Conversion and Validation of Rectal Constraints for Prostate Carcinoma Receiving Hypofractionated Carbon-ion Radiotherapy With a Local Effect Model

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Research

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Abstract

Purpose: The study objective was to convert the microdosimetric kinetic model (MKM) rectum constraints for 16-fraction carbon-ion radiotherapy (CIRT) to local effect model (LEM) constraints for 12-fraction, 8-fraction, and 4-fraction CIRT for prostate carcinoma patients (PCAs).

Methods: Two strategies were employed. To understand the fractionation effects, MKM linear-quadric (LQ) strategy first converted MKM rectum constraints for 16-fraction CIRT to 12-fraction, 8-fraction, and 4-fraction CIRT. To examine the differences in the biophysical models, MKM constraints were converted to LEM constraints using an RBE-conversion model. The LEM LQ strategy first converted MKM rectum constraints for 16-fraction CIRT to LEM constraints using the RBE-conversion model. Then, the LEM constraints converted the 16-fraction constraints to the rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRT using the LQ model. The LEM rectum constraints for 16 and 12-fraction CIRTs were compared to the rectum doses and the clinical follow-ups in 40 patients.

Results: The 16-fraction NIRS rectum constraint Dmax < 60.8 Gy(RBE) and CNAO rectum constraint D1cc < 66.00 Gy(RBE) were converted by MKM LQ strategy to LEM constraints 58.01 and 55.97 Gy(RBE) (12fx), 45.47 and 43.97 Gy(RBE) (8fx), and 29.64 and 28.67 Gy(RBE) (4fx) and by LEM LQ strategy to 61.73 and 59.69 Gy(RBE) (12fx), 53.03 and 51.33 Gy(RBE) (8fx), and 40.10 and 38.88 Gy(RBE) (4fx). Differences of 36.13% were found. No late rectum complications were reported.

Conclusions: The LEM rectum constraints from MKM LQ strategy were more conservative and can be used as the reference constraints for starting the hypofractionated CIRT.

Introduction

From the experimental carbon-ion radiotherapy (CIRT) started in 1950s [1, 2] to the clinical carbon ion radiotherapy started in 1994[3, 4], up to now, more than half a century of experience demonstrated the outstanding physical and biological advantages of CIRT for treating human malignant tumors, such as prostate carcinoma (PCA) [5]. Since 1995, the National Institute for Quantum and Radiological Science and Technology, the former National Institute of Radiobiological Science (NIRS) in Japan, has investigated the use of hypofractionated CIRT to treat PCAs [6, 7] and have long-time follow-up data [8].

Since the α/β ratio for PCA is lower than the surrounding rectum, bladder, and urethra [6], hypofractionated CIRT not only improves local tumor control, but also reduces gastrointestinal and genitourinary morbidities. Therefore, since 1995, the total fractionations for PCA CIRT in NIRS has been decreased from 20 to 16, then to 12. Now a 4-fraction PCA CIRT clinical trial is ongoing [6].

Hypofractionated CIRT clinical trials with PCA have been well described [6, 9]. However, the dose constraints for rectums were only published for 16-fraction and 20-fraction CIRT [10]. Furthermore, these dose constraints are based on the microdosimetric kinetic model (MKM). By converting from their constraints, the local effect model (LEM) rectum constraints were established [11] and successfully applied to our dose-escalation clinical trial, which examined dose escalations to 4.10 Gy(RBE) per fraction by 16 fractions. A new 12-fraction protocol has also been in use since September 2019. The major issue for starting shorter course protocols, even the 4-fraction protocol, is how to impose feasible rectum dose constraints for the LEM-based centers.

In photon radiotherapy, a linear-quadratic (LQ) model [12] has been widely used to convert doses between different fractionations, based on biological equivalent doses. Our previous study [11] established an RBE-conversion model to

convert RBE-weighted doses with MKM (MKM doses) to the RBE-weighted dose with LEM (LEM doses). In this study, based on the LQ model and the RBE-conversion model, two strategies were established to convert the MKM NIRS rectum constraints (referred to as MKM rectum constraints) for 16-fraction CIRT to LEM constraints for 12-fraction, 8-fraction, and 4-fraction CIRTs. In addition, follow-ups in 40 previously treated patients were used to validate the established constraints.

