

ORIGINAL ARTICLE

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Active Breathing Coordinator reduces radiation dose to the stomach in patients with left breast cancer

Ying Piao^a , Hongtao Chen^a, Fengshun Yuan^b, Juan Fan^a, Shihai Wu^a , Xianming Li^a and Dong Yang^a 

^aDepartment of Radiation Oncology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen, Guangdong, People's Republic of China; ^bSichuan Provincial Center for Disease Control and Prevention, Center for AIDS/STD Control and Prevention, Chengdu, Sichuan, People's Republic of China

ABSTRACT

Background/Purpose: Gastric dose parameters comparison for deep inspiration breath-hold (DIBH) or free breathing (FB) mode during radiotherapy (RT) for left-sided breast cancer patients (LSBCPs) has not been investigated before. This study aimed to analyze the impact of Active Breath Coordinator (ABC)-DIBH technique on the dose received by the stomach during RT for LSBCPs and to provide organ-specific dosimetric parameters.

Materials and methods: The study included 73 LSBCPs. The dosimetric parameters of the stomach were compared between FB and DIBH mode. The correlation between the stomach volume and dosimetric parameters was analyzed.

Results: Compared to FB mode, statistically significant reductions were observed in gastric dose parameters in ABC-DIBH mode, including Dmax (46.60 vs 17.25, $p < 0.001$), D1cc (38.42 vs 9.60, $p < 0.001$), Dmean (4.10 vs 0.80, $p < 0.001$), V40Gy (0.50 vs 0.00, $p < 0.001$), V30Gy (6.30 vs 0.00, $p < 0.001$), V20Gy (20.80 vs 0.00, $p < 0.001$), V10Gy (51.10 vs 0.77, $p < 0.001$), and V5Gy (93.20 vs 9.60, $p < 0.001$). ABC-DIBH increased the distance between the stomach and the breast PTV when compared to FB, from 1.3 cm to 2.8 cm ($p < 0.001$). Physiologic decrease in stomach volume was not found from FB to ABC-DIBH (415.54 cm³ vs 411.61 cm³, $p = 0.260$). The stomach volume showed a positive correlation with V40Gy ($r^2 = 0.289$; $p < 0.05$), V30Gy ($r^2 = 0.287$; $p < 0.05$), V20Gy ($r^2 = 0.343$; $p < 0.05$), V10Gy ($r^2 = 0.039$; $p < 0.001$), V5Gy ($r^2 = 0.439$; $p < 0.001$), Dmax ($r^2 = 0.269$; $p < 0.05$) and D1cc ($r^2 = 0.278$; $p < 0.05$) in FB mode. While in ABC-DIBH mode, most stomach dosimetric parameters were not correlated with gastric volume.

Conclusions: The implementation of ABC-DIBH in LSBCPs radiotherapy resulted in lower irradiation of the stomach. Larger stomach volume was associated with statistically significantly higher dose irradiation in FB mode. To reduce radiotherapy related side effects in FB mode, patients should be fast for at least 2 hours before the CT simulation and treatment.

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Left-sided breast cancer; radiotherapy; stomach dose; stomach volume; ABC-DIBH

Introduction

Breast cancer is the most prevalent malignant tumor in women around the world, and managing it often involves surgery, chemotherapy, radiotherapy (RT), and endocrine therapy. Adjuvant RT after surgery has been proved to reduce the risk of local-regional recurrence (LRR) and improve overall survival (OS) in breast cancer patients [1,2]. However, RT can incidentally expose organs at risk (OARs), including heart, left anterior descending artery (LAD), and ipsilateral lung, to radiation, increasing the risk of cardiac damage, lung fibrosis, and secondary malignancies, especially in left-sided breast cancer patients (LSBCPs) [3,4].

Up to now, seldom research focused on the relationship between RT of LSBCPs and the increased risk of gastric symptoms. In our previous study, an increased incidence rate

of radiation-induced nausea and vomiting (RINV) in LSBCPs, especially those received hypofractionated RT, had been demonstrated [5]. RT associated gastric mucosal injury is not well known, hard to manage, and sometimes easy to be ignored. Actually, the problem of RINV is undervalued in the clinical practice by radiation oncologists in clinical practice [6–8]. RINV may produce weight loss, changes in body shape, and even further cause an adverse effect on the patient's therapeutic effect. In addition, the second primary cancer in stomach after breast radiotherapy cannot be neglected [9,10].

