Reports of Practical Oncology and Radiotherapy 25 (2020) 760–764

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Case report

Definitive single fraction stereotactic ablative radiotherapy for inoperable early-stage breast cancer: A case report

Manasa Veluvolu [a], Mausam Patel [a], Ganesh Narayanasamy [a], Thomas Kim [b,*]

[a] Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, United States
[b] Department of Radiation Oncology, Rush University Medical Center, Chicago, IL, 60612, United States

ARTICLE INFO

Article history:
Received 6 April 2020
Received in revised form 2 June 2020
Accepted 29 June 2020
Available online 11 July 2020

Keywords:
SABR
SBRT
Breast
Definitive
Case

ABSTRACT

We review a case of inoperable early stage breast cancer treated definitively with the use of stereotactic ablative radiotherapy (SABR). A 57-year-old female with a history of decompensated cirrhosis with early stage breast cancer was treated with 25 Gy in one fraction. At her 7-month follow up visit, there was a complete resolution of disease on imaging. This case represents a novel approach for the treatment of breast cancer with SABR when surgery is contraindicated.

1. Introduction

Advances in both surgery and radiation therapy have led to the development of breast conserving therapy for early stage breast cancer. Indeed, the paradigm shift from mastectomy to lumpectomy and adjuvant radiation has changed the current standard of care. Similar to the surgical trend of preserving breast tissue with lumpectomy, there has been a trend in radiation oncology towards decreasing the treated volume of breast while increasing the dose per fraction. Indeed, studies have shown that hypofractionated radiotherapy yields the same results as conventional fractionation when treating the whole breast.[1–4] Accelerated partial breast irradiation (APBI) involves not only increased fractional dose but also a reduction in the treatment of normal breast with brachytherapy, intraoperative radiotherapy and external-beam radiotherapy. However, no matter what radiation technique is applied, surgery remains part of the standard of care in operable patients.[5]

Unfortunately, there is no consensus on the optimal approach among women who are not candidates for surgery. Stereotactic ablative radiotherapy (SABR), or stereotactic body radiation therapy (SBRT), has been increasingly used in lieu of surgery among various disease sites, including the lung, kidney, liver, spine, and brain, and is often considered the standard of care in many of these sites.[6–8] Studies have shown SABR to be a suitable alternative to surgery; furthermore, it can yield superior local control rates as compared to conventional radiotherapy in inoperable cases.[9] In this case report, we discuss the use of SABR in one fraction for early stage breast cancer in a patient where surgery was contraindicated (Figs. 1–3).

2. Case report

A 57-year old-woman with a history of decompensated cirrhosis secondary to alcohol abuse was referred to radiation oncology after being diagnosed with a malignant neoplasm of the left breast. She initially presented to her primary care physician for a self-palpated left breast mass. She was then referred for a diagnostic mammogram revealing an irregular-shaped 3.4 cm mass in the lower-outer quadrant of the left breast. The biopsy revealed an invasive lobular carcinoma (ILC), Nottingham grade 2, estrogen receptor staining strongly positive (95%, 3+), progesterone staining negative (0), Her2/neu staining negative (1+), ki-67 of 60%. Computed tomography (CT) of the chest, abdomen and pelvis revealed no evidence of metastatic disease. A nuclear medicine bone scan revealed no metastatic disease. No clinical or radiographic evidence of axillary lymphadenopathy was noted. While a bilateral breast MRI was ordered as part of her diagnostic work up, the exam was aborted as she was unable to tolerate the procedure due to anxiety.

* Corresponding author at: Department of Radiation Oncology, Rush University Medical Center, 500 South Paulina Street, Atrium Building, Ground Floor, Chicago, IL 60612-3833, United States.
E-mail address: Thomas_Kim@rush.edu (T. Kim).

