NICE advice

Axxent electronic brachytherapy system for early stage breast cancer

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the Axxent electronic brachytherapy (eBx) system. It delivers single-dose intraoperative radiotherapy (SD-IORT) during breast-conserving surgery for people with early-stage breast cancer.
- The **innovative aspects** are that it incorporates a miniaturised 50 kV X-ray source in which no radioisotopes are needed, and is provided to any suitable hospital as a managed service using a mobile platform.
- The intended **place in therapy** for the Axxent eBx system is in the current NHS pathway for patients offered SD-IORT in place of external beam radiotherapy (EBRT), which is usually given in daily radiotherapy sessions for 3 weeks.

- The **key points from the evidence** summarised in this briefing are from 6 non-comparative studies including 452 patients. There is a lack of robust evidence evaluating the Axxent eBx system for early-stage breast cancer. In general, SD-IORT using Axxent eBx was well tolerated with a low rate of adverse events and good cosmetic outcomes.
- **Key uncertainties** around the evidence are that the available studies include patients for whom the technology is not recommended by the manufacturer, and there is a lack of long-term follow-up evidence.
- The **cost** per patient of the Axxent eBx managed service is £3,750 (excluding VAT). There is no capital equipment purchase, maintenance cost or servicing charge. In comparison, external beam radiotherapy costs £2,821 per patient (15 fractions) in addition to the initial purchase and maintenance costs of a linear accelerator.

The technology

The Axxent eBx system (Xoft) is a mobile platform for treating early-stage breast cancer. It can also be used to treat non-melanoma skin cancer and gynaecological cancers, but these uses are beyond the scope of this briefing. It uses an isotope-free miniaturised X-ray source, which generates a 50 Kv photon spectrum in order to deliver single-dose intraoperative radiotherapy (SD-IORT).

Patients have SD-IORT immediately following breast-conserving surgery, before the surgery is completed and while the patient is still under general anaesthetic. A saline-filled balloon-shaped applicator is placed into the breast tissue where the tumour was removed, at the tumour bed. A single dose of 20 gray (Gy) X-ray radiation is delivered from the generator to the balloon surface, from where it is passed on to the breast tissue. Once SD-IORT has been delivered, the single-use disposable applicator is removed and the surgery can be completed.

Delivery of SD-IORT using the Axxent eBx system takes approximately 10 minutes and generally adds up to 40 minutes to the total breast-conserving surgery procedure.

The innovation

Axxent eBx allows SD-IORT to be delivered at local or regional hospitals at the point of surgery.

The Axxent eBx system does not use isotopes and so there are minimal radiation protection implications and no bespoke construction or specialist shielding is needed. Treatment with the system is done through a managed service agreement, which avoids the cost of capital equipment purchase, maintenance costs or service charges; the only direct costs are per-patient treatment costs.

Current standard practice with external beam radiotherapy (EBRT) for breast cancer involves, post-operatively, 3 weeks of daily radiotherapy sessions. SD-IORT treatment with the Axxent eBx system is given once at the time of surgery. The system is also designed to allow for targeted radiotherapy, the aim of which is to spare surrounding tissues from radiation exposure. Standard EBRT is delivered to the whole breast. Furthermore, because it is a mobile platform, Axxent eBx can be used to deliver SD-IORT in multiple hospitals, including those that do not have specialist radiotherapy centres.

Current NHS options

For early-stage breast cancer, breast-conserving surgery is usually the first treatment option (NHS Choices). The NICE guideline on early and locally advanced breast cancer: diagnosis and treatment recommends that patients should have EBRT after surgery to destroy any remaining cancer cells. This should be delivered as 40 Gy in 15 fractions (5 days for 3 weeks).

NICE is aware of the following CE-marked device that appears to fulfil a similar function to the Axxent eBx system:

- Intrabeam (Zeiss).

NICE is currently developing guidance on the intrabeam radiotherapy system for the adjuvant treatment of early breast cancer.

Population, setting and likely place in therapy

The Axxent eBx system would be used in secondary care for people with early-stage breast cancer who are offered SD-IORT as an alternative to EBRT. Detailed selection would apply in such cases which are outside the scope of this briefing.

Axxent eBx is provided in the UK as a managed service by Oncotherapy Resources. The referrer for treatment with the Axxent eBx system would either be the breast surgeon

responsible for the patient, or the clinical oncologist who prescribed the radiotherapy dose. The surgeon doing the breast surgery must be trained and certified in SD-IORT by Oncotherapy Resources, and should observe at least 1 procedure before doing their own. Oncotherapy Resources provides a qualified mentor to oversee the first treatment in theatre who will then certify the surgeon if deemed competent.

SD-IORT using the Axxent eBx system is done by a certified Oncotherapy Resources radiographer, whose time is provided within the cost of the service. They act as the radiation protection supervisor (RPS) in accordance with ionising radiation regulations (including for medical exposure). Before treatment, the operator (as the RPS) and local radiation protection advisor (RPA) liaise with Oncotherapy Resources' own RPS and RPA representatives to agree local rules, risk assessment and employer liability. The Ionising Radiation (Medical Exposure) Regulations require that a medical physics expert is also involved.