Convincing evidence of a decreased dose of heart, LAD and lung during irradiation in deep inspiration breath hold (DIBH) mode for LSBCPs exists [11–13]. Active Breath Coordinator (ABC) system, an effective respiratory

CONTACT Dong Yang  yangdongyifan888@sina.com  Department of Radiation Oncology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen, Guangdong, People's Republic of China

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management strategy that monitors the patient's breathing cycle and implements breath hold at a predefined lung volume, has been widely used. It offers improved cardiac sparing and planning target volume (PTV) coverage in breast cancer RT, providing the advantage of separating the heart and PTV by altering internal anatomy during DIBH [14]. To the best of our knowledge, gastric dose parameters comparison for DIBH or free breathing (FB) mode during RT for LSBCPs has not been investigated before. Therefore, following our previous retrospective study reported the gastric symptoms in LSBCPs treated with RT [5], here we present this exploratory research comparing dosimetric parameters of the stomach in patients treated using ABC-DIBH mode to FB mode.

Materials and methods

Patient population

A total of 73 consecutive patients diagnosed with left-sided breast cancer undergoing whole breast or thoracic wall RT between October 2020 and June 2021 were enrolled in this retrospective study, which was approved by the institutional review board. All the 73 patients were able to hold their breath for at least 40s at 70% to 80% of maximum deep inspiration in the supine position and were treated in ABC-DIBH mode. Patient characteristics are presented in Table 1.

CT simulation

Siemens SOMATOM Definition AS scanner was used to obtain computed tomography (CT) simulation images. The breath-hold technique was managed using the Active Breathing Coordinator device (ELEKTA). Each patient underwent two CT scans, including the FB mode and the ABC-DIBH mode. Patients were scanned in the supine position

with both arms raised above the head. Prior to the scan, a radio-opaque dot was placed 2cm inferior to the lower boundary of the breast on the affected side to delineate the caudal bound of the breast tissue. For the patients treated with modified radical mastectomy, the border was marked referred to the healthy side. Spiral CT scans were taken from the upper border of the third cervical vertebrae. The radiation oncologist evaluated each CT scan to determine the lower border in order to contain the whole chest and stomach in both FB and ABC-DIBH modes. CT datasets for both FB and ABC-DIBH modes were acquired with 3mm thick adjacent slices. After the planning CT was done, the images were submitted to the treatment planning system (TPS).

Contouring and treatment planning

Target contouring was conducted in Eclipse (Varian Medical Systems Inc, Version 13.6). The clinical target volume (CTV), as well as all OARs, such as heart, lungs, and contralateral breast, were contoured according to the Radiation Therapy Oncology Group (RTOG) delineation guideline (www.rtog.org). Whole breast CTV or chest wall CTV was contoured in both FB and ABC-DIBH CT image. To ensure consistency, regional nodal CTV was not included in the plan. On each CT scan, contouring of the OARs, CTV and PTV was performed by the same qualified oncologist and reviewed by two senior oncologists. The clinical treatment prescription was given according to the condition of individuals, surgical method, pathological stage, treatment implementation, and physician discretion, which was 5000 centi-Gray (cGy)/25 Fractions (F), 4320 cGy/16F or 4050 cGy/15F. In this study, a prescription dose of 5000 cGy/25F was conducted in all plans to maintain consistency. For the same reason, boost dose was not included in the prescription.

For each patient, two CT datasets were contoured, and both two plans were generated by Monaco TPS v5.11.0 (Elekta) software with a grid size of $0.2 \times 0.2 \text{ cm}^2$. An intensity-modulated radiation therapy (IMRT) technique was used, consisting of 2 tangential inverse planned conformal beams and 2-3 additional beams. The latter were planned to improve target dose coverage and homogeneity. All plans were optimized to achieve 95% of the PTV receiving 95% of the prescribed dose, while minimizing the dose to OARs as much as possible. The stomach in FB and DIBH CT was delineated according to the RTOG atlas and guidance [15] after the completion of full-course radiotherapy to calculate the dosimetric data. The stomach was not considered as an OAR during the plan formulation.

