Recommendations for hypofractionated whole-breast irradiation

Author: SBRT, Brazilian Society of Radiotherapy

Participants: *Nilceana Maya Aires Freitas*[1], *Arthur Accioly Rosa*[2], *Gustavo Nader Marta*[3,4], *Samir Abdalla Hanna*[4], *Rodrigo de Morais Hanriot*[5], *Allisson Bruno Barcelos Borges*[6], *Guilherme Rocha Melo Gondim*[5,7], *Antonio Cassio Assis Pellizzon*[7], *Igor Moreira Veras*[8], *Wilson José de Almeida Júnior*[9], *Claudia Regina Scaramello Hadlich Willis Fernandez*[10], *Eronides Salustiano Batalha Filho*[11], *Marcus Simões Castilho*[12], *Felipe Quintino Kuhnen*[13], *Rosa Maria Xavier Faria Najas*[14], *Renato José Affonso Júnior*[6], *André Campana Correia Leite*[15], *Homero Lavieri Martins Ribeiro*[16], *Ruffo Freitas-Junior*[17], *Harley Francisco de Oliveira*[18].

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1. Radiotherapy Department of the Araújo Jorge Hospital of the Góias State Association Against Cancer, Goiânia/GO, Brasil. **2.** Radiotherapy Department of the Bahia State Portuguese Hospital, Salvador/BA and President of the Brazilian Radiotherapy Society (SBRT), São Paulo/SP, Brasil. **3.** Department of Radiology and Oncology, Division of Radiation Oncology, Instituto do Câncer do Estado de São Paulo (ICESP), Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. **4.** Department of Radiation Oncology, Hospital Sírio-Libanês, São Paulo, Brazil **5.** Radiotherapy Department of the Oswaldo Cruz German Hospital, São Paulo/SP, Brasil. **6.** Radiotherapy Department, Barretos Cancer Hospital, Barretos/SP, Brasil. **7.** Radiotherapy Department of the AC Camargo Hospital, São Paulo/SP, Brasil. **8.** Radiotherapy Department of the Regional Integrated Oncology Center, Fortaleza-CE. **9.** Radiotherapy Department of the Moinhos dos Ventos Hospital, Porto Alegre-RS. **10.** Radiotherapy Service of the José Alencar Gomes da Silva National Cancer Institute, Rio de Janeiro/RJ, Brasil. **11.** Radiotherapy Department of the Brasilia State University Hospital and representative of the Ministry of Health, Brasili/DF, Brasil. **12.** Radiotherapy Department of the Felicio Rocho Hospital, Belo Horizonte/MG, Brasil. **13.** Radiotherapy Department of the Charity Hospital of Florianópolis, Florianópolis/SC, Brasil. **14.** Radiotherapy Department of the Rio Grande do Norte State League Against Cancer, Natal/RN, Brasil. **15.** Department of Radiation Oncology, Fundação Centro de Controle de Oncologia Manaus- AM. **17.** Mastology Program of the Goias Federal University, Goiânia-GO and representative of the Brazilian Mastology Society, São Paulo/SP, Brasil. **18.** Centro de Tratamento em Radio-Oncologia (CTR) and Ribeirão Preto Medical School (FMRP) da Universidade de São Paulo (USP) - Ribeirão Preto/SP; Hospital Márcio Cunha (HMC) - Ipatinga/MG, Brasil.

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SUMMARY

This recommendation consensus for hypofractionated whole-breast radiotherapy (RT) was organized by the Brazilian Society of Radiotherapy (SBRT) considering the optimal scenario for indication and safety in the technology applied. All controversies and contraindication matters (hypofractionated RT in patients who underwent chemotherapy [CT], hypofractionated RT in lymphatic drainage, hypofractionated RT after mastectomy with or without immediate reconstruction, boost during surgery, hypofractionated RT in patients under 50 years old, hypofractionated RT in large breasts, hypofractionated RT in histology of carcinoma in situ [DCIS]) was discussed during a meeting in person, and a consensus was reached when there was an agreement of at least 75% among panel members. The grade for recommendation was also suggested according to the level of scientific evidence available, qualified as weak, medium, or strong. Thus, this consensus will aid Brazilian radiotherapy experts regarding indications and particularities of this technique as a viable and safe alternative for the national reality.

