Journal of Radiotherapy in Practice

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Stereotactic body radiotherapy in Cyberknife® for partial breast irradiation: a review

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Literature Review

Cite this article: De la Pinta C and Fernández-Lizarbe E. (2022) Stereotactic body radiotherapy in Cyberknife® for partial breast irradiation: a review. *Journal of Radiotherapy in Practice* **21**: 411–415. doi: 10.1017/S146039692000120X

Received: 30 October 2020
Revised: 8 December 2020
Accepted: 9 December 2020
First published online: 18 January 2021

Key words:
APBI; breast cancer; Cyberknife; SABR; SBRT

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Abstract

Introduction: Partial breast irradiation (PBI) can reduce the volume of treatment and number of treatment sessions in low-risk breast cancer patients. Stereotactic body radiotherapy (SBRT) allows the administration of high doses per fraction thereby reducing the number of fractions and reducing the dose to the surrounding tissues. The objective of this study is to review the literature on the use of SBRT in PBI using the Cyberknife® (CK) unit.
Material and methods: In this review, we analysed the literature in PubMed and MEDLINE with articles published in the last 10 years. All citations were evaluated for relevant content and validity.
Results: We include articles in the English language with information about PBI, SBRT in PBI, the use of the CK unit in PBI and other applications of SBRT in breast carcinoma. A total of 68 articles were found and 28 articles were selected for inclusion in this review.
Conclusions: The treatment of PBI using the CK unit has clear advantages in reducing the treatment volume, and therefore theoretically reducing side effects and good cosmetic results with adequate tumour control. However, the placement of fiducial markers is necessary, requiring an adequate learning curve for the placement of the markers and longer treatment times.

Introduction

The Cyberknife® (CK) system uses the combination of robotics and image guidance to deliver concentrated and accurate beams of radiation to the target volume while reducing the dose to the surrounding tissues. Due to the acquisition of images every 20–60 seconds, it makes it possible to monitor intrafraction tumour lesions movement. The CK unit improves the precision of stereotactic body radio therapy (SBRT) treatment by the use of the tracking system.

Several studies have shown that the most frequent recurrences after lumpectomy in breast cancer occur in the same quadrant as the primary tumour. The lumpectomy cavity and 1·5 cm–2 cm around the tissue may present microscopic spread.[1,2] Relapses are usually found approximately 10 mm around the resection cavity.[3] This indicates that partial breast irradiation (PBI) treatment can be effective in decreasing the toxicity of whole breast irradiation (WBI) for low-risk selected patients.[4-6] The results of phase III trial NSABP 39/Radiation Therapy Oncology Group (RTOG) 0413[7] comparing conventional whole breast radiotherapy and PBI for stages 0, I and II showed that the 10-year cumulative incidence of ipsilateral breast tumour recurrence between PBI and WBI was only 0·7% (4·6% versus 3·9%) with an HR 1·22 (90% CI 0·94–1·58), this difference in ipsilateral breast irradiation was less than 1% at 10 years suggesting that PBI is an acceptable option for patients followed by breast cancer surgery, with no difference in G3-5 toxicities. In the study by Whelan et al.[8] after 8·6 years of median follow-up, the local control was 2·8% in WBI and 3% in PBI, with no statistically significant differences (HR = 1·27 (90% CI, 0·84–1·91). G2 and G3 toxicities were 28% and 4% in WBI and 12% and 1% in WBI, failure or poor cosmetic outcome occurred in 31% and 15%, respectively. Another study[9] demonstrated equivalent local control with both treatments with lower toxicity in PBI.

ASTRO[10] recommendations in PBI include >=48 years, E 0-I, invasive non-lobular or ductal in situ =<2 cm, negative margins >=2 mm, negative GCS, as was Vermeulen in 2011 >45 years, E 0-IIA, non-lobular or in situ <=3 cm, negative BGC and MRI staging. PBI candidate patients according to GEC-ESTRO[11] guidelines are >50 years, infiltrating ductal, mucinous, colloidal, tubular or medullary carcinoma, lobular carcinoma in situ allowed, ductal carcinoma in situ absent, grades 1–3, pT1-2 <30 mm, pN0, margins >2 mm, unicentric, unifocal, lymphovascular invasion absent, no neoadjuvant chemotherapy.

The objective of this study is to review the current literature on the use of SBRT in PBI using the CK unit.

Material and Methods

This review analysed studies on the treatment of PBI in breast cancer using the CK system. The articles included were in English with full-text articles available in PUBMED and MEDLINE in

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the last 10 years (from January 2010 to January 2020). The criteria for inclusion were: comparison with other systems, technical requirements, immobilisation, treatment volumes, dose and fractionation; as also results and toxicities. After the literature review, we use the following terms: PBI OR APBI AND breast OR breast cancer AND CK. A total of 68 articles were found. After examining them, we included series with PBI, local control and toxicity data, published were included in the last 10 years. Finally, 28 articles were selected for inclusion in this review.