The dose-volume histograms (DVHs) were utilized to evaluate dosimetric parameters for the stomach, including Dmax (max dose), Dmean (mean dose), D1cc (dose delivered to a 1 cm^3 volume of the stomach), V5Gy (volume receiving 5 Gy), V10Gy, V20Gy, V30Gy, V40Gy and V50Gy. The stomach volumes and DVHs from both FB-CT and DIBH-CT image sets were recorded and analyzed. In two respiratory modes, the distance between stomach and breast PTV was measured in transverse, coronal, and sagittal CT images, respectively, and the shortest distance was selected for statistical analysis.

Table 1. Patient and tumor characteristics.

Characteristics	<i>n</i> = 73 (%)
Age (y)	
Median (range)	44(27-64)
Breast conserving surgery	
Yes	45(61.6)
No	28(38.4)
Tumor stage	
Is	5(6.8)
1	35(47.9)
2	26(35.6)
3	4(5.5)
4	3(4.1)
N category	
0	29(39.7)
1	30(41.1)
2	5(6.8)
3	4(5.5)
x	5(6.8)
Hormone receptor status	
Positive	53(72.6)
Negative	13(17.8)
Not assessed or unknown	7(9.6)
HER2/neu status	
Overexpressed	21(28.8)
Not overexpressed	45(61.6)
Not assessed or unknown	7(9.6)

Statistical analysis

The Kolmogorov-Smirnov test was used to detect normality of the measurement data. Then appropriate statistical analysis method was selected. Variables with normal distribution were expressed as mean and 95% CI (confidence interval), while variables with non-normal distributions were expressed as median and 95% CI. The stomach volume between FB and ABC-DIBH mode was compared using the paired samples t-test. The paired samples Z-test was used to assess the differences in stomach dose parameters and the distance between stomach and PTV in the two respiratory modes. Spearman's rank correlation test was used to investigate the relationship between the gastric volume and the gastric dose parameters. Statistical analyses were conducted using SPSS 23.0 (SPSS IBM Inc., Armonk, New York), with a p-value less than 0.05 considered statistically significant.

Results

The analysis included a total of 73 LSBCPs, and their characteristics are outlined in Table 1. All the patient data from 146 CT scans and 146 treatment plans were evaluated.

Stomach dose

Based on the Kolmogorov-Smirnov test, the stomach dose parameters and the distance between stomach and breast PTV did not follow a normal distribution. As a result, the data were expressed as median and 95% CI (Table 2). For most dosimetric parameters analyzed, ABC-DIBH significantly reduced the dose to the stomach: Dmax was reduced from 46.60 Gy to 17.25 Gy (-63.0%, $p < 0.001$), D1cc was reduced from 38.42 Gy to 9.60 Gy (-75.0%, $p < 0.001$), Dmean was reduced from 4.10 Gy to 0.80 Gy (-80.4%, $p < 0.001$). Statistically significant reductions were also observed in other stomach dose parameters, including V40Gy(0.50 vs 0.00, $p < 0.001$), V30Gy(6.30 vs 0.00, $p < 0.001$), V20Gy(20.80 vs 0.00, $p < 0.001$), V10Gy(51.10 vs 0.77, $p < 0.001$), and V5Gy(93.20 vs 9.60, $p < 0.001$). For demonstration purpose, the cumulative DVHs of plans computed on FB-CT and DIBH-

CT image for a representative patient are shown in Figure 1. Figure 2 illustrates that, for the same patient, during DIBH, the stomach moved caudally and posteriorly compared to FB. In other words, ABC-DIBH techniques increased the distance between the stomach and the breast PTV when compared to FB, from 1.3 cm to 2.8 cm ($p < 0.001$).