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CORRESPONDING AUTHOR: Harley Francisco de Oliveira
Brazilian Society of Radiotherapy -SBRT – Pça. Oswaldo Cruz, 124 – cj. 52 – 5º andar
Paraíso – São Paulo – SP – CEP 04004-070 – Phone/Fax: (11) 3262-3976
E-mail: sbradioterapia@sbradioterapia.com.br, sbradioterapia@uol.com.br

INTRODUCTION

Breast cancer represents around 29.5% of all cancer types in Brazil, and it is the most prevalent type amongst women. It is estimated there were 59,700 new cases in the country in 2018[1], around 56 cases for every 100,000 women.

Radiotherapy (RT) is an essential part of Breast cancer treatment during early stages, with proved benefits of survival after conservative surgery[2]. The conventional fractionation (1.8-2 Gy per fraction) has been used as the standard over the last decades, with a total dose of 50-50.4 Gy over 25-28 sections, distributed over 5 consecutive weeks.

Hypofractionated radiotherapy is an RT technique in which the total dose is administered over a shorter time range with fractionated doses that are higher than the conventional ones. The scientific evidence for its use is established by prospective and randomized studies, including a considerable number of patients submitted to the conventional treatment for breast cancer, with comparable safety, effectiveness, local control, and survival observed on conventional treatment. It is a technique widely used in several countries[3,4,5].

The implementation of the whole-breast hypofractionated RT in the clinical routine was larger amongst academics than in community hospitals[6]. Variations in indication, considering anatomical aspects, planning parameters, technical and prognostic factors had a significant influence in that scenario. Recent recommendations allowed for a larger scope of indications for the use of whole-breast hypofractionated radiotherapy so that the slightest variations in medical decisions could intervene in treatment individualization[6].

Brazil faces the same difficulty to include hypofractionated radiotherapy in current clinical practice, whether it is for funding reasons or technical matters; so far, it has only been implemented in reference centers. In the current Brazilian reality, the lack of RT equipment has caused difficulty of access, long waiting lines, and delays for beginning treatment, all of which can compromise the oncology effectiveness[7,8,9]. The reduction in RT time could allow for an increased in installed capacity and, consequently, expand the access:

This article aims to report the consensus for recommendation of the Brazilian Society of Radiotherapy (SBRT) for the use of whole-breast hypofractionated RT.

METHODOLOGY

A meeting was organized to take place in the city of São Paulo on March 3rd, 2018, for which were invited the leading members of SBRT with renowned expertise and dedicated to the treatment of breast cancer. Representatives of some of the main reference centers for RT from each of the country's regions were invited, both from the Public Health System (SUS) as well as from the supplementary healthcare network. The panel was attended by 18 radio-oncologists, a physician representative of the Brazilian Association of Medical Physics (ABFM) and a mastologist representing the Brazilian Society of Mastology (BSM), the last two chosen as ad hoc consultants. Only the radio-oncologists had voting rights.

The literature available on the subject was reviewed, presented and discussed during plenary. Questions were raised regarding the indications and safety of whole-breast hypofractionated RT in different clinical contexts[10], which were put to the vote of panel members according to the Delphi Method[11].

There were three possible answers to the questions: agree, disagree, abstains. The consensus was reached when there was an agreement amongst at least 75% of the panel members. The grade for recommendation was also suggested according to the level of scientific evidence available, qualified as weak, medium, or strong, as follows.

Level of scientific evidence:

Strong Level – Data obtained from multiple randomized studies of good size, concordant and/or of a robust meta-analysis of randomized controlled trials.

Medium Level – Data obtained from a less robust meta-analysis, from a single randomized trial or from non-randomized trials (observational).

Weak Level – Data obtained from experts' consensual opinions.

For organization purposes, the meeting was divided into three main discussion section:

Section I – Who is the ideal patient for whole-breast hypofractionated RT?

Section II – Controversies and contraindications

All controversial issues were discussed in section II. Since there is still no strong evidence in the current literature on certain clinical contexts, particularities and subgroup analyses were conducted for consensus on the following subjects: Hypofrac-

tionated RT in patients who underwent chemotherapy (CT), hypofractionated RT in lymphatic drainage, hypofractionated RT after mastectomy with or without immediate reconstruction, boost use during surgery, hypofractionated RT in patients under 50 years old, hypofractionated RT in large breasts, hypofractionated RT in histology of carcinoma in situ (DCIS).