Methods And Materials

Patient information

Forty PCAs, who received 16-fraction and 12-fraction CIRT at our center from October 2018 to January 2020, were selected from our clinical database. Syngo (V13B, Siemens, Germany) with a LEM was used for their clinical treatment planning. Thirty-eight patients received 16-fraction CIRT with 4.00 Gy(RBE) to 4.10 Gy(RBE) dose per fraction and two patients received 12-fraction CIRT with a dose per fraction of 4.50 Gy(RBE). Rectum dose-volume histograms (DVH) from Syngo were collected for validation purposes.

Framework of the study

Figure 1 describes the framework of the study. Two strategies were employed, the MKM LQ strategy and the LEM LQ strategy,

For the MKM LQ strategy, in Step 1.1 (LQ), the MKM rectum constraints for 16-fraction CIRT were converted to the MKM rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRTs based on a LQ model. This conversion was conducted in line with previous work by Uhl M et al. An a/b ratio of 3.9 Gy for the rectum [13] was used. In Step 1.2 (RBE conversion), three MKM rectum constraints were converted to the LEM rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRTs using a RBE-conversion model.

For the LEM LQ strategy, in Step 2.1 (RBE conversion), the MKM rectum constraints for 16-fraction CIRT were converted to the LEM rectum constraints for 16-fraction CIRT using the RBE-conversion model. In Step 2.2 (LQ), the LEM rectum constraints for 16-fraction CIRT were converted to the LEM rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRTs, based on the LQ model.

RBE-conversion model and LQ model

Our previous study [11] established a RBE-conversion model for 16-fraction CIRT, this study additionally developed three RBE-conversion models respectively for 12-fraction CIRT with MKM prescriptions 5.3 Gy(RBE)/fx, for 8-fraction CIRT with MKM prescription 7.0 Gy(RBE)/fx, and for 4-fraction CIRT with MKM prescription 10.0 Gy(RBE)/fx. These works were done with our research treatment planning system Raystation (8A, Raysearch, Sweden). Similarly, 10 patients were randomly selected from 40 enrolled patients. Their planning CTs and contouring from Syngo were exported to the Raystation (V8A, Raysearch, Sweden). The clinical target volumes included the prostates and the periphery seminal vesicles at high risk. The planning target volumes were generated based on the clinical target volumes by adding 10.0 mm in the left-right directions, 5.0 mm in the head-feet directions, and 3.0 mm in the superior-inferior directions. The process of model establishment in brief were that the MKM plans were generated and optimized to fulfill the MKM prescriptions, and then LEM plans were generated by recalculating the physical doses from MKM plans. Based on the isodose volumes from the MKM and LEM plans, a conversion curve for converting the MKM doses to LEM doses was established.

For the LQ model, the following equation was used:

$$N_2 * d_2 * (1 + d_2/(\alpha/\beta)) = N_1 * d_1 * (1 + d_1/(\alpha/\beta))$$

where α/β is 3.9 Gy, *d* is the dose per fraction, and *N* is the total fractionation.

Rectum constraints for 16-fraction CIRT

NIRS published their rectum dose constraints for 16-fraction CIRT [10, 14] with MKM, which were percentage volume constraints. Choi [15] et al. from Centro Nazionale di Adroterapia Oncologica (CNAO), Italy, first converted NIRS constraints to LEM. Based on that, they additionally injected their experience and published their own constraints, which were absolute volume constraints. In this study, CNAO constraints were compared to the constraints from our previous study and then converted to the LEM rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRT based on our two strategies. To perform MKM LQ strategy on the CNAO constraints, their LEM constraints were converted backward to the corresponding MKM constraints based on our RBE-conversion model.

Conversion uncertainty

The LQ model is an analytical approach. However, the RBE-conversion model were based on only 10 patients. To evaluate its conversion uncertainty, the other 30 patients were used to generate a new RBE-conversion model for 16-fraction CIRT and compared to the counterpart which based on 10 patients.

Clinical evaluation

Clinical follow-up data were collected and compared to the LEM rectum constraints for 16-fraction CIRT and 12-fraction CIRT. Patients were followed up by a radiation oncologist at one month, then every three months after CIRT completion in the first two years, every six months in the next three years, and yearly afterward. Late toxicity was evaluated according to the toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer [16].

Results

CNAO converted the following MKM rectum constraints in terms of percentage volume to LEM for 16-fraction CIRT: dose received by 20% of the rectum (D20%) ≤ 28.8 Gy(RBE), D10% ≤ 46.40 Gy(RBE), D5% ≤ 60.00 Gy(RBE), and Dmax ≤ 66.00 Gy(RBE). The LEM doses converted by our RBE-conversion model [11] versus their LEM doses were D20% ≤ 43.14 Gy(RBE) versus 42.90 Gy(RBE), D10% ≤ 58.48 Gy(RBE) versus 57.70 Gy(RBE), D5% ≤ 68.68 Gy(RBE) versus 68.20 Gy(RBE), and Dmax ≤ 73.09 Gy(RBE) versus 72.00 Gy(RBE).

