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Breast Cancer
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1 Introduction

Breast cancer is the most frequent cancer in women in developed countries, accounting for 25 to 30% of cancers, with an incidence of about 100 cases per 100 000 women per year. Most of these tumours arise between 45 to 65 years.

Due to screening programmes, the disease is more often discovered at an early stage, in which breast conserving treatment, including brachytherapy, can be offered to the patient. Standard approach for small tumours combines breast conserving surgery and radiotherapy, with long-term survival rates similar to those obtained with mastectomy.

Brachytherapy may play a role as boost irradiation to the tumour bed after external beam irradiation of the whole breast or may be used in selected cases as a sole radiation modality after conservative surgery. For tumours not amenable to primary conservative surgery, treated with initial systemic treatment and / or external beam irradiation, a conservative approach including brachytherapy boost can be proposed to selected patients.

2 Anatomical Topography

The upper outer quadrant is the most common site of origin of breast cancer (38.5%), followed by the central area (29%), the upper inner quadrant (14.2%), the lower outer quadrant (8.8%) and the lower inner quadrant (5%). Breast cancer is more common in the left than in the right breast (16).

Tumour spreads along the ducts as well as invading adjacent lobules, ducts, fascia strands, and the mammary fat, and permeates through the lymphatic vessels of the breast to the regional lymph nodes. The skin of the breast is rarely invaded in early stages, but in advanced T3-T4a tumours microscopic invasion of the lymphatic vessels of the skin may be present, as well as macroscopic invasion in T4b, T4c and T4d tumours.

3 Pathology

Most cancers are invasive. Usually, they are well to poorly differentiated ductal adenocarcinomas (70%). Next most common are lobular adenocarcinomas (20%). Since the implementation of screening, the incidence of non-invasive ductal carcinoma has been rising (up to 15 - 20 % of all cases). Lobular Carcinoma in situ is an incidental finding in premenopausal women and is nowadays not considered to be an indication for radiotherapy.

Multifocal disease is seen less frequently with invasive ductal carcinoma (20%) than with invasive lobular cancer (50%) and intraductal carcinoma (80%). The incidence of multicentric ductal carcinoma is also less frequent in < 20 mm invasive ductal carcinoma (12%) than in > 20 mm invasive ductal carcinoma (23%) (15).

Depending on stage selection and the definition criteria used, about 16% to 39% of invasive cancers will be associated with an extensive component of ductal carcinoma in situ (EIDC) (1, 5, 24, 39). These tumours have more often a subclinical extension beyond the tumour mass 74 - 88% when EIDC + in stead of 42 - 48% when EIDC- (24, 43) and at a distance (30% at a distance of 20 mm
when EIDC+ versus 2% when EIDC- (24). They are therefore more frequently associated with positive section margins after tumour excision and have higher local recurrences rates after breast conserving treatment. Local recurrence is between 9 and 32% when EIDC + in stead of 1 - 10% when negative, the range depending on the surgical technique (tumourectectomy versus quadrantectomy), and the radiation doses delivered (1,39,56,57).

4 Work Up

Clinical examination, with measurement and documentation of the localisation of the tumour mass with pictures in supine position, mammography, ultrasonography and if indicated MRI, are mandatory to document local tumour extension. The diagnosis of malignancy should be documented by fine needle aspiration cytology, core biopsy or microscopic examination of the resection specimen. Nodal and distant spread must be investigated and the tumour stage assessed according to the UICC TNM classification.

The breast surgeon, radiation oncologist and if indicated a medical oncologist jointly make the decision about the modalities of breast cancer treatment to be used.

During breast conserving surgery, the surgeon should mark the tumour bed with 4 to 6 clips indicating the cranio-caudal, medio-lateral and (antero)-posterior limits of the resected volume. If there is doubt about residual micro-calcifications, postoperative mammography must be performed.

If initial treatment with systemic neo-adjuvant hormono- or chemotherapy, and/or external beam radiotherapy, regression and localisation of possible residual disease must also be documented by mammography, ultrasonography, or MRI.

5 Indications, Contra-indications

The main indications for brachytherapy in breast cancer are as a boost in radiotherapy in breast conserving treatment and less frequent as sole treatment of selected small tumours after surgery, or as treatment of thoracic wall recurrences in already irradiated areas.

- Interstitial boost irradiation of the primary tumour site after breast conserving surgery. For that reason, interstitial boosts may be preferred to external beam boosts with electrons or photons for of deeply seated tumour sites. When the CTV extends deeper than 28 mm under the epidermis, implants have a better dose distribution in terms of the volume of the irradiated breast tissue and dose to the skin blood vessels than electron beam boosts (53,54). If there is a high risk of local recurrence (eg. if the section margins are positive) and a higher boost dose is planned, the ballistic advantage of an interstitial implant over electron beams is even more important.

