

Original Research Article

VMAT radiation-induced nausea and vomiting in adjuvant breast cancer radiotherapy: The incidental effect of low-dose bath exposure

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ARTICLE INFO

Article history:

Received 24 August 2017

Revised 29 September 2017

Accepted 30 September 2017

Available online 6 November 2017

Keywords:

Volumetric modulated arch therapy

Gastroesophageal junction

Coeliac plexus

Nausea

Vomit

ABSTRACT

Background and purpose: To investigate the hypothesis on low-dose bath exposure related to radiation-induced nausea and vomiting (RINV) in adjuvant breast volumetric modulated arch therapy (VMAT).

Methods and materials: A total of 106 consecutive breast cancer patients (pts) treated with adjuvant radiotherapy (RT) with VMAT from January 2013 to May 2016 were evaluated retrospectively. For each pt, a planning CT was reimported and the coeliac plexus and gastroesophageal junction with gastric mouth (GEJCPs) were contoured as a new organ at risk (OAR) in the upper abdominal area. RINV was associated with Dmax and Dmean to GEJCPs. Univariate analysis with χ^2 , *t*-test, and Pearson's covariance was used for statistical analysis.

Results: Of 106 pts, 64% complained of acute RINV according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. RINV was related to Dmax > 10 Gy and Dmean > 3 Gy to GEJCPs ($P < 0.005$). The radiation breast side and planning target volume (PTV) correlated with RINV.

Conclusions: RINV in VMAT breast radiotherapy could be a new emerging acute side effect due to a low dose bath to upper abdominal structures such as the GEJCPs. A Dmax < 10 Gy and Dmean < 3 Gy to GEJCPs should be constrained in VMAT planning to minimize RINV risk in breast radiotherapy.

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Introduction

Meta-analyses have clearly demonstrated that adjuvant breast cancer (BC) radiotherapy (RT) reduces the risk of any first recurrence with a beneficial effect on survival in node-positive patients (pts) [1,2]. Two randomised trials failed to show an overall survival benefit, but an advantage of locoregional control and disease- and distant recurrence-free survival with a reduction of mortality have been recorded [3,4]. Traditionally, the total administered dose to the whole breast or to the chest wall is 50 Gy in standard fractionation followed by an additional 10 Gy boost on the surgical bed when indicated. Recently, technical developments in radiation oncology such as intensity-modulated radiation therapy (IMRT) techniques and volumetric modulated arch therapy (VMAT) are ongoing to better optimise the dose homogeneity for targets and organs at risk compared to three-dimensional conformal radiotherapy (3D-CRT) [5,6]. Moreover, VMAT is an interesting option in cases of complex and different anatomical sites being treated

simultaneously, in unfavourable anatomy conditions such as the pectus excavatum and in other particular situations such as bilateral breast irradiation [7,8].

A well-known limitation of VMAT in BC is the low-dose bath exposure of healthy structures because of the possibility of an increased risk of secondary cancer or undesirable acute side effects [9]. One of these effects is radiation-induced nausea and vomiting (RINV) due to a low-dose bath to the upper abdominal anatomical structures underlying the planning target volume (PTV).

Radiation to the breast and extremities causes a minimal emetogenic risk that has been estimated at <30% in Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guidelines, but these data antedated IMRT [10]. In our study, we formulated a hypothesis of some parameters to explain RINV in our BC pts treated with VMAT.

Materials and Methods

A retrospective study of BC pts treated using VMAT in our institution was conducted. The study was approved by the appropriate ethics committee. From January 2013 to May 2016, 106

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consecutive BC pts were treated with adjuvant RT using the VMAT modality.

Patients first planned to undergo 3D-CRT with unacceptable dosimetry according to International Commission on Radiation Units and Measurements (ICRU) recommendations on PTV coverage of the breast, chest wall, supraclavicular fossa, and internal mammary chain (IMC) or on the organ at risk (OAR) dose for the lungs, heart, left anterior descending artery (LAD), and contralateral breast were then selected for the treatment using VMAT modality [11].

Patient characteristics

Stage I/III invasive BC was found in 95 pts and DCIS in 11 pts. In 95 pts, the left side breast was irradiated, while in 11 pts, the right side breast was treated. The mean patient age was 54.4 years (32–76 years).

