

Investigation of the efficacy of the change ratio of brain natriuretic peptide for predicting the cardiac effects of chemoradiotherapy on esophageal cancer

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Abstract. The aim of this study was to investigate the effectiveness of brain natriuretic peptide (BNP) as a predictor of radiological effects on the heart. A total of 41 patients with esophageal cancer who underwent chemoradiotherapy (CRT) were retrospectively investigated. The BNP levels were measured on the first day of CRT (pre-CRT) and the last day of CRT (post-CRT), and the median concentration of BNP and dosimetric parameters of the heart were calculated. The change ratio of BNP was calculated as follows: $[(\text{BNP post-CRT}) - (\text{BNP pre-CRT})] / (\text{BNP pre-CRT})$. The comparison of BNP pre-CRT with post-CRT was performed using a Wilcoxon signed-rank test. The relationship between dosimetric parameters and change ratio was analyzed using Spearman's correlation coefficient. The median levels of BNP of pre-CRT and post-CRT were 10 and 22 pg/ml, respectively, and the difference was statistically significant ($P < 0.0001$). Significant correlations (all $P < 0.05$) were observed between the change ratio and mean dose, V5, V10, V20, and V30. Of the cohort, 14 patients developed acute-to-subacute cardiac events, such as pericardial effusion, cardiomegaly, acute exacerbation of chronic heart failure, and a decreased ejection fraction. The change ratios of BNP, V5, V10, V20, and V30 were significantly higher in patients who experienced cardiac events compared with those who did not. The results of this study showed that BNP measurement, particularly the change ratio of BNP pre- and post-CRT, may be a useful cardiac event predictor in addition to dosimetric parameters.

Introduction

Radiotherapy is a treatment option for esophageal cancer, and chemoradiotherapy (CRT) is the standard method of treatment for patients with unresectable esophageal cancer (1,2). The number of elderly patients diagnosed with unresectable esophageal cancer is increasing given the aging population and the occurrence of complications. Consequently, the number of patients undergoing CRT is also increasing. Notably, the radical irradiation field in esophageal cancer, including the prophylactic lymph node region, is quite large. Furthermore, the dose delivered to the heart is increased, particularly if the primary tumor is located in the middle thoracic esophagus or below. Pericardial effusion, pericarditis, and myocarditis are acute adverse events of the heart, and ischemic heart disease, coronary artery disease, atherosclerosis, and valvular disease are late adverse events (3,4). The development of radiotherapy-induced cardiotoxicity is a well-recognized complication in the treatment of left breast cancer. Additionally, a correlation between cardiac mortality and the dose delivered to the heart has been reported (5-8). However, several reports of cardiotoxicity are delayed effects, and the acute effects on the heart remain to be clarified. Brain natriuretic peptide (BNP) is a peptide hormone synthesized in the ventricle that protects the heart. Moreover, its secretion is increased in response to the damage to the heart. Hence, it is clinically used as a biochemical marker of heart failure (9,10). The present study focused on the fluctuations of BNP levels to investigate the early effects of radiotherapy on the heart. The purpose of this study was to investigate the effectiveness of BNP as a predictor of the effects of radiotherapy on the heart of patients with esophageal cancer.

Materials and methods

Patients. A total of 41 patients with esophageal cancer were enrolled in the present study. Following a thorough explanation of the clinical stage and prognosis, treatment goals,

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schedules, and adverse events, all included patients provided written informed consent for chemoradiotherapy. All patients underwent definitive CRT at Hirosaki University Hospital (Hirosaki, Japan) between September 2014 and June 2019. The median age of the cohort, including 34 men and 7 women, was 68 years (age range, 54-78 years). Patient evaluation included physical examination, biopsy using esophagogastroduodenoscopy, blood counts, blood chemistry tests, respiratory function tests, blood gas analysis, and electrocardiography. The levels of BNP were determined in all patients before and after CRT. According to the 8th edition of the Union for International Cancer Control guidelines, the clinical staging was performed using chest radiographs, chest-pelvic computed tomography (CT) scans, and positron-emission tomography/CT (PET/CT) scans. This study was approved by the institutional research review board of our institution (approval no. 2020-089).