- Interstitial boost irradiation of the primary tumour site after neo-adjuvant systemic chemotherapy and / or external radiotherapy of the whole breast with clinical complete or partial remission in tumours not amenable to primary conservative surgery. This category includes tumours 30 - 70 mm in diameter, non-metastatic or with limited nodal extension, which are usually treated by mastectomy. Interstitial brachytherapy boost after whole breast irradiation has been shown to provide significantly higher local control rate than electron or cobalt beam boost in retrospective (35) and randomised studies (10). In case of partial remission, conservative resection of residual tumour can be carried out before implantation (4).

It has also been advocated as boost method in the treatment of locally advanced breast cancer after primary chemo or hormonotherapy and external beam irradiation (14)

- Postoperative interstitial irradiation alone of the primary tumour site after breast conserving surgery in selected low risk T1 and small T2N0-1 breast cancer, (26,36,59). Since the follow-up
of this new approach is rather short, this treatment should be reserved still only for randomised trials.

- **Thoracic wall irradiation** with a moulded cast for breast cancer recurrences after mastectomy and previous irradiation to the thoracic wall. Limited recurrences can also be treated by interstitial implantation, definitively or after surgical resection (13).

Contra-indications for interstitial breast implants are the following clinical situations:

- Multicentric breast cancer.
- Paget’s Disease alone or in association with a breast lump.
- Poor cosmetic outcome after previous breast conserving surgery, since there is no rationale then to use complex techniques to obtain optimal cosmetic outcome.
- Locally advanced breast cancer with extensive skin involvement, invasion of the thoracic wall or inflammatory carcinomas.
- Metastatic disease making long term local control not the main consideration.
- For thoracic wall recurrences (mould technique), target areas larger than 40 cm² or lesions thicker than 5mm.

### 6 Target Volume

The PTV for the primary site boost irradiation in breast conserving treatment is defined by a rim of 20 - 30 mm breast tissue surrounding the primary tumour, since this area contains 80% of the microscopic tumour extensions around the primary tumour (23). This means that a safety margin of breast tissue of 15 mm may be adequate after complete tumour excision. In case of incomplete resection, a safety margin up to 30 mm may be more appropriate. In most cases, these margins include into the clinical boost target volume a large amount of ducts in the direction to the nipple.

Breast skin or tissues beyond the fascia such as thoracic wall muscle or ribs are never CTV for boost irradiation in T1 or T2 breast cancer since there is no significant amount of tumour cells supposed to be left there in deeply seated tumours. In superficially located tumours, the overlying skin is usually surgically removed with the tumour, and the residual skin has not to be boosted.

On the contrary, irradiation of the skin should be carefully avoided to prevent the occurrence of late skin telangiectases. When a dose of 50 Gy is delivered to the skin vessels, late telangiectases may occur already in 30% of cases. (49). Vessels may have received already 20 to 40 Gy from the breast irradiation, depending on the photon energy and the beam angle. Therefore, there is usually only a small dose amount left in skin vessel tolerance for telangiectases.

### 7 Technique

#### 7.1 Localisation of the PTV

Although some experienced brachytherapists, based on their clinical experience and stereotactic intuition, are able to do freehand implantation, it is advisable to use one of the following techniques to accurately localise the PTV and the breast skin, which is a critical organ for cosmesis.

Implants can be carried out during surgery. This allows direct vision to the CTV and appropriate covering of it by the implant. On the other hand, the positioning of the sources in relation to the overlying skin may be less precise, since the skin is closed over the implant when the source carriers are already fixed in the breast tissue.
When implants are carried out postoperatively, haemoclips can help the radiation oncologist to localise the target area and estimate the depth of the PTV under the overlying skin (21,27,33,44,45). This helps to define the dimensions of the boost volume, as well as the choice between electron beam boost and interstitial implant (53). Usually, 5 clips are placed: cranial, caudal, left and right to the excision cavity as well as at the deepest point of the posterior resection margin.

With the help of these clips, the target centre, as well as the inclination of the needles, can be defined with a conventional or with a CT-simulator, and entrance, and exit points can be marked on the skin. (Fig 18.1)

![Fig 18.1A,B: Using marker clips to localise the boost target volume and simulate entrance points of guide needles at the skin of the breast (with courtesy of H. Jacobs)](image)

When clips are lacking, it is still possible to localise the target volume isocentre with a clinical “3D” reconstruction, starting from the frontal and lateral views of the pre-treatment mammogram and the preoperative pictures taken in supine position. Although the surgical intervention may displace the target area according to the preoperative situation, especially when large resections or remodelling have been performed, clinical experience and control (see point 2) have taught us this being a quite reliable method to localise the PTV in the breast.

First, the position of the tumour centre (TC) relative to the nipple is measured on the frontal and lateral views of the affected breast (Fig 18.2).

On the frontal, we measure the depth from the tumour centre to the nipple DF and the distance from the breast midline in medial or lateral sense (ML). On the lateral view, the depth DP and the cranial-caudal distance from the nipple position CC.