Stomach volumes

Both stomach volume in FB and ABC-DIBH modes conformed to a normal distribution (ZFB = 0.07, $p = 0.200$; ZDIBH = 0.08, $p = 0.200$), and the parameter was expressed as mean and 95% CI (Table 2).

A physiologic decrease in stomach volume was not found during DIBH. The mean volume of the stomach was 415.54 cm³ in the FB cohort vs 411.61 cm³ in the ABC-DIBH cohort ($p = 0.260$).

Correlation between the gastric volume and stomach dose parameters

The Spearman's rank correlation test was used to investigate the association between gastric volume and different dosimetric parameters (Table 3). In FB mode, the stomach volume showed a positive correlation with V40Gy ($r^2 = 0.289$; $p = 0.013$), V30Gy ($r^2 = 0.287$; $p = 0.014$), V20Gy ($r^2 = 0.343$; $p = 0.003$), V10Gy ($r^2 = 0.039$; $p < 0.001$), V5Gy ($r^2 = 0.439$; $p < 0.001$), Dmax ($r^2 = 0.269$; $p = 0.021$) and D1cc ($r^2 = 0.278$; $p = 0.017$) (Figure 3a-g). In other words, a larger stomach volume was associated with statistically significantly higher dose irradiation in FB mode. There was a weak correlation between stomach volume and stomach V5Gy ($r^2 = 0.283$; $p = 0.015$) in ABC-DIBH mode (Figure 4).

Discussion

Traditionally, cardiotoxicity and radiation pneumonitis have been correlated with left breast cancer RT [3,4]. It is generally believed that the DIBH mode offers dose advantages in heart, LAD and lungs [11-13]. In the patients who receive adjuvant RT for the left breast, the stomach is located below the left diaphragm and sometimes inside the RT field. Gastric mucosa is sensitive to radiation. Clayman C [16] noted that low levels (1800 cGy) radiation elicited a 50% reduction in gastric acid. Despite previous studies, little attention has been given to the dosimetric data of stomach in left breast cancer RT. Hence, we examined the dose parameters of the stomach with or without the ABC-DIBH technique in our clinical patients who received left breast RT. This is, to the best of our knowledge, the largest and only dataset of patients with detailed dosimetric information both in FB and ABC-DIBH modes, and a broad range of radiation doses to the stomach.

As the gastrointestinal tract is highly vulnerable to radiation, several studies have reported on gastric toxicities in breast cancer RT, such as RINV and second primary cancer. Some retrospective studies suggested that RT for breast cancer increased the risk of gastric reactions [5,6,17]. Gastric

Table 2. Comparison of dosimetric data of stomach for free breathing (FB) and Active Breathing Coordinator (ABC) plans ($n = 73$).

Parameter	FB Median (95%CI)	ABC Median (95% CI)	Z-value	P-value
Volume (cc)*	415.54(378.35-452.74)	411.61(374.70-448.51)	1.14	0.260
Dmax (Gy)	46.60(40.91-48.30)	17.25(9.84-25.60)	10.13	0.000
D1cc (Gy)	38.42(29.10-44.00)	9.60(5.20-16.75)	10.24	0.000
Dmean (Gy)	4.10(2.90-4.98)	0.80(0.55-1.27)	9.59	0.000
V50Gy (cc)	0.00(0.00-0.00)	0.00(0.00-0.00)	1.73	0.088
V40Gy(cc)	0.50(0.00-2.99)	0.00(0.00-0.00)	5.11	0.000
V30Gy(cc)	6.30(1.54-12.30)	0.00(0.00-0.00)	6.13	0.000
V20Gy(cc)	20.80(9.06-29.70)	0.00(0.00-0.29)	7.76	0.000
V10Gy(cc)	51.10(31.90-67.60)	0.77(0.00-6.70)	8.85	0.000
V5Gy(cc)	93.20(62.70-115.95)	9.60(1.10-18.70)	8.25	0.000
Distance	1.30(1.20-1.60)	2.80(2.50-3.40)	12.32	0.000

CI = confidence interval, Gy = Gray, cc = cubic centimetre, Distance = distance between stomach and breast PTV.