Chemoradiotherapy. A 3D conformal radiotherapy planning procedure was performed in all patients. Serial CT images at 2.5 mm intervals were obtained. The gross tumor volume was defined as the volume of the primary tumor and metastatic lymph nodes determined by esophagogastroduodenoscopy, CT, and PET/CT imaging prior to treatment. Metastatic lymph nodes were defined as lymph nodes measuring ≥ 1 cm in size on CT imaging or positive on PET/CT imaging. The clinical target volume was defined as the primary tumor plus longitudinal margins of ≥ 5.0 cm, lateral margins of 0.5 cm, metastatic lymph nodes plus 0.5-cm margins, and prophylactic lymph node area. The planning target volume was the clinical target volume plus 0.5-cm margins. A 10 MV linear accelerator (Varian Clinac iX, Varian Medical Systems) was used, and radiotherapy was performed using the anterior-posterior opposing field technique until a dose of 40 Gy was delivered. The field-in-field method was used depending on the location of the primary lesion, as appropriate. Following the delivery of 40 Gy, the spinal cord was avoided using oblique opposing fields with the target volume, excluding the prophylactic lymph node area from the planning target volume. The total irradiation dose for the primary lesion and lymph node metastasis ranged from 50-60 Gy (median, 60 Gy) at the isocenter. All patients received concurrent chemotherapy. The chemotherapy regimen included a combination of cisplatin (70 mg/m² on day 1) and fluorouracil (700 mg/m²/day on days 1-4) as intravenous infusion. One or two cycles of chemotherapy were administered during radiation therapy.

Evaluation and analysis. The BNP measurement was outsourced to LSI Medience Corporation (license no. 220AIAMX0000200) using a chemiluminescent immunoassay. The upper limit of normal BNP was defined as 18.4 pg/ml, which is the reference value utilized by the company. The range, median, mean and change ratio (\pm SD) of the BNP levels on the first (pre-CRT) and the last (post-CRT) day of CRT were calculated. The change ratio was calculated as follows: [(BNP post-CRT)-(BNP pre-CRT)]/(BNP pre-CRT). The heart, including the pericardium, was contoured based on the CT scans used for actual radiotherapy planning to calculate the cardiac dosimetric parameters. The upper end of the heart on CT was defined as the area immediately below the left pulmonary artery (11). Following heart contouring, the

mean dose, V5, V10, V20, V30, V40, and V50 for the heart were obtained from dose-volume histograms using radiotherapy planning software (Monaco, version 5.11; Elekta). V5, V10, V20, V30, V40, and V50 are the heart volume ratio irradiated with 5, 10, 20, 30, 40, and 50 Gy, or more radiation, respectively. Subsequently, the range, median, and mean \pm SD of the mean dose, V5, V10, V20, V30, V40, and V50 were calculated. The BNP levels pre- and post-CRT were compared using the Wilcoxon signed-rank test. The relationships between the cardiac dosimetric parameters and the ratio of change in BNP were analyzed using Spearman's correlation coefficient. The relationship between BNP and survival was investigated using the Kaplan-Meier method. The cumulative survival rate was calculated from the first day of CRT, and the differences were compared using a log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference. All analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, Inc.). Treatment toxicity was evaluated using the Common Terminology Criteria for Adverse Events (version 4.0) established by the U.S. National Cancer Institute (12).