https://doi.org/10.1016/j.rpor.2020.06.011
1507-1367/

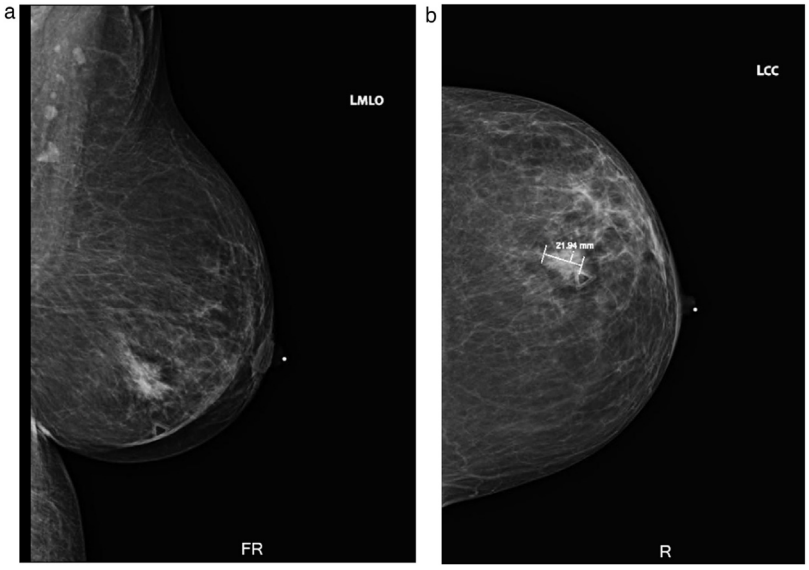

Fig. 1. Pre-treatment left breast mammogram in (a) MLO and (b) CC orientations.

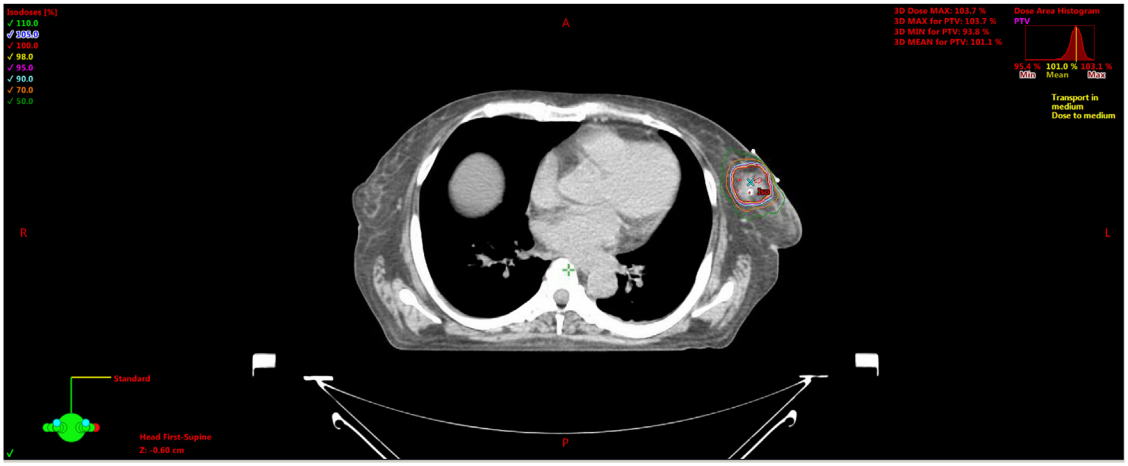

Fig. 2. Treatment planning and dosimetry.

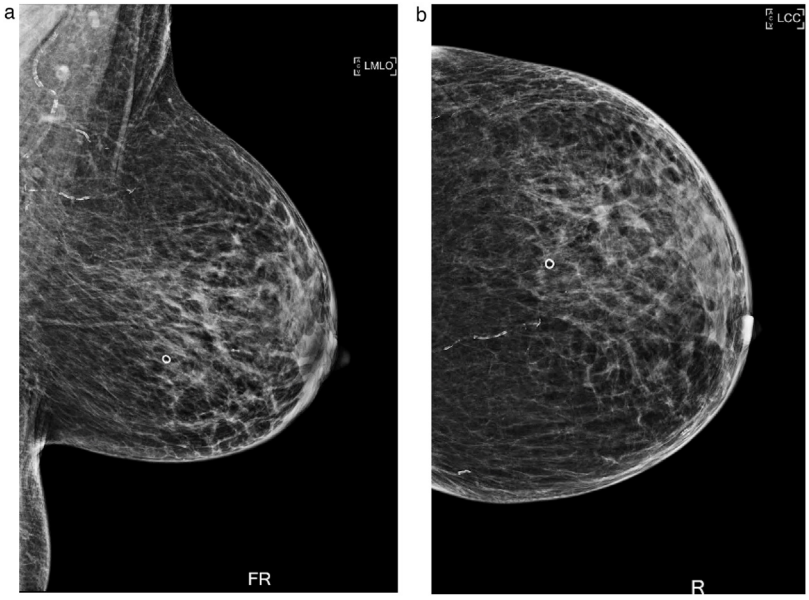

Fig. 3. Post-treatment left breast mammogram in (a) MLO and (b) CC orientations at 7 months follow up.