The Axxent eBx system will fit in the current NHS pathway during breast-conserving surgery for early-stage breast cancer in patients for whom SD-IORT is offered and would replace post-operative EBRT.

Costs

Device costs

The list price per patient of SD-IORT with the Axxent eBx system is £3,750 (excluding VAT). No capital equipment purchase is needed, and there are no maintenance costs or service charges. The list price for the service includes:

- machine delivery to and collection from the hospital
- machine calibration and testing
- a mobile lead screen
- radiation protection documentation and advice
- a treatment dose of 20 Gy
- a sterile balloon applicator

- a certified radiographer to deliver treatment in theatre.

Costs of standard care

The NHS costs (HRG codes) for a standard course of EBRT delivered 5 days per week for 3 weeks (15 fractions) are:

- SC23Z – Deliver a fraction of complex treatment on a megavoltage machine: £1,980.
- SC52Z – Preparation for complex conformal radiotherapy: £1,453.

The costs above exclude the initial purchase of a linear accelerator and maintenance. These costs vary depending on usage and specification but, on average, linear accelerators cost around £1.4 million to purchase with an equivalent running cost over a 10-year lifespan (National Audit Office 2011).

Resource consequences

The Axxent eBx system is available to but not currently used in any NHS centre. However, it is being used by several private hospitals.

The main resource consequence would be training (provided by Oncotherapy Resources at no additional charge) for the surgeon to carry out a procedure, which will involve SD-IORT delivered by an Oncotherapy Resources operator. Few adjustments are needed in theatre to deliver SD-IORT in addition to standard breast-conserving surgery, although it adds 30 to 40 minutes to the procedure.

Regulatory information

The Axxent eBx system was CE marked as a class IIb device in December 2011.

A search of the Medicines and Healthcare Products Regulatory Agency website revealed that no manufacturer Field Safety Notices or Medical Device Alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

A diagnosis of cancer is a protected characteristic under the Equality Act (2010). SD-IORT may be particularly advantageous for older people or people with physical disabilities, who may find it difficult to attend daily EBRT sessions for 3 weeks.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies (table 1) were selected for inclusion in this briefing. These included 452 patients, with follow-up ranging from 1 to 5 years. The studies were reported in 1 full-text paper and 5 conference abstracts, so information was limited. All of the studies included patients with breast cancer classed as ductal carcinoma in situ (DCIS) which is not currently an Oncotherapy Resources-recommended indication for treatment with Axxent eBx. Ivanov et al. (2011) justified the inclusion of patients with DCIS, stating that the rate of recurrence in this group is high enough to warrant SD-IORT. In addition, 4 of the 6 studies included patients who are younger than those for whom Oncotherapy Resources recommends SD-IORT.

Overall the studies reported on the following outcomes: recurrence, adverse events and cosmetic outcomes. No recurrences were reported at 1-year follow-up, but at 5 years

Dickler et al. (2015) reported 4 recurrences in 68 patients. This was stated to be comparable to accelerated partial breast irradiation. In general, SD-IORT with the Axxent eBx system was well tolerated with a low rate of adverse events and positive cosmetic outcomes.

Table 1 summarises the clinical evidence, and its strengths and limitations.

Table 1: Included studies of SD-IORT with the Axxent eBx system

Study	Details of intervention [and comparator]	Outcomes	Strengths and limitations
Arterberry 2013 22 patients, 18 enrolled Prospective case series Single centre US Follow-up: 1 year (median)	Xoft Axxent electronic brachytherapy system. Single dose of 20Gy.	No grade 3 to 4 adverse events. Cosmetic outcome was excellent in most patients. No local recurrence. One patient needed whole breast irradiation due to close margins at re-excision.	Strengths: Prospective study. Limitations: Conference abstract only; case series; single centre; included patients with DCIS which is not a recommended criteria for treatment with SD-IORT; longer follow-up would allow recurrence to be fully assessed.
Costa 2015 30 patients Retrospective case series Single centre Portugal Follow-up: 18 months (median)	Xoft Axxent electronic brachytherapy system. Single dose of 20 Gy.	Mean treatment time of 9 minutes 10 seconds. No grade 3 to 4 adverse events. No local recurrence, 1 axillar recurrence 1 year post-treatment.	Limitations: Conference abstract only; retrospective; single-centre case series; included patients <50 years of age which is not a recommended criteria for treatment with SD-IORT; longer follow-up would allow recurrence to be fully assessed.