Table 1 shows the MKM rectum constraints of percentage volume for 16-fraction CIRT and the converted LEM constraints for 16-fraction, 12-fraction, 8-fraction, and 4-fraction CIRT resulting from the two strategies.

Table 1
The MKM rectum constraints for 16-fraction CIRT and the converted LEM constraints for 16-fraction, 12-fraction, 8-fraction, and 4-fraction CIRT from two strategies.

$^{4}D_{MKM}$16fx	$^{5}D_{LEM}$16fx	$^{1}D_{LEM}$ 12fx			$^{2}D_{LEM}$ 8fx			$^{3}D_{LEM}$ 4fx		
		^{6}MKM LQ	^{7}LEM LQ	^{8}Diff	MKM LQ	LEM LQ	Diff	MKM LQ	LEM LQ	Diff
D20%≤28.80	43.14	37.60	39.55	5.18%	30.40	34.60	13.82%	20.80	26.83	28.98%
D10%≤46.40	58.48	49.74	53.08	6.72%	39.25	45.86	16.83%	25.66	34.96	36.24%
^{9}D5%≤56.00	65.11	55.27	58.91	6.58%	43.41	50.69	16.76%	28.33	38.42	35.59%
^{10}Dmax≤60.80	68.33	57.60	61.73	7.16%	45.13	53.03	17.50%	29.46	40.10	36.13%
1 The LEM rectum constraints for 12-fraction CIRT [Gy(RBE)];										
2 The LEM rectum constraints for 8-fraction CIRT [Gy(RBE)];										
3 The LEM rectum constraints for 4-fraction CIRT [Gy(RBE)];										
4 The MKM rectum constraints for 16-fraction CIRT [Gy(RBE)];										
5 The LEM rectum constraints for 16-fraction CIRT from our previous study [Gy(RBE)];										
6 The LEM rectum constraints converted from MKM LQ strategy;										
7 The LEM rectum constraints converted from LEM LQ strategy;										
8 Difference= (LEM LQ-MKM LQ)/MKM LQ*100%;										
9 Based on the publication [14], NIRS used D5%≤56.00 Gy(RBE) as their constraints;										
10 Based on the publication [14], NIRS used Dmax ≤ 60.80 Gy(RBE) as their constraints.										

CNAO also proposed absolute volume constraints for clinics. Table 2 shows the CNAO constraints for 16-fraction CIRT were converted to constraints for 12-fraction, 8-fraction, and 4-fraction CIRT using our two strategies.

Table 2
LEM CNAO rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRT converted based on two strategies

[4]D_{LEM}16fx	[1]D_{LEM} 12fx			[2]D_{LEM} 8fx			[3]D_{LEM} 4fx		
	[5]MKM LQ	[6]LEM LQ	[7]Diff	MKM LQ	LEM LQ	Diff	MKM LQ	LEM LQ	Diff
$D_{10cc} \leq 54.00$	45.97	49.14	6.90%	36.53	42.59	16.58%	23.94	32.60	36.19%
$D_{5cc} \leq 61.00$	51.70	55.30	6.96%	40.73	47.70	17.12%	26.62	36.28	36.30%
$D_{1cc} \leq 66.00$	55.97	59.69	6.65%	43.97	51.33	16.75%	28.67	38.88	35.59%
1 The LEM rectum constraints for 12-fraction CIRT [Gy(RBE)];									
2 The LEM rectum constraints for 8-fraction CIRT [Gy(RBE)];									
3 The LEM rectum constraints for 4-fraction CIRT [Gy(RBE)];									
4 The CNAO rectum constraints for 16-fraction CIRT of absolute volumes [Gy(RBE)];									
5 The LEM rectum constraints converted from MKM LQ strategy;									
6 The LEM rectum constraints converted from LEM LQ strategy;									
7 Difference= (LEM LQ-MKM LQ)/MKM LQ*100%.									

Table 3 lists the DVH parameters for the 38 patients receiving 16-fraction CIRT. Eight patients slightly exceeded the D20% constraints, and four of eight patients slightly exceeded D10% constraints (see the dark grey in Table 3). The DVH parameters for two patients receiving 12-fraction CIRT were within the LEM constraints for the 12-fraction CIRT by the MKM LQ strategy.