Cyberknife® versus other PBI systems

For the application of PBI, different techniques such as brachytherapy, intraoperative radiotherapy (IORT), three-dimensional radiotherapy (3DRT) or intensity-modulated radiotherapy (IMRT) have been studied with similar results.[12] SBRT in CK has emerged as a possible alternative in PBI (Stereotactic-PBI, S-PBI). It has a clear advantage over other techniques of external radiotherapy due to its tracking system. This system minimises setup error and allows to reduce treatment margins, from 2 to 2·5 cm expansion to 1–1·5 cm of PTV, considering patient movement, this is a clear advantage compared to other systems such as 3DRT or IMRT. In addition, SBRT compared to brachytherapy is a non-invasive technique with less risk of infection.

Goggin et al.[13] performed a dosimetric comparison between CK and other external radiotherapy systems in PBI. Nine patients treated with lumpectomy were included. The treatment volume in CK was defined as the lumpectomy cavity with a total margin of 12 mm. In this study, a dose of 30 Gy in five fractions was prescribed. In 3DRT, the lumpectomy cavity was defined with a total margin of 25 mm. In this study, the prescription dose was 38·5 Gy in 10 fractions. Planning target volume (PTV) coverage and dose to critical structures were similar in both plans, except V5 was lower in 3DRT, 6·2% versus 39·4% in CK Iris collimator and 17·9% in multileaf collimator (MLC). CK showed a contralateral breast V50 of 25·5% in Iris collimator and 24·2% in MLC compared to 3DRT (56·2%). Plans with CK were more conformant than with 3DRT. Treatment times were approximately 50% shorter and the number of monitor units was 50% less, with MLC being more common than Iris collimator. Treatment time was similar to MLC and 3DRT. However, it should be considered that comparing two dosimetric methods with different margins and different prescriptions includes an important variable of confusion. Heinzerling et al.[14] compared 3DRT and CK. The authors reported better coverage with CK, V15% in ipsilateral lung, maximum dose in heart, and V50% and V100% lower ipsilateral breast, but higher dose in skin. However, the same treatment volume was used ignoring the tracking advantages of CK. Fan et al.[15] compared CK, IMRT, mini-photon tangents and electrons as a boost. Of the four modalities, CK showed better dose distribution, low maximum dose in lung, low V20 and V40 in ipsilateral lung, low dose in skin and heart using MLC. Xu et al.[16] compared their results with the available literature, CK was superior to IMRT or 3DRT except for the very low doses. Treatment with IMRT or 3DRT requires the inclusion of large volumes of breast, which has led to significant rates of fibrosis with poor cosmetic outcomes.[17,18]

The major disadvantage for PBI with IORT is that the definitive pathological anatomy is not always available. In addition, the dose is administered at 1 cm, but recurrences have been described at more than 1 cm. S-PBI is performed with the definitive pathological anatomy, being a less invasive treatment, the volume of the PTV is covered by the prescribed dose, and the plan is image based. The differences between IORT and interstitial brachytherapy are the inclusion of the cavity and 1 cm or 1·5 cm, respectively.[19]

Technical requirements in PBI in CK

After clinical selection of patients, 4–5 weeks up to 12 weeks after lumpectomy, administration of PBI treatment in CK requires placement of fiducial markers in the proximity of the lumpectomy cavity.

Surgical clips assist in the delineation of the post-operative seroma cavity and fiducials, usually of gold, are used to allow the tracking. Fiducials can be implanted intraoperatively during surgery, but the definitive pathological results will not be available until a few weeks later, so the indication for PBI at that time will not be definitive. The placement of ultrasound-guided fiducials has been studied.[20]

A number of recommendations should be followed for their placement. First, the oncologist and radiologist delineate the cavity area on the skin and local anaesthesia is injected. The fiducial markers should be placed inside the parenchyma, at least 1–2 cm outside the cavity and with a separation between them of more than 18–20 mm, with a distance of less than 10 cm. It is important to place them in different planes, with a 15º angulation avoiding overlapping in the X-ray at 45º. The placement of a minimum of three fiducials is recommended.[21] After the procedure, a mammography is performed to check the correct placement of the fiducials in different planes.

Rahimi et al.[22] used three–four ultrasound-guided gold fiducials around the lumpectomy cavity and two on the breast surface. In the study by Obayomi-Davies et al.,[23] they used four gold fiducials of 2 mm implanted in the seroma cavity guided by ultrasound, using at least three for tracking. Patients with poor breast integrity or large seromas were not considered as candidates. Vermeulen in 2011[24] used four–five CT-guided 2 mm gold fiducials, if there were difficulties, it was defined by MRI. In 11 tumours, the fiducials were sutured into the cavity by the surgeon, one upper, one lower, medial, lateral and in-depth.

