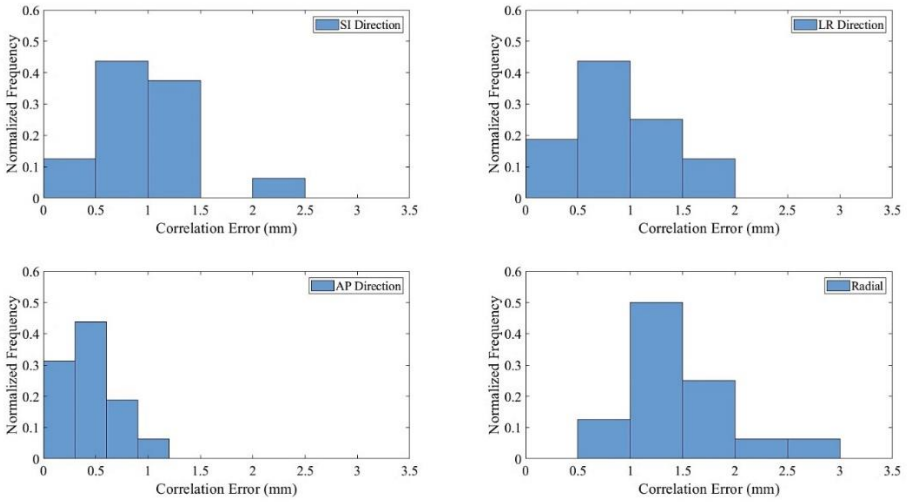

Figure 2a. Histogram analysis of the absolute mean correlation error for all treatment fractions (SI= superior-inferior, LR=left-right, and AP=anteroposterior)

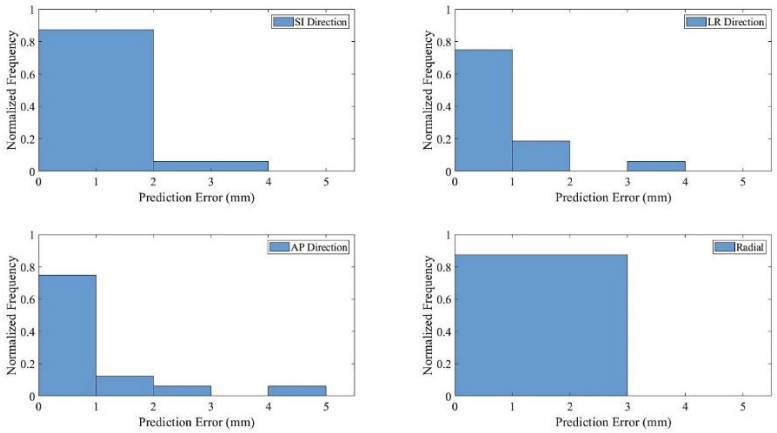

Figure 2b. Histogram analysis of the absolute mean prediction error for all treatment fractions (SI= superior-inferior, LR=left-right, and AP=anteroposterior)

Table 2. A systematic review of different CyberKnife generations regarding the correlation and predictor tracking errors

CyberKnife type		Number of patients &Tumor location	Correlation error (mm) Absolute Mean ± SD			Prediction Error (mm) Absolute Mean ± SD		
			SI	LR	AP	SI	LR	AP
In this study	CyberKnife G3	33 patients (116 fractions) with thoracic cancers	0.95±0.22	0.93±0.20	0.49±0.19	0.71±0.30	0.69±0.29	0.58±0.24
In this study	CyberKnife G3	13 patients (44 fractions) with abdomen cancers	1.11±0.29	0.86±0.19	0.36±0.15	3.40±1.05	1.89±0.68	2.32±0.84
Hoogeman et al. [8]	CyberKnife G4	44 patients (158 fractions) with lung cancers	0.80±0.40	0.40±0.30	0.80±0.40	00±00	00±00	00±00
Floriano et al. [20]	CyberKnife VSI	16 patients (54 fractions) with thoracic cancers	1.93±0.26	1.18±0.26	1.42±0.17	0.60±0.16	0.20±0.1	0.25±0.13
Winter et al. [16]	CyberKnife VSI	27 patients (118 fractions) with liver cancers	1.15±1.55	0.7±0.98	0.63±0.83	0.18±0.10	0.15±0.09	0.09±0.07
Nakayama et al. [17]	CyberKnife VSI	42 patients (211 fractions) with lung cancers	0.70±0.43	0.36±0.16	0.44±0.22	0.13±0.11	0.03±0.02	0.03±0.02
Yang Z-Y et al. [22]	CyberKnife VSI	22 patients (92 fractions) with lung cancers	0.39±1.12	0.19±0.81	0.25±1.02	0.0±0.14	0.0±0.14	0.0±0.08
Yang B et al. [27]	CyberKnife M6	Phantom study with 15 (mm) motion amplitude	0.11±0.09	0.10±0.06	0.12±0.09	0.10±0.02	0.001±0.003	0.10±0.02
		Phantom study with 20 (mm) motion amplitude	0.13±0.10	0.10±0.08	0.13±0.10	0.16±0.03	0.001±0.001	0.16±0.03