Table 3
DVH parameters from 40 patients versus the LEM constraints

Constraints (16fx)	[1]LEM Constraints	[2]DVH Summary	
		[3]Median	[4]Maximum
Our previous study	D20%≤43.14	37.91	[5]49.96
	D10%≤58.48	53.53	[6]62.12
	D5%≤65.11	59.96	65.18
	Dmax ≤ 68.33	62.91	66.61
CNAO study	$D_{10cc} \leq 54.00$	37.58	53.52
	$D_{5cc} \leq 61.00$	53.43	60.30
	$D_{1cc} \leq 66.00$	62.54	65.86
Constraints (12fx)	[7]LEM Constraints	Patient 1	Patient 2
Constraints from MKM LQ	D20%≤37.60	24.27	30.53
	D10%≤49.74	38.65	46.75
	D5%≤55.27	46.45	52.86
	Dmax ≤ 57.60	54.11	55.37
	D10cc ≤ 45.97	29.89	27.10
	D5cc ≤ 51.70	42.17	44.55
	D1cc ≤ 55.97	53.20	54.80

1 LEM rectum constraints for 16-fraction CIRT, the percentage volume constraints were from our previous study, the absolute volume constraints were from CNAO [Gy(RBE)];

2 The value of D20%, D10%, D5%, Dmax, D_{10cc}, D_{5cc}, and D_{1cc} parameters processed from each patients' rectum DVH of 38 patients who received 16-fraction CIRT and 2 patients who received 12-fraction CIRT [Gy(RBE)] ;

3 The median value of DVH parameters among the 16-fraciton group and 12-fraction group [Gy(RBE)];

4 The maximum value of DVH parameters among the 16-fraciton group and 12-fraction group [Gy(RBE)];

5 Eight patients were over the D20% constraints for 16-fraction CIRT;

6 Four of 8 patients were over the D10% constraints for 16-fraction CIRT;

7 The LEM rectum constraints converted from MKM LQ strategy for 12-fraction CIRT.

Up until Aug 2020, the median follow-up was 10.8 months (7.1–20.8). None of the patients reported late rectum complications. For the 16-fraction CIRT, the differences between the RBE-conversion model based on 10 patients and the model based on 30 patients was – 0.62% (-3.02–2.49%). Detailed information is presented in figure A.1, Appendix.

Discussion

Two strategies were established to convert the MKM rectum constraints for 16-fraction CIRT to the LEM rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRTs, and up to 36.30% difference was found. The RBE-conversion model based on 10 patients were comparable to the conversions based on 30 patients. The follow-up data shows that the LEM rectum constraints for 16-fraction and 12-fraction CIRT were safe.

NIRS published their rectum constraints for 16-fraction and 20-fraction CIRT, in which they used the LQ model to convert their rectum constraints from 16-fraction to 20-fraction [5]. Based on their success, a similar process was carried out to generate new constraints for our shorter treatment protocols. Furthermore, an RBE-conversion model was introduced to convert the MKM dose to LEM dose or vice versa. Based on these models, the MKM prescription and organs at risk (OAR) constraints can be converted between MKM and LEM.

Former 20-fraction to 12-fraction CIRT with MKM indicated that the shorter CIRT course could greatly reduce treatment costs while maintaining the same clinical outcomes [6, 9]. Therefore, for the benefit of patients in our center, a new clinical trial of 12-fraction CIRT for PCA patients with LEM was initiated to escalate the prescription from 54.00 Gy(RBE) to 58.80 Gy(RBE). To prepare for this new study, we sought to derive the rectum constraints for this protocol. If our clinical trial validates the feasibility of the converted rectum constraints, other OAR constraints may also be converted by these methods and used for shorter CIRT.

The major difference between the LEM rectum constraints from the two strategies was whether the overall conversions included the RBE-conversion model conversions. Previous studies showed that LEM Gy(RBE) is smaller than MKM Gy(RBE) when doses are more than 5.00 Gy(RBE)[17, 18], e.g. MKM dose 10 Gy(RBE)/fx equals 7.95 Gy(RBE)/fx, a 20.05% difference. Therefore, the constraints from the MKM LQ strategy were smaller than the constraints from the LEM LQ strategy, especially for the 4-fraction CIRT. However, since the LQ model is mostly used for photon radiotherapy, not CIRT, dose-escalation studies are still needed to confirm the feasibility of the constraints. A reasonable choice would be to start with the LEM constraints based on the MKM LQ strategy.