Immobilisation in PBI in CK

It is recommended that the planning CT should be performed at least 1 week after the placement of the fiducials.[23] Simulation and planning were performed 3 days prior to treatment in the study by Vermeulen et al. Vermeulen et al.[24] in their study placed the patients in supine, head first and arms at the sides with an alpha cradle. The light-emitting diodes (LEDs) were placed on the ipsilateral breast. The CT included an extension from the mandible and several centimetres below the inframammary line. The CT slices were 1·25 mm. However, Meszaros et al.[25] performed the CT slices every 5 mm. Rahimi[22] used a vacuum mattress, and a bra system for breast immobilisation, thus also holding the contralateral breast, preventing it from being placed on the other breast.

PBI contouring in CK

Treatment volumes included CTV and PTV, as there was no GTV. In the study by Seiler et al[21], CTV included the surgical bed with the surgical clips and the seroma, and 20 mm of expansion limited to the breast, the pectoral muscle and 5 mm of the skin surface. The PTV included the CTV and 2 mm of margin. However, Vermeulen et al.[24] used a CTV margin of 10–15 mm using MRI contouring with T2 or STIR sequences. Yoo et al.[26] included a CTV margin of 10–15 mm and a PTV margin of 3–5 mm. Obayomi-Davies

https://doi.org/10.1017/S146039692000120X Published online by Cambridge University Press

et al.[23] included a CTV to PTV margin of 5 mm. Rahimi et al.[22] used a CTV margin of 15 mm, without a PTV margin. There is no clear consensus on this.[27]

Treatment dose in PBI at CK

The justification for hypofractionation in breast cancer is due to the low alpha/beta rate of the breast.

The single dose in PBI has been investigated with promising results,[28–34] allowing reduction of treatment. However, the most widely used schemes are hypofractionated.

Rahimi et al.[22] published a phase 1 study of dose escalation from 30 Gy to 40 Gy in five fractions. The prescription isodose was 95% and 99% of the PTV received a minimum of 90%. Meszaros et al.[25] in a phase II study included 27 patients treated with 25 Gy/4 fractions daily. Vermeulen et al.[24] used doses of 30 Gy in 5 fractions in 2 patients, and 34 Gy in 10 fractions in 7 patients, with estimates based on breast cancer alpha/beta rate of 4·6 Gy and alpha/beta rate of 3·4 Gy for late toxicity. The mean prescription isodoses was 70% (range 65–76%) at PTV and the mean PTV volume was 114 cc (range 39–241 cc). Yoo et al.[26] treated 8 patients with 15 Gy, 8 patients with 18 Gy and 34 patients with 21 Gy. Obayomi-Davies et al.[23] included 10 patients treated with 30 Gy in 5 daily fractions, equivalent to 50 Gy in 25 fractions with an alpha/beta for 4 Gy tumour control. Prescription isodoses was 80% with Monte Carlo, 100% of the PTV received the prescription dose, the mean PTV was 70 cc. Ipsilateral lung V9 was 3%, and contralateral lung V1·5 Gy was 31%. The maximum skin dose was 36 Gy. The mean number of beams was 155 (119–194 beams). Lozza et al.[35] included 20 patients using CK with the Iris collimator with a prescription dose of 30 Gy in five fractions at 95% isodoses to PTV, with a median PTV of 88·1 cc and 60 minutes treatment duration (35–120 minutes).

Results and toxicity

Vermeulen et al.[24] described no recurrence after a median follow-up of 7 months (range 4–26 months). In the study by Obayomi-Davies et al.,[23] there were also no relapses at 3 years. In the study by Lozza et al.[35] after a median follow-up of 2 years, no relapse was observed. Acute toxicity occurs in the first 90 days after treatment and late toxicity after 90 days of treatment.

Rahimi et al.[22] described in their dose-escalation study 65 patients with acute toxicities and 47 patients with late toxicities. Most patients presented acute grade 1 toxicity, only two patients presented grade 2 acute toxicity consisting of axillary paresthesia and dermatitis. Most of the late toxicities were grade 1, five patients presented grade 2 late toxicities including breast pain, rib fracture and fibrosis. In the rib fracture patient, the V100 was 1·71 cc, with a maximum dose of 45·24 Gy, conformance index of 1·48. Only three patients experienced grade 3 toxicity at the 37·5 Gy dose level consisting of cellulite with grade 3 fibrosis and grade 3 dermatitis resolved without problems. Only one grade 3 dermatitis was dose limiting at 40 Gy in five fractions. Ten patients presented fat necrosis and four patients asymptomatic. Of the 10 patients with fat necrosis, the cut point was at a PTV $\geq$ to 124 cc. 95·9%, 100%, 96·7% and 100% at 6, 12 and 24 months were classified as excellent and good aesthetic results. Other constraints included skin $<$ 39·5 Gy (exceeded in two patients), the protocol suggested the use of separate fractions at least 40 hours apart. In the study by Meszaros et al.,[25] there were no major grade 2 toxicities. Toxicities included grade 1 dermatitis in 22·2% of patients, grade 1 oedema in 11·1% and grade 1 pain in 3·4%. Cosmetic results were excellent in 62·9% and good in 37·1%. Vermeulen et al.[24] found minimal-to-moderate fatigue 2–3 weeks after the start of treatment, similar to fatigue after surgery. All toxicities were mild. The late cosmetic result was between excellent and good.

