NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision

Treatment for breast cancer usually involves surgery to remove part or all of the breast. This is sometimes followed by radiotherapy, particularly if only part of the breast has been removed. Brachytherapy is a type of radiotherapy in which the source of radiation is placed in or close to the area being treated. It can be used as an additional treatment (known as adjuvant) after surgery. It typically involves the insertion of radioactive implants into the space in the breast where tissues has been removed. The implants are usually in place for 1 to 5 days. The aim of the procedure is to minimise the chance of the cancer recurring.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2007.

Procedure name

- Adjuvant brachytherapy for breast cancer
- Accelerated partial breast irradiation

Specialty societies

The following societies were approached to nominate Specialist Advisers:

- Association of Cancer Physicians
- British Association of Surgical Oncology
- Royal College of Radiologists

- Society of Radiographers

Description

Indications

Breast cancer

Breast cancer is the most common cancer in England (36,939 newly diagnosed cases of breast cancer in women were registered in 2004)[1]. The most common symptom of breast cancer is a lump in the breast. However, patients within certain age groups may be diagnosed with breast cancer at an asymptomatic stage, through the breast screening programme.

There are several types of breast cancer. Ductal carcinoma in situ (DCIS) is a very early form of breast cancer. The cancer cells are contained inside the ducts and have not spread into the surrounding breast tissue. If it is not treated, it may develop into an invasive cancer. The most common type of invasive breast cancer is invasive ductal breast cancer (also known as ductal carcinoma). Other types of breast cancer include lobular breast cancer and medullary breast cancer.

Breast cancer is usually categorised into four stages and three grades. Stage 1 describes a tumour of less than 2 cm in diameter, the lymph nodes in the armpit are not affected and the cancer has not spread. At stage 4, the tumour can be any size, the lymph nodes may or may not contain cancer cells but the cancer has spread to other parts of the body such as the lungs, liver or bones. Grade 1 or low-grade cancer is slow growing and the tumour cells resemble normal cells. In grade 2 or intermediate grade cancer the cells are moderately differentiated and grow at a faster rate. Grade 3 or high-grade cancer is fast growing and the cells are poorly differentiated.

Current treatment and alternatives

Treatment depends on the type, stage and grade of the breast cancer. Surgery is usually the first option and may involve removing the whole breast (mastectomy) or part of the breast (‘conservative’ or ‘breast-conserving surgery’), which can involve lumpectomy, wide local excision or segmentectomy. Breast tissue excision can be accompanied by axillary lymph node clearance or sentinel node sampling, if appropriate. External beam radiotherapy may be administered after surgery, particularly if surgery is conservative. The aim is to lower the risk of local cancer recurrence. In cases of conservative surgery, radiotherapy is usually given to the whole of the remaining breast, often with a localised boost of irradiation targeted at the estimated position of the tumour bed. This boost may be given as external beam radiotherapy, usually given in short daily sessions, over a number of weeks. Alternatively, the radiotherapy boost may be given as radioactive implants (brachytherapy).

Chemotherapy and hormone therapy may also be given before or after breast cancer surgery.

More recently radiotherapy is being used as the sole method of adjuvant radiotherapy after breast conservation surgery. Newer techniques have been developed that deliver shorter, more intense courses of radiotherapy (accelerated irradiation) to a more focused part of the breast (partial breast irradiation).

There are several methods of accelerated partial breast irradiation including intensity-modulated radiotherapy, three-dimensional conformal radiotherapy and brachytherapy (interstitial and balloon).

This overview assesses accelerated partial breast irradiation using brachytherapy in the treatment of breast cancer after local excision.

What the procedure involves

Brachytherapy as the sole method of adjuvant radiotherapy can be delivered as either interstitial or balloon brachytherapy.

Interstitial brachytherapy involves inserting a number of catheters individually into the breast tissue surrounding the lumpectomy cavity. The catheters can be placed intraoperatively or postoperatively (under local or general anaesthesia). The catheters are usually positioned in two to four planes, approximately 1 to 1.5 cm apart and typically, between 4 and 20 catheters are used, although the exact number of catheters and planes is determined by the size and shape of the target. Image guidance may be used to ensure that the catheters are positioned correctly. Wires with radioactive implants can then be inserted, or a machine can be used to insert small radioactive sources into the catheters. Radiation can be delivered in low or high dose rates. In general, the higher the dose rate the more radiation is delivered in a shorter time (although total doses may in fact be lower with high dose rate therapy).

