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Beyond the heart in hypofractionated radiotherapy and in the transition from 3D to IMRT/VMAT

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ABSTRACT

Background: The knowledge of the risks induced by radiation with hypofractionation regimens has only recently been estimated together with its implementation as a management standard. However, the dose to other risk organs with intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) is not clear, that is why this is only a reference study of radiation doses to organs at risk in hypofractionation in our center.

Materials and methods: We completed a retrospective and observational analysis of 1398 patients treated with adjuvant hypofractionated radiotherapy from 2015 to 2018, using the clinical records and dose-volume histogram of patients treated with moderate hypofractionated adjuvant radiotherapy. To analyze the institutional experience on the dosimetry of the esophagus and liver as risk organs in the use of moderate adjuvant hypofractionated radiotherapy in breast cancer.

Results: The dosimetry of the esophagus was 3271 cGy DMax, 177 cGy DMed, 68 cGy D50%, 500 cGy DcMAX with 3D RT and 4124 cGy DMax, 1242 cGy DMed, 934.50 cGy D50%, 3213 cGy DcMAX with IMRT/VMAT and the dosimetry for the liver was for right breast cancer 466 cGy DMed, 102 cGy D50% and 8% V20, for left breast cancer 22 cGy DMed, 6.10 cGy D50% and 0.3% V20.

Conclusion: The statistically significant differences in irradiation show the lack of consensus on the optimal restrictions in hypofractionation regimens to reduce clinical sequela; consequently, the variability in the specification of each radiation oncologist is observed; standardization in our center can lead to improvement in the quality of treatments.

Key words: breast cancer; liver; esophagus

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Introduction

Radiotherapy (RT) represents a cornerstone of breast cancer treatment, because it is unavoidable to irradiate surrounding healthy tissues, the treatment is associated with a significant number of non-cancer deaths. In the first trials that included breast irradiation, an increase in the number of cardiac deaths was observed [1] so the investigation was directed to the evaluation of radiation doses to these structures.

The great advances in RT techniques during the last decades have led to a continuous reduction of the radiation dose to the heart, however, the benefit of lower toxicity continues to be paradoxically minimized by exposing the pa-

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tient to a personalized multidisciplinary therapeutic approach, which has resulted not only in an increase in life expectancy, but also carries the price of additional associated toxicity, analyzing its impact on each organ at risk and establishing preventive care strategies is important in this comprehensive approach.

In line with these advances, moderate hypofractionation (40–42.56 Gy with daily doses of 2.5–2.67 Gy) has recently become the standard for adjuvant RT to the breast [2]. The data available for the estimation of radiation-induced risks refer mainly to conventional fractionation regimens, so it is necessary to ask, if this information is applicable to new hypofractionation regimens?

Intensity modulated radiation therapy (IMRT) has been used to reduce side effects and improve therapeutic effects in various solid tumors, including head and neck cancer, prostate cancer, and anal cancer [3–6].

For breast cancer, the results of randomized studies regarding the benefit in toxicity and efficacy of IMRT compared to 2-dimensional (2D) or 3-dimensional (3D) conformal radiotherapy in early breast cancer should be taken with caution [7–9].

Radiation exposure from cancer treatment has been shown to increase the risk of a number of second primary malignancies (SPM).

Its incidence has been underestimated because most patients had a short life expectancy after treatment or their follow-up was less than 15 years; for which this phenomenon became more evident as the survival time increased.

The cumulative incidence of PMS could be as high as 20% of patients treated with radiotherapy, and this cumulative proportion varies with several factors: depending on the tissue and organs, the patient's age at the time of treatment, hereditary factors, the distribution of dose, the size of the irradiated volume, the dose per fraction and the dose rate [10].

Several observational studies have shown an increased risk of esophageal cancer after radiation therapy [11–14]. A dose-response relationship based on 252 women who developed esophageal cancer after radiation therapy for breast cancer suggests that the risk of esophageal cancer increases by 7.1% for each Gy [95% confidence interval (CI): 1.9–20.6] of median dose in the esophagus [15]. Currently, a systematic review of the esophageal dose in modern adjuvant radiotherapy in breast cancer has been carried out, it included 42 studies from 2010 to 2020 with a total of 112 regimens where the average mean dose in the esophagus ranged from 0.2 Gy in partial breast irradiation, from 1.8 to 6.7 Gy for total breast or chest wall radiotherapy and for radiotherapy that included the nodal region, the mean esophageal doses were higher: mean 11.4 Gy and maximum of 34.4 Gy, which can double the risk of esophageal cancer [16].