Section III – Safety in the technology applied

RESULTS

Section I – Optimal scenario for the indication of whole-breast hypofractionated RT

The SBRT consensus considered hypofractionated RT to be safe and effective for women who meet all the following clinical criteria:

- Have underwent conservative treatment for breast cancer;
- Are over 50 years old.
- Have invasive carcinoma of no special type, grades I and II;
- Have clinical stages T1 and T2;
- Have negative axillary lymph nodes;
- There is no particularity regarding the laterality of the affected breast;
- There is no restriction regarding the immunohistological profile (patients with positive hormone receptors, HER2 super-expressed or triple negative).

Level of agreement	Level of evidence
100%	Strong

Dose and fractionation:

The models of moderate fractionation of 42.5 Gy in 16 fractions and of 40 Gy in 15 fractions are equally safe and effective.

Level of agreement	Level of evidence
100%	Strong

Comments: The hypofractionated models are those that use a dose above 2 Gy/fraction. The fractionation models used in the Start B[12] studies of 40 Gy in 15 fractions and in the Canadian study[4] of 42.5 Gy in 16 fractions present consistent results regarding late toxicity, survival free of locoregional recurrence, and quality of life with 10-year average follow-up[4].

Section II – Areas of controversy and contraindications

Mastectomy and reconstruction:

The panel considers the post-mastectomy hypofractionated RT of solely the thoracic wall with NO immediate breast reconstruction to be safe.

Level of agreement	Level of evidence
100%	Moderate

Comments: Despite Start studies (A[13] and B[12]) not having as the assessment of post-mastectomy hypofractionated RT as the initial objective, this group represented 8% (513 patients) of the sample[3]. There was no statistical power for a recommendation. However, locoregional recurrence happened in 6.8% of these patients. The toxicity was not different for patients who underwent mastectomy and hypofractionated RT[3]. Radiobiological ratios of similar remaining-tissue sensibility, regardless of the surgical technique, and the potential reduction of late events from breast α/β encourage the use of hypofractionated models[14].

There was NO agreement as to the safety of the indication of post-mastectomy hypofractionated RT after immediate breast reconstruction WITH prosthesis/tissue expander.

Level of agreement	Level of evidence
28%	Weak

Comments: The Start studies (A[13] and B[12]) excluded post-mastectomy patients with immediate reconstruction, and there are no other studies that can be used as a reference for the procedure.

There was NO agreement as to the safety of the indication of post-mastectomy hypofractionated RT after immediate breast reconstruction WITH autologous tissue.

Level of agreement	Level of evidence
39%	Weak

Comments: The Start studies (A[13] and B[12]) excluded post-mastectomy patients with immediate reconstruction and, to the present day, there are no other studies with results that can be used as a reference for the procedure.

The panel considers the treatment with hypofractionated RT to be safe for breasts of all sizes, as long as the recommended technical criteria presented in this document are followed.

Level of agreement	Level of evidence
100%	Strong

Comments: The Start studies (P[15], A[13], and B[12]) did not limit breast size, and classified them into small, medium, and large. There was no toxicity difference amongst different breast sizes. The restriction should be made according to dosimetric parameters[3]. The Canadian study[4] limited the inclusion of breasts with latero-lateral diameter above 25 cm². This panel strongly suggests the use of the technical parameters established in Section III - Safety in the hypofractionated RT technology applied to treat breast cancer.

CHEMOTHERAPY

The panel considers the treatment of exclusively the breast with hypofractionated RT, AFTER adjuvant CT, to be safe.

Level of agreement	Level of evidence
100%	Strong

Comments: Several randomized clinical trials allowed CT patients in their adjuvant treatment protocols. Adjuvant CT was used in 13.9%, 35.5%, 22.2%, and 11% in the Start-P[15], Start A[13], Start[12] and Canadian[4] studies, respectively. In addition, in the Cochrane meta-analysis[16], 1,728 patients (21%) received adjuvant CT.

There was no difference in local control in the Start (P[15], A[13], and B[12]) and Canadian[4] studies in the subgroup of adjuvant CT, regardless of the RT model used (hypofractionated RT or conventional RT). Similarly, upon evaluating cosmesis and regular tissue toxicity, there was no difference amongst the study groups, regardless of the the use of adjuvant CT. The use of hypofractionated RT for breast cancer has been increasing considerably over the years.