Results

A summary of the patient's characteristics is provided in Table I. All 41 patients were diagnosed with squamous cell carcinoma. The clinical stages were as follows: stages I, II, III, and IV in 10, 5, 13, and 13 patients, respectively. The site of the primary lesion was the cervical, upper thoracic, middle thoracic, and lower thoracic esophagus in 6, 12, 13, and 10 patients, respectively. The number of radiotherapy fractions ranged from 25-33, with a fraction size of 1.8-2 Gy. The median total dose was 60 Gy (range, 50-60 Gy). Prior to the diagnosis of esophageal cancer, cardiovascular complications were observed in 26 patients (63%). Hypertension was a cardiovascular complication that occurred in the majority of patients. During the period of analysis, 18 patients were alive and 23 patients died. For all patients, the median follow-up period was 29.2 months (range, 1.7-82 months). For the surviving patients, the median follow-up period was 55.6 months (range, 31.3-82 months).

The BNP levels pre- and post-CRT and the change ratio of BNP in all 41 patients are shown in Table II. The BNP levels pre-CRT ranged from 3-18 pg/ml; the median and mean levels were 10 and 10.15 pg/ml, respectively. The BNP levels post-CRT ranged from 5-95 pg/ml; the median and mean levels were 22 and 29.02 pg/ml, respectively. The change ratio of BNP ranged from -50-766.67%; the median and mean levels were 200 and 246.11%, respectively. Following CRT, 63% of patients had abnormally high BNP levels. In the group with a higher change ratio (that is, above the median), only 19% of patients (4/21) remained within the normal range after CRT. However, in the group with a lower change ratio (that is, below the median), 51% of patients (11/20) remained within the normal range after CRT. The results of the comparison of BNP levels pre- and post-CRT are shown in Fig. 1. The BNP levels were significantly elevated post-CRT compared with pre-CRT ($P < 0.0001$).

The range, median, and mean \pm SD values of the mean dose, V5, V10, V20, V30, V40, and V50 for the heart are shown

Table I. Patient characteristics.

Characteristic	Value
Sex	
Male	34 (83)
Female	7 (17)
Age, years	
Median	68
Range	54-78
Performance status, n (%)	
0-1	40 (98)
2	1 (2)
Stage, n (%)	
I	10 (24)
II	5 (12)
III	13 (32)
IV	13 (32)
Site of primary lesion, n (%)	
Cervical	6 (15)
Upper thoracic	12 (29)
Middle thoracic	13 (32)
Lower thoracic	10 (24)
Radiation doses, Gy	
Median	60
Range	50-60
Cardiovascular complications, n (%) ^a	
Hypertension	25 (61)
Diabetes	6 (15)
Dyslipideamia	5 (12)
Follow-up duration, months	
Median	29.2
Range	1.7-82
Status, n (%)	
Alive	18 (44)
Dead	23 (56)

^aMore than one complication per patient in some cases.

in Table III. The median values were 33.9 Gy, 83.0, 76.8, 70.8, 62.3, 51.9, and 20.0%, respectively. The mean values were 28.3 Gy, 70.5, 65.6, 59.8, 52.7, 42.2, and 19.6%, respectively. The correlation coefficients for cardiac dosimetric parameters and the change ratio are shown in Table IV. Significant correlations were observed between the change ratio and mean dose (P=0.041), V5 (P=0.004), V10 (P=0.004), V20 (P=0.006), and V30 (P=0.016). Scatter diagrams between the change ratio and mean dose, V5, V10, V20, and V30 are shown in Fig. 2.

A list of adverse events following CRT is shown in Table V. Adverse events were investigated using medical records and imaging tests, such as CT and PET/CT scans. Cardiac events occurred in 14 patients. Pericardial effusion, cardiomegaly, acute exacerbation of chronic heart failure, and decreased ejection fraction (defined as a decrease of <50%) were observed

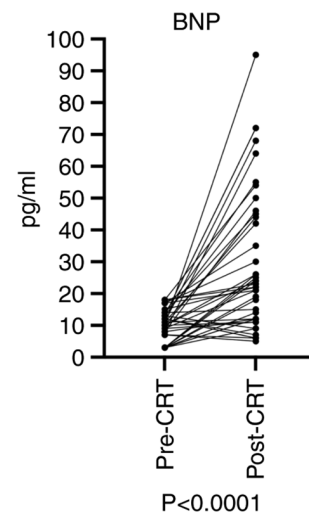


Figure 1. Before-after plot of BNP levels pre and post-CRT. There was a significant difference between the BNP levels post-CRT vs. pre-CRT. BNP, brain natriuretic peptide; CRT, chemoradiotherapy.