If the brachytherapy is high dose rate, the radioactive sources are left in place for a few minutes and then removed. In low dose rate brachytherapy, the implants are left in place for a few days.

In **balloon brachytherapy**, a balloon device attached to a catheter is placed into the lumpectomy cavity, either at the time of surgery or during a separate procedure. If it is inserted postoperatively, it may be done using an open or percutaneous approach with ultrasound guidance. A small portion of the catheter remains outside the breast. The balloon is inflated with a saline-contrast mixture allowing the surrounding breast tissue to conform to the balloon. A computed tomography (CT) scan is used to ensure conformity and the absence of air pockets between the balloon and surrounding tissue. If an air pocket or seroma are present, treatment is usually delayed until resolution.The catheter is connected to a computer-controlled high dose rate machine that inserts a radiation seed to deliver the radiotherapy. After each treatment session, the seed is removed and the catheter is disconnected.

Treatment is typically done over 5 days, with two treatment sessions per day. After the final treatment, the balloon device is removed through the same incision that was used to insert it.

Efficacy

Local or regional recurrence and survival

In a randomised controlled trial of 258 patients receiving either interstitial brachytherapy or whole breast external beam radiotherapy, the 5-year actuarial rate of local recurrence was 4.7% and 3.4%, respectively (p = 0.50)[2]. There were no statistically significant differences in the 5-year probability of overall survival (94.6% vs 91.8%), cancer-specific survival (98.3% vs 96.0%) and disease-free survival (88.3% vs 90.3%).

In a non-randomised controlled trial of 398 patients, there was no statistically significant difference in 5-year actuarial rate of ipsilateral breast tumour recurrence between interstitial brachytherapy and external beam radiotherapy (1% in both groups, p = 0.65)[4]. The 5-year actuarial rates of overall survival were also similar (87% for brachytherapy and 93% for external beam radiotherapy, p = 0.23). A second non-randomised controlled trial reported local or regional recurrences in 7.8% (4/51) of tumours in the brachytherapy group compared with 5.3% (5/94) in the external beam radiotherapy group after a median follow-up of 75 months (p = 0.23)[5]. Regional node recurrences were reported in 5.9% (3/51) of patients in the brachytherapy group and 0% (0/94) of patients in the external beam radiotherapy group (p = 0.04). Disease-free survival at final follow-up was 88% in the brachytherapy group and 92% in the external beam group (p value not stated).

One case series of balloon brachytherapy reported a 3-year actuarial overall survival rate of 95.8% in 400 patients[13]. The 3-year actuarial rate of ipsilateral breast tumour recurrence was 1.79%.

Cosmesis and patient satisfaction

The randomised controlled trial reported that significantly more patients treated with HDR brachytherapy had excellent to good cosmetic result compared with those treated with whole breast irradiation using photons (81.2% vs 65.6%, p = 0.014)[2].

One non-randomised controlled trial of 144 patients reported excellent or good cosmetic result at median follow-up of 20 months for 75% of patients in the brachytherapy group and 84% in the external beam group (p = not significant)[5].

Procedure aborted for device-related issues

In one case series, 6.7% (5/75) interstitial brachytherapy procedures and 25% (7/28) balloon brachytherapy procedures were aborted because of device-related issues[6].

Safety

One study of 103 patients reported that 17% of patients treated with interstitial brachytherapy had grade 1 skin erythema and 5% had skin erythema of a higher grade, compared with 43% and 0%, respectively, for patients treated with balloon brachytherapy (p = 0.01 and 0.06, respectively)[6]. Subcutaneous fibrosis was reported in 32% of patients treated with interstitial brachytherapy and 11% of patients treated with balloon brachytherapy (p = 0.04). There was no statistically significant difference in symptomatic fat necrosis (12% for interstitial brachytherapy vs 7% for balloon brachytherapy, p = 0.73).