Dickler 2015 68 patients with 69 breast cancers Prospective case series Multicentre (n=not reported) US Follow-up: 5 years	Xoft Axxent electronic brachytherapy system. Single dose of 20 Gy.	Mean time to deliver the radiation was 13 minutes (range 7 to 30 minutes). No grade 4 to 5 adverse events. Cosmetic outcomes were excellent or good in most patients. Four local recurrences occurred.	Strengths: Multicentre study, 5-year follow-up. Limitations: Conference abstract only, case series; included patients with DCIS and of <50 years of age which are not recommended criteria for treatment with SD-IORT.
Hanna 2015 78 patients Prospective case series Multicentre (n=12) US Follow-up: 12 months (median)	Xoft Axxent electronic brachytherapy system. Single dose of 20 Gy (n=77), 21 Gy (n=1).	Mean treatment time was 10.5 minutes. A low rate of adverse events. Cosmetic outcomes were excellent or good in most patients.	Strengths: Multicentre study Limitations: Conference abstract only; case series; included patients with DCIS and of <50 years of age which are not recommended criteria for treatment with SD-IORT; longer follow-up would allow recurrence to be fully assessed.

Ivanov 2011 11 patients Prospective case series Single centre US Follow-up: 12 months (mean)	Xoft Axxent electronic brachytherapy. Single dose of 20 Gy.	Mean time for radiation delivery was 22 minutes (range 20 to 24 minutes). At 12-month follow-up, 10/11 patients rated overall cosmesis as excellent. Cancer recurrence did not occur within follow-up period. Potential adverse events such as rib fracture, infection, fat necrosis or desquamation did not occur.	Strengths: Prospective study Limitations: Case series; small sample size; single centre; included patients with DCIS which is not a recommended criteria for treatment with SD-IORT; longer follow-up would allow recurrence to be fully assessed.
Syed 2016 243 patients Prospective case series Multicentre (n=17) US Follow-up: 16.5 months (median)	Xoft Axxent electronic brachytherapy system. Single dose of 20 Gy (n=242), 21 Gy (n=1).	The mean treatment time was 10.2 minutes. A low rate of adverse events. Cosmesis was excellent to good in most patients.	Strengths: Multicentre study Limitations: Conference abstract only; case series; included patients with DCIS and of <50 years of age which are not recommended criteria for treatment with SD-IORT; longer follow-up would allow recurrence to be fully assessed.

Strengths and limitations of the evidence

There is a lack of robust published evidence evaluating SD-IORT for early-stage breast cancer using the Axxent eBx system. The studies identified in this briefing were all non-comparative. However, there are 2 ongoing trials that are likely to provide further data

when completed: Syed 2016 is a multicentre trial of 243 patients and Dickler 2015 reports 5-year follow-up data.

Recent and ongoing studies

A search of Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform for 'XOFT OR Axxent AND breast' found the following 3 results:

- Intraoperative radiation therapy immediately following resection of early stage breast cancer. Status: active; not recruiting; enrolled 75; preliminary results published in Dickler et al 2015. Indications: breast cancer.
- Intraoperative radiotherapy for early stage breast cancer. Status: active; target of 200; not recruiting. Indications: breast cancer.
- Safety and efficacy study of the Xoft Axxent eBx IORT System. Status: Recruiting; target of 1200; preliminary results published in Syed et al. 2016. Indications: invasive ductal carcinoma; DCIS.

Specialist commentator comments

It was generally felt that there is a lack of data and long-term follow-up data on the Axxent eBx system, and that larger and longer studies are needed. It was noted that the Axxent eBx system is indicated for a very specific group of patients who typically have a low rate of recurrence, so 5- and 10-year data are needed to determine non-inferiority compared with EBRT. One commentator noted that the length of follow-up in the current evidence base is insufficient.

One commentator also raised concerns that unlike EBRT, SD-IORT with the Axxent eBx system would be delivered before gaining pathology data which would have indicated that the patient needed EBRT. This commentator noted that SD-IORT is recommended for a specific group of early breast cancer patients, and so some people would not be eligible to have this treatment. Nevertheless, commentators acknowledged that SD-IORT would improve patient accessibility, where appropriate.

One commentator reflected that the use of SD-IORT has the potential to increase capacity at radiotherapy centres in the UK because it reduces patient visits compared with EBRT. The commentator added that avoidance of daily transport for EBRT may also offer

advantages for patients with limited access to transport.

Specialist commentators

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

The following clinicians contributed to this briefing:

- Ms Siobhan Laws, consultant surgeon at Hampshire Hospital NHS Trust. Ms Laws acted as a clinical advisor for an international multicentre clinical trial on the data and safety reporting committee (Lifecell/Acelity). This was an unpaid position. She has been paid to teach (lecture and practical) on a commercial course sponsored by Baxter. Her unit has published their experience of Intrabeam and contributed to patient accrual in the TARGIT A trial. They also published a commentary on Intrabeam in the ABS yearbook 2015.
- Ms Claire Reynolds, senior radiographer CT Sim/IORT pathway radiographer at Royal Free London NHS Foundation Trust. Ms Reynolds has co-authored research papers on the IORT technique and also presented on the topic of patient selection for the TARGIT Academy, which is sponsored by Zeiss.
- Mrs Camarie Welgemoed, breast specialist radiographer at Imperial College Healthcare NHS Trust. No conflicts to declare.
- Mrs Sairanne Wickers, consultant breast radiographer , University College London Hospitals. No conflicts to declare.

Development of this briefing

This briefing was developed for NICE by Cedar. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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