in 8, 4, 1, and 1 patients, respectively. These cardiac events occurred between 1.4 and 52 months after CRT. All cardiac events were grade ≤ 2 . A Mann-Whitney U-test was used to compare the median dosimetric parameters, the median change ratio, and median pre-CRT BNP levels between 14 patients who experienced cardiac events and 27 patients who did not (Fig. 3). Significant differences were observed in the V5 (P=0.002), V10 (P=0.007), V20 (P=0.012), V30 (P=0.009), and change ratio (P=0.009). There was no significant difference in pre-CRT BNP levels. In addition to cardiac events, dermatitis, esophagitis, and myelosuppression were observed as acute adverse events. A Mann-Whitney U-test was used to compare the median change ratio and median pre-CRT BNP levels between low and intermediate grades of these adverse events, but there was no significant association with BNP. The relationship between BNP and survival was investigated using the Kaplan-Meier method. However, there was no significant difference between 20 patients with a lower change ratio (that is, below the median) and 21 patients with a higher change ratio (that is, above the median) (Fig. 4).

Discussion

The present study focused on the fluctuations of BNP levels. Thus far, only a few previous studies have investigated the relationship between radiotherapy and atrial natriuretic peptide (ANP). Wondergem *et al* (13) investigated 121 patients with Hodgkin's disease and breast cancer. They reported that patients who experienced cardiac events after radiotherapy had significantly higher ANP levels compared with those who did not. Additionally, studies conducted on rhesus monkeys or rats reported similar findings, indicating that ANP levels were increased after total-body irradiation or whole-heart irradiation (14,15). No reports were published on the relationship between radiotherapy and BNP until around the year 2000. Nevertheless, a few studies have suggested that BNP is an effective predictor of various cardiac dysfunctions in patients with heart failure (9,10). To the best of our knowledge,

Table II. BNP before and after CRT and change ratio of BNP.

Measurement	BNP pre-CRT, pg/ml	BNP post-CRT, pg/ml	Change ratio, %
Range	3-18	5-95	-50-850
Median	10	22	200
Mean \pm SD	10.15 \pm 4.78	29.02 \pm 21.95	246.11 \pm 255.97

BNP, brain natriuretic peptide; CRT, chemotherapy.

Table III. Dosimetric parameters of heart.

Measurement	MD, Gy	V5 (%)	V10 (%)	V20 (%)	V30 (%)	V40 (%)	V50 (%)
Range	0.9-44.8	3.5-96.9	1.8-94.2	0.3-89.3	0-82.7	0-75.4	0-51.8
Median	33.9	83.0	76.8	70.8	62.3	51.9	20.0
Mean \pm SD	28.3 \pm 12.3	70.5 \pm 26.9	65.6 \pm 26.4	59.8 \pm 25.5	52.7 \pm 24.1	42.2 \pm 23.6	19.6 \pm 14.8

Table IV. Spearman's correlation coefficient by rank for Change ratio of BNP and dosimetric parameters of heart.

Dose	R (95% confidence interval), n=41	P-value
Mean dose	0.32 (0.005-0.578)	0.041
V5	0.44 (0.146-0.665)	0.004
V10	0.44 (0.146-0.665)	0.004
V20	0.42 (0.122-0.651)	0.006
V30	0.37 (0.066-0.618)	0.015
V40	0.24 (-0.081-0.518)	0.128
V50	0.14 (-0.181-0.440)	0.370

Table V. Adverse events of chemoradiotherapy.

