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Research Letter

Cone Beam CT-Based Daily Adaptive Planning or Defined-Filling Protocol for Neoadjuvant Gastric Cancer Radiation Therapy: A Comparison

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Abstract

Purpose: This study aimed to investigate, in the setting of neoadjuvant gastric irradiation with integrated boost, whether cone beam computed tomography (CBCT)-based adaptive radiation therapy compared with a defined-filling protocol would be beneficial in terms of feasibility and achieving daily reproducible dose volume indexes of the planning target volume (PTV) and organs at risk (OARs) and workflow.

Methods and materials: Planning computed tomography (PCT) and 25 CBCT scans of a previously treated patient were used, and neoadjuvant therapy of gastric carcinoma was simulated offline. PTVs and OARs were defined per the TOPGEAR protocol (PTV: 45 Gy/1.8 Gy), and an integrated boost (gross tumor volume [GTV]: 50.4 Gy/2.016 Gy) was added. The patient followed a filling regimen consisting of 12-hour fasting followed by 200 mL of water intake (2 glasses of water) immediately before irradiation. OARs and PTVs were newly contoured on each CBCT. Nonrigid registration of PCT and CBCT scans was performed. Nonadapted plans were recalculated on each CBCT (R-CBCT). Furthermore, an adapted plan was created for the new anatomy (A-CBCT). Dose parameters and comparison of R-CBCT and A-CBCT for the kidneys, liver, and heart were analyzed using a paired *t* test.

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Data-sharing statement: The data used and generated in this work may be available under ethical and data protection considerations upon request on an individual basis.

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Results: A total of 200 plans for R-CBCT and A-CBCT were obtained. Mean gastric volumes were 277.32 cm^3 ($\pm$54.40 cm^3) in CBCT scans and 519.2 cm^3 in PCT. Mean doses to the PTV did not differ meaningfully within the CBCT scans, with an average of 1.54%. The D_{95} improved in GTV coverage by 5.26% compared with the R-CBCT plan. Mean heart, liver, and right kidney doses were reduced with the A-CBCT plan by 35.74%, 10.71% and 29.47%, respectively. The R- and A-CBCT comparison for GTV and OARs was significantly different in all cases ($P < .0001$).

Conclusions: Adaptive radiation therapy through deformable registration represents an important tool in neoadjuvant gastric irradiation, encompassing daily variability and organ motion, compared with the defined-filling protocol while improving OAR sparing.

Introduction

One of the main problems radiation oncologists have to overcome in a neoadjuvant setup is the daily planning target volume (PTV) motion, which is an inherent feature for this organ.[1] Although the defined-filling protocol has been widely applied, this approach might not represent a reliable alternative for achieving daily similar volumes throughout the treatment, as confirmed by previous experiences.[2,3]

Therefore, a comparison between a novel cone beam−based adaptive radiation therapy approach and a defined-filling protocol is presented herein, accounting for daily changes in the PTV, organs-at-risk (OARs) sparing, and potential workflow benefit.

Methods and Materials

Imaging of a previously treated patient was used and a neoadjuvant treatment simulation of gastric carcinoma was performed retrospectively (planning computed tomography [PCT]; Brilliance Big Bore, Philips Healthcare, Best, The Netherlands; and cone beam computed tomography [CBCT]; XVI/Versa HD, Elekta AB, Stockholm, Sweden). PTVs and OARs (heart, lungs, kidneys, liver, spinal cord) were defined on the PCT per the TOPGEAR study protocol (PTV 45 Gy/1.8 Gy)[4] with an additional integrated boost (gross tumor volume [GTV]: 50.4 Gy/2.016 Gy) localized on the greater curvature and including nodal areas. For each fraction, the patient followed a defined gastric filling regimen of a fasting period of 12 hours, followed by an intake of 200 mL of water shortly before daily irradiation. Daily CBCT images (n = 25) were exported to an image registration platform (Velocity V3.2.1, Varian Medical Systems, Palo Alto, CA), and OARs and PTVs were recontoured on each data set. Registration of the PCT and daily CBCT scans were performed throughout organ-guided deformable matching and controlled through the spyglass function and warp map (voxel migration map). CBCT imaging does not support Hounsfield units (HU); thus, a resampled PCT was created (based on the registration and anatomy of the CBCT). The treatment plan without adaptation was recalculated this way on each CBCT (R-CBCT). Furthermore, an adapted treatment plan was created and optimized for the modified anatomy (A-CBCT). All plans were calculated with a Monte Carlo-based algorithm (Monaco V5.11, Elekta AB).

