REVIEW ARTICLE
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RADIOTHERAPY IN BREAST DUCTAL CARCINOMA *IN SITU*

Radioterapia em carcinoma ductal *in situ* de mama

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ABSTRACT

Breast ductal carcinoma *in situ* (DCIS) comprises a heterogeneous group of lesions with different forms of clinical and pathological presentation. Postoperative radiotherapy is usually performed in DCIS patients who underwent conservative breast surgery. The objective of the present study was to describe indications and clinical evidences of radiotherapy for breast DCIS patients.

KEYWORDS: Breast; Ductal Carcinoma in Situ; Radiotherapy.

RESUMO

O carcinoma ductal *in situ* (CDIS) de mama compreende um grupo heterogêneo de lesões com diferentes formas de apresentação clínica e patológica. A radioterapia pós-operatória é normalmente realizada nas pacientes com CDIS submetidas à cirurgia conservadora de mama. O presente estudo teve o objetivo de apresentar as indicações e as evidências para a utilização da radioterapia na abordagem do CDIS de mama.

PALAVRAS-CHAVE: Mama; Carcinoma Ductal in Situ; Radioterapia.

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INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast comprises a heterogeneous group of lesions with different forms of clinical and pathological presentation. Traditionally, DCIS is classified according to its architectural pattern, which is usually encompassed in five main subdivisions: comedo, cribriform, micropapillary, papillary or solid[1]. It's a distinctive set of proliferative lesions with heterogeneous invasion potential. Therefore, identifying lesions with more aggressive potential is necessary to establish the most appropriate therapeutic proposal[1].

DCIS diagnosis has increased very markedly over the last years due to population-based mammography screening programmes[1]. When radical mastectomy was the method of choice to approach DCIS, cure rate was close to 98%, with low recurrence rate after surgical procedure[2].

With the advent of conservative treatment (quadrantectomy/lumpectomy followed by whole breast radiotherapy) for invasive breast carcinomas, this type of therapy started being used for DCIS (specially for small and unicentric tumors), though it's important to mention that there are only retrospective studies backing this kind of approach for DCIS. Therefore, there are no prospective or randomized clinical trials comparing conservative therapy and radical mastectomy for these patients[3,4].

Whole breast radiotherapy after conservative surgery reduces the risk of local recurrences (both *in situ* and invasive). Local control benefits are the most significant gains of this approach and the results are more significant when combined with radiotherapy, even though there are no direct gains regarding overall survival rates.

THE ROLE OF ADJUVANT WHOLE BREAST RADIOTHERAPY FOR DUCTAL CARCINOMA *IN SITU*: CLINICAL EVIDENCE

Randomized clinical trials

Four randomized clinical trials with over 4,000 patients showed local control benefit when adjuvant radiotherapy was added to the treatment of DCIS patients who underwent conservative surgery.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-17 involved 818 patients randomly divided into two groups: whole breast isolated or radiotherapy-associated surgery. The main result was local recurrence (invasive or intraductal). In a 12-year follow-up, radiotherapy reduced the cumulative local recurrence rate (16.0 *versus* 32.0%). Considering invasive and non-invasive recurrences, in both subgroups the gains were maintained though the invasive recurrence decrease was higher than non-invasive recurrence (16.8 *versus* 7.7% and 14.6 *versus* 8.0%, respectively). There was no impact over overall or cancer-specific survival rates[5]. An update of this study (with conjoint analysis of NSABP B-24 data) corroborates the benefits of adjuvant radiotherapy[6].

The European Organization for Research and Treatment of Cancer (EORTC 10853) assessed 1,010 DCIS patients (with ≤5-cm tumors) treated with conservative surgery. The patients randomly received whole breast radiotherapy or a clinical approach. After 4.3 years of trial, the group treated with radiotherapy showed lower invasive (4.8 *versus* 8.0%) and non-invasive (5.8 *versus* 8.8%) recurrence rates when compared to the non-adjuvant group[7]. In 15 years, there was a 48% decrease in the risk of local recurrence, with a longer recurrence-free interval, over the same period for the radiotherapy group (82 *versus* 69%). No difference was observed between cancer-specific and overall survival[8].