Her clinical prognostic stage (AJCC 8) was: Stage IIA (cT2, cN0, cM0, G2, ER: Positive, PR: Negative, HER2/neu: Negative).

Aside from her breast cancer diagnosis, the primary healthcare concerns for this patient were related to her decompensated cirrhosis. She had a history of alcohol abuse (3 large bourbon drinks a day for 20–30 years) which she quit at the same time as her breast cancer diagnosis. She had a history of multiple paracenteses for large volume abdominal ascites. She has also experienced esophageal varices, portal hypertension, mild splenomegaly, body wall edema, low blood pressure, elevated INR and scleral icterus.

Her case was discussed in the multidisciplinary breast tumor board with surgical oncology, medical oncology, radiation oncology, radiology, pathology and gastroenterology present. Various treatment options including surgery, systemic therapy and radiation were discussed. The usual standard treatment approach with initial breast conserving surgery or mastectomy was not feasible given the severity of her decompensated cirrhosis and coagulopathy. Stereotactic ablative radiotherapy (SABR), a form of highly focused radiation treatment used in many other extracranial sites, was then offered as a definitive treatment option.

With the patient's consent, she underwent a non-enhanced CT simulation for treatment purposes in the supine position. A wingboard with a vacuum modified cushion was used to stabilize her arms above her head and keep her immobilized. The images were reconstructed at 2 mm slice spacing. The gross tumor volume (GTV) was defined as the clip placed during biopsy and the surrounding mass-like hyperdense region on planning CT. The clinical target volume (CTV) was defined to be the same volume as the GTV. The GTV/CTV was expanded by 0.3 cm to create the planning target volume (PTV). The prescription dose was 25 Gy in a single fraction on a linear accelerator targeting the PTV. A volumetric modulated arc therapy plan with 2 partial arcs was used to cover the target. The plan was normalized for 100% of the dose to cover 95% of the target PTV.

The following max dose constraints to organs at risk (OARs) were used for single fraction treatment, as summarized by the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC radiotherapy: heart/pericardium, 22 Gy; ribs, 30 Gy; and skin, 26 Gy.[10] For the bilateral lungs, at most 1500 mL was to receive less than 7 Gy and 1000 mL was to receive less than 7.4 Gy.[11] The final plan demonstrated a max dose of 4.4 Gy to the heart/pericardium and 11 Gy to the ribs. Because the max dose in the entire plan was determined to be 25.9 Gy, the skin dose constraint was also met. Finally, 2115.9 mL of bilateral lung tissue received less than 7 Gy and 2116.2 mL of tissue received less than 7.4 Gy. After quality assurance checks were completed, the patient was immobilized in the treatment position, and the treatment dose was initiated after the pre-treatment cone beam CT (CBCT) showed that the isocenter agreed with the computerized stereotactic treatment plan, and the alignment and tumor location were verified by the treating physician.

The SABR treatment was tolerated well by the patient. The following month, she was started on endocrine therapy with goserelin, as a 3.6 mg subcutaneous injection given every 28 days. She was also started on 1 mg anastrozole PO daily a couple of weeks later. Three months following the SABR, and two months after initiation of endocrine therapy, the patient returned for thickening and pruritis of the skin over the previously treated region which she first noticed two months following SABR. She did not notice any nipple discharge, pain, enlarged lymph nodes, or other symptoms. Physical examination revealed skin thickening, dimpling and hyperpigmentation.

Due to persistent inflammatory changes on the treated side, the patient's medical oncologist ordered a breast MRI four months post SABR. However, this time, she was instructed to take diazepam 5 mg PO prior to her exam and thus, she was able to tolerate the entirety of the procedure. The MRI showed the treated lesion measuring 1.3 cm with surrounding skin thickening and edema in the lateral left breast. The surrounding skin changes were attributed as radiation-induced changes by the radiologist. A CDK4/6 inhibitor palbociclib 125 mg was added to her treatment plan for 21 days followed by a 7 day break. Mammography and ultrasound at seven months post SABR showed no discrete mass in the area of concern, although the trabecular parenchymal thickening of the left breast due to radiation was noted. Vascular calcifications were seen but no new masses or suspicious microcalcifications were observed. Benign axillary lymph nodes and edema were also visualized. The patient is currently on goserelin and continues to take anastrozole and palbociclib with no clinical or radiographic evidence of recurrence.