Complications of interstitial and balloon brachytherapy reported by the studies included fat necrosis in 1.5% (22/1449) to 16% (8/50) of patients, symptomatic seromas in 10% (8/80) and 10.6% (153/1449) of patients, fibrosis in 10% (5/50), and 19% (53/274) of patients, telangiectasia in 2% (1/50) and 13% (35/274) of patients, breast pain in 3% (3/89) and 7% (20/274) of patients, infection in 3% (9/274), 8% (92/1140) and 9% (4/43) of patients[5,3,7,9,10,13]. One case series specified that two cases of infection were severe (one case of mastitis and one abscess)[10].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to adjuvant brachytherapy for breast cancer. Searches were conducted via the following databases, covering the period from their commencement to 30/11/2007: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with breast cancer.
Intervention/test	Adjuvant brachytherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on one randomised controlled trial (two reports), two non-randomised controlled trial and five case series[2–11].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing reviews on this procedure

There are several reviews on accelerated partial breast irradiation. One review, which was published in 2007, stated that accelerated partial breast irradiation alone after breast conserving surgery is still an experimental treatment even in patients with a low risk, such as older women with favourable prognostic factors[12]. The various techniques have a marked difference in dose distribution and homogeneity. The published range of local recurrence rates varied between 0% and 37%, the median follow-up was from 8 to 72 months. The review states that the relevant oncology societies in Germany support randomised clinical studies comparing accelerated partial breast irradiation with whole breast radiotherapy in a well-defined subset of low-risk patients.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

- High dose rate brachytherapy for carcinoma of the cervix. NICE interventional procedures guidance 160 (2006). Available from www.nice.org.uk/IPG160
- High dose rate brachytherapy for prostate cancer. NICE interventional procedures guidance 174 (2006). Available from www.nice.org.uk/IPG174
- Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedures guidance 201 (2006). Available from www.nice.org.uk/IPG201
- Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedures guidance 132 (2005). Available from www.nice.org.uk/IPG132
- Interstitial laser therapy for breast cancer. NICE interventional procedures guidance 89 (2004). Available from www.nice.org.uk/IPG089

Technology appraisals

- None

Clinical guidelines

- A Clinical Guideline on early breast cancer is in development (final scope August 2006) – the scope includes radiotherapy (external beam and brachytherapy). The guideline is due to be published in January 2009.

Cancer service guidance

- Improving outcomes in breast cancer – manual update. Cancer service guidance (2002). Available from www.nice.org.uk/nicemedia/pdf/Improving_outcomes_breastcancer_manual.pdf

Public health

- None

Table 2 Summary of key efficacy and safety findings on brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy

Study details	Key efficacy findings	Key safety findings	Comments
Polgar C et al. (2002, 2007)[2,3] **Randomised controlled trial** Hungary Study period: 1998–2004 **n = 258** Population: patients with T1, N0-1mi, Grade 1-2, nonlobular breast cancer • Partial breast irradiation = 49.6% (128/258) (88 interstitial brachytherapy only, 40 limited field electron beam) • Whole breast RT (external-beam) = 50.4% (130/258) Mean age (years): • Partial breast irradiation = 59 (range 30–84) • Whole breast RT = 58 (range 31–80) Histological Grade 1: • Partial breast irradiation = 63.3% (81/128) • Whole breast RT = 50% (65/230) Inclusion criteria: wide excision with microscopically negative surgical margins; unifocal tumour, primary tumour size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micrometastasis >0.2 mm and ≤2.0 mm) axillary status; histological Grade 2 or less. Exclusion criteria: bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (expect basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; extensive intraductal component. **Median follow-up (months): 66 (range 18–101)**	**Ipsilateral breast recurrence**: • Partial breast irradiation = 4.7% (6/128) • Whole breast RT = 3.1% (4/130) p value not reported **Regional recurrence:** • Partial breast irradiation = 1.6% (2/128) • Whole breast RT = 0.8% (1/130) p value not reported **Distant metastasis:** • Partial breast irradiation = 3.9% (5/128) • Whole breast RT = 5.4% (7/130) p value not reported **Any first relapse (local, regional or distant):** • Partial breast irradiation = 10.2% (13/128) • Whole breast RT = 9.2% (12/130) p value not reported **Contralateral breast cancer:** • Partial breast irradiation = 6.2% (8/128) • Whole breast RT = 2.3% (3/130) p value not reported **5-year actuarial rate of local recurrence:** • Partial breast irradiation = 4.7% (95% CI 0.7 to 8.7) • Whole breast RT = 3.4% (95% CI 0.1 to 6.7) RR = 1.24, 95% CI 0.65 to 2.34, p = 0.50	**Late side effects for patients with minimum follow-up of 18 months (n = 104)** **Slight telangiectasia (grade 2):** • Tumour bed RT = 2.0% (1/50) • Whole breast RT = 3.7% (2/54) **Grade 2–3 fibrosis:** • Tumour bed RT = 10.0% (5/50) • Whole breast RT = 13.0% (7/54) **Fat necrosis:** • Tumour bed RT = 16.0% (8/50) • Whole breast RT = 9.3% (5/54)	Randomisation described. Efficacy data has been presented from the 2007 paper. This paper did not report any safety data, which was taken from the 2002 paper. All comments relate to the 2007 paper unless otherwise specified. For 40 patients allocated to the partial breast irradiation group there was a technical contraindication for interstitial brachytherapy. These women were treated with wide local electron field. Two patients did not receive allocated intervention (one in each group) – one patient had distant metastasis identified before RT and one patient opted for mastectomy without RT. Intention-to-treat analysis. Two patients were lost to follow-up (both in whole breast irradiation group). The authors note that the study may be underpowered to detect small possible differences in local tumour control between the two treatment arms. The partial breast irradiation group