A cooperative study conducted by researchers from England, Australia and New Zeeland randomly submitted 1,701 patients to DCIS surgery with free margins to the following groups: isolated surgery, surgery with whole breast radiotherapy, surgery with tamoxifen treatment and surgery with both whole breast radiotherapy and tamoxifen treatment. After 53 months of follow-up, on average, radiotherapy was able to decrease the recurrence rate of *in situ* and ipsilateral invasive carcinoma. Hormone therapy did not reduce the occurrence of ipsilateral invasive tumors, although DCIS overall recurrence was shown to be lower[9]. After 12.7 years of study, it was once again confirmed that radiotherapy decreased the incidence of ipsilateral invasive tumors recurrence (*hazard ratio* 0.32; 95% confidence interval — 95%CI 0.19–0.56; p<0.0001) and *in situ* recurrence (*hazard ratio* 0.38; 95%CI 0.22–0.63; p<0.0001)[10].

An investigation by the Swedish Breast Cancer Group analyzed the role of whole breast radiotherapy after conservative surgery in 1,046 DCIS patients. After 5.2 years of study, the group that underwent radiotherapy showed less recurrences (44 *versus* 117 cases). No difference was observed between groups regarding contralateral breast cancer, distant metastasis and death rates[11]. A recent 20-year follow-up update of this study placed radiotherapy as related to a 37.5% reduction of ipsilateral recurrence risk. Once again, no impact on overall survival rates was observed[12].

The study 9.804 by the Radiation Therapy Oncology Group (RTOG) randomly submitted 636 DCIS patients (with unicentric tumor smaller than 2.5 cm and low or intermediate nuclear grade) to whole breast radiotherapy or to observation. The use of tamoxifen was optional (62% of the patients received it). With average follow-up of 7.17 years, local ipsilateral recurrence in the radiotherapy group was rare (2 *versus* 19 occurrences). In a seven-year period, local recurrence rate was 0.9% in the radiotherapy group and 6.7% in the observation group (*hazard ratio* 0.11; 95%CI 0.03–0.47; p<0.001)[13].

It is worth noting that studies NSABP B-17[6] and EORTC[8] pointed out the benefits of radiotherapy even for the subgroup of patients considered at low risk (free surgical margins, >2-cm tumors and low-grade lesion). Also importantly, even though there were no direct overall survival benefits, breast cancer mortality rate was higher among patients with ipsilateral breast invasive carcinoma recurrence.

Some of the aforementioned studies, however, have limitations mainly regarding pathological evaluation (measurement of the tumor size and definition of free margins), surgical specimen radiography, and postoperative mammography.

Table 1 sums up the characteristics and results of randomized clinical trials selected.

Meta-analysis

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published in 2010 a meta-analysis compiling data from clinical trials and showed an absolute risk reduction of 15.2% over ten years when whole breast radiotherapy was combined with conservative surgery. The benefits of radiotherapy were the same regardless of age, surgery type (quadrantectomy or lumpectomy), use of tamoxifen, diagnosis method (clinical or radiologic), surgical margin (free, narrow or unknown), nuclear grade, presence of comedonecrosis, architectural subtype or tumor size. Furthermore, the impact of radiotherapy on the outcome was similar in terms of *in situ* and invasive local recurrences: 6.5 versus 14.9% and 6.9 *versus* 15.4%, respectively. The analysis of the subgroup of patients rated as low-risk (≤2-cm tumor, grade 1 and free margins) showed that radiotherapy was able to reduce the absolute risk of local recurrence by 18% (12 *versus* 30%; p=0.002)[14].

Another meta-analysis carried out by the Cochrane Group confirmed the statistically significant benefits of radiotherapy in cases of ipsilateral local recurrence (*hazard ratio* 0.49; 95%CI 0.41–0.58; p<0.00001), ipsilateral invasive recurrence (*hazard ratio* 0.50; 95%CI 0.32–0.76; p=0.001), and ipsilateral *in situ* recurrence (*hazard ratio* 0.61; 95%CI 0.39–0.95; p=0.03). Analysis of all subgroups showed benefits of adopting radiotherapy, with no long-term toxicity associated to this treatment[15].

RADIATION BOOST AFTER WHOLE BREAST RADIOTHERAPY FOR DUCTAL CARCINOMA *IN SITU*

The role of booster doses in the treatment of breast invasive tumors has been stablished through randomized clinical trials[16].

Regarding DCIS, a retrospective multicenter study showed, in a 72-month follow-up, that women younger than 45 years had local recurrence rates after conservative breast treatment of 54, 28 and 16%, considering patients treated exclusively with surgery, with surgery combined with whole breast radiotherapy, and with surgery combined with whole breast radiation boost on surgical bed, respectively[17]. Corroborating those results, other

Table 1. Randomized clinical trials.