Adverse events	Grade 1, n	Grade 2, n	Grade 3, n
Cardiac events			
Pericardial effusion	0	8	0
Cardiomegaly	4	0	0
Acute exacerbation of chronic heart failure	0	1	0
Decreased ejection fraction	0	1	0
Dermatitis	34	7	0
Esophagitis	8	30	3
Myelosuppression	4	17	20

Jingu *et al* (16) was the first to report that BNP levels were significantly increased ≥ 9 months vs. < 9 months after radiotherapy. In the present study, BNP levels were determined on the last day of CRT. The BNP levels post-CRT were also significantly elevated compared with those recorded pre-CRT. This finding suggests that BNP levels in the heart may have been elevated by radiotherapy.

A previous study reported that the change ratio of BNP is a predictor of cardiac events. In patients with nonischemic chronic heart failure, a $\geq 15\%$ increase in BNP levels was considered a risk factor for the occurrence of cardiac events (17). In another study, involving patients with chronic heart failure, the relationship between the change ratio and mortality in the N-terminal-pro-BNP, a precursor BNP was investigated. The results demonstrated that the rate of all-cause mortality was increased in parallel with the change ratio (18). Based on these reports showing the usefulness of the change ratio of BNP, the correlation between dosimetric parameters of the heart and change ratio was investigated to explore the relationship between the degree of BNP elevation after radiotherapy and the dose delivered to the heart. In the present study, significant correlations were observed between the dosimetric parameters of the heart and the change ratio, except

for V40 and V50. However, the correlation coefficients were ~ 0.4 for these parameters, and although there were significant differences, the correlations were weak. In contrast, there were no significant correlations observed between the absolute BNP levels after radiotherapy and dosimetric parameters of the heart (data not shown).

Similarly, there was a prospective study that investigated the correlation coefficients between dosimetric parameters of the heart and BNP in 43 cases of left breast cancer (19). This study examined the normalized BNP concentration, which is defined as the post-treatment BNP levels divided by the pre-treatment BNP levels. The results demonstrated significant correlations in V20, V25, V30, and V45 with the mean dose of the heart. This evidence is consistent with the findings of the present study, suggesting that an elevation in BNP levels due to radiotherapy is associated with low- to medium-dose irradiation rather than high-dose irradiation.

A long-term toxicity study used the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme to investigate 139 patients with thoracic esophageal cancer