These distances are transferred to the patient, while the breast is compressed in the same way as at mammography (no correction for magnification needed). With frontal compression, the distance ML is marked medially or laterally from the nipple and the depth DF both at the upper and underside of the breast. Then, with lateral compression, the cranio-caudal distance from the nipple CC is marked and the depth DP at both sides of the breast.
Fig 18.2: Measuring distances from tumour centre, relative to nipple position on face and profile mammography to define the boost target localisation in breast conserving treatment.

The position of the TC is reconstructed by drawing the equatorial plane through the four depth points (2 DF and 2 DP) and orthogonal lines through ML and CC (Fig 18.3A).

Fig 3: Defining the implantation isocentre and definitive needle entrance and exit points at the skin for a breast implant.

A: Reconstruction boost target isocentre from mammography, by simulator, or CT. The indicated entrance points are too close to the target volume.

B: Inclination of the implantation equator plane away from the target to avoid an overlap of the boost PTV and needle exit points at the skin.
C: Indication of new entrance and exit points, further away from the boost CTV, to avoid skin teleangiectases.

D: Occurrence of severe teleangiectasic “stars” at skin entrance or exit points if rules for implantation are not followed (see text)

Ultrasonography, CT (Fig 18.4) and MRI may also be used for locating the tumour area more precisely and may possibly help to reduce side effects and breast recurrences by eliminating geographic misses (33,43). By means of CT and marker clips it has been possible to further reduce the volume of the boost which still improving local control rates (20).

Fig 18.4 : Using CT and clip localisation for localising the boost PTV (with courtesy of J. Hammer) In some cases, after localisation of the PTV and inclination of the needle implant, the presumed entrance or exit points may be too close to the target area. Then, it may be advised to change the inclination of the equator, so that target area and the skin points got sufficiently separated (Fig 18.3B,C) and the occurrence of star-like tele-angiectasia at exit and entrance points (Fig 18.3D) is avoided.

7.2 Technique of implantation

Breast implants can easily be carried out under local anaesthesia and pre-medication with f.i. 2.5 to 5mg midazolam (Dormicum®) given 15-30 minutes before the implantation. The patient is installed in supine position, with the homolateral arm in 90° abduction.

7.2.1 Design of the implant geometry:

Once the tumour centre is localised, and the three dimensions of the clinical target volume and the PTV (length, width, and thickness) are defined, the implant geometry is designed according to the rules of the Paris System (see physics chapter):
• Needles are implanted parallel and equally distant from each other. In most cases, they are inserted in a medio-lateral direction. However, in very medially or laterally located tumour sites it might be advisable to implant in a cranio-caudal direction to enable adequate PTV covering without having source positions in the breast skin. In some rare cases, the upper outer quadrant has to be implanted with needles orientated in a 45° angle to avoid overlap of source positions and skin.

• Two planes of needles are usually needed to cover the PTV. A single plane may be sufficient in case of flat breast (target thickness of less than 12 mm). Three planes are occasionally required in a large breast (target thickness of more than 30 mm) when the targeted breast tissue between pectoral fascia and skin is thicker than 30 mm.

• If two or more planes have to be implanted, needles are disposed either in a triangle or a square pattern. When the PTV extends close to the skin, a triangular configuration adapted to follow the breast skin contour is better than a square configuration. This is the case in a very cranially or caudally located PTVs in regular implants, or in a very medially or laterally located PTV when craniocaudally orientated implants are carried out.

• Number and spacing between needles are chosen to cover adequately the width and the thickness of the PTV. Five to nine needles spaced to 15 - 20 mm are usually required.

7.2.2 Anaesthesia:
After decontamination of the skin, the entrance and exit points are localised (see supra), and infiltrated with 1% lidocaine (+/- 1 ml for each point). If the needles have to pass through the retro-areolar area, it is also infiltrated with 3 to 5 ml. General anaesthesia may be required for very sensitive patients.

7.2.3 Guide needle technique:
First, a reference needle is implanted at the posterior (deepest) side in to the centre of the PTV. By performing implants either by freehand or helped by the methods described above, it is always possible to control the position of the first implanted needle relatively to the inner scar. This is possible by moving the tip of the needle up and down in the scar. This causes a visible retraction of the scar at the skin while moving with the needle. For definitive positioning, the needle should pass about 5 mm behind the internal scar. The other needles of the posterior plane are then implanted parallel to the first one.

Spacing templates are disposed around the posterior plane of needles. Then the superficial plane of needles is implanted through the corresponding holes in the templates. It is important to respect a sufficient distance between the superficial needles and the overlying skin. To avoid overlap of the high dose region around the needles (MSM: Maximal Security Margin (51)) and the skin vessels located in the first 5 mm under the skin surface (Fig 18.5), a minimum skin-source distance has to be respected.

![Fig 18.5: Positioning of the Maximum Security Margin (MSM) around an interstitial implant at 5mm under the epidermis (from 51).](image-url)
This distance depends on source configuration and spacing between needles, and corresponds to 0.4 \times (\text{spacing} + 1 \text{ mm}) for single plane implants, 0.4 \times \text{spacing} for squares, and 0.4 \times (\text{spacing} - 1 \text{ mm}) for triangles (Fig 18.6).