All patients underwent surgery consisting of quadrantectomy in 82 pts and mastectomy in 24 pts. Node sampling as sentinel or axillary dissection were assessed in all patients. Node irradiation was prescribed for 36 pts (36 pts for supraclavicular nodes including 10 pts for IMC). Adjuvant chemotherapy was delivered in 63 patients and hormone therapy was administered to 85 pts (in 44 pts alone and in 41 after chemotherapy). See Table 1 for patient characteristics.

Radiotherapy

An immobilising device was used to place the pts in the supine position with both arms above the head. A CT data set was acquired with 2.5-mm-thick adjacent slides and included the chest from C6 to a mean level of D12-L2 (D11-L3) vertebrae in all pts. Clinical target volumes (CTVs) were similar to those for 3D-CRT. The breast or chest wall CTVs and nodal (supraclavicular, IMC) CTVs delineation was defined according to established RTOG guidelines [12]. An expansion margin to the breast and chest wall CTVs of 10 mm over and below the palpable breast and 5 mm in all other directions was provided to obtain PTVs. For nodal CTVs, an expansion of 5 mm was allowed in all directions. OAR delineation included both lungs, the spinal cord from C6 to D12, the heart, the LAD, the pharynx, the entire oesophagus, the contralateral lung and breast [13].

For patients with supraclavicular or IMC nodal irradiation, a single procedure was performed for the entire treatment course with a differential dose of the 3 PTVs. According ICRU 83, treatments were in 25 fractions; the prescribed dose was 50 Gy total in 2 Gy/f to the breast chest wall and IMC, while a total dose of 48 Gy was prescribed to the supraclavicular nodes (1.92 Gy/f) [14]. VMAT was planned using Oncentra MasterPlan (collapsed cone algorithm) for 10 pts or Monaco (Monte Carlo photon algorithm treatment planning systems) for 96 pts and consisted of a dual arc plan

of 6 MV photon beams (170°/340° for the left breast and 190°/20° for the right breast). To minimize the dose to the unspecified tissues the “serial function” Monaco tool was applied.

Dosimetric evaluation was based on the dose-volume histogram (DVH) analysis of the PTVs and OARs. For the retrospective analysis on RINV, all the 106 effective VMAT treatment plans were reviewed and the original planning CTs were reimported. An experienced radiation oncologist contoured on the CT slices of each patient a new volume below the diaphragm containing the anatomical structures of the parasymphathetic-symphathetic afferent-efferent pathways responsible for emesis [15,16].

Because the whole gastric volume was not included in the original planning CTs, only the upper gastric structures were contoured. The anatomical volume of interest was identified in fixed structures as the coeliac plexus and the gastroesophageal junction with gastric mouth (GEJCPs) because the important peripheral pathways in emesis are through the phrenic and visceral nerves from the stomach and oesophagus. These structures identified a new OAR, and this was the key point of our analysis related to RINV. The total and mean volume of the PTVs (breast or chest wall) and GEJCPs were calculated for each patient by the DVH. For the GEJCPs, Dmax and Dmean were assessed.

Statistical analysis

Univariate analysis with the χ^2 test was applied to evaluate the correlation between RINV and dosimetric for the GEJCPs (Dmax and Dmean), geometric (breast side, PTVs and GEJCPs, and volumes), and clinical variables (age, chemotherapy, and surgery). Data were reanalysed using the t-test. Multivariate analysis was conducted using Pearson's covariance test to confirm an independent role of these variables on RINV. Statistical significance was considered at $P < 0.05$; the data were processed using SPSS Version 2.1 (SPSS Inc., Chicago, IL, USA).

RINV toxicity

Acute gastric toxicities consisting of nausea and vomiting as indicative parameters for RINV were assessed according to CTCAE version 4.03 for gastrointestinal disorders [17].

To correlate nausea and vomiting toxicities with radiation doses to the GEJCPs, the number and frequency of emetic symptoms (nausea and vomiting) were extracted from the Oncentra patients' medical charts where these symptoms had been previously recorded during the patients' weekly management visit while in treatment. Grade 1 (G1) and grade 2 (G2) nausea and vomiting G1 (V1) were scored according to the CTCAE version 4.03. Data on adjuvant systemic treatments (chemotherapy or hormone) and surgery (mastectomy or quadrantectomy) were also recorded.