This study aims to analyze the institutional experience on the current use of adjuvant hypofractionated RT for patients with breast cancer, regarding the dosimetry of the esophagus and liver as risk structures, since there are no data to establish whether its irradiation is potentially related to relevant clinical sequela in the patient's quality of life, either short or long term.

Materials and methods

A retrospective and observational research study of patients with non-metastatic breast cancer treated with adjuvant radiotherapy at the Oncology Hospital of the National Medical Center XXI Century, in the period from January 1, 2015, to December 31, 2018. The inclusion criteria were histopathologically proven non-metastatic breast cancer, treatment with moderate hypofractionated adjuvant radiation therapy, age > 18 years, treatment planning records available, available dose-volume histograms, no prior RT involving the current treatment field. The exclusion criteria were those patients for whom treatment planning data are not available.

Results

We included 1,398 patients treated with adjuvant hypofractionated radiotherapy from 2015 to 2018 in our center and who met the inclusion criteria.

The main characteristics of the patients and the treatment received are shown in Table 1. On average, there were 349 patients treated per year, 63.7% (890) received treatment to the rib cage and/or residual breast with lymph nodes areas. Axillary and supraclavicular, which from now on will be referred to in this text as regional nodal irradia-

Table 1. Characteristics of patients treated with adjuvant radiotherapy (RT) for breast cancer, in the period 2015–2018

	% (N)
Technique	
3D	92.6% (1294)
VMAT/IMRT	7.4% (104)
Fields	
RNI	63.7% (890)
Tangential	36.3% (508)
Dose	
40 Gy en 15 Fx	33.9% (474)
42.56 Gy en 16 Fx	65.1% (910)
Other Schemes	1% (14)
Side	
Right	49% (685)
Left	51% (713)
Boost	
No	99.3% (1388)
Yes	0.7%(10)
Year	
2015	26% (364)
2016	27% (378)
2017	25.2% (352)
2018	21.7% (304)

3D — 3-dimensional conformal radiotherapy; IMRT — intensity-modulated radiation therapy; VMAT — volumetric modulated arc therapy

tion (RNI); in 36.3% (508) only the rib cage or residual breast is included.

The dose of 42.56 Gy in 16 fractions was the main fraction used in 65.1% of the series, while 40 Gy in 15 fractions was established for 33.9%.

92.6% of the treatments were planned with the 3D conformal technique and only 7.4% with the IMRT or volumetric modulated arc therapy (VMAT) techniques. It should be highlighted that the VMAT technique was increased through the years of treatment from 0.8% in 2015 to 17.1% for in 2018.

Of 1,398 patients, only 10 (0.7%) patients received a sequential boost to the surgical site with electrons or photons, representing less than 1% of the cohort.

Esophageal analysis

The dosimetry for the esophagus is shown in Table 2. In its analysis, the planning technique used drastically influenced the irradiation received by the organ, with doses of 3271 cGy (99.50–4089), 177 cGy (58–483), 68 cGy (51–88.50), 500 cGy (126–2350) with 3D RT and 4124 cGy (3572–4405), 1242 cGy (1021–1571), 934.50 cGy (735.50–1172), 3213 cGy (2583–3756) with IMRT/VMAT for Dmax, Dmed, D50%, and DcMAX, respectively.

On the other hand, a dosimetry difference was documented for the same parameters evaluated (Dmax, Dmed, D50% and DcMAX), consistent with the treatment field, with a higher irradiation dose for the esophagus in its cervical portion, logically in the treated patients, with RNI with the following values: 3942.50 cGy (3187.75–4247.75), 392.50 cGy (177.25–806), 83 cGy (66.77–127), 150 cGy (400–3287) compared to 77cGy (64–96), 46 cGy (38–57), 45cGy (37–56), 61 cGy (51–74.50) for those with tangential fields.