Fig 18.6: Linear relation of the Maximum Security Margin (MSM) to source spacing distance (S) for single plane and double plane in squares or triangular geometry. MSM = 0.4 (S+1) for single plane, 0.4 S for double plane squares, and 0.4 (S-1) for triangles (from 42).

To verify this distance, the use of a skin source measuring bridge is recommended (Fig 18.7) (52, 54).

Fig 18.7: The Source Skin Measuring Bridge (E. Van Limbergen et al. 1989)

If the superficial needles are too close to the skin, the templates are moved towards each other so that the overlying skin moves up and away from the needles. If this is not sufficient, templates with a smaller spacing between the needles are used, resulting in compression of the breast tissue and upward movement of the skin. If this is still not sufficient, needles must be replaced or irradiation of the overlying skin has to be accepted, depending on the clinical situation.

Once the implant is approved, and the needles immobilised to the templates by fixation buttons, the position of the target centre relative to the implant (distance to the needlepoint or entrance) must be measured and recorded.

The minimum distance from the skin above the implant is recorded as well, and the critical positions of the skin at the exit and entrance points of the needles (the medial and lateral epidermal points) are also measured relatively to the needle ends.

In case of open tip needles that will be manually afterloaded by iridium wires, it is advisable to crush the needle at the tip to occlude the lumen to facilitate and secure the loading by preventing dummy wires and active sources to sort.

Finally, some gauze is placed between the templates and the skin of the thoracic wall at both sides of the implant to avoid skin necrosis secondary to continuous pressure of these templates.
7.2.4 Plastic tube technique:

Guide needles may be replaced by plastic tubes immobilised by buttons at both sides of the breast. The main advantage is that it is probably better tolerated by the patient, but it is more difficult to contain the optimal geometry (parallelism, inter needle spacing and distance to the overlying skin).

8 Dosimetry

Source lengths and spacing have to be adequate to cover the PTV. Spacing and number of needles have been calculated previously to the implantation, according to the Paris system rules (see physics chapter 2).

The length of the sources has to be adapted to the length of the PTV, which has to take the position of the skin vessels also into account. These vessels are, as mentioned above, no target volume at all for boost irradiation. For sources with equal linear activity, sources should be 1.43 times longer than the PTV. With stepping source PDR or HDR afterloaders and using geometrical optimisation, this source / target length ratio can be reduced to 1.18, which reduces the active source length needed by 15%. This allows adequate covering of the target, without loading source positions that are very close to or even inside the skin.

For this, the following data must be entered into the planning system, using projection images (radiographs) or sectional images (CT images) and dummy sources:

- The central dose points in the implant at the level of the tumour centre TC, measured from the hollow or pointed end of the implantation needles.
- The medial and lateral edges of the PTV. For example, if we want to treat 15 mm both sides from a primary tumour of 20 mm, the edges will be at 25 mm both sides of the central dose points. These lateral and medial target limits can either be drawn on to the simulator films or defined mathematically in the planning system by shifting the co-ordinates of the central dose points medially and laterally along the needle direction.
- The critical dermal dose points. These points are situated 5 mm deeper than the epidermal entrance and exit points, measured at the time of implantation.
- Overlying skin points, using either a metal wire fixed to the skin in the central plane or a metal marker at those points where the skin surface seems to be the closest to the active sources (28). Again, reference dermal points are situated 5 mm deeper.

The dose is prescribed at an isodose representing 85% of the Mean Central Dose. However the dose to the dermal points should not exceed the prescribed dose to the PTV. If so, it is a clinical decision either to accept the source positions and having a higher risk of creating late teleangiectasic stars at the entrance or exit points of the needles or at the overlying skin (Fig 18.4D) or to spare the skin while accepting a smaller safety margin. This can be achieved as follows:

- With classical low dose rate, by reducing source length to decrease the dose at entry points or with a partial withdrawal of the sources to reduce the dose to the overlying skin.
- With stepping source afterloaders implants, using the geometrical optimisation facility. Doing this, skin doses are lowered, while keeping the target unchanged in most cases. Another solution is by not loading source positions into the skin but 2 to 3 positions outside the skin, allowing a better covering of the lateral limit of the target, while avoiding hot spots in the skin itself.
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**Dose, Dose Rate, Fractionation**

LDR, PDR, and HDR brachytherapy are feasible as interstitial brachytherapy for breast cancer. Using LDR or PDR as a boost, a typical dose of 15 Gy is given after complete resection and 45 to 50 Gy whole breast irradiation. After incomplete resection, a dose of 20 to 25 Gy may be recommended. In definitive non-surgical treatment, this boost dose may escalate to 25 to 30 Gy. The recommended dose rate is 60 to 80 cGy.h⁻¹ for LDR (8,30) and 0.6 to 0.8 Gy pulses every hour for PDR (12).