Results

A total of 106 consecutive VMAT cases were included in the data set; of these, 67 (64%) patients complained about acute RINV according CTCAE version 4.03 criteria. RINV acute toxicity G1 nausea was assessed in 46 pts (43%), G2 nausea in 13 (12%), and G1 vomiting in 8 (7%). Symptoms occurred at a mean 30 Gy delivered dose (range 20–34) almost at the beginning of the third week of the treatment. RINV occurred in 3 pts with right side irradiated breasts (27%); in left side irradiated breasts, 64 pts (67%) were symptomatic. On DVH analysis, the PTV mean volume was 781.13 cc (180–2166); the GEJCPs mean volume was 32.7 cc (23.06–64.7). For GEJCPs, the mean Dmean dose was 5.11 Gy (0.5–11 Gy) and the mean Dmax dose was 11.6 Gy (1.3–21 Gy); see Table 2.

Table 1
Patient characteristics and clinical parameters.

Number of patients	106
Stage I/III	95
DCIS	11
Mean age	54.4 years (32–76)
Hormone therapy	85
Chemotherapy	63
Left breast RT	95 (89%)
Right breast RT	11 (10%)
Quadrantectomy	82
Mastectomy	24
Nodal RT	36
Internal mammary chain	10

Table 2
Dosimetric parameters.

GEJCPs mean volume (cc)	32.7 (23.06–64.7)
PTV mean volume (cc)	781.13 (180–2166)
Mean Dmax of GEJCPs (Gy)	11.6 (1.3–21)
Mean Dmean of GEJCPs (Gy)	5.11 (0.5–11)

Univariate analysis

In the χ^2 test, RINV correlated with the Dmax and the Dmean of the GEJCPs; a statistically significant correlation of Dmax > 10 Gy ($P < 0.001$, odds ratio [OR] 20 [95%CI 15–30]) and RINV was observed. Further, Dmean > 3 Gy significantly correlated with RINV ($P < 0.001$, OR 15 [95% CI 10–25]; see Table 3. Moreover, OR RINV risk seemed to increase for the Dmax and Dmean of GEJCPs (Figs. 1 and 2). G1 vomiting (V1) and G2 nausea were related to a Dmax > 17 Gy ($P < 0.001$) and a Dmax > 15 Gy ($P < 0.001$), respectively.

Regarding geometrical variables, both the left side irradiated breast and a PTV (breast or chest) >700 cc significantly correlated with RINV. The GEJCPs volume ($P = 0.34$, OR 0.67 [95% CI 0.3–1.53]) did not correlate significantly with RINV.

No statistically significant correlation was found for age ($P = 0.2$, OR 1.72 [95% CI 0.8–3.95]), hormone therapy ($P = 0.38$, OR 0.63 [95% CI 0.2–31.8]), chemotherapy ($P = 0.12$, OR 0.52 [95% CI 0.2–1.2]), and nodal radiation ($P = 0.110$, OR 0.51 [95% CI 0.22–1.17]). Surgery (mastectomy vs quadrantectomy) ($P = 0.046$, OR 2.55 [95% CI 1–6.44]) was weakly significant for RINV. *t*-test also

confirmed the significant correlation of RINV with Dmax and Dmean to GEJCPs; the irradiated breast side and PTV volume were also statistically significant.

Multivariate analysis

Pearson's covariance correlation test confirmed the significant correlation of RINV with Dmax and Dmean to the GEJCPs. Moreover, a weak correlation was found for the breast irradiated side and PTV as shown in Table 3 and Fig. 3. Mastectomy had only a slight statistical significance ($P = 0.05$).

Discussion

The occurrence of RINV in breast radiation is considered an uncommon acute symptom. In MASCC/ESMO guidelines, breast and extremity radiotherapy yields a minimal emetogenic potential with a risk of emesis <30%, but these data antedated VMAT treatment modality [10]. VMAT is a feasible technique in cases of unfavourable situations or complex adjuvant breast and nodal irradiation SIB protocols [18,19]. Furthermore, VMAT has many dosimetric advantages because it provides excellent target volume coverage with good OAR sparing, but it may inadvertently allow a large low-dose bath delivery to previously unirradiated healthy structures. The consequence could be the shift in the radiation-related morbidity, defining new distinct toxicity profiles from those seen in the pre-VMAT era [9].