Table 2. Dosimetry of the esophagus of patients treated in the period 2015–2018

	Esophagus		
	RNI	Tangential	p-value
DMax[a]	3942.50 cGy (3187.75–4247.75)	77 cGy (64–96)	0.001
DMed[a]	392.50 cGy (177.25–806)	46 cGy (38–57)	0.001
D50%[a]	83 cGy (66.77 - 127)	45 cGy (37–56)	0.001
DcMÁX[a]	1450 cGy (400–3287)	61 cGy (51–74.50)	0.001
	3D	IMRT/VMAT	
DMax[a]	3271 cGy (99.50–4089)	4124 cGy (3572–4405)	0.001
DMed[a]	177 cGy (58–483)	1242 cGy (1021–1571)	0.001
D50%[a]	68 cGy (51–88.50)	934.50 cGy (735.50–1172)	0.001
DcMaX[a]	500 cGy (126–2350)	3213 cGy (2583–3756)	0.001

RNI — regional nodal irradiation; 3D — 3-dimensional conformal radiotherapy; IMRT — intensity-modulated radiation therapy; VMAT — volumetric modulated arc therapy

Table 3. Dosimetry of the esophagus of patients treated with nodal irradiation in the period 2015–2018

Esophagus			
	Right	Left	p-value
DMax[a]	2893 cGy (104.50 – 3946)	3883 cGy (136–4276)	0.001
DMed[a]	150.50 cGy (58.50 – 362.50	397 cGy (77.50–791.50)	0.001
D50%[a]	70 cGy (49 - 96)	80 cGy (58–112.75)	0.001

Table 4. Dosimetry of the liver of patients treated in the period 2015–2018.

Liver			
	Right	Left	p-value
Dmed[a]	466 cGy (301–709)	22 cGy (14–44)	0.001
D50%[a]	102 cGy (71–151.10)	6.10 cGy (4–10.55)	0.001
V20[a]	8 cGy (5–13)	0.30 cGy (0.09–1.22)	0.001
	3D	IMRT/VMAT	
Dmed[a]	245 cGy (25–504)	908 cGy (607–1289)	0.001
D50%[a]	64 cGy (8–110)	644 cGy (393.25–1175.75)	0.001
V20[a]	7 cGy (3–11)	10 cGy (3.10–23)	0.002

3D — 3-dimensional conformal radiotherapy; IMRT — intensity-modulated radiation therapy; VMAT — volumetric modulated arc therapy

Of the 890 patients treated with RNI, 676 were identified to have had their esophagus bypassed, and their dosimetry was calculated by laterality, with the dose received being higher in those with left breast cancer, with a difference of up to 10 Gy more in Dmax and 2 Gy in Dmed, as broken down in Table 3.

Liver analysis

We identified 685 (49%) patients with right-sided breast cancer who received breast or rib cage irradiation with or without lymph node irradiation. Of this group, liver dosimetry was only documented for 646 patients.

The difference in Dmed, D50% and V20 was related to the laterality of the treatment [466 cGy (301–709), 102 cGy (71–151.10) and 8% (5–13) for right breast cancer *vs* 22cGy (14–44), 6.10 cGy (4–10.55) and 0.30% (0.09–1.22) in left breast cancer].

When comparing the 3D RT technique *vs.* IMRT/VMAT, it corresponded to an increase in the dosimetry of Dmed, D50% and V20 with the following doses: 245 cGy (25–504), 64 cGy (8–110) 7% (3–11) compared to 908 cGy (607–1289), 644 cGy (393.25–1175.75), 10% (3.10–23), respectively.

The global analysis of restrictions of the study has shown that the doses to each of the organs at risk are minimized in planning with the 3D conformal technique in a statistically significant way, as shown in Tables 2 and 4.

Discussion

This systematic review of dosimetry to organs at risk in adjuvant hypofractionated radiotherapy regimens for breast cancer during 2015–2018 in our unit shows that the wide variation in dose received by the liver and esophagus derives from the technique used as the main factor.

As a result of the analyses, it was confirmed that the increase in the implementation of the IMRT/VMAT technique over the years has generated a significantly higher dose received in the organs evaluated, it was specifically evidenced in the liver that the dose was higher even without taking into account the laterality of the treatment field.