Superior-Inferior (SI), Left-Right (LR), and Anterior-Posterior (AP).

The reported results from the CyberKnife G3 were compared to other CyberKnife generations, including G4, VSI, and M6, to enhance understanding of accuracy, errors, and uncertainties [8, 16, 17, 20, 22, 27]. The results (mean ± SD) are summarized in Table 2. In the CyberKnife G3 system, the prediction model operates with a latency of 200 ms latency, whereas in CyberKnife G4, VSI, or M6 systems, the temporal delay was reduced to 115 ms. Additionally, Table 1 in the Supplementary Material provides a summary of the correlation and prediction error ranges for each CyberKnife generation, including CyberKnife G3, G4, VSI, and M6 systems in the lung region.

Error Modeling in CyberKnife System

The proposed models for the correlation and prediction errors, based on tumor motion in the lung and abdomen, are presented in Supplementary Table 2. According to this Table, all data across different regions passed the F-test with a P-value less than 0.05, demonstrating a significant relationship between all the input-output data. In the second step, only the linear and quadratic models for all regions were considered, and the F/Fc and P-value tests for these models were conducted. Passing these tests shows that the regression model is statistically significant. As shown in Supplementary Table 2, the tests for the linear models in lung (right lower lung - RLL) (correlation error) and liver (correlation and prediction errors) failed, as detailed in Supplementary Table 3. In addition, both the linear and quadratic models for the lung (right middle lung - RML) (correlation error) and pancreas (correlation and prediction errors) also failed, as indicated in Supplementary Table 3. A more detailed description of the reported results (Supplementary Tables 2 and 3) can be found in the Supplementary Materials - Section 1.

Discussion

This study was conducted to evaluate the errors and uncertainties associated with the SRTS in the CyberKnife system. Understanding these errors and uncertainties, along with their relationship to tumor

motion, is critical for accurately calculating treatment margins. In addition, a comparison analysis across different CyberKnife generations was performed to provide deeper insights into the accuracy, errors, and uncertainties throughout the system's evolution.

The histogram analysis demonstrates that the largest correlation and prediction errors occurred in the SI direction (Figure 2a and Figure 2b). Given that the CyberKnife G3 system uses a historical pattern-matching filter for the prediction model, relatively high prediction errors are expected. In this regard, Hoogeman et al. [8] reported that the SDs of prediction errors could reach up to 2.90 mm using the CyberKnife G3 system. Furthermore, they observed a roughly 50% reduction in error when comparing the old and new versions of the prediction model, as the system latency was reduced from 200 ms to 115 ms. Murphy et al. [28] also show that the total tracking error significantly improves when the system latency is reduced by 40%. As shown in Table 2, the prediction error decreases substantially with system latency reductions or the use of newer software versions. However, throughout the evolution of the CyberKnife system, the correlation error has remained dominant. Supplementary Table 1 highlights the range of correlation and prediction errors for various CyberKnife generations, supporting this observation. Overall, the radial Synchrony error in the CyberKnife G3 system was 2.60±0.93 mm, while in the CyberKnife G4, VSI, and M6 systems, this error decreased to was 2.00±0.60 mm, 1.79±1.16 mm, and 0.66±0.23 mm, according to studies by Liu et al. [21], Winter et al. [16], and Yang et al. [27].