Yosuke et al. [9] published the preliminary results of CIRT using spot scanning for treating PCAs. They used a 12-fraction protocol. This fractionation was similar to the NIRS apparatus [6] and our new clinical trials. The spot scanning delivery was the same as ours. The five-year results of the Yosuke study independently verified the NIRS clinical results, demonstrating that the 12-fraction protocol has similar clinical outcomes and OAR complications as the 16-fraction CIRT. These results gave us confidence in the future of our clinical study. However, since the total fractionation decreased, the accuracy and consistency of the patient setups became more important. In the Yosuke study, patient immobilization and treatment were similar to the NIRS study [6]. Furthermore, they developed a 2D positioning system to make sure the patient setup error was less than 1 mm, and an in-room CT was utilized to verify the patient setup at the end of the first treatment and the first treatment of every week. In our center, a similar method was applied; a 2D-X-ray positioning system was used to correct patient bone anatomy and in-room CTs were conducted to verify the patient setup again before every fraction treatment.

The prescription and rectum constraints in the Yosuke study, with 12-fraction CIRT, support the feasibility of our conversion. In their study, the rectum constraint was given as V80% < 10 cc and the prescription was 51.6 Gy(RBE)/12fx. Based on the RBE-conversion model for 12-fraction CIRT, the corresponding LEM constraint and prescription were 49.00 Gy(RBE) < 10 cc and 55.71 Gy(RBE)/12fx (4.64 Gy(RBE)/fx). These parameters were similar to the D10cc < 49.14 Gy(RBE) converted from LEM CNAO constraints using LEM LQ strategy (see Table 3) and our clinical prescription for 12-fraction CIRT.

Based on the LEM rectum constraints for 12-fraction CIRT and the Japanese experience with 12-fraction CIRT, a proposed clinical procedure for performing the 12-fraction CIRT were that: use the LEM constraints from MKM LQ

strategy as the starting constraints; as the prescription is escalated, if a patient's rectum dose was more than the LEM constraints from the MKM LQ strategy but lower than the LEM LQ strategy, this patient could still receive CIRT; however, during treatment and post-treatment follow-up, physicians may closely monitor rectum complications, since the complication report is crucial in adapting the constraints; for the patient whose rectum doses were more than the constraints from the LEM LQ strategy, the physician may ask the patient to receive another treatment first until his prostate is small enough so the rectum dose is lower than the LEM constraints from the LEM LQ strategy.

The LEM rectum constraints for 12-fraction, 8-fraction, and 4-fraction CIRT are based on clinical experience with 16-fraction CIRT. Whether the 16-fraction experience applies to smaller fractionations is still unknown. Furthermore, the translation from 16-fraction CIRT to smaller fractionation CIRTs is based on the LQ model, which may not be sufficiently precise for CIRT. In addition, NIRS applied a one-beam-per-day, four-fraction-treatment-per-week protocol. However, our center applies a two-beam-per-day, five-fraction-treatment-per-week protocol. The impact of these differences on the RBE-conversion model and rectum complication has not been investigated. Furthermore, our median patient follow-up time was only 10 months, but the longer NIRS follow-up time showed that 81% of the late rectum toxicities occurred within two years after CIRT. Thus, the follow-up times for late toxicities in this study may not be long enough. However, based on the limited follow-up, the complication reports related to the overdoses of urethra were more frequent after the prescription was escalated from 4.0 Gy(RBE) to 4.1 Gy(RBE) per fraction of 16-fraction CIRT and 12-fraction CIRT. It may be more frequent as the fractionation decreased, which may need more consideration.

Conclusions

Two strategies were established to convert the MKM rectum constraints for 16-fraction CIRT to the LEM constraints for 12-fraction, 8-fraction, and 4-fraction CIRT for PCAs. Significant differences were found in the converted constraints. The clinical follow-ups from the patients receiving 16-fraction and 12-fraction CIRT showed the LEM rectum constraints were safe so far. Therefore, our 12-fraction CIRT for PCAs could refer to the LEM rectum constraints from the MKM LQ strategy as the starting constraints. However, since the patient setup plays an important role, special attention should be paid to managing the patient setup in the future.