Table 3
Univariate and multivariate analyses of RINV.

	N	Univariate model				N	Multivariate model	
		OR	95% CI	χ^2	<i>P</i>		Pearson's covariance (95% CI)	<i>P</i>
Max dose (Dmax)								
<10 Gy	37	ref			37			
≥10 Gy	69	20	15–30	97.64	<0.001	69	0.755**	<0.001
Mean dose (Dmean)								
<3 Gy	28	ref			28			
≥3 Gy	78	15	10–25	45.087	<0.001	78	0.646**	<0.001
Hormonal therapy								
No	21	ref			21			
Yes	85	0.63	0.2–1.8	0.761	0.383	85	–0.085	0.39
Chemotherapy								
No	43	ref			43			
Yes	63	0.52	0.2–1.2	2.456	0.117	63	–0.088	0.37
Side								
Dx	11	ref			11			
Sx	95	5.51	1.4–22.2	6.815	0.009	95	–0.254*	0.01
PTV								
≤700 cc	56	ref			56			
>700 cc	50	2.47	1.1–5.61	0.030	0.030	50	0.211*	0.03
GEJCP volume								
<30 cc	45	ref			45			
≥30 cc	51	0.67	0.3–1.53	0.902	0.342	51	–0.097	0.35
Age								
>50	65	ref			65			
≤50	41	1.72	0.8–3.95	1.628	0.202	41	–0.124	0.21
Surgery								
Mastectomy	24	ref			24			
Breast conservation	82	2.55	1.0–6.44	4.027	0.046	82	–0.195	0.05
Nodal RT								
No	70	ref			70			
Yes	36	0.51	0.22–1.17	2.55	0.110	36	–0.155	0.11

Bold values are highlights the high statistical significance.

* One tail test.

** Two tail test.

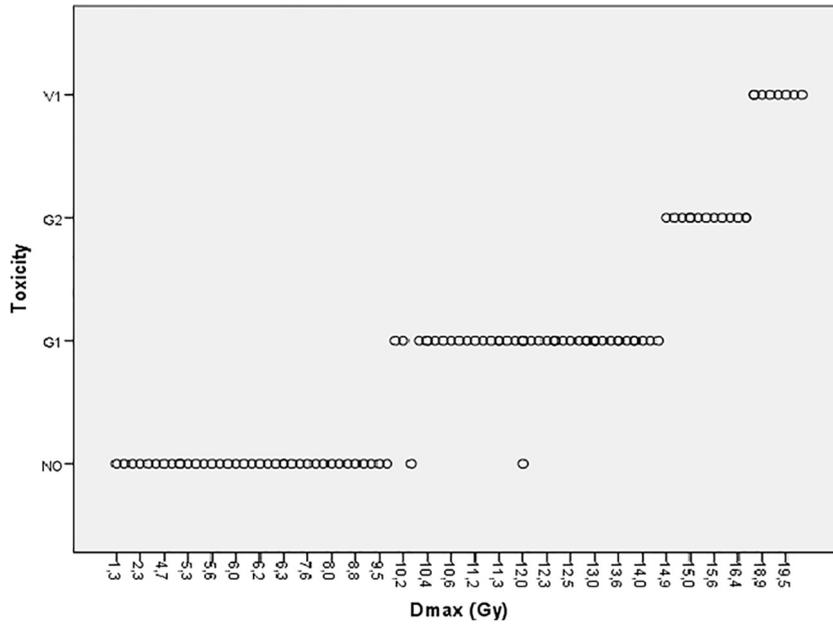


Fig. 1. Correlation of RINV risk and Dmax to GEJCPs: risk increases for Dmax > 10 Gy.