The paired *t* test was employed for statistical significance assessment with the R-project software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Complete abdominal imaging was obtained from daily CBCT images (n = 25). In total, 200 plans were performed for R-CBCT (n = 100) and A-CBCT (n = 100). In the PCT, the stomach volume was 519.2 cm^3, which was found to differ in CBCT images (277.32 $\pm$ 54.4 cm^3 average; V_{min} 193.7; V_{max} 365.7). The GTV in the PCT was 7.9 cm^3 (Fig 1).

The PTV D_{mean} distributions were 45.23 Gy, 45.79 Gy, and 45.09 Gy for PCT, R-CBCT, and A-CBCT, respectively, yielding a difference of −1.54% between A-CBCT and R-CBCT, 1.25% between R-CBCT and PCT, and −0.32% between A-CBCT and PCT. As for the D_{95}, 43.39 Gy, 42.96 Gy, and 43.40 Gy were found for PCT, R-CBCT, and A-CBCT, respectively. The difference rates were 1.02%, −0.98, and 0.03 between A-CBCT and R-CBCT, R-CBCT and PCT, and A-CBCT and PCT, respectively. Other parameters are shown in Table 1. The PTV covered by 45 Gy (V_{45}) was 60.47%, 81.20%, and 53.50% for PCT, R-CBCT, and A-CBCT, respectively (Fig 2).

The GTV D_{mean} was 50.36 Gy, 49.47 Gy, and 50.30 Gy for PCT, R-CBCT, and A-CBCT, respectively. The differences between the plans were 1.68% between A-CBCT and R-CBCT, −1.76% for R-CBCT and PCT, and −0.11% for A-CBCT and PCT. The D_{95} profile was 49.48 Gy, 46.79 Gy, and 49.26 Gy, respectively, with absolute differences of 5.26% between A-CBCT and R-CBCT, −5.43% for R-CBCT and PCT, and −0.45% for A-CBCT and PCT. Additional characteristics are shown in Table 1.