Abbreviations

MKM: microdosimetric kinetic model; CIRT: Carbon-ion Radiotherapy; LEM: local effect model; PCA: prostate carcinoma; LQ model: linear-quadratic model; CNAO: Centro Nazionale di Adroterapia Oncologica (CNAO), Italy; NIRS: National Institute of Radiobiological Science, Japan; 16fx: 16-fraction CIRT; 12fx: 12-fraction CIRT; 8fx: 8-fraction CIRT; 4fx: 4-fraction CIRT; MKM dose: RBE-weighted doses with MKM; LEM dose: RBE-weighted doses with LEM; OAR: organ at risk.

Declarations

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Authors' Contributions

WW, P, K, and Q designed the study. WW and P performed the study. YXZ, ZJ, JF, K and GL helped analyzed the results. P and ZS helped collect patients' follow-ups. WW and P wrote the manuscript. All authors reviewed and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The retrospective study was approved by the Ethical Review Board of Shanghai Proton and Heavy Ion Center, and written informed consent could be obtained from all patients prior to inclusion into the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

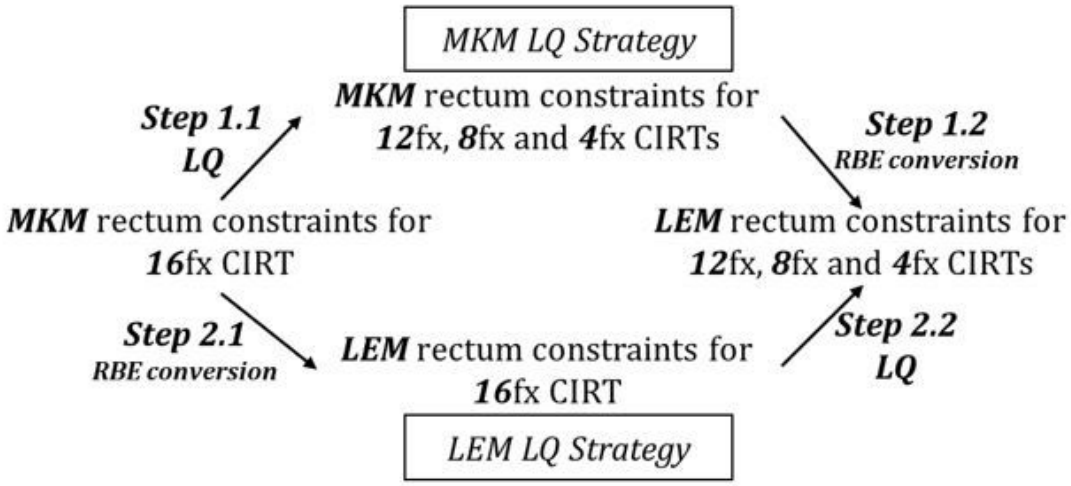

Figure 1

The framework of this study

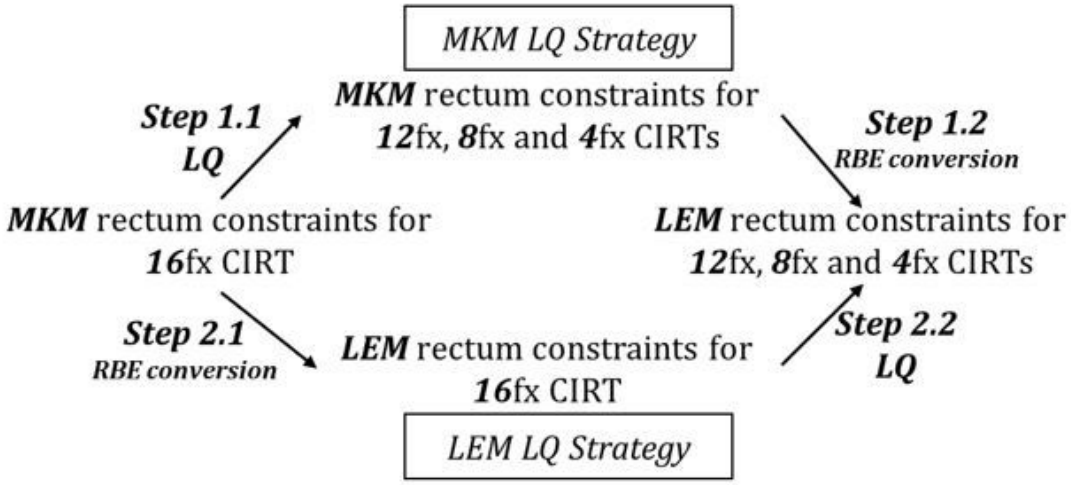

Figure 1

The framework of this study

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix.docx
- Appendix.docx