Typical HDR after resection of the tumour and 45-50 Gy whole breast irradiation schedules use 10 Gy in 1 fraction or doses up to 20 Gy in 4 to 6 Gy fractions (18). Assuming an (α/β)-ratio of 10 Gy for acute reactions this corresponds in 18.6 Gy in 2 Gy fractions per day. Assuming an α/β-ratio ratio of 3Gy for late effects, this corresponds in 27.6 Gy in 2 Gy fractions.

With brachytherapy alone, performed in selected cases after complete surgery, the recommended dose is 45- 50 Gy LDR / PDR delivered in 96 h or 32 Gy in 8 HDR fractions in 4 days (26,59)

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**Results**

Local control rates after breast conserving treatment are dose dependent. Recently three randomised trials (2,41,47), have confirmed the hypothesis based on retrospective studies (50) that an increase in dose may lead to a decrease in local recurrence rates by a factor 2. The absolute impact however seems to be higher in women under 40 years old (LR 10.2% with boost versus 19.5% for no boost) than in postmenopausal women (LR 2.8% with boost versus 4.6% without boost)(2).

On the other hand, poor cosmetic outcome has also been correlated with radiation dose to the breast skin (radiation teleangiectases), and breast tissue (retraction due to fibrosis), the latter depending not only on RT doses but also on the treated boost volume.

Analysis of the Leuven data, showed an upward nipple retraction of 1 mm on the average for every Gy above 50 Gy (51). Several groups have also indicated the influence of boost volume on cosmetic outcome (3,31,32). Data reported by the Amsterdam group relate the incidence of severe fibrosis to the boost volume: every doubling of the boost volume (starting from 50 cc) shifted the tolerance dose for severe fibrosis with 11% (3).

For developing skin teleangiectases, the tolerance dose is rather low: A dose of 50 Gy delivered in 2 Gy fractions to these vessels results in teleangiectases in 30% of cases (49). These vessels are located in the first 5 mm of the breast skin beneath the epidermis (52). Depending on the energy and the beam angle of the photon beam, these vessels already receive 20 to 40 Gy from whole breast irradiation. Therefore, the contribution of the boost to skin dose should be kept minimal.

Different methods for boosting the tumour bed are available for the radiation oncologist. External beam irradiation with reduced field photon beams, an electron beam, intra-operative electron beam radiation, interstitial implants carried out either peri-operatively or postoperatively performed and recently also IMRT. The choice is often based on the personal preference and training of the radiation oncologist involved or on the available infrastructure in the hospital. In many cases, patients in the same hospital receive a boost with the same treatment technique. However the choice should rather depend on objective individual patient characteristics such as the size of the breast and the size and localisation of the target volume. For deeply seated tumours, it can be theorised that techniques such as interstitial implants or IMRT might offer a potential advantage because of better adaptation of the treated volume to the target. In those cases, smaller volumes can be treated and lower skin doses delivered, compared to standard external electron beam boost. (Fig 18.8)

Analysis of irradiated boost volumes in the EORTC boost no boost trial (unpublished data 1995) and from the Graz-Linz study (18,19) shows indeed a 3 fold volume decrease in patients treated by
interstitial implants as compared to external beam techniques. Despite the lower boost volumes treated with BT no decrease in local control rate was observed in the studies concerned. (18,19, data presented at the ECCO meeting in Istanbul 2000 (6), and Bartelink personal communication at the GEC-ESTRO Breast Consensus Meeting in Stresa, 2001). So, if appropriately applied, interstitial boosts can treat the boost PTV more conformably and reduce the amount of non target breast tissue in the boost irradiation.

Fig 18.8: Different boost modalities in breast conserving treatment. For deeply located tumours, brachytherapy offers the possibility to treat less non-target breast tissue and to spare the skin.

On the other hand, the skin sparing effect of an interstitial boost depends on the depth of the boost PTV. Depth determines the choice of the electron beam energy, and the fall-off dose to the skin vessels of the implant. The poor cosmetic outcome related to high-energy electron beam boosts was already recognised in 1983 by Ray and Fish (38). They found irradiation with a 12 MeV or higher energy electron beams the most significant parameter related to poor cosmetic outcome. Also, at Guys Hospital, the incidence of late skin teleangiectasia was only seen in patients who received skin doses above 50 Gy (17).

For target depths deeper than 28 mm beneath the epidermis, an electron beam energy higher than 9 MeV is needed and the skin doses delivered by an implant to cover the same target are significantly lower (53), offering the possibility of reducing the incidence of teleangiectasia when the sources are implanted at a sufficient distance from the epidermal surface. In this way the Leuven group was able to reduce the incidence of skin anegetia in patients with a 15 Gy implant from 51% to 4.6% (54).

Despite the theoretical advantage of delivering a highly conformal boost to the tumour bed, with reduction in unnecessary treatment of non target breast tissue and skin, published data, particularly the cosmetic outcome are not always supporting this concept.