3. Discussion

Multiple published and ongoing studies have assessed the efficacy of SABR in breast cancer both in the adjuvant and neoadjuvant settings.[12–23] Indeed, Vasmel et al. performed a single arm prospective trial assessing the role of neoadjuvant magnetic resonance (MR) guided partial breast radiation among low risk breast cancer patients.[23] Low risk was defined as that with non-lobular histology, unifocal disease, without indications for chemotherapy, and with node negative, non-metastatic disease. Thirty-six patients were treated with an ablative dose of 20 Gy to a 3 mm expanded GTV volume (PTV-GTV) and 15 Gy to a 3 mm expanded CTV volume (PTV-CTV). Breast conserving surgery was performed 6–8 months after radiation. Primary outcome was a pathologic complete response, achieved in 42% of patients.[23]

While studies have assessed the role of both pre- and post-op SABR, few have assessed the effect of definitive radiation among inoperable patients or those who refuse surgery. Arriagada et al. and Van Limbergen et al. reported some of the earliest known retrospective studies of definitive radiotherapy in inoperable patients.[1,24,25] Both demonstrated a significant correlation between dose and local control. Moreover, given that they were among some of the first to report on definitive radiation for breast cancer, they used older radiation techniques and large treatment fields as compared to current standards.[1]

Shibamoto et al. performed one of the most recent studies evaluating the effect of definitive radiation on Stage IA-IIIC breast cancer patients refusing surgical intervention.[26] Eighteen patients were treated with conventional whole-breast irradiation consisting of 50 Gy in 25 fractions followed by a SBRT or intensity modulated radiation therapy (IMRT) boost. SBRT was delivered to the primary tumor in 18.0–25.5 Gy in 3 fractions in patients without nodal disease while IMRT was delivered in 20 Gy in 8 fractions to the tumor and axillary lymph nodes in patients with nodal involvement. Additionally, 9 patients received hormone therapy, 4 received chemotherapy, and 9 received a hydrogen peroxide injection. Three-year overall and progression free survival were 93% and 85%, respectively, while the 3-year local control rate was 92%. Furthermore, there were no grade 3 or higher toxicities. While the authors conclude that definitive radiation results in favorable tumor control and cosmetic outcomes, they acknowledge the limitations of their small, heterogeneous patient population.[26]

To our knowledge, there has been only one case report thus far assessing definitive SABR on clinical outcomes in a patient who was not deemed a surgical candidate. *Gao et al.* reported a case of a 69-year-old female with stage III chronic kidney disease and end stage liver disease who was diagnosed with Stage IIA, ER/PR -, HER2 + invasive ductal carcinoma (IDC) of the right breast.[27] While her right breast lesion was initially found on mammogram measuring

$2.6 \times 2.1 \times 1.3$ cm, she was also found to have a left sided lesion measuring $0.9 \times 07 \times 0.6$ cm on breast MRI upon further imaging work up. Unfortunately, she was not deemed a surgical candidate given her comorbidities. Similarly, systemic therapy was also contraindicated. Thus, she was ultimately treated with definitive bilateral SBRT to each lesion with the PTV of each lesion receiving 40 Gy in 5 fractions with a simultaneous integrated boost of 50 Gy in 5 fractions to the GTV. Her 3-month follow up demonstrated resolution of the left lesion and decrease in size of the right lesion. At 22 months, there was no evidence of residual disease in either breast. Finally, no visible radiation induced toxicity was observed.[27]

One important difference between the current case and that of Gao et al. is the different histology between the 2 cases, with our patient presenting with ILC as opposed to the more common IDC. Lobular histology has long been thought to be associated with an increased rate of multifocality and multicentricity, and thus; it was initially thought to be a relative contraindication to breast conserving therapy (BCT).[28] However, studies eventually demonstrated equivalent local control rates between ILC and IDC after BCT. While BCT is now standard for ILC, lobular histology is still considered a "cautionary" category per ASTRO consensus guidelines when treating with APBI.[29] This is partly due to the lack of patients with ILC in APBI prospective studies. Nonetheless, per the GEC-ESTRO working group guidelines, the presence of a lobular histology should not be considered a contraindication for either BCT or APBI.[28]