Table 2 provides a comprehensive comparison across four CyberKnife generations, detailing tumor locations, and tracking errors for both the correlation and prediction models in each direction. As expected, the largest correlation and predictor errors were in the SI direction. Masao Nakayama et al. [17] and Floriano et al. [20] reported overall mean±SD correlation errors of 0.95±0.43 and 1.50±0.80, respectively, for 42 and 16 lung cancer patients. The correlation error estimated in this study (1.47±0.45 mm) aligns with these finding. However, due to the older version of the prediction model used in CyberKnife G3 system, our prediction error was higher compared to other studies. Winter et al. [16] and Malinowski et al. [29] also reported the correlation model error in liver cancer patients, founding 1.70±1.10 mm and 1.60±1.00 mm for the absolute mean±SD correlation error, respectively [16, 29]. The correlation error estimated in this work (1.57±0.60 mm) closely matches these results.

In this study, various regression models, including linear, non-linear, or piecewise regressions, were implemented to explain the SD of errors as a function of tumor motion across different regions. Using the F-test, P-value, and R^2 values, statistically sound and well-fitted models were identified. Previous researches have treated the lung region as a unified region [8, 17]; however, in this work, the lung tumors were categorized into five distinct groups (left lower lung - LLL, left upper lung - LUL, right lower lung - RLL, right middle lung - RML, and right upper lung - RUL), and a suitable regression model was developed for each group. The results in Supplementary Table 3 show that for all lung regions, linear, non-linear, or piecewise regression models exist, correlating the SD of correlation and prediction errors with the target amplitude exist. In other words, the correlation and prediction errors are influenced by both tumor amplitude and position. The results indicate that the correlation error models for the lung LLL, LUL, and RUL, as well as the prediction error models for the lung LUL and RML, exhibit linear behavior. The correlation error models for the lung RLL and RML, along with the prediction error models for the lung LLL, RLL, and RUL, follow a quadratic pattern. These findings demonstrate a moderate relationship between model errors and target amplitude in the lung region, aligning with the conclusions of Nakayama et al. [17]. In the liver region, the correlation error model ($R2=0.61$, $P<0.05$) has a strong relationship, while the prediction error model ($R2=0.37$, $P<0.05$) demonstrates a moderate relation with the amplitude, both exhibiting non-linear behavior. In contrast, in the pancreas region, both the correlation error model ($R^2=0.80$, $P<0.05$) and prediction error model ($R^2=0.78$, $P<0.05$) show a strong relationship with tumor motion amplitude, with fully non-linear behavior. Note that the relations between the SD of errors and tumor motion varies based on the tumor size and position.

There are few limitations to the current study that should be taken into consideration. First, the clinical log data analysis was performed using the CyberKnife G3 system; applying the same approach to new CyberKnife generation would provide more comprehensive insights. Second, the number of treatment fractions in the liver region is relatively small, which may limit the robustness of the error model in relation to tumor motion. Third, the regression models presented in this work represent only the average behavior of SD errors relative to the tumor motion. In future research, by factoring in tumor size and precise location, and following the systematic strategy outlined here, the models can be refined and enhanced.

Conclusion

This study compares the errors and uncertainties of correlation and prediction models across different CyberKnife systems for different tumor locations. The radial Synchrony error was 2.60±0.93 mm for the CyberKnife G3 system, 2.00±0.60 mm for the CyberKnife G4 system, 1.79±1.16 mm for the CyberKnife VSI system, and 0.66±0.23 mm for the CyberKnife M6 system. The results also show that while the correlation error remains dominant in the lung and abdomen regions, the prediction error has been significantly reduced by the changes introduced in the latest generation. Given that the CyberKnife G3 system uses the historic pattern-matching filter to compensate for the system latency, whereas the CyberKnife G4,

VSI, and M6 systems employ a combination of the historic pattern-matching filter and a least mean square filter for improved accuracy.

The study investigated well-fitted models with strong statistical support for the SD of errors versus tumor motion across different regions of the lung, liver, and pancreas. The findings reveal that: 1) the lung region exhibits a more linear behavior between model errors (both the correlation error and prediction error models) and target amplitude, 2) the liver region demonstrates a more non-linear behavior between model errors and target amplitude, and 3) the pancreas region show a non-linear behavior between the both correlation and prediction errors and tumor motion amplitude.

Acknowledgment

The authors acknowledge Sonja Dieterich for providing access to the clinical database. Also, this work was kindly supported by the Iran National Elites Foundation (INEF) [grant no.15/32930] and Amirkabir University of Technology.

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