*The parameter of stomach volume was expressed as mean and 95% CI. The paired samples t-test was used to compare the stomach volume between FB and DIBH mode, and paired samples Z-test was used to determine the differences in stomach dose parameters and the distance between stomach and PTV in FB and DIBH mode.

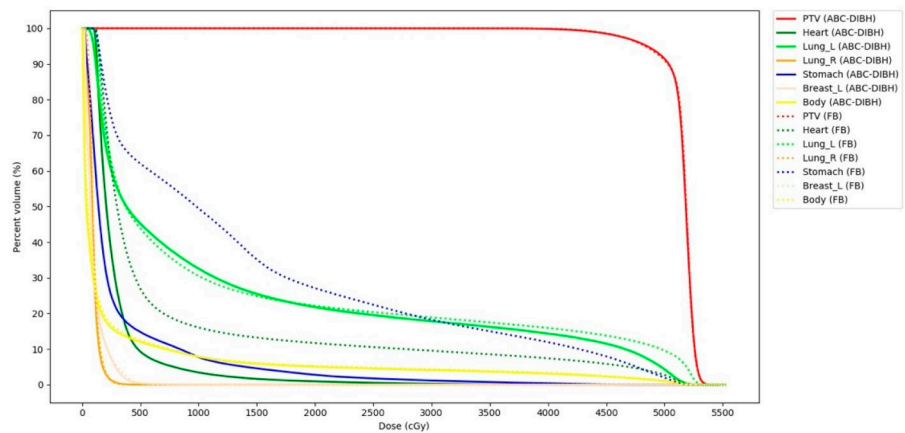


Figure 1. The cumulative DVH comparison between the plans on FB-CT and DIBH-CT image sets. This comparative DVH graphically illustrate the dosimetric scenario presented in Figure 2.

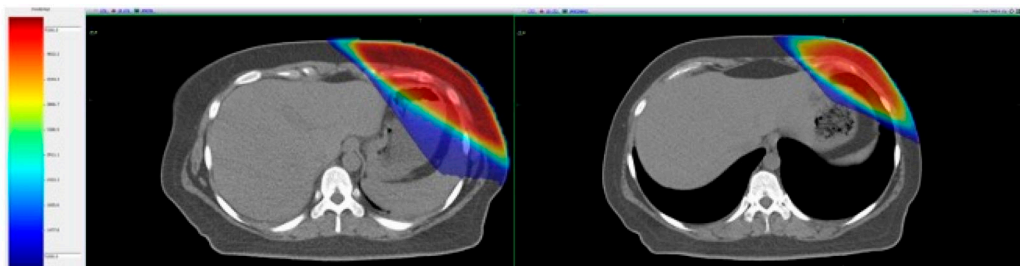


Figure 2. Isodose distribution from the same level of the same patient calculated in FB CT (left panel) and DIBH CT (right panel) images.

Table 3. Correlation (spearman's correlation coefficient r^2) between gastric volume and the stomach dose-volume histogram (DVH) parameters in FB and DIBH modes.

Mode	V50Gy	V40Gy	V30Gy	V20Gy	V10Gy	V5Gy	Dmean	Dmax	D1cc
FB	0.197 ^a	0.289 ^b	0.287 ^b	0.343 ^b	0.039 ^c	0.439 ^c	0.065 ^a	0.269 ^b	0.278 ^b
DIBH	-0.104 ^a	0.091 ^a	0.049 ^a	0.153 ^a	0.225 ^a	0.283 ^b	0.130 ^a	0.201 ^a	0.224 ^a

^aStatistically insignificant $p > 0.05$, ^bStatistically significant $p < 0.05$, ^cStatistically significant $p < 0.001$.

symptoms, including anorexia, vomiting, or nausea, would reduce the quality of life of the affected patient. A Korean study [18] identified 37,966 breast cancer patients who received adjuvant RT after surgery and reported that the incidence rate of gastric cancer in the RT group was higher than that of the general Korean population. Similarly, several population-based studies [19,20] have confirmed that patients undergoing post-operative RT for their primary breast cancer, especially with left breast cancer [9,21], presented with significantly higher risks of secondary gastric cancer than those patients who had not been irradiated.