The main reason is probably an incorrect positioning of the boost to the target and to the breast skin, at least in the oldest reported series.
Local Control Rates:

Table 1 shows the local control rates reported after external beam boosts and interstitial implants. Most studies such as the retrospective analysis by Mansfield (29) and Hammer (19), and a randomised trial published by Fourquet (10), show better local control for implanted patients. Also in the EORTC boost no boost trial subgroup analysis showed a non significant, but probably better local control rate was seen in implanted patients (2.5% versus 4.5%, P = 0.09) but patients were not randomised for boost modality in this large study (Data presented by at the ECCO meeting in Istanbul 2000 (6). Touboul et al. (48) found difference but not significant in local failure rate. These were at 10 years 8.1% for interstitial and 13.5% for electron boosts (p = 0.32). However, both groups were not strictly comparable: Implanted patients were younger (91% below 50y, versus 70% below 50 y for electrons) and less frequently treated with quadrantectomy.

Table 18.1: Local control rates after Brachytherapy boost, compared to external beam boost in breast conserving treatment.

<table>
<thead>
<tr>
<th>Breast Conserving Surgery + RT</th>
<th>n</th>
<th>Five-year Local Failure Rates</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De le Rochefordiere et al. 1992 (7)</td>
<td>T1-T2</td>
<td>337</td>
</tr>
<tr>
<td>Mansfield et al. 1995 (29)</td>
<td>T1-T2</td>
<td>1070</td>
</tr>
<tr>
<td>Touboul et al. 1995* (48)</td>
<td>T1-T2</td>
<td>329</td>
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<tr>
<td></td>
<td></td>
<td>19.5%(10y)</td>
</tr>
<tr>
<td>Perez et al. 1996 (34)</td>
<td>T1-T2</td>
<td>619</td>
</tr>
<tr>
<td>Wazer et al. 1997 (61)</td>
<td>T1-T2</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2 % (7y)</td>
</tr>
<tr>
<td>Hammer et al. (18)</td>
<td>T1-T2</td>
<td>420</td>
</tr>
<tr>
<td>Colette 2000 (6)</td>
<td>T1-T2</td>
<td>5312</td>
</tr>
<tr>
<td>Polgar et al. 2001 (37)</td>
<td>T1-T2</td>
<td>207</td>
</tr>
</tbody>
</table>

Radiotherapy only

| Fourquet et al. 1995***(10) | T2(>3cm)-T3(< 7cm) | 255 | 30% (5y) | 16% (5y) | p< 0.03 |
|                            |   | 39% (8y) | 24% (8y) |

* Groups not strictly comparable: Implanted patients were younger (91% below 50y, versus 70% below 50 y for electrons) and less frequently treated with quadrantectomy.

** all pts had close margins < 2 mm, but implanted patients had, were younger 51y versus 62y(p 0.0001)

** Randomised trial
Only the data from Wazer et al. (1997) suggest a worse outcome of implanted cases, although not significant, in a small series, with a very unbalanced risk profile: implanted patients were markedly younger (51y) than non-implanted patients (62y). p=0.00001

These better local control rates could be attributed to the higher nominal and biological effective doses that are delivered by an implant, or maybe to better boost localisation methods and this despite the smaller boost volumes treated.

**Cosmetic Outcome:**

For cosmetic outcome the data are less consistent (Table 18.2)

The earlier reports on cosmetic outcome after interstitial implants, of the early experience in the USA have put the use of iridium implants in breast conserving treatment somewhat in disgrace. Ray and Fish (38) reported in 1983 on their first experiences in 23 patients and compared cosmetic outcome to those in 107 patients treated with electron beams. It might be assumed that technical performance in their early experience was not optimal and correct skin-source distances may not have been respected in the way which was proposed later as a logical strategy to improve cosmetic outcome (52). Fowble reported in 1986 in an abstract (11) a worse cosmetic outcome in interstitial boost patients, but there was a major difference in follow up time (only 29 months in the Electron Beam group versus 54 months in the Iridium group). It is clear that at least a follow up time of 36 months is needed to evaluate late effects of radiation on breast retraction (51) and skin damage (49).

Olivotto et al. (32), reporting on the early Harvard experience, noted a significantly worse cosmetic outcome with interstitial boosts (58% excellent results) than with external beam boosts or if no boost was given (85% excellent results, p<0.03). This may have been related to the volume implanted and dose delivered which both were significantly higher in the implanted group.

De la Rochefordière et al. (7), and Taylor et al. (46) found no differences between both boost types, but the cosmetic result in their series was influenced primarily by the surgical technique (resected breast volume, scar orientation and skin resection) and by the use of concomitant chemotherapy.