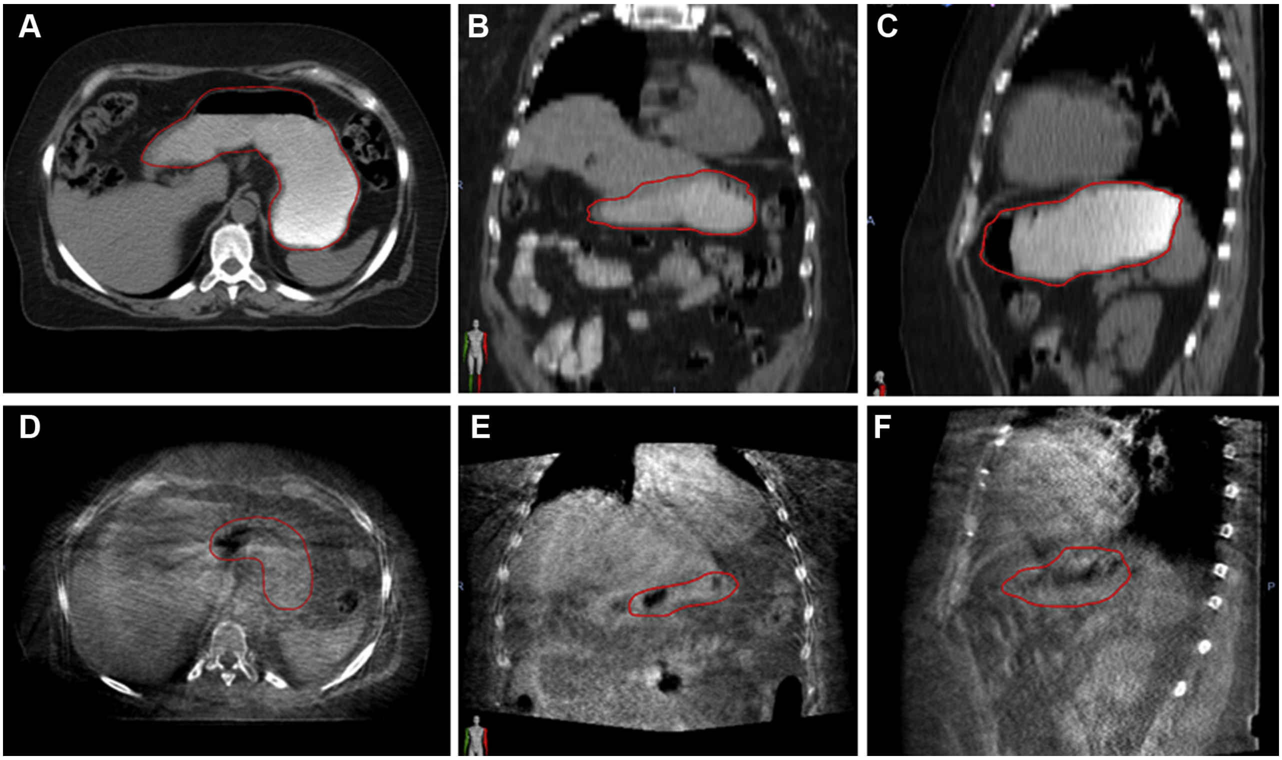

Figure 1 Morphologic differences between planning and representative cone beam computed tomography stomach contours in (A, D) axial, (B, E) coronal, and (C, F) sagittal views, respectively.

The mean dose to the heart, liver, and right kidney could be reduced with the A-CBCT plan by −35.74%, −10.71%, and −29.47%, respectively, compared with the R-CBCT (Fig 3). No differences were found in the left kidney, spinal cord, or overdosing (V >110%) parameters. Further dose-distribution details are shown in Table 2.

The comparison for R-CBCT and A-CBCT differences regarding GTV D_{min} and D_{95}; right kidney D_{mean}, D_{30}, and D_{60}; liver D_{mean}; and heart D_{mean}, were significant according to the paired t test ($P < .0001$). Additional details are shown in Table 3.

Discussion

According to the results presented herein, with a wide range of volume variability (V_{min}: 193.7; V_{max}: 365.7),

Table 1 Planning and gross tumor volume dose parameters

	D_{min}	D_{mean}	D_{max}	D_{99}	D_{95}	D_{90}	D_{50}
Planning target volume dose, Gy							
PCT	34.28	45.23	51.6	41.37	43.39	43.94	45.24
Recalculated	27.88	45.79	53.28	37.70	42.69	44.31	45.94
Adapted	33.22	45.09	52.02	41.99	43.40	43.88	45.06
Difference, %							
A − R	19.16	−1.54	−2.38	11.38	1.02	−0.98	−1.92
R − PCT	−18.67	1.25	3.26	−8.88	−0.98	0.85	1.55
A − PCT	−3.08	−0.32	0.81	1.49	0.03	−0.14	−0.41
Gross target volume dose, Gy							
PCT	48.42	50.36	51.6	48.79	49.48	49.67	50.37
Recalculated	45.30	49.47	52.99	46.07	46.79	47.32	49.53
Adapted	48.17	50.30	52.02	48.83	49.29	49.49	50.35
Difference, %							
A − R	6.35	1.68	−1.83	6.0	5.26	4.59	1.65
R − PCT	−6.45	−1.76	2.69	−5.58	−5.43	−4.73	−1.67
A − PCT	−0.51	−0.11	0.81	0.08	−0.45	−0.35	−0.05

Abbreviations: A = new anatomy; PCT = planning computed tomography; R = recalculated