Furthermore, RT-induced gastric mucosal damage has been reported in a few case reports, mostly due to lung cancer, gastrointestinal malignancy, or other tumors located in the upper abdomen. Prajnan Das [22] reported that the absolute and percent volumes of V40 and V50 in the stomach were significantly correlated with the incidence of gastric bleeding in intrahepatic cholangiocarcinoma RT. Qi Liu [23] reported that the volume percent of the stomach V50 was strongly related with the rates of Grade 2 and above acute and late toxicities for patients with thoracic esophageal squamous cell carcinoma. H. Yoon [24] reported that stomach

V25 > 6.3% and duodenum V35 > 5.4% were predictive factors for $\geq$ grade 2 gastroduodenal toxicities according to esophagogastroduodenoscopy (EGD) before and after RT were enrolled. The absolute volumes of stomach V50, V40 and V35 were also proved to be significant predictive factors of acute GI toxicity [25–27]. Taking those evidence into account, we chose absolute volume of V5-V50 for calculation. Our results showed statistically significant reductions in stomach Dmax, D1cc, V40, V30, V20, V10, and V5 in ABC-DIBH mode, suggesting that the implementation of the ABC technique may reduce the incidence rate of radiation-induced gastric side effects. And The hypothesis was consistent with our previous study [5], which demonstrated that the incidence of gastric symptoms in the ABC-DIBH mode was significantly lower than in the FB mode.

In a retrospective study by Feng et al. that included 139 intrahepatic cancer patients received three-dimensional conformal RT (3D-CRT) to partial liver [28], the stomach Dmean was not found to be associated with the subsequent gastric bleed events, such as gastric haemorrhage requiring transfusion, or radiologic, endoscopic, even elective operative intervention. The response of the stomach to radiation seemed to resemble a serial organ structure in terms of severe gastric side effects. However, in a work from Van den Belt-Dusebout AW [29], the risk of stomach cancer was found to be 3.4 times higher compared with the general population in long-term survivors who received abdomen RT. The mean stomach dose was identified as a prominent predictor of secondary stomach cancer. In another study conducted on atomic bomb survivors, the likelihood of death from most solid cancers, including stomach cancer, continued to rise over the