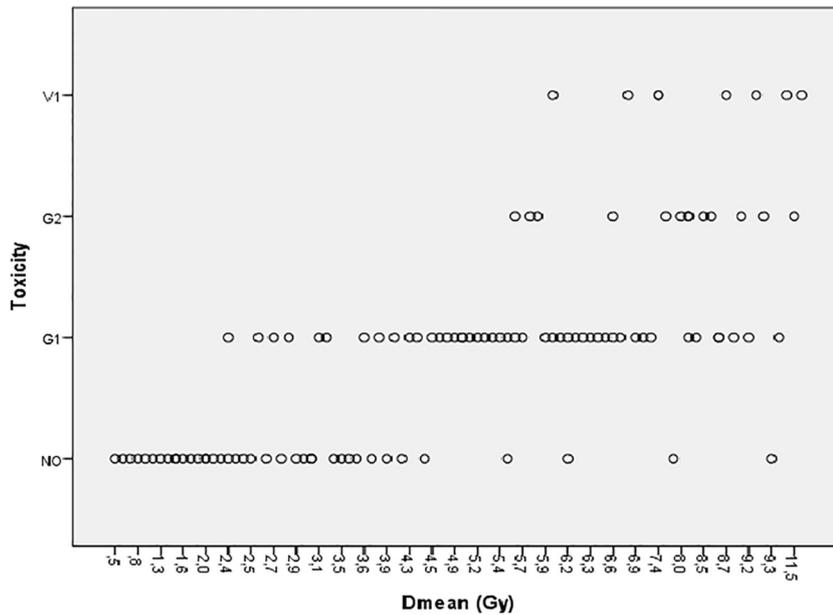


Fig. 2. Correlation of RINV risk and Dmean to GEJPS: risk increases for Dmean > 3 Gy.

This retrospective analysis of 106 VMAT-treated BC pts found that 64% pts complained about acute RINV. This result is similar to the estimated risk for upper abdominal irradiation according to MASCC/ESMO guidelines reporting a moderate emetogenic potential risk of RINV (60–90%) for this site. RINV has been related to many RT variables such as the site of irradiation, RT techniques, irradiation volume, dosing, and fractionation as the Italian Group for Antiemetic Research in Radiotherapy (IGAAR) had previously assessed in a prospective observational trial [20].

Supported by these concepts, to explain our findings, we have presumed an incidental low-dose delivery to a non-target OAR in the upper abdomen-like gastric structures. We did not find available data in the literature on this issue. Very few 2D- and 3D-CRT studies have been published on the acute toxicity of stomach radiation, but all failed to report information on toxicity and

DVH-related data [21]. Currently, to improve the use of VMAT in breast radiation, many studies have investigated and constrained the doses to conventional structures such as the heart, lungs, breast, ribs, and skin but not to the upper abdominal structures [22]. The recognition of RINV as an effect of incidental low-dose exposure to IMRT on healthy surrounding CNS tissues was recently widely investigated by Kocak-Uzel et al. [23]. The authors showed that RINV in pts receiving definitive head and neck IMRT was associated with increased doses to specific CNS structures. Rosenthal et al. focused on the estimation of the doses and toxicities to non-target structures during HNC IMRT and had previously assessed the cause of RINV in IMRT HNC related to the dose to the brain stem, especially to the area postrema [24]. This finding was confirmed by Ciura et al. in a retrospective study on the correlation of brainstem dose to RINV in a population of oropharyngeal