Fourquet (10) and Perez (34) also did not find significant differences, while Touboul et al. had worse outcome with implants. However, in this study, implanted patients received whole breast beam radiotherapy with Co60, while electron beam boost patients had whole breast RT delivered by a 4-6 MV linear accelerator which lead to better dose homogeneity and lower skin doses.
### Table 18.2: Percentage Excellent (E) and Good (G) cosmetic results after Brachytherapy boost, compared to electron beam boost. Retrospective studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Fup</th>
<th>EBRT Dose</th>
<th>External beam Boost Dose</th>
<th>Interstitial Dose</th>
<th>P</th>
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<tbody>
<tr>
<td>Ray and Fish 1983 (38)</td>
<td>130</td>
<td>2y</td>
<td>45-50 Gy</td>
<td>15-25 Gy variable energy</td>
<td>15-25 Gy LDR</td>
<td>74% (23pts) na</td>
</tr>
<tr>
<td>Fowble et al. 1986 (11)</td>
<td>29mos (E) 54mos(Ir)</td>
<td>45-50 Gy</td>
<td>16 Gy (7-11MeV)</td>
<td>97% (73% E)</td>
<td>20 Gy LDR</td>
<td>95% (79% E) NS</td>
</tr>
<tr>
<td>Olivotto et al. 1989 (32)</td>
<td>497</td>
<td>3y</td>
<td>46(+6) Gy</td>
<td>16 Gy (7-11MeV)</td>
<td>97% (73% E)</td>
<td>20 Gy LDR</td>
</tr>
<tr>
<td>De le Rochefordiere et al.1992 (7)</td>
<td>337</td>
<td>3y</td>
<td>46(+6) Gy</td>
<td>16 Gy (7-11MeV)</td>
<td>97% (73% E)</td>
<td>20 Gy LDR</td>
</tr>
<tr>
<td>Mansfield et al. 1995 (29)</td>
<td>1070</td>
<td>10y</td>
<td>45 Gy</td>
<td>20 Gy</td>
<td>95%</td>
<td>20Gy</td>
</tr>
<tr>
<td>Sarin et al. 1993 (42)</td>
<td>289</td>
<td>3.5y</td>
<td>45Gy(5Gy)</td>
<td>15-20Gy (8-11MeV)</td>
<td>40%</td>
<td>15-20Gy (8-11MeV)</td>
</tr>
<tr>
<td>Touboul et al. 1995 (48)</td>
<td>329</td>
<td>2.5-11y</td>
<td>45-50 Gy</td>
<td>15 Gy (9-12MeV)</td>
<td>83% (31%E)</td>
<td>10-20Gy LDR</td>
</tr>
<tr>
<td>Perez et al. 1996 (34)</td>
<td>701</td>
<td>5.6y</td>
<td>48-50 Gy</td>
<td>10-20Gy (9-12MeV)</td>
<td>81%</td>
<td>10-20Gy LDR</td>
</tr>
<tr>
<td>Wazer et al. 1997 (61)</td>
<td>517</td>
<td>5y</td>
<td>50 Gy</td>
<td>20 Gy (9-12MeV)</td>
<td>88%</td>
<td>20Gy LDR</td>
</tr>
<tr>
<td>1998 (19)</td>
<td>420</td>
<td>5y</td>
<td>50 Gy</td>
<td>10.8 Gy</td>
<td>70%</td>
<td>10 Gy HDR</td>
</tr>
<tr>
<td>Fourquet et al. 1995 (10)</td>
<td>255</td>
<td>3-7.3 y</td>
<td>57.6 Gy</td>
<td>20 Gy (CO 60)</td>
<td>75% (48%E)</td>
<td>20 Gy LDR</td>
</tr>
</tbody>
</table>

EL pts received whole breast RT with cobalt 60, IS pts with 6 MV Linac

Sarin et al. (42) and recent publications by Wazer et al. (61) and Hammer et al. (19) found the cosmetic results after interstitial brachytherapy superior to external boosts with less fibrosis and skin telangiectases. In the Graz-Linz series, it is interesting to note that the significant decrease in fibrosis (from 29% for electron beam boost to 17% for implants) was consistent with a 3 fold reduction of the treated boost volume (from 70-130 ml in electrons to 21-64 ml). Furthermore, there was as well a significant reduction in radiation telangiectasia (from 28% for electrons to 9% for implants), leading to good and excellent results in 88% of brachytherapy boost patients and 70% in electron beam boosts (p<0.001)
It is clear that the outcome for local control and cosmesis outcome of an interstitial boost strongly depends on dose delivery and technical performance. In technical performance, the major factors are the boost target localisation technique and the already discussed techniques for avoiding skin blood vessels with the boost (52,54).

Another important factor is dose rate of boost delivery: Mazeron et al (30) reported a significant effect of dose rate on local control. Five-year local control was 84% with dose rates higher than 50cGy/h and 74% for lower dose rates. These authors recommended a dose rate of 60 cGy/hr to maximise local control. Deore et al (8) reported on 289 cases and found a significant increase in local failure rate when LDR dose rates were < 30 cGy/h. They noted 24% local failures versus 5 - 9% for higher dose rates up to 160 cGy/h, (p<0.05). They also noted. significantly more complications and poor cosmesis if the dose rate was > 100 cGy/h (p<0.05). A dose rate of 60-80 cGy/h is currently advocated as probably being the optimal dose rate for LDR and PDR (12) brachytherapy.