Study	Recruitment period	Duration (years)	Number of patients	Pathology central revision (%)	Negative margins (%)	RT doses	*Booster doses*
NSABP B-17	1985–1990	17.25	818	76	78	50Gy/25 fractions	10 Gy/5 fractions (9% of the patients)
EORTC 10853	1986–1996	15.8	1.010	85	83	50Gy/25 fractions	10 Gy/5 fractions (5% of the patients)
UK/ANZ DCIS	1990–1998	12.7	1.030	0	100	50Gy/25 fractions	-
SweDCIS	1987–1999	20	1.067	26	80	50 - 54Gy/25 -27 fractions	-
RTOG 9804	1998–2006	7.17	636	100	100	50 - 54Gy/25 -27 fractions or 42,5Gy/16 fractions	-

Study	Local recurrence (%)						Overall survival (%)	
	Total		Invasive		*In situ*			
	With RT	Without RT	Without RT	With RT	Without RT	With RT	Without RT	With RT
NSABP B-17	35.0	19,8	19,6	10,7	15,5	9,0	86,0	87,0
EORTC 10853	30.0	17,0	15,0	9,5	15,0	7,5	90,0	88,0
UK/ANZ DCIS	19.4	7,0	9,1	3,3	9,7	3,8	97,9	96,2
SweDCIS	20.0	32,0	-	-	-	-	77,7	73,0
RTOG 9804	6.7	0,9	-	-	-	-	95,1	91,7

RT: radiotherapy; NSABP: National Surgical Adjuvant Breast and Bowel Project; EORT: European Organization for Research and Treatment of Cancer; RTOG: Radiation Therapy Oncology Group.

retrospective studies reported low local recurrence rates when booster radiation doses were systematically used[18,19].

However, some studies reported no benefit related to the use of radiation boost in the treatment of DCIS patients[21].

This matter remains open, and currently two randomized clinical trials are ongoing with the goal of evaluating booster doses for DCIS patients.

WHOLE BREAST HYPOFRACTIONATED RADIOTHERAPY FOR DUCTAL CARCINOMA *IN SITU*

The hypofractionated radiotherapy, which has a fraction number smaller than the standard 25 to 30, is becoming popular after the publishing of two studies that evaluated the long-term evolution of patients submitted to this procedure[22,23]. Treatment schemes with 15 and 16 radiotherapy fractions have been assessed. No differences between local control, survival rate and toxicity were observed, and schemes were deemed equivalent to standard, if not better in terms of late toxicity. Most patients included in both studies were aged over 50 years and had low-risk invasive tumors in early stages. Regarding DCIS, however, the hypofractionated schemes were not randomly tested.

Despite that, the appeal for a shorter-term, more efficient treatment led several health centers to evaluate the effects of hypofractionated radiation on DCIS, and the outcomes were all gathered in a meta-analysis of observational studies published in 2015. Among the 13 studies analyzed, four (2,534 patients) compared the hypofractionated radiation to standard fractioning, but found no differences in local recurrence rate between the groups (*hazard ratio*: 0.78, 95%CI 0.58–1.03). The authors concluded that hypofractionated radiotherapy seems to be safe and efficient for DCIS patients and can be used as long as professionals keep in mind that the studies included in the meta-analysis carry a low level of evidence[24].

WHOLE BREAST ADJUVANT RADIOTHERAPY IN ELDERLY PATIENTS WITH DUCTAL CARCINOMA *IN SITU*

The benefits of radiotherapy for low-risk DCIS patients is a controversial question, especially in advanced ages. Also, women over 70 years old either are generally not included in clinical trials or represent a small portion of the studied population. According to a data collection in France, only 13.4% of the studied DCIS patients were aged 70 years or older[25].

The best available data about conservative breast cancer treatment with or without radiotherapy in elderly patients (above 70 years old) come basically from two randomized studies conducted with early-stage invasive tumor patients. The patients submitted to radiation had good results as to local control, but overall survival rates were not impacted[26,27].