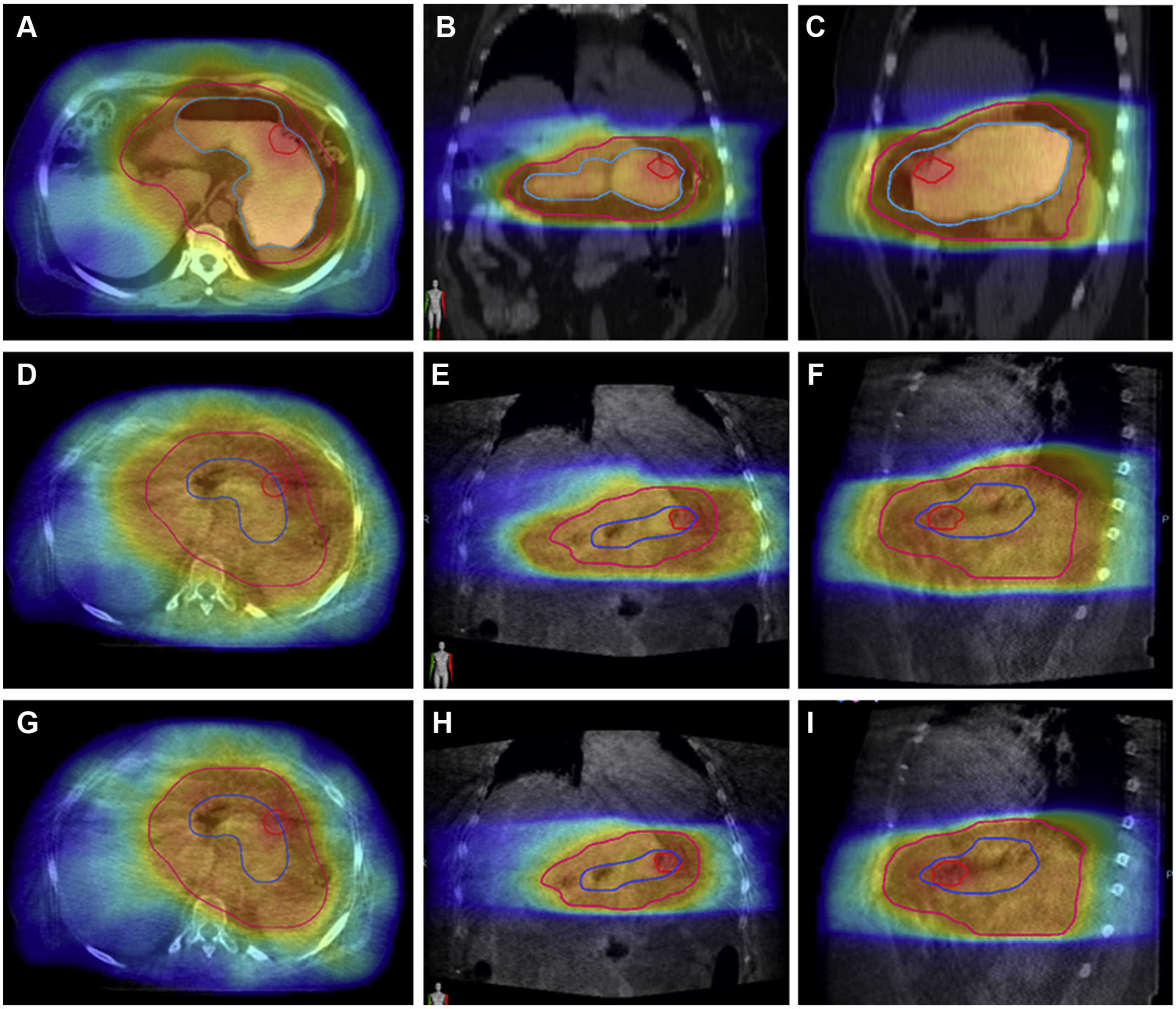

Figure 2 Planning target volume (red), stomach (blue), and gross tumor volume (red) dose distribution and anatomic and contour variations between planning, recalculated cone beam, and new anatomy cone beam computed tomography in (A, B, C) axial, (D, E, F) coronal, and (G, H, I) sagittal representative views, respectively.

the adaptive radiation therapy approach emerges as a solid alternative option to overcome this problem.[5] Previously published experiences have pointed out the value of this concept, due to the inherent motion of this organ, which could exceed the established margins according to most guidelines.[1,6-8]

The advantage of deformable registration lies with improved OARs sparing while assuring an accurate PTV delimitation.[9,10] The results obtained herein regarding doses reaching critical structures, such as the heart, kidney, or liver, confirm the value of this procedure, because rigid matching might result in inaccurate structure dosimetry. Despite the low intended doses, sparing of large abdominal areas due to variable daily volumes could also translate into better intestine sparing, therefore diminishing potential clinically acute toxicity, which tends to impair treatment compliance in this set of patients.[11,12] Part of the limitations of this study encompasses the variability of registered PTV sizes from the PCT and the subsequent CBCT images, which could result in biased outcomes due to the nature of these organs and the single-patient design; however, these results should not be disregarded because they show the same trend toward potential benefits of plan adaptation as previous publications and describe the feasibility of a workflow not previously reported. Although not measured, the entire process, from image acquisition, recontouring, deformable registration, and computed tomography resampling to completed treatment planning, required approximately 40 to 60 minutes, which is not