During the 1980s and 1990s, breast cancer radiation therapy was generally field-based, with the medial border positioned away from the midline, with the esophagus outside the field [17]. The current standard practice is the use of international contour guides, where the volume to be treated has been established more medially, so that the esophagus may be more involved in the irradiation fields. This reflects the complexity of limiting the dose due to its anatomical proximity to the treatment field. The same reason causes greater susceptibility to radiation of the esophageal cervical portion that entails unwanted side effects.

According to our results, to date, the main advantage of treatment with the 3D technique in planning for breast cancer is a greater potential to reduce doses to organs at risk compared to the VMAT technique. These results support the lack of consensus on the suitability of this type of technique against 3DC RT.

On the other hand, the second determinant to mention of the dosimetry to the esophagus was the inclusion of lymph nodes, reporting higher irradiation doses in patients treated with NI compared to tangential fields.

The magnitude of this information can be exemplified by an individual patient data meta-analysis of about 40,000 women in 75 randomized trials, where radiotherapy approximately doubled the rate ratio for esophageal cancer [relative risk (RR) = 2.42, 95% CI: 1.19–4.92] [18]. The average mean dose received in the esophagus was 8.4 Gy, more than double that reported in our cohort: 3.92 Gy in those with NI, however, the records showed a higher mean dose (12.42 Gy) when analyzing the planned treatments with IMRT/VMAT.

Another aspect evaluated was the distribution of the dose received in the liver. The variation was evident for the laterality of treatment in patients treated for right breast cancer, the distribution of greater irradiation was focused on segments IVA and VIII, today there is no certainty as to what clinical impact this profile of curves may have on it.

The risks that have been considered to be associated with radiotherapy at present are likely to be lower than for irradiated patients in previously published studies. Radiotherapy can be delivered with greater precision now than in the past, and doses to organs at risk with modern 3DC radiotherapy are likely to be lower. As there are few or no previous dosimetry reports of organs such as the esophagus and liver, the data presented will serve as a reference for future research.

The wide ranges between dosimetry show a high degree of variability in the restrictions specified and accepted by radiation oncologists in each planning, related to the lack of well-established parameters to limit the radiation dose received by these organs in breast cancer patients treated with hypofractionations. The lack of studies showing the acute and, more rarely, the long-term clinical relationship of RT-induced toxicities means that these organs are often neglected in terms of dosimetric protection.

There is a significant benefit from inverse-planned IMRT compared with 3DCRT in reducing acute toxicity of breast radiation therapy, like less skin toxicity, also the target volume coverage may be better and the dosimetry more homogeneous. There are potential advantages for IMRT and it is difficult to balance with 3D [19].

Finally, although due to the nature of the study, it is not possible to establish any association with clinical outcomes, the statistically significant differences in irradiation show that the contouring of these organs must be carried out methodically in those treatments that include the supraclavicular area, patients with the right-sided disease or in whom IMRT/VMAT planning is considered and always establish the lowest possible restrictions as an objective to be considered within the review of treatment plans since it is not uncommon for patients to refer data during treatment of esophagitis, dysphagia, odynophagia, gastroesophageal reflux disease and abdominal pain, the same data that should not be considered in the context of advances in the quality and safety of our treatments.

Conclusion

To considering the structural complexity and its organic consequence of each organ at risk, this study allows us to reflect on the evaluation beyond just the indications to determine the need for adjuvant radiotherapy in the multimodal management of these patients.

As the data supporting the pathophysiology of RT-induced injury of specific events do not yet establish whether certain events are more likely to occur with specific dose distributions and exposures and/or in different substructures, in addition to the high hope of life of these patients, justifies a stricter threshold and the implementation of more than one parameter to consider for restrictions when evaluating an RT plan.

Finally, and as shown above, the presented results of the doses to the esophagus and liver, become relevant as it is the largest registry in our country, which serves to identify potential areas of learning, considering the sum of the multiple treatments received during this period.

The data on the involvement of radiotherapy in the toxicity of adjuvant treatment for breast cancer is derived from conventional fractionations, requiring the establishment of prospective studies designed to establish a relationship between tissue tolerance, new fractionation schemes and their impact. Without compromising the probability of tumor control.

Having sufficient evidence to adequately communicate the current real risk of treatment side effects leads to trust and acceptance of radiotherapy as an irreplaceable pillar in cancer treatments.

Conflict of interest

None declared.

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