Regarding DCIS, the EBCTCG[15] meta-analysis also showed good outcomes of adjuvant radiotherapy after conservative surgery. Results were proportionally better in patients aged 50 years or older, with absolute risk of ipsilateral recurrence after 10 years of 18,5 *versus* 29,1% for patients below the age of 50 , and of 10,8 *versus* 27,8% for the other age groups. It is worth noting that the cut-off age was 50 years old, and still the risks with or without adjuvant radiotherapy in this group were lower compared to patients under this age. There are no specific data addressing patients over 70 years old, however, the proportional reduction of occurrences in the group receiving radiation therapy increased with aging, for every decade added: 60 to 69 and 70 and above (p=0.02).

Even elderly DCIS patients benefit in terms of local control from radiotherapy after conservative surgery and, to the present moment, there is not a subgroup of patients that can be safely kept from radiation therapy. Age alone can not be a contraindication for the treatment. In the long run, the potential impact of local recurrence on elderly patients' quality of life and psychological state should not be underestimated.

However, at least for patients with lower life expectancy, whether by presence of comorbidities or advanced age, the extent of risk reduction should be evaluated, keeping in mind that at least nine patients must be submitted to radiation therapy as a means of preventing ipsilateral recurrence[15]; among the elderly, this number can range from 20 or 21 (70 to 80 years old) to 160 (80 years and older) patients[28].

The International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA)[29] recommend that, once survival rates do not change, the level of local control must be assessed considering individual risk, physiological age, life perspective, treatment tolerance, patient's preference and other potential matters such as daily visits to the radiotherapy service for adjuvant therapy.

ACCELERATED PARTIAL BREAST RADIATION FOR DUCTAL CARCINOMA *IN SITU*

Accelerated partial breast radiation (APBR) has been evaluated in several randomized clinical trials. When compared to whole breast radiotherapy, results are controversial when it comes to local control rates. Some studies report similar local recurrence rates, while others point out lower rates in the group of patients submitted to APBR. It's important to emphasize that the number of DCIS patients included in such studies is small, hence it's difficult to outline the true effect of APBR in this subgroup of patients[30].

The American Society for Radiation Oncology (ASTRO)[31] and the American Brachytherapy Society (ABS)[32] consider DCIS patients good candidates to APBI. On the other hand, the European

Society for Radiotherapy and Oncology (ESTRO) states that new studies are necessary to prove the efficiency of APBI for DCIS patients and they do not recommend this therapy as a routine procedure[33].

CONCLUSIONS

- Whole breast adjuvant radiotherapy is related to reduction of *in situ* and invasive recurrences in breast DCIS patients. Therefore, it should be adopted as a routine procedure;
- The action of booster radiation doses in the treatment of DCIS patients is not clear;
- Hypofractionated radiotherapy can strongly be regarded as a procedure for DCIS patients, following the same selection criteria used for invasive tumors;
- For elderly DCIS patients, the indication of radiotherapy must be based on the balance between treatment benefits and patients' life perspective;
- APBI for DCIS patients is a controversial matter despite some international guidelines supporting its use in clinical practice.

REFERENCES

1. Allred DC. Ductal carcinoma in situ: terminology, classification, and natural history. J Natl Cancer Inst Monogr. 2010;2010:134-8. https://doi.org/10.1093/jncimonographs/lgq035
2. Rosner D, Bedwani RN, Vana J, Baker HW, Murphy GP. Noninvasive breast carcinoma: results of a national survey by the American College of Surgeons. Ann Surg. 1980;192:139-47.
3. Solin LJ, Fourquet A, Vicini FA, Taylor M, Olivotto IA, Haffty B, et al. Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. Cancer. 2005;103:1137-46. https://doi.org/10.1002/cncr.20886
4. Cutuli B, Cohen-Solal-le Nir C, de Lafontan B, Mignotte H, Fichet V, Fay R, et al. Breast-conserving therapy for ductal carcinoma in situ of the breast: the French Cancer Centers' experience. Int J Radiat Oncol Biol Phys. 2002;53:868-79.
5. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. Semin Oncol. 2001;28:400-18.
6. Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst. 2011;103:478-88. https://doi.org/10.1093/jnci/djr027
7. Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. J Clin Oncol. 2001;19:2263-71. https://doi.org/10.1200/JCO.2001.19.8.2263
8. Donker M, Litière S, Werutsky G, Julien JP, Fentiman IS, Agresti R, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol. 2013;31:4054-9. https://doi.org/10.1200/JCO.2013.49.5077
9. Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet. 2003;362:95-102.
10. Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21-9. https://dx.doi.org/10.1016%2FS1470-2045(10)70266-7
11. Emdin SO, Granstrand B, Ringberg A, Sandelin K, Arnesson LG, Nordgren H, et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol. 2006;45:536-43. https://doi.org/10.1080/02841860600681569
12. Wärnberg F, Garmo H, Emdin S, Hedberg V, Adwall L, Sandelin K, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. J Clin Oncol. 2014;32:3613-8. https://doi.org/10.1200/JCO.2014.56.2595
13. McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, et al. RTOG 9804: A Prospective Randomized Trial for Good-Risk Ductal Carcinoma In Situ Comparing Radiotherapy With Observation. J Clin Oncol. 2015;33(7):709-15. https://doi.org/10.1200/JCO.2014.57.9029
14. Early Breast Cancer Trialists' Collaborative Group, Correa C, McGale P, Taylor C, Wang Y, Clarke M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr. 2010;2010:162-77. https://doi.org/10.1093/jncimonographs/lgq039
15. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev. 2013;11:CD000563. https://doi.org/10.1002/14651858.CD000563.pub7
16. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):47-56. https://doi.org/10.1016/S1470-2045(14)71156-8
17. Omlin A, Amichetti M, Azria D, Cole BF, Fourneret P, Poortmans P, et al. Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network. Lancet Oncol. 2006;7:652-6. https://doi.org/10.1016/S1470-2045(06)70765-3