A study conducted by the US National Cancer Database showed an increase in hypofractionated RT indication for patients who received CT, with an absolute increase of 13.6% over the last decade (from 4.6% to 18.2%)[17].

The panel considers the treatment of exclusively the breast with hypofractionated RT, AFTER neoadjuvant CT, to be safe.

Level of agreement	Level of evidence
94%	Weak

Comments: None of the clinical trials that assessed hypofractionated RT included neoadjuvant CT in their respective treatment protocols[16]; however, the indication in this scenario has substantially increased over the last few years[16,17].

Randomized prospective studies are being conducted with indications and models of hypofractionated RT posterior to neoadjuvant CT. In current clinical practice, the exposure to CT, both adjuvant as neoadjuvant, prior to surgery did not alter the toxicity patterns for hypofractionated RT.

The panel does NOT consider to be safe the treatment of exclusively the breast with hypofractionated RT and concurrent CT.

Level of agreement	Level of evidence
100%	Weak

Comments: The is no data in the literature that addresses the oncologic safety of hypofractionated RT concurrent with CT since the main clinical trials available did not use that combination[17].

The panel considers the treatment of exclusively the breast with hypofractionated RT, exclusively concurrent with anti-HER2 drugs, to be safe.

Level of agreement	Level of evidence
89%	Weak

Comments: Trastuzumab, as well as other anti-HER2 drugs, were not clinically assessable during recruiting for breast hypofractionated RT. Trastuzumab can be safely used after and concurrent with conventional RT. In a mitigating scenario, trastuzumab was administered with hypofractionated RT in several clinical situations, and no increased toxicity was observed[17].

DCIS

The panel considers the treatment of exclusively the breast with hypofractionated RT to be safe in patients with pure Ductal Carcinoma IN SITU.

Level of agreement	Level of evidence
100%	Moderate

Comments: In a meta-analysis of breast hypofractionated RT conducted by Cochrane[16], only 0.15% of patients presented a diagnosis of pure DCIS, and there was no evidence of a difference in local con-

trol and toxicity. The retrospective Montreal study showed similarities in the relapse patterns for the ipsilateral breast with the hypofractionated models for the pure DCIS histology[18]

AGE

The panel considers the treatment of exclusively the breast with hypofractionated RT to be safe in patients between 40 and 50 years old.

Level of agreement	Level of evidence
100%	Strong

Comments: The Start A[13], Start B[12] and Canadian[4] studies included, respectively, 23%, 21%, and 25% of women under 50 years old. The local control was similar among different ages.

There was NO agreement regarding the safety of indication of hypofractionated RT of exclusively the breast for patients with age under 40 years.

Level of agreement	Level of evidence
61%	Strong

Comments: The Start studies (P[15], A[13], and B[12]) included only 5.8% women under 40 years old. The local control and toxicity of normal tissue presented similar results among groups; however, without the due safety of indication to this day.

DRAINAGE

There was NO agreement regarding the safety of indication of hypofractionated RT exclusively of the breast in lymphatic drainage of the supraclavicular fossa (SCF).

Level of agreement	Level of evidence
56%	Moderate

Comments: The Start studies (P[15], A[13], and B[12]) used hypofractionated RT in the SCF, respectively, in 20%, 14%, and 7% of a total of 470 patients. The Cochrane[16] meta-analysis grouped only 10% of patients who underwent hypofractionated RT in the SCF. The Canadian[4] study did not include patients for lymphatic drainage irradiation.

A Chinese[19] study randomized 811 patients with high-risk breast cancer, stage II, for conventional or hypofractionated RT in the SCF and did not observe any difference in locoregional recurrence, distant metastasis, disease free survival, and global survival. Locoregional recurrence was also similar in meta-analysis[20] [relative risk [RR]= 1.03; 95% CI (0.87; 1.23), P=0.72], and in the Start[14] studies (0.5% vs 0.3%; p=0.71). The risks of pulmonary toxicity, rib fracture, plexopathy, and upper limb lymphedema were similar between the conventional and hypofractionated RT models[14,20].

There was NO agreement regarding the safety of indication of hypofractionated RT exclusively of the breast in lymphatic drainage of the supraclavicular fossa (SCF) and axilla.