Boost localisation:

Breast irradiation is usually performed in a postoperative setting. To be able to localise the boost target area, the radiation oncologist should have knowledge of the exact size and location, by a careful clinical description, preoperative mammogram, ultrasound etc. The surgeon should make his incision directly over the tumour bed and placement of surgical clips may help to localise the target volume. The use of postoperative ultrasound or CT may improve the localisation precision, and reduce side effects and possibly breast recurrences by eliminating geographic misses localisation boost (20,33,44). By means of CT and marker clips it has been possible to reduce the volume of the boost and to apply the boost with increasing accuracy and further improving local control rates. Hammer (20) reported a reduction of the 5-year local failure rate in T1 and T2 stages from 5.1 %, (without clips) to only 3.4% (with clips), while at the same time boost volumes were further reduced from 39 ml (range 21 to 64 ml without clips) to 29 ml (range 21 to 40 ml with clips). However the increase in local control may be also have been due to an improvement in surgical methods and in pathological evaluations. In addition, the indications for pre- and post-menopausal systemic therapy have been extended in the last years and this could also have contributed to improve treatment results.

Intra-operative boosts have been advocated to improve the localisation of interstitial implants but this approach has not resulted in better local control rates (5.1 - 7% 5 year failure rates) and certainly no better cosmetic outcome (22,29).

Based on the same concepts of ballistic selectivity, treated boost volumes and skin doses delivered by external beam RT can also be improved by intra-operative EBRT or IMRT. However, up to now, for breast cancer, there are no mature data available that have demonstrated any advantage for local control or cosmesis.

Besides using brachytherapy as a boost after breast conserving surgery and external beam radiotherapy (see Table 18.1A), or after external beam only in more advanced cases (see Table 18.1B), there is another indication which still is controversial but potentially very attractive because of being time and money sparing: the use of wide field interstitial brachytherapy as the sole radiation treatment after breast conserving surgery, without whole breast irradiation.

The rationale for this is that a selection of low risk patients has a very low risk of having multifocal disease in the breast and may not need whole breast RT. In the well known study by Holland et al. (23), it was demonstrated that when tumour was removed, residual tumour was still present in 42% when a margin of 2 cm was taken; 17% beyond a margin of 3 cm, and 10% beyond 4 cm. However, in a later study, the same group (24) concluded that in patients with no extensive intraductal
component, only 2% had residual disease beyond a 2 cm margin. In a similar study by Gump (15), excluding invasive lobular and EIC positive patients, residual tumour was found in only 12% beyond a 2 cm margin in tumours less than 2 cm.

The early results in unselected patients were however not encouraging. Local recurrence rates of 15-37% with a follow up from 1.5 to 8 years have been noted (9). However, there is some indication that this approach might be of value in strictly selected low risk patients over 50 years old, low or moderate grade, T1-T2 with negative section margins and no presence of an extensive component of intraductal carcinoma. (Table 18.3). Initial findings of these trials are promising with local recurrence rates of 0.45% per year of follow up in the first years, which is comparable to local recurrence rates after BCS and whole breast irradiation in low and moderate risk patients. However, longer follow up and careful assessment in phase III trials is needed before this could be considered as a routine treatment in patients with a low or moderate risk for local recurrence.

<table>
<thead>
<tr>
<th>Institute</th>
<th>Selection</th>
<th>BT type</th>
<th>n</th>
<th>Median Follow-up</th>
<th>Local failure</th>
<th>LF per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>William Beaumont Hospital (59)</td>
<td>&lt;3cm,N0 N1bi SM clear &gt;2mm</td>
<td>LDR/HDR 50/32-34Gy</td>
<td>133</td>
<td>3.2 y</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ochsner Clinic USA (26)</td>
<td>&lt;4cm , N0 N1bi SM clear</td>
<td>LDR/HDR 45/32-34Gy</td>
<td>150</td>
<td>3.8 y</td>
<td>1.3 %</td>
<td>0.3%</td>
</tr>
<tr>
<td>London Reg. C.C. Canada (33)</td>
<td>&lt;4;5cm N0-1 SM clear</td>
<td>HDR 37.2 Gy</td>
<td>39</td>
<td>1.7 y</td>
<td>2.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Örebro Medical Center (25)</td>
<td>&lt; 5cm N0-1 SM clear</td>
<td>PDR 50 Gy</td>
<td>43</td>
<td>2.8 y</td>
<td>2.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>NIO Budapest (36)</td>
<td>&lt;2 cm N0-1a SM clear</td>
<td>HDR 30.3-36.4</td>
<td>87</td>
<td>2.8 y</td>
<td>2.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Total :</strong></td>
<td></td>
<td></td>
<td>452</td>
<td></td>
<td>1.3 %</td>
<td>0.45%</td>
</tr>
</tbody>
</table>

11 References