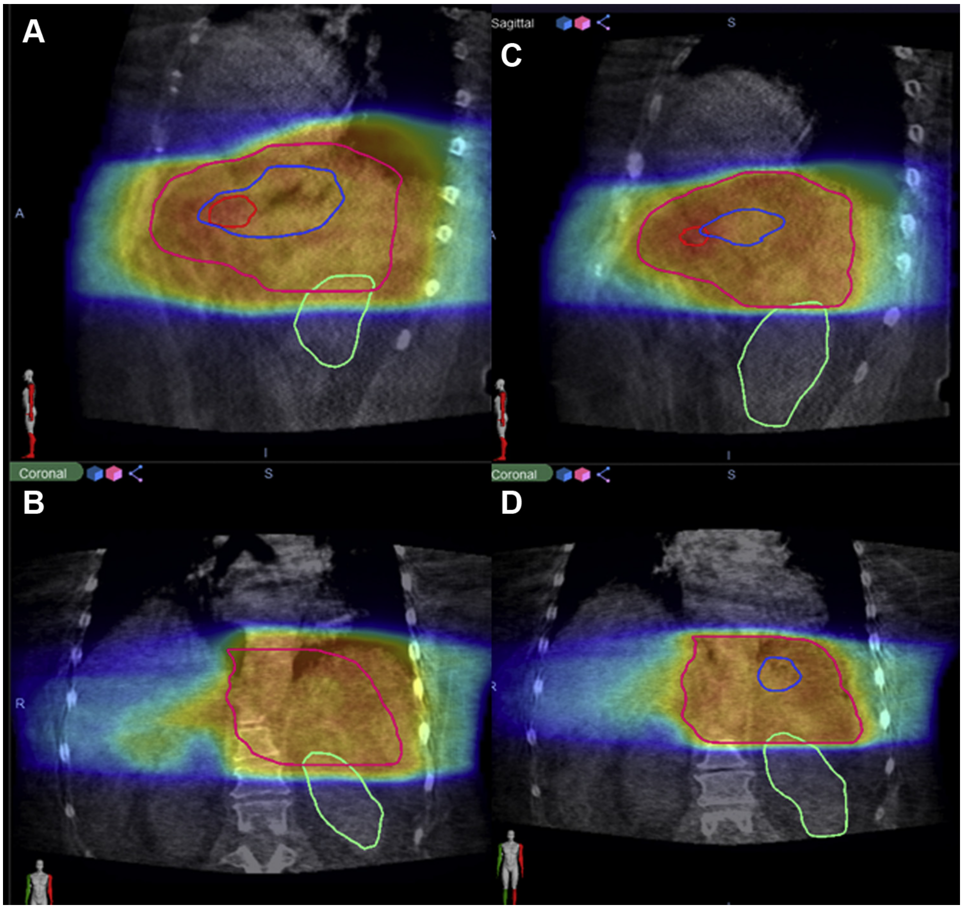

Figure 3 Representative sagittal and coronal views for (A, B) recalculated and (C, D) new anatomy cone beam computed tomography dose delivered to the left kidney.

suitable in this form for daily routine. A proposed alternative to overcome the timing problem could be limiting the workflow days. This plan-of-the-day strategy, selecting the most accurate plan according to daily imaging, has been already reported in the setting of bladder and uterine cervix irradiation and published by different groups worldwide.[13,14]

Conclusions

Adaptive radiation therapy through deformable registration represents an important tool in neoadjuvant gastric irradiation, encompassing daily volume variability, compared with daily defined-filling protocol. OAR sparing could be significantly improved with this approach.

Table 2 Organ-at-risk dose parameters

Dose, Gy	D_{30}	D_{60}	D_{30}	D_{60}	D_{mean}	D_{mean}	D_{mean}
Structure	Left kidney		Right kidney		Liver	Spinal cord	Heart
PCT	3.02	1.44	13.66	3.32	21.23	40.06	8.97
Recalculated	2.67	1.35	13.84	2.59	22.87	38.27	12.20
Adapted	2.66	1.24	10.58	2.14	20.42	37.25	7.84
Difference, %							
A − R	−6.62	−8.15	−23.55	−17.37	−10.71	−2.67	−35.74
R − PCT	−4.97	−6.25	−0.14	−21.99	7.72	−4.52	36.01
A − PCT	−11.26	−13.89	−23.67	−35.54	−3.82	−7.06	−12.60

Abbreviations: A = new anatomy; PCT = planning computed tomography; R = recalculated.