Level of agreement	Level of evidence
33%	Weak

Comments: There were no randomized clinical trials that included the axilla in RT volumes. Despite some studies suggesting the model were equivalent regarding acute and late toxicities, most panel members did not consider hypofractionated radiotherapy to be appropriate in this context due to a lack of safety for recommendation to this day.

There was NO agreement regarding the safety of indication of hypofractionated RT exclusively of the breast in lymphatic drainage of the internal mammary chain.

Level of agreement	Level of evidence
22%	Weak

Comments: The randomized studies did not include the internal mammary chain in the RT volumes. Despite some studies suggesting equivalent levels of acute and late toxicity, it is not possible to exclude the possibility of increased pulmonary, costal arch, and heart toxicity with hypofractionated radiotherapy due to lack of scientific evidence[20].

BOOST

The panel considered the administration of a boost in patients who undergo breast hypofractionated RT to be safe.

Level of agreement	Level of evidence
100%	Strong

Comments: The use of a boost during surgery, when indicated, was used in different randomized controlled trials. In the Start studies (P[15], A[13], and B[12]) and the Cochrane[16] meta-analysis compilation, a boost

was used in 75%, 60%, 43%, and 44% of patients, respectively. In MD Anderson[21] and a Chinese[22] study, all patients had a boost after the whole-breast hypofractionated RT. No increased toxicity was observed with the addition of a boost to the hypofractionated models when compared to conventional therapy[16,20,22].

The models used were: 3x3 Gy, 4x2,5 Gy, 3x2,67 Gy and 5x2 Gy.

T3 STAGE

The panel considered the use of breast hypofractionated RT to be safe in patients with T3 tumors.

Level of agreement	Level of evidence
77%	Weak

Comments: The T3 stage was included in the Start studies (P[15], A[13], and B[12]), with tumors equal or larger than T2 representing 42.5%, 48.6%, and 35.9%, respectively. There is no analysis of the results; however, the randomized controlled trials considered that the size of the resected tumor, on its own, should not be an exclusion factor for hypofractionated radiotherapy[14].

GRADE III HISTOLOGY

The panel considered the use of breast hypofractionated RT to be safe in patients with grade-III-histology tumors.

Level of agreement	Level of evidence
100%	Strong

Comments: The compilation of the Start[3] studies showed that the tumor grade was not an isolated prognostic factor. Amongst the 5,861 patients grouped in the Start studies (P[15], A[13], and B[12]), it was observed 9% of locoregional recurrence for tumors with grade III histology, and 4.5% and 3.4%, respectively, for grade II and I. In the subgroup analysis of the Canadian[4] study, grade III histology was a risk factor linked to an increase in local recurrence. However, regardless of histological grade, those patients who underwent hypofractionated RT did not present an increase in relapse when compared with conventional RT. A specific population cohort study with grade II patients who underwent hypofractionated RT also did not show evidence of increased risk of locoregional recurrence in early-stage breast cancer[23].

The summary of accepted considerations that are recommended by the panel members with over 75% of agreement is presented in Table 1.

SECTION III – SAFETY IN THE HYPOFRACTIONATED RT TECHNOLOGY APPLIED TO TREAT BREAST CANCER

This panel of specialists recommends, for the breast hypofractionated RT, the use of the three-dimensional conformal technique (3DCRT). This technique uses dedicated computer tomography, with which it is possible to assess the distribution of the radiation dose in the target volume and the adjacent organs at risk (OARs), providing increased quality and safety during the treatment.

TABLE 1. PROFILE OF PATIENT FOR WHICH THE SBRT CONSENSUS RECOMMENDS THE USE OF HYPOFRACTIONATED RT FOR BREAST CANCER TREATMENT (AGREEMENT > 75% AMONGST PANEL MEMBERS)

Variable	Level of agreement (%)	Level of evidence
Surgery Conservative	100	Strong
Mastectomy		
Without reconstruction	100	Moderate
Age		
>40 years	100	Strong
Stage of the tumor		
T1 – T2	100	Strong
T3	77	Weak
Histological grade		
G1 – G2 – G3	100	Strong
Histology		
Invasive carcinoma of no special type	100	Strong
DCIS	100	Moderate
Regardless of IHC	100	Strong
Axillary lymph nodes		
Absent	100	Strong
Breast size		
Any size	100	Strong
Systemic treatment		
After adjuvant CT	100	Strong
After neoadjuvant CT	94	Weak
Concurrent with anti-HER2 drugs	89	Weak
Boost	100	Strong