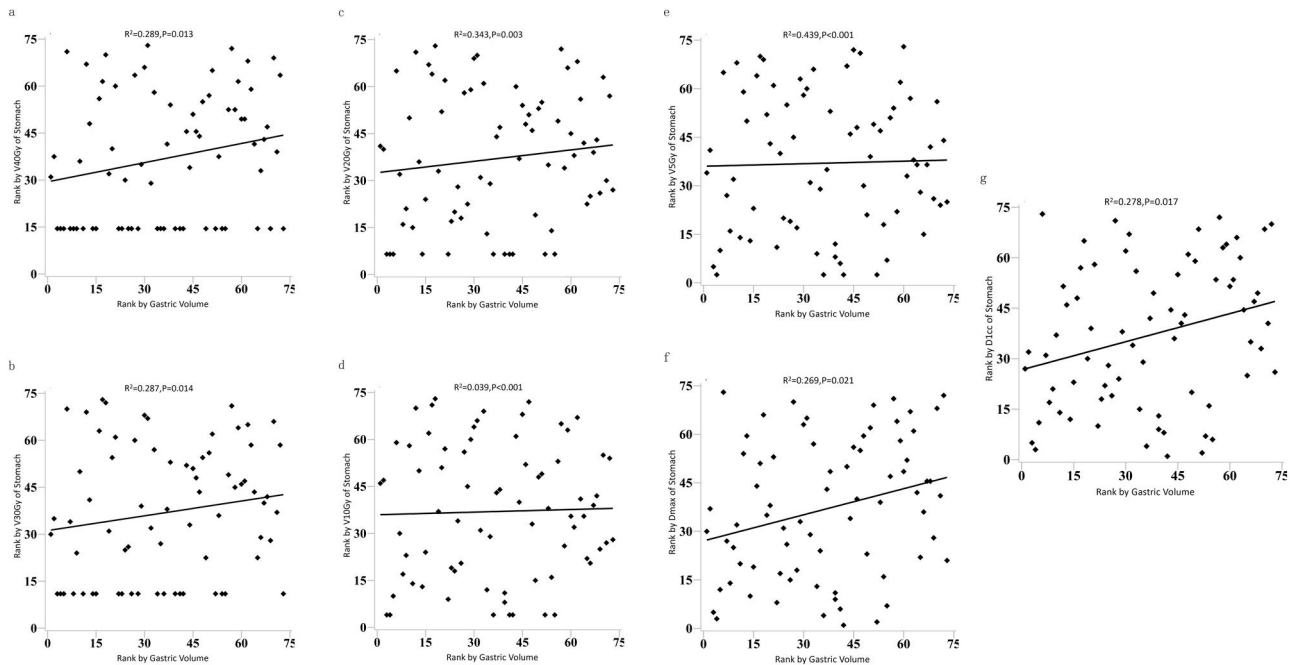


Figure 3. Correlation between gastric volume and different dosimetric parameters in FB mode evaluated with the spearman's rank correlation test: V40Gy (a), V30Gy (b), V20Gy (c), V10Gy (d), V5Gy (e), Dmax (f), D1cc (g).

*Each dot represents a patient, plotted by the rank order of gastric volume and dosimetric parameters on the horizontal and vertical axis respectively.

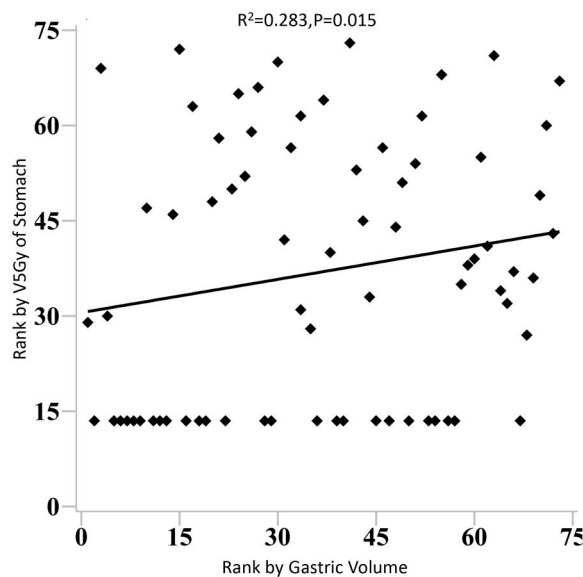


Figure 4. Correlation between gastric volume and V5Gy in DIBH mode evaluated with the spearman's rank correlation test.

*Each dot represents a patient, plotted by the rank order of gastric volume and dosimetric parameters on the horizontal and vertical axis respectively.

course of their lifetimes in approximate proportion to radiation exposure dose [30]. Based on these studies, stomach Dmean was associated with late radiation toxicity. According to our research, a significant reduction in stomach Dmean was demonstrated when utilizing the ABC-DIBH technique.

Based on a work from Yonsei University College [31], the incidence of severe gastroduodenal complications was notably higher among patients with liver cirrhosis than those without cirrhosis. Similarly, according to the records of intrahepatic cancer patients treated with RT, a lower TD50 value(22 Gy) for the cirrhosis patients compared with normal

patients(56 Gy) pointed out their greater sensitivity of radiation-induced gastric bleeding [28]. In liver cirrhosis patients, gastric mucosa under portal hypertension has functional abnormalities, such as mucus secretion decrease, gastroepithelial proliferation inhibition, and mucosal defense mechanism damage [32]. As a result, the portal hypertensive gastric mucosa is susceptible to radiation. Taking this into account, the dose of the stomach should be meticulously monitored when administering adjuvant RT to LSBPs with liver cirrhosis, and appropriate preventative management techniques, such as ABC-DIBH, should be considered.