Table 3 Dose-distribution difference between recalculated and new anatomy cone beam computed tomography for GTV and organs at risk

Recalculated − adapted difference	Paired differences					t	dF	Significance
	Mean	SD	Mean standard error	95% confidence interval				
				Lower	Upper			
GTV D_{mean}	−0.11484	0.05177	0.01035	−0.13621	−0.09347	−11.092	24	**<.0001**
GTV D_{95}	−0.9840	0.04930	0.00986	−0.11875	−0.07805	−9.980	24	**<.0001**
Right kidney D_{mean}	0.12064	0.06702	0.01340	0.09297	0.14831	9.000	24	**<.0001**
Right kidney D_{30}	0.12644	0.13011	0.02602	0.07273	0.18015	4.859	24	**<.0001**
Right kidney D_{60}	0.02056	0.02488	0.00498	0.01209	0.03083	4.131	24	**<.0001**
Liver D_{mean}	0.09836	0.05890	0.01178	0.07405	0.12267	8.349	24	**<.0001**
Heart D_{mean}	0.18200	0.08940	0.01788	0.14510	0.21890	10.179	24	**<.0001**

Abbreviations: GTV = gross tumor volume; SD = standard deviation.

References

1. Watanabe M, Isobe K, Takisima H, et al. Intrafractional gastric motion and interfractional stomach deformity during radiation therapy. *Radiother Oncol*. 2008;87:425-431.
2. Bouchard M, McAleer MF, Starkschall G. Impact of gastric filling on radiation dose delivered to gastroesophageal junction tumors. *Int J Radiat Oncol Biol Phys*. 2010;77:292-300.
3. Brandner ED, Wu A, Chen H, et al. Abdominal organ motion measured using 4D CT. *Int J Radiat Oncol Biol Phys*. 2006;65:554-560.
4. Leong T, Smithers BM, Michael M, et al. TOPGEAR: A randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). *BMC Cancer*. 2015;15:532.
5. Sonke JJ, Aznar M, Rasch C. Adaptive radiotherapy for anatomical changes. *Semin Radiat Oncol*. 2019;29:245-257.
6. Wu AJ, Bosch WR, Chang DT, et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. *Int J Radiat Oncol Biol Phys*. 2015;92:911-920.
7. Schernberg A, Rivin Del Campo E, Rousseau B, et al. Adjuvant chemoradiation for gastric carcinoma: State of the art and perspectives. *Clin Transl Radiat Oncol*. 2018;10:13-22.
8. Wo JY, Yoon SS, Guimaraes AR, Wolfgang J, Mamon HJ, Hong TS. Gastric lymph node contouring atlas: A tool to aid in clinical target volume definition in 3-dimensional treatment planning for gastric cancer. *Pract Radiat Oncol*. 2013;3:e11-e19.
9. Oh S, Kim S. Deformable image registration in radiation therapy. *Radiat Oncol J*. 2017;35:101-111.
10. Liao Y, Wang L, Xu X, et al. An anthropomorphic abdominal phantom for deformable image registration accuracy validation in adaptive radiation therapy. *Med Phys*. 2017;44:2369-2378.
11. Boda-Heggemann J, Hofheinz RD, Weiss C, et al. Combined adjuvant radiochemotherapy with IMRT/XELOX improves outcome with low renal toxicity in gastric cancer. *Int J Radiat Oncol Biol Phys*. 2009;75:1187-1195.
12. Buergy D, Lohr F, Baack T, et al. Radiotherapy for tumors of the stomach and gastroesophageal junction—a review of its role in multimodal therapy. *Radiat Oncol*. 2012;7:192.
13. Sharfo AW, Breedveld S, Voet PW, et al. Validation of fully automated VMAT plan generation for library-based plan-of-the-day cervical cancer radiotherapy. *PLoS One*. 2016;11:e0169202.
14. Krishnan A, Tsang YM, Stewart-Lord A. The impact of intrafractional bladder filling on "Plan of the day" adaptive bladder radiotherapy. *Tech Innov Patient Support Radiat Oncol*. 2019;9:31-34.