DCIS = Ductal Carcinoma IN SITU. IHC = Immunohistochemical. CT = Chemotherapy. RT = Radiotherapy

The panel members suggest complying with the following criteria:

- Image acquisition and treatment in the supine position;
- Use of proper restraining devices that allows the patient to be comfortable and the position to be reproduced;
- The delineation of target structures and OARs as recommended by breast cancer contouring atlas by the RTOG[24] (https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx) or the ESTRO[21] (https://www.ncbi.nlm.nih.gov/pubmed/25630428).
- Evaluation of the dose-volume histogram (DVH); the constraints and prescription doses according to the RTOG 1005[25] are suggested by this panel.
- PTV_Eval – Breast CTV + 5-10 mm margin for setup, editing 5 mm of skin and excluding the volume of the costal arches.
- D95%=95% in an optimal scenario, being acceptable up to D90%=90%;
- DMAX=115% in an optimal scenario, being acceptable up to 120%;
- Compliance index (CI): volume covered by 95% of the prescription isodose/ PTV_Eval volume, this being from 0.95-2 (optimal) and the acceptable value of 0.85-2.5;

OARs constraints, such as ipsilateral lung, heart, contralateral lung, thyroid, and contralateral breast, according to the RTOG 1005 – Annex IV – p. 83[25].

(https://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?action=openFile&FileID=9366 rtog 1005 protocol) (Table 2);

- It is recommended to always use a linear accelerator;
- It is recommended to confirm the positioning with, at least, planar imaging on the first day of treatment and weekly, according to the RDC20[26].

TABLE 2. DOSE-VOLUME CONSTRAINTS FOR PLANNING WHOLE-BREAST HYPOFRACTIONATED RADIOTHERAPY, ACCORDING TO THE RTOG 1005[25] CRITERIA

Structure	Criteria
Breast CTV	D95% ≥ 38 (≥ 36)Gy D50% ≤ 43.2 (≤ 44.8)Gy
Boost CTV	D95% ≥ 9.5(9.0)Gy V11Gy ≤ 5(10)%
Heart	V16(20)Gy ≤ 5% V8Gy ≤ 30(35)% MeanD≤ 3.2(4)Gy
Lung	V16Gy ≤ 15(20)% V8Gy ≤ 35(40)% V4Gy ≤ 50(55)%
Contralateral lung – IMRT	V4Gy ≤ 10(15)%
Contralateral breast	MaxD ≤ 240(384)cGy D5% ≤ 144(240)cGy

CTV = clinical tumor volume, IMRT = Intensity-modulated radiotherapy, D_x = dose that receives the % the volume, V_{Gy} = volume that receives the dose in Gy, MeanD = mean dose, MaxD = maximum dose

FINAL CONSIDERATIONS

These recommendations presented by the SBRT for the use of whole-breast hypofractionated radiotherapy will aid Brazilian radiotherapy experts regarding indications and particularities of this technique as a viable and safe alternative for the national reality.

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RESUMO

Este consenso de recomendações para a radioterapia (RT) hipofracionada de toda a mama foi organizado pela Sociedade Brasileira de Radioterapia (SBRT) considerando o cenário ideal para indicação e segurança na tecnologia aplicada. Questões de controvérsias e contraindicações (RT hipofracionada em pacientes submetidas à quimioterapia [QT], RT hipofracionada nas drenagens linfáticas, RT hipofracionada após mastectomia com ou sem reconstrução imediata, a realização de reforço de dose em leito cirúrgico [ou boost], RT hipofracionada em pacientes com idade menor que 50 anos, RT hipofracionada em mamas volumosas, RT hipofracionada em histologia de carcinoma in situ [CDIS]) foram discutidas em encontro presencial, sendo o consenso atingido quando existisse concordância de pelo menos 75% dos panelistas. O grau de recomendação foi também sugerido de acordo com o nível de evidência científico disponível, qualificado entre fraco, médio ou forte. Assim, este consenso deverá servir para auxiliar os especialistas da radioterapia brasileira em relação às indicações e particularidades dessa técnica, como uma alternativa segura e viável para a realidade nacional.

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