In our previous study [5], the larger stomach volume was related with a significantly higher risk for acute radiotherapy toxicity. According to a study published in 2021, there was a linear correlation between stomach volume and stomach Dmax, as well as left lung V4 and V5 [33]. A gastric volume of approximately 170cc or less was associated with improved incidental radiation dose for the stomach, left lung, and heart. In our current study, some patients had a smaller gastric volume in ABC-DIBH mode because of the compression of the stomach by the air-filled lungs. Some had a larger volume in ABC-DIBH mode due to the gas inhaled entering the stomach. The causal relationship between the gastric volume and the ABC-DIBH condition is difficult to elucidate.

The role of the gastric volume on the dose-effect relationship stomach was investigated. In our current study, we observed that gastric volume in FB scans was positively correlated with stomach Dmax, D1cc, and V40-V5. Based on the statistical results, with any increase in gastric volume, the related DVH of the stomach will increase in FB mode. While in ABC-DIBH mode, with the stomach moved caudally and posteriorly away from PTV, most stomach dosimetric parameters were not correlated with gastric volume (Supplementary Figure 1). Therefore, in FB mode, proper management of the

patient's gastric volume should be taken into consideration. Based on previous studies [34,35], a 2-hour fasting period can result in 60-90% emptying of gastric contents. So, our recommendation is for patients to fast for at least 2 hours before undergoing CT simulation and RT treatment in order to reduce gastric volume.

Despite being the first to analyze dose parameters of the stomach in LSBCPs with RT, our study has several limitations. First, there is inevitable discrepancy between the planned dose and delivered dose for planned targets and OARs in both FB and DIBH mode. Due to the respiratory motion, the position and shape of thoracic and abdominal organs change during the breathing process, which may lead to dosimetric inaccuracies in planning and treatment. The applicability of our findings in the real world may be compromised. Fortunately, based on the relevant studies, it can be deduced that the motion of OARs during the course of CT simulation and treatment remains within an acceptable range both in FB [36] and DIBH [37] mode. To some extent, it ensures that errors fluctuate within a certain range, ensuring the reliability of our results. Another potential limitation of our analysis is that most of our references about gastric side effects are studies of tumors located in the upper abdomen cases. As a result, the role of radiation in gastric complications was derived from chemoradiation treatment in a considerable proportion of studies. Chemotherapy itself can be associated with gastric mucosal damage or changing radiosensitizing effects of the stomach. Finally, there's a natural variability in the stomach position, which may confound the dose calculation. Any differences in stomach filling would influence the position and shape. However, it was our practice to instruct patients to take the two CT scans in FB and ABC-DIBH modes within 5 min, which eliminated the content alteration, stomach dose with the two modes in the same patient was relatively comparable.

Many studies have demonstrated liver dose reduction by DIBH technique in right-sided breast RT [38,39]. Similarly, as organs adjacent to the diaphragm, the dose advantage of the stomach was confirmed in the ABC-DIBH mode for LSBCPs RT, based on organ-specific dosimetric parameters provided by our study, which is a unique contribution. Another suggestion of our results is that patients should fast for at least 2 hours before CT simulation and treatment in FB mode to reduce gastric volume. While the patients who received RT in ABC-DIBH mode don't need to control the volume of stomach. We believe that these results could help clinicians perform safer radiotherapy in this region.

In summary, in a series of clinical patients, we exclusively demonstrated that implementation of ABC-DIBH in LSBCPs RT resulted in lower irradiation of the stomach. Larger stomach volume was associated with statistically significantly higher dose irradiation in FB mode. To reduce radiotherapy related side effects, patients should be fast for at least 2 hours before the CT simulation and treatment in FB mode.

Author contributions

Y. Piao and H. Chen contributed equally to this work.

D Yang is the guarantor of integrity of the entire study. D Yang, H Chen and Y Piao were responsible for study concepts and design. H Chen and Y Piao were responsible for the clinical studies. D Yang and F Yuan carried out the experimental studies/data analysis. F Yuan carried out the statistical analysis. Y Piao, J Fan and S Wu prepared the manuscript. X Li and D Yang edited the manuscript.

Disclosure statement

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ORCID

Ying Piao  <http://orcid.org/0000-0002-6829-3538>
Shihai Wu  <http://orcid.org/0000-0002-5833-9723>
Dong Yang  <http://orcid.org/0009-0007-8746-7445>

Data availability statement

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

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