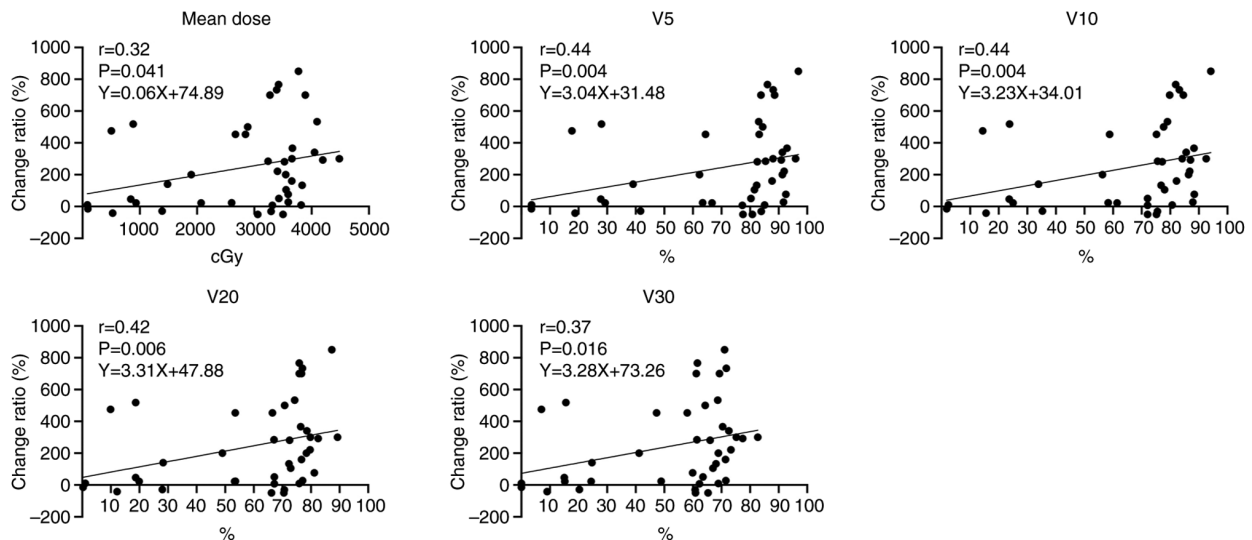


Figure 2. Scatter diagrams between the ratio of change in BNP and mean dose, V5, V10, V20, and V30. There were significant correlations between the ratio of change in BNP and mean dose, V5, V10, V20, and V30 BNP, brain natriuretic peptide, V, volume.

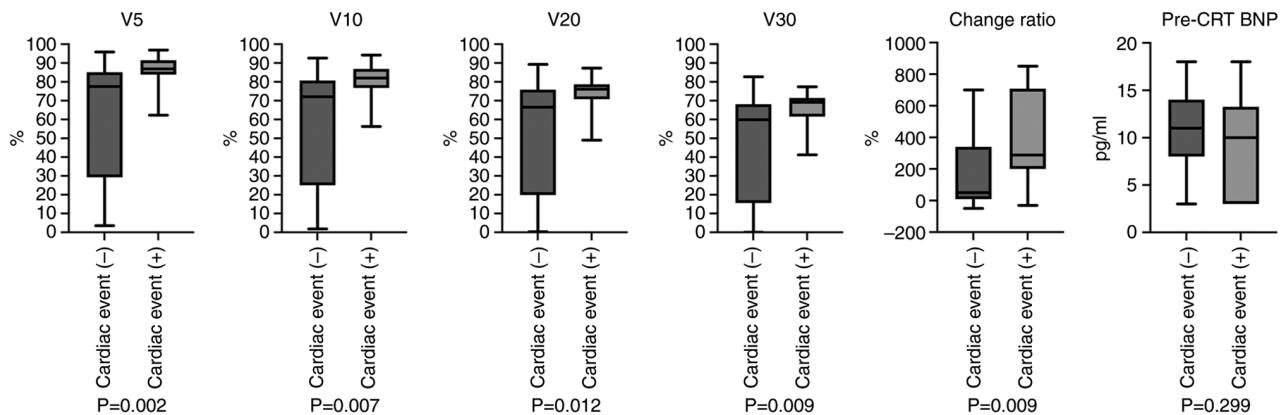


Figure 3. Box-and-whisker plot of the ratio of change in BNP, V5, V10, V20, and V30 in patients with and without cardiac events. The median values of all parameters were significantly elevated in patients who experienced cardiac events vs. those who did not. BNP, brain natriuretic peptide, V, volume.

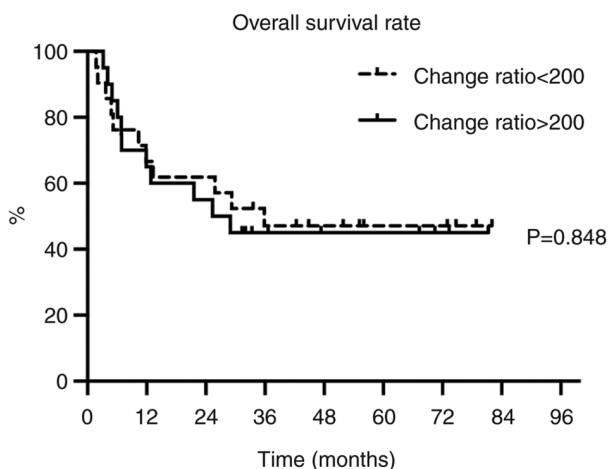


Figure 4. Overall survival rate according to change ratio of BNP. BNP, brain natriuretic peptide.