In the Obayomi-Davies study,[23] all patients presented excellent cosmetic results. The side effects described in the study by Lozza et al.[35] were all mild, and more than 80% of the patients presented excellent cosmetic results.

Some recommendations for follow-up of these patients are included in the study by Vermeulen et al[24], recommending follow-up at 4 weeks, 6 months and annually, including quality of life questionnaires and mammography at 6 months and annually thereafter.

Other indications for breast SBRT

In addition to PBI, the use of SBRT in breast cancer is expanding in other scenarios including inoperable patients as definitive treatment or as neoadjuvant treatment.

The radiobiological advantages of SBRT include the ablative effect on the tumour, enhancing different mechanisms of tumour destruction. This treatment increases the direct cytotoxic damage derived from the double breakage of the DNA and the stem cell, in addition to the microvascular and stromal damage in the tumour tissues. SBRT can enhance the anti-tumour immune response. Some studies, such as that of Shibamoto et al[36], have analysed the use of exclusive radiotherapy in conventional linear accelerators. In this study, 18 patients were included with 3 dose levels: 50 Gy/25 fractions; 18–25·5 Gy/3 fractions and 20 Gy/8 fractions. Overall survival, progression-free survival and local control were 93%, 85% and 92%, respectively, at 3 years. One patient died from lung metastases, another patient developed liver metastases at 90 months and a patient with local relapse with a tumour at diagnosis of 51 mm. Seven patients presented grade 1 dermatitis and 11 patients presented grade 2 dermatitis.

Neoadjuvant radiotherapy in breast cancer improves tumour oxygenation by irradiating small volumes and reducing the dose to healthy tissue. In addition, it allows to include the area of carcinoma in situ assisting the use of MRI.

Guidolim et al.[37] included patients with early stage, less than 3 cm, oestrogen receptor positive, axilla clinically negative, with tumours at least 2cm from the skin, limited to 5 mm, and chest wall in a phase I preoperative single-dose study. All patients underwent prone MRI and CT scans. The prescription dose was 21 Gy to the primary tumour followed by surgery 1 week later. Twenty-seven patients with excellent cosmetic results and preserved quality of life were included. There were no major toxicities at grade 3. The cosmetic result was good or excellent in more than 92% of the patients. The authors conclude that this treatment is feasible and safe. Bondiau et al.[38] in their phase I study according to the chemotherapy scheme, SBRT with doses of 19·5 Gy/3 fractions and 22·5 Gy/3 fractions followed by WBI at 50 Gy. With CTV including GTV and 5 mm, and PTV including CTV and 2 mm. Surgery was performed at 4–8 weeks, with two complete responses and four patients with partial response, without increased toxicity.

CK has advantages in PBI over radiotherapy in LINAC, IORT or brachytherapy. In 3D radiotherapy or IMRT in LINAC, the treatment volumes are higher than CK. IORT is performed without having the definitive pathological anatomy with treatment volumes limited by the technique itself. Organisation with surgical teams is another complication. The correct placement in the tumour bed is operator and situation of the tumour bed dependent,

https://doi.org/10.1017/S146039692000120X Published online by Cambridge University Press

without being able to correct coverage defects once placed. Finally, brachytherapy is an invasive technique. For the administration of PBI in CK, the placement of fiducial markers is necessary. A week later, a planning CT scan is performed with the patient placed on a mat and a breast support system is recommended. Treatment volumes include CTV and PTV. The extent of these volumes varies according to the authors. Doses vary from 25 to 34 Gy and between 4 and10 fractions. No long-term local control results are available. Side effects are very limited. SBRT in breast cancer is being studied in inoperable patients or as a neoadjuvant strategy.

Limitations

The study has several limitations. On the one hand, the number of studies available is low, data of these patients are limited, with few patients and variable dose and fractionation schedules are reported. On the other hand, the follow-up period for patients included in studies is short.

Conclusions

The treatment of PBI in the CK unit has clear advantages in reducing the treatment volume, and therefore theoretically reducing side effects and good cosmetic results with adequate tumour control. However, the placement of fiducial markers and longer treatment times are necessary.

Author Contribution. The manuscript has been fully developed by all the authors.

Acknowledgements. None.

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