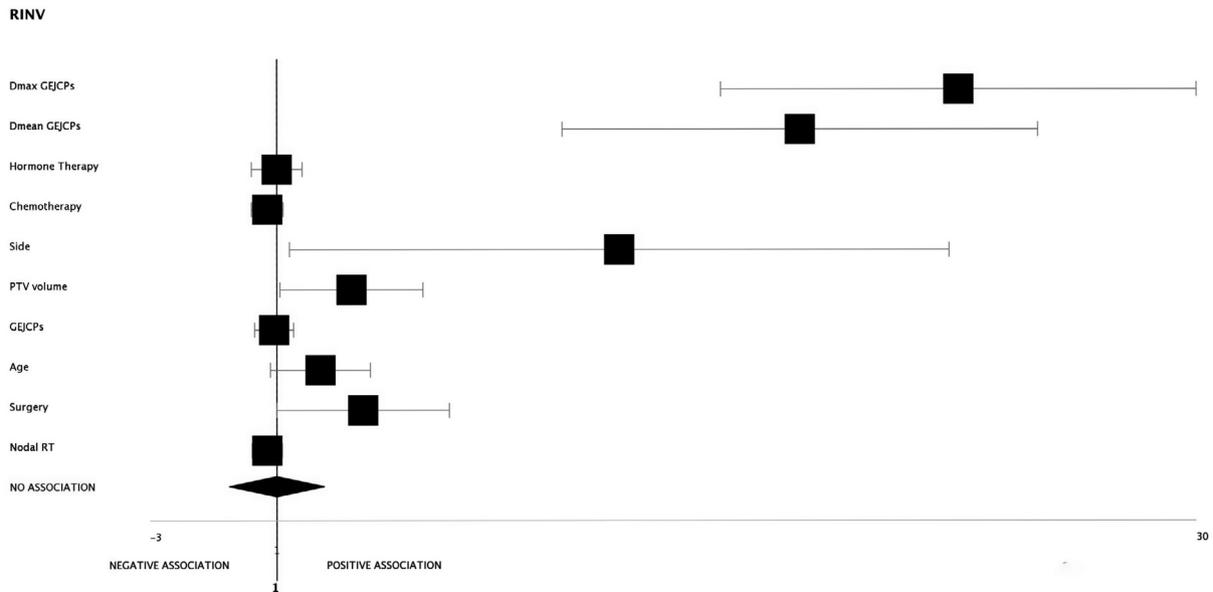


Fig. 3. Forest plot of multivariate analysis: Dmax and Dmean for GEJCPs are statistically correlated to RINV, but there is less statistical correlation for the side breast, PTV, age, and surgery.

cancer pts treated with IMRT. They correlated dosimetry for the brainstem, area postrema, and dorsal vagal complex and found that the mean brainstem dose is a key parameter of interest [25].

On the basis of these investigations, we investigated factors that could explain RINV in our cohort. Starting from the symptomatic RINV results that were similar to abdominal irradiation, we have identified an OAR in the upper abdomen called the GEJCPs as the peripheral trigger zone of emesis [15,16]. This anatomical area contains the neural vagal connections, fibres collected in the coeliac plexus, gastroesophageal junction, and gastric mouth through which the afferent pathway of emesis to the brain stem develops. The coeliac plexus, also known as the solar plexus, is a complex network of interconnecting nerves through the coeliac ganglia that is located in the abdomen near the coeliac trunk, behind the stomach and in front of the crura of the diaphragm on the level of 12th dorsal-1st lumbar vertebrae. The gastroesophageal junction consists of the lower third of the oesophageal tract through the diaphragmatic hiatus into the gastric mouth to the phrenic nerves. Because of this deep abdominal location, the GEJCPs is normally excluded from low radiation doses in breast 3D-CRT; therefore, this yields a minimal emetic potential. Utilising the VMAT modality,

this structure may be incidentally involved in low-dose bath exposure ranging from 10 Gy to 20 Gy isodoses as seen in Fig. 4a and b.

In our study, the delivered doses to the GEJCPs were evaluated for dose–response effects confirming a radiation dose–response correlation for this OAR if Dmean > 3 Gy or Dmax > 10 Gy. Further, RINV toxicity increased as Dmax increased, rising from Dmax > 10 Gy to 17 Gy for G1–G2 nausea and Dmax > 17 Gy for G1 vomiting (V1). We found the same results for Dmean, recording G1–G2 nausea for Dmean within 3 and 6 Gy and V1 for Dmean > 6 Gy. The dose-constraint threshold for Dmax suggests a dose–effect correlation typical of a serial organ such as the spinal cord [26]. The irradiated GEJCPs volume did not affect RINV. About the treated volume in the IGAAR study, a field size >400 cm² was a significant risk factor for RINV, while in our study the PTV of the residual breast or chest was an interesting RT-related variable with a significant risk at a value >700 cc [18]. Regarding the role of surgery, mastectomy appeared to have a significant impact due to the anatomical continuity of the chest wall into the upper abdomen and to the thickness of the chest wall compared to the breast.

Additionally, nodal radiation and breast side were considered in our analysis. Nodal radiation was the main reason to treatment