Advantages of using SABR over conventional fractionation and APBI include the ability to deliver a highly conformal dose distribution in fewer treatment sessions. Additionally, steep dose fall off results in lower toxicity to normal structures, potentially giving better outcomes with fewer side effects. Treatment margins are reduced down to 1–2 mm from 5–10 mm as compared to conventional methods. Moreover, the shorter treatment time and ability to forgo surgery reduces healthcare costs.[30] Challenges associated with SABR include those still seen from radiation therapy, such as potential off-target effects and difficulties with monitoring for recurrence in regions of radiation induced fibrosis.[9]

SABR was ultimately decided as choice of treatment for our patient as she was inoperable, and this technique offered great potential for treatment given its convenience, dosimetric advantages, and demonstrated high rates of local control among other disease sites. Because our patient presented with gross disease at the time of radiation, we elected to proceed with an ablative dose of radiation as is typically done with SABR rather than with conventional fractionation. Indeed, ablative doses have generally been defined as greater than 8 Gy per fraction and are characterized by termination of cell division and function by overwhelming cellular repair mechanisms.[11] The radiotherapy was completed in one sitting and the patient remains in remission at 7 months. While we noted tissue changes at the site of radiotherapy normally reported for this technique, our radiologists were able to confirm that the changes were not causes for concern and were expected radiation induced sequela.

While definitive radiation in place of surgical resection has demonstrated favorable outcomes more recently in the literature, additional studies are necessary to determine what role SABR plays in definitive care. Thus, surgery should remain part of the standard regimen whenever possible. Nonetheless, SABR may be a suitable alternative in patients deemed unsuitable for surgery. NCT03585621 is a phase I/II prospective study of SBRT among breast cancer patients deemed either inoperable or refusing surgery.[31] The primary outcome measure will be acute toxicity 12 weeks post treatment with secondary objectives assessing quality of life and tumor control.

4. Conclusion

This case represents one of the few studies illustrating the potential of SABR for early-stage, inoperable breast cancer. SABR has many potential advantages including decrease in cost, time, and side effects as compared to surgery with general anesthesia. The 25 Gy single fraction regimen in this case resulted in favorable tumor control and cosmetic outcomes. Large, prospective studies with long term follow up are necessary to further define the role of SABR in patients who have inoperable disease or refuse surgery. Currently, prospective trials are under way to help establish the role of SABR among the neoadjuvant, adjuvant, and definitive settings.

Conflict of interest

None declared.

Financial disclosures

None declared.

CRediT authorship contribution statement

Manasa Veluvolu: Writing - original draft. **Mausam Patel:** Writing - review & editing. **Ganesh Narayanasamy:** Writing - review & editing, Supervision. **Thomas Kim:** Conceptualization, Writing - review & editing, Supervision.