who underwent CRT. The results demonstrated that 16 patients (11.5%) developed symptomatic grade ≥ 2 pericarditis (20). In

the present study, 14 patients (34%) developed cardiac events, with the majority of events being pericardial effusions (20%). In addition, all cases of pericardial effusion were asymptomatic and grade 2, as evaluated using Common Terminology Criteria for Adverse Events version 4. Of note, lethal events were not observed in the present study. The median period for the development of cardiac events was 12 months (range: 1.4-43 months). However, as pericardial effusion and cardiomegaly are often detected through imaging, the actual time of development may have been earlier. It is hypothesized that performing imaging analyses every 3-6 months at our institution may have resulted in this delay. Therefore, numerous cardiac events observed in this study were acute to subacute adverse events. The relationship between the development of cardiac events and the change ratio of BNP and dosimetric parameters of the heart was investigated. The median change ratio, V5, V10, V20, and V30 were significantly higher in patients who developed a cardiac event vs. those who did not. The results indicated that BNP might be an early predictor of cardiac stress due to radiotherapy, similar to previous reports (16,19). It was also suggested that the change ratio of

BNP and percentage of low- to medium-dose area irradiated to the heart might be an effective predictor of cardiac event development.

Due to aging, CRT is frequently utilized in Japan for the treatment of esophageal cancer, including cases of medically unresectable stage I cancer (21,22). A previous report indicated that the 4-year survival rate for stage I esophageal cancer is ~80% (23). Additionally, the outcomes of CRT have improved over the past few years. The effects of chemotherapy on the heart should also be considered when administering CRT. A study on the cardiac effects of preoperative treatment for esophageal cancer reported more cardiac complications with CRT vs. chemotherapy alone (24,25). Therefore, to reduce the risk of adverse events in the hearts of patients for longer-term survival, it is necessary to decrease the dose delivered to the heart.

This study has some limitations. As this was a single institute study, the number of included patients was small, the follow-up period was short, and the development of cardiac events may not have been fully grasped. The reason for the short follow-up period was that 26 patients with stage III or IV disease were included in the study and >50% of the 26 patients succumbed to cancer or other coexisting complications at a relatively early time following CRT. Therefore, the value of BNP as a predictor of survival could not be determined. Imaging tests such as echocardiography, nuclear medicine examination, and cardiac MRI have been reported to be useful in evaluating myocardial damage associated with cancer therapy (26,27). As this study was a retrospective study, unfortunately, these imaging tests were not performed in all patients. Regarding irradiation technology, numerous institutions have recently begun using intensity-modulated radiation therapy. In this study, several patients received conventional radiotherapy; thus, it is important to use intensity-modulated radiation therapy to reduce the cardiac dose and investigate patients treated with intensity-modulated radiation therapy in the future.

In conclusion, the present study revealed that BNP levels after CRT were significantly increased in patients with esophageal cancer, and the change ratio pre- and post-CRT correlated with the dose delivered to the heart, particularly the percentage of low- to medium-dose areas. Furthermore, it was found that the change ratio and the percentage of the low- to medium-dose areas were significantly higher in patients who experienced a cardiac event compared with those who did not. The change ratio of BNP pre- and post-CRT may thus be a useful predictor of cardiac events.

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Availability of data and materials

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

Authors' contributions

YH, MT, CY, KI, IF, MS, HK and MA contributed to the study conception and design. SK, RO, and AK collected and analyzed the data. YH wrote the manuscript, analyzed data, and performed the literature search. All authors have read and approved the final manuscript. YH, SK, RO, and AK confirm the authenticity of all raw data.

Ethics approval and consent to participate

This study was approved by the institutional research review board of the Hirosaki University Graduate School of Medicine (approval no. 2020-089). The Institutional Research Review Board of the Hirosaki University Graduate School of Medicine waived the requirement for informed consent due to the retrospective nature of the study. This study was performed using the opt-out method on the hospital website.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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