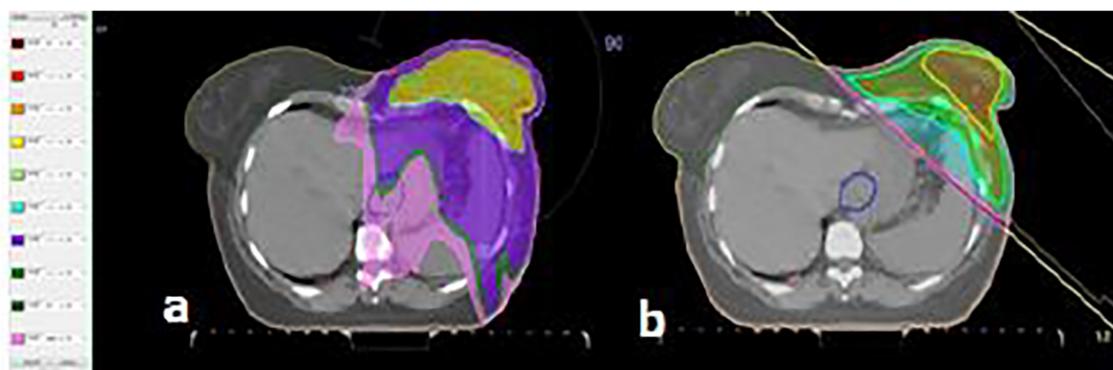


Fig. 4. a: A dose image of VMAT left breast radiation: note the blue ring (including the GEJCPs) in the blue and green isodose corresponding to 15–20 Gy. b: The same patient treated with 3D conformal RT using 2 tangential half beams: note that the distribution of 15–20 Gy isodose is far from the GEJCPs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

using VMAT in almost all the right and some of the left BC pts, but this variable did not significantly affect the RINV incidence. In contrast, left breast side was significantly related to RINV in our analysis, occurring in 60% of left side irradiated breast symptomatic patients. An anatomical explanation could underlie this phenomenon because the GEJCPs is on the left side in the upper abdomen. These data should be considered with caution because in 106 patients treated with VMAT, 89% had left breast irradiation due to the advantages of IMRT in left side breasts as a better dose reduction to the heart, left ventricle, and LAD than other techniques [27]. Patient factors such as age or chemotherapy could also affect the potential for RINV as reported by the IGAAR multifactorial analysis in which previous cancer chemotherapy had an unfavourable impact, but in our study, age, chemotherapy, and hormone therapy did not significantly affect symptoms [18].

In this retrospective study, low dose levels of Dmax and Dmean of a previously uncountoured upper abdominal structure incidentally involved in the VMAT pathway appeared as a new point of interest to explain RINV in breast cancer adjuvant RT. More information obtained by whole stomach contouring could be helpful.

Conclusion

VMAT modality has become an increasingly implemented radiation treatment technique for breast cancer, but arch beams' paths traverse healthy structures that were not directly irradiated in previous 3D-CRT techniques, providing a new acute morbidity profile unseen before the IMRT era. It has been assumed that RINV yields a minimal emetogenic potential in 2D-3D CRT breast cancer treatment, but with VMAT, we recorded a symptomatic incidence of RINV similar to MASCC/ESMO upper abdominal irradiation guidelines. This comparison led us to focus on the low dose-related effect on uncountoured structures at risk (GEJCPs) that lie in the upper abdomen near the PTV. This study has several limitations, including the low number of patients analysed and the very limited gastric contoured volume on the CT planning abdominal slides. Nevertheless, this research describes a new toxicity profile in BC adjuvant RT with VMAT modality and could provide benchmark data for future studies. An editorial by Alongi et al. on low-dose bath with VMAT in BC defined this issue as "much ado about nothing," but this concept should be stressed in light of new emerging toxicity profiles such as RINV in VMAT BC RT [28]. A routine monitored and constrained dose to relevant structures such as the GEJCPs or whole stomach could be useful to minimize RINV risk.

Conflict of interest statement

All authors declare no financial and personal relationships with other people or organisations that could inappropriately influence this work.