References

1. Barry A, Fyles A. Establishing the role of stereotactic ablative body radiotherapy in early-stage breast cancer. *Int J Breast Cancer*. 2018;2018:2734820.
2. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. 2008;371(9618):1098–1107.
3. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol*. 2008;9(4):331–341.
4. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *JNCI: J National Cancer Inst*. 2002;94(15):1143–1150.
5. Wenz F, Sedlmayer F, Herskind C, et al. Accelerated partial breast irradiation in clinical practice. *Breast Care (Basel)*. 2015;10(4):247–252.
6. David S, Tan J, Savas P, et al. Stereotactic ablative body radiotherapy (SABR) for bone only oligometastatic breast cancer: a prospective clinical trial. *Breast*. 2020;49:55–62.
7. Tian S, Higgins KA, Curran WJ, Cassidy RJ. Stereotactic body radiation therapy vs. Surgery in early-stage non-small cell lung cancer: lessons learned, current recommendations, future directions. *J Thorac Dis*. 2018;10(3):1201–1204.
8. Lo SS, Loblaw A, Chang EL, et al. Emerging applications of stereotactic body radiotherapy. *Future Oncol*. 2014;10(7):1299–1310.
9. Shirvani SM, Chang JY, Roth JA. Can stereotactic ablative radiotherapy in early stage lung cancers produce comparable success as surgery? *Thorac Surg Clin*. 2013;23(3):369–381.
10. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 4.2020). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 22 May 2020.
11. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol*. 2008;18(4):215–222.
12. Haas JA, Witten MR, Cotrutz C, et al. Stereotactic body radiation therapy for early-stage breast Cancer Using a robotic linear accelerator. *Int J Radiat Oncol Biol Phys*. 2017;99(2, Supplement):S7.
13. Rahimi A, Thomas K, Spangler A, et al. Preliminary results of a Phase 1 Dose-escalation trial for early-stage breast cancer using 5-fraction stereotactic body radiation therapy for partial-breast irradiation. *Int J Radiat Oncol Biol Phys*. 2017;98(1), 196-205.e192.
14. Rahimi A, Timmerman R. New techniques for irradiating early stage breast cancer: stereotactic partial breast irradiation. *Semin Radiat Oncol*. 2017;27(3):279–288.
15. Horton JK, Blitzblau RC, Yoo S, et al. Preoperative single-fraction partial breast radiation therapy: a novel phase 1, dose-escalation protocol with radiation response biomarkers. *Int J Radiat Oncol Biol Phys*. 2015;92(4):846–855.
16. Obayomi-Davies O, Kole TP, Oppong B, et al. Stereotactic accelerated partial breast irradiation for early-stage breast cancer: rationale, feasibility, and early experience using the CyberKnife Radiosurgery Delivery Platform. *Front Oncol*. 2016;6:129.

17. Preoperative Stereotactic Ablative Body Radiotherapy (SABR) for Early-Stage Breast Cancer. In: https://ClinicalTrials.gov/show/NCT03137693.
18. Stereotactic Image-Guided Neoadjuvant Ablative Radiation Then Lumpectomy. In: https://ClinicalTrials.gov/show/NCT02212860.
19. Preoperative Single-Fraction Radiotherapy in Early Stage Breast Cancer. In: https://ClinicalTrials.gov/show/NCT02482376.
20. Charaghvandi RK, van Asselen B, Philippens ME, et al. Redefining radiotherapy for early-stage breast cancer with single dose ablative treatment: a study protocol. *BMC Cancer*. 2017;17(1):181.
21. Bondiau PY, Courdi A, Bahadoran P, et al. Phase 1 clinical trial of stereotactic body radiation therapy concomitant with neoadjuvant chemotherapy for breast cancer. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1193–1199.
22. Feasibility Study of Stereotactic Body Radiotherapy for Early Breast Cancer. In: https://ClinicalTrials.gov/show/NCT02065960.
23. Vasmel JE, Charaghvandi RK, Houweling AC, et al. Tumor response after neoadjuvant magnetic resonance guided single ablative dose partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2020;106(4):821–829.
24. Van Limbergen E, Van der Schueren E, Van den Bogaert W, Van Wing J. Local control of operable breast cancer after radiotherapy alone. *Eur J Cancer*. 1990;26(6):674–679.
25. Arriagada R, Mouriesse H, Sarrazin D, Clark RM, Deboer G. Radiotherapy alone in breast cancer. I. Analysis of tumor parameters, tumor dose and local control: the experience of the Gustave-Roussy Institute and the Princess Margaret Hospital. *Int J Radiat Oncol Biol Phys*. 1985;11(10):1751–1757.
26. Shibamoto Y, Murai T, Suzuki K, et al. Definitive radiotherapy with SBRT or IMRT boost for breast cancer: excellent local control and cosmetic outcome. *Technol Cancer Res Treat*. 2018;17, 1533033818799355.
27. Gao RW, Park SS, Jakub JW, et al. Durable response of early-stage breast cancer to bilateral definitive SBRT in a medically inoperable patient. *Pract Radiat Oncol*. 2018;8(6):361–365.
28. Polgár C, Van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol*. 2010;94(3):264–273.
29. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol*. 2017;7(2):73–79.
30. MB M. Stereotactic body radiation therapy for breast cancer: benefits, challenges and choices. *Appl Rad Oncol*. 2018;7(1):50–54.
31. Stereotactic Body Radiation Therapy for Breast Cancer. In: https://ClinicalTrials.gov/show/NCT03585621.