18. Alvarado R, Lari SA, Roses RE, Smith BD, Yang W, Mittendorf EA, et al. Biology, treatment, and outcome in very young and older women with DCIS. Ann Surg Oncol. 2012;19:3777-84. https://dx.doi.org/10.1245%2Fs10434-012-2413-4

19. Halasz LM, Sreedhara M, Chen YH, Bellon JR, Punglia RS, Wong JS, et al. Improved outcomes of breast-conserving therapy for patients with ductal carcinoma in situ. Int J Radiat Oncol Biol Phys. 2012;82:e581-6. https://doi.org/10.1016/j.ijrobp.2011.08.015

20. Rakovitch E, Narod SA, Nofech-Moses S, Hanna W, Thiruchelvam D, Saskin R, et al. Impact of boost radiation in the treatment of ductal carcinoma in situ: a population-based analysis. Int J Radiat Oncol Biol Phys. 2013;86:491-7. https://doi.org/10.1016/j.ijrobp.2013.02.031

21. Meattini I, Livi L, Franceschini D, Saieva C, Meacci F, Marrazzo L, et al. Role of radiotherapy boost in women with ductal carcinoma in situ: a single-center experience in a series of 389 patients. Eur J Surg Oncol. 2013;39:613-8. https://doi.org/10.1016/j.ejso.2013.03.002

22. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086-94. https://doi.org/10.1016/S1470-2045(13)70386-3

23. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513-20. DOI: 10.1056/NEJMoa0906260

24. Nilsson C, Valachis A. The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies. Radiother Oncol. 2015;114(1):50-5. https://doi.org/10.1016/j.radonc.2015.01.001

25. Cutuli B, Lemanski C, Fourquet A, Lafontan B, Giard S, Meunier A, et al. Breast-conserving surgery with or without radiotherapy vs mastectomy for ductal carcinoma in situ: French Survey experience. Br J Cancer. 2009;100:1048-54. https://dx.doi.org/10.1038%2Fsj.bjc.6604968

26. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004;351:971-7. https://doi.org/10.1056/NEJMoa040587

27. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266-73. https://doi.org/10.1016/S1470-2045(14)71221-5

28. Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst. 2006;98:681-90. https://doi.org/10.1093/jnci/djj186

29. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13:e148-60. https://doi.org/10.1016/S1470-2045(11)70383-7

30. Marta GN, Macedo CR, Carvalho H de A, Hanna SA, da Silva JL, Riera R. Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. Radiother Oncol. 2015;114:42-9. https://doi.org/10.1016/j.radonc.2014.11.014

31. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017;7:73-9. https://doi.org/10.1016/j.prro.2016.09.007

32. Hepel JT, Arthur D, Shaitelman S, Polgár C, Todor D, Zoberi I, et al. American Brachytherapy Society consensus report for accelerated partial breast irradiation using interstitial multicatheter brachytherapy. Brachytherapy. 2017;16(5):919-28. https://doi.org/10.1016/j.brachy.2017.05.012

33. Polgár C, Van Limbergen E, Pötter R, Kovács G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol. 2010;94:264-73. https://doi.org/10.1016/j.radonc.2010.01.014