References

- [1] Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomised trials. *Lancet* 2011;378:1706–7.
- [2] Early Breast Cancer Trialists Collaborative Group (EBCTCG). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–35.
- [3] Poortmans PM, Collette S, Kirkow C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015;373:317–27.
- [4] Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional nodal irradiation in early stage breast cancer. *N Engl J Med* 2015;373:307–16.
- [5] Yim J, Suttie C, Bromley R, Morgia M, Lamoury G. Intensity modulated radiotherapy and 3D conformal radiotherapy for whole breast irradiation: a comparative dosimetric study and introduction of a novel qualitative index for plan evaluation, the normal tissue index. *J Med Radiat Sci* 2015;62(3):184–91.
- [6] Popescu CC, Olivetto IA, Beckham WA, et al. Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. *Int J Radiat Oncol Biol Phys* 2010;76:287–95.
- [7] Hahn C, Kavanagh B, Bhatnagar A, et al. Choosing wisely: the American Society for Radiation Oncology's top 5 list. *Pract Radiat Oncol* 2014;4(6):349–55.
- [8] Hartford AC, Galvin JM, Beyer DC, et al. American college of radiology (ACR) and American society for radiation oncology (ASTRO). Practice guideline for intensity-modulated radiation therapy (IMRT). *Am J Clin Oncol* 2012;35:612–7.
- [9] Hall EJ, Wu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;56(1):33–83.
- [10] Feyer PC, Maranzano E, Malassiotis A, et al. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer* 2011;19(Suppl. 1):S5–S14.
- [11] Tyran M, Mailleux H, Tallet A, et al. Volumetric-modulated arc therapy for left-sided breast cancer and all regional nodes improved target volumes coverage and reduces treatment time and doses to heart and left coronary artery, compared with a field-in-field technique. *J Radiat Res (Tokyo)* 2015;56(6):927–37.
- [12] White J, Tai A, Arth D et al. Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions. RTOG Radiation Therapy Oncology Group Web site. Available from: <http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx>.
- [13] Nielsen MH, Berg M, Pedersen AN, et al. Delineation of targets volumes and organ at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. *Acta Oncol* 2013;52:703–10.
- [14] ICRU 83 (2010) International Commission on Radiation Units and Measurements, Prescribing, Recording and Reporting Photon Beam Therapy, ICRU Report 50 (International Commission on Radiation Units and Measurements, Bethesda, Maryland).
- [15] Gray H. Anatomy of the human body. thirteenth American ed. Philadelphia: Lea & Febiger; 1985. 367–370.
- [16] Guyton AC, Hall JE. Textbook of medical physiology. eleventh ed. Philadelphia: Elsevier; 2006. p. 823–4.
- [17] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03: June 14, 2010. U.S. Department of Health and Human Services.
- [18] Nicolini G, Fogliata A, Clivio A, Vanetti F, Cozzi I. Planning strategies in volumetric modulated arc therapy for breast. *Med Phys* 2011;38:4025–31.
- [19] Nicolini G, Clivio A, Fogliata A, Vanetti F, Cozzi I. Simultaneous integrated boost radiotherapy for bilateral breast: a treatment planning and dosimetric comparison for volumetric modulated arc and fixed field intensity modulated radiotherapy. *Radiat Oncol* 2009;4:27.
- [20] Maranzano E, De Angelis V, Pergolizzi S, et al. A prospective observational trial on emesis in radiotherapy: analysis on 1020 patients recruited in 45 Italian radiation oncology centres. *Radiother Oncol* 2010;94:36–41.
- [21] Kavanagh BD, Pan CC, Lawson LA, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76(3):101–7.
- [22] Fogliata A, Seppälä J, Reggiori G et al. Dosimetric trade-offs in breast treatment with VMAT technique. *BJR* 90: Issue 1070.
- [23] Kocak-Uzel E, Gunn Brandon G, Kolen RR, et al. Beam path toxicity in candidate organs-at-risk: assessment of radiation emetogenesis for patients receiving head and neck intensity modulated radiotherapy. *Radiother Oncol* 2014;111(2):281–8.
- [24] Rosenthal DI, Chambers MS, Fuller CD, et al. Beam path toxicities to non-target structures during intensity modulated radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008;72(1):747–55.
- [25] Ciura K, McBurney M, Nguyen B, et al. Effect of brain stem and dorsal vagus complex dosimetry on nausea and vomiting in head and neck intensity modulated radiation therapy. *Med Dosim* 2011;36(1):41–5.
- [26] ICRU 62 (1999) International Commission on Radiation Units and Measurements, Prescribing, Recording and Reporting Photon Beam therapy (Supplement to ICRU report 50) (International Commission on Radiation Units and Measurements, Bethesda, Maryland).
- [27] Nieder C, Schill S, Kneschaurek P, Molls M. Influence of different treatment techniques on radiation dose to the LAD coronary artery. *Radiat Oncol* 2007 Jun;5(2):20.
- [28] Alongi F, Giaj-Levra N, Fiorentino A et al. Low-dose bath with volumetric modulated arc therapy in breast cancer: "Much ado about Nothing?". *Editorial. Tumori* 2016; 102 (4): 335–336.