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Technique: brachytherapy was delivered with HDR remote afterloading equipment using an iridium-192 isotope. Implantations were performed postoperatively under local anaesthesia, 4–6 weeks after surgery. 4–13 catheters were inserted in 1–4 planes using template guidance. 69.5% (89/128) partial breast irradiation patients and 72.3% (94/130) whole breast irradiation patients received chemotherapy and/or hormonal therapy (p = 0.37). Disclosure of interest: none stated.	**5-year actuarial rate of true recurrence/marginal miss:** • Partial breast irradiation = 1.6% (95% CI 0.0 to 3.8) • Whole breast RT = 1.7% (95% CI, 0.0 to 4.1) **5-year actuarial rate of elsewhere breast failure:** • Partial breast irradiation = 3.1% (95% CI 0.0 to 6.7) • Whole breast RT = 1.7% (95% CI, 0.0 to 4.0) **Overall survival at 5 years:** • Partial breast irradiation = 94.6% (95% CI 90.2 to 99.1) • Whole breast RT = 91.8% (95% CI, 86.3 to 97.4) **Cancer-specific survival at 5 years:** • Partial breast irradiation = 98.3% (95% CI 96.0 to 100) • Whole breast RT = 96.0% (95% CI, 92.4 to 99.6) **5-year actuarial rate of contralateral breast cancer:** • Partial breast irradiation = 7.1% (95% CI, 1.9 to 12.2) • Whole breast RT = 2.4% (95% CI, 0.0 to 5.2) p = 0.12 Significantly more patients treated with HDR brachytherapy had excellent to good cosmetic result compared with those treated with whole breast irradiation using photons (81.2% vs 65.6%, p = 0.014)		included some patients with external beam RT. There were significantly more patients in the partial breast irradiation group with Grade 1 tumour (63% vs 50%), which has better prognosis The authors assumed that histological grade had no significant impact on survival results and univariate analysis did not show a statistically significant difference in local tumour control between Grade 1 and Grade 2. Overall, reported 5-year survival rates for both groups are excellent and well above the 5-year survival rates encountered in the general patient population (75-80%) –this is indicative of relatively low risk patient population (as selection criteria would also have implied). This feature makes the detection of significant differences between the two treatment arms for several outcomes difficult (lack of power); it also, in principle, diminishes the generalisability of the findings to other women with breast cancer.

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Vicini FA et al. (2003)[4] **Non-randomised controlled trial (historical controls)** USA Study period: 1993–2001 for brachytherapy cases and 1980–1997 for controls **n = 398** Population: patients with invasive early stage breast cancer • Brachytherapy = 50% (199/398) • Whole breast external beam RT = 50% (199/398) Mean age at diagnosis (years): • Brachytherapy = 65.2 • External beam RT = 63.5 Inclusion criteria: age > 40 years, infiltrating ductal histology, absence of an extensive intraductal component, negative margins ≤ 2 mm, tumour size < 3 cm, performance of an axillary lymph node dissection and cancer involvement of ≤ 3 lymph nodes. Technique: interstitial brachytherapy. 120 patients were treated with LDR implant on an inpatient basis. The remaining patients were treated with HDR implant as outpatients. **Mean follow-up (years):** • **Brachytherapy = 5.0** • **External beam RT = 8.9, p < 0.001** Disclosure of interest: none stated.	**5-year actuarial rate of ipsilateral breast recurrence:** • Brachytherapy = 1% • External beam RT = 1% p = 0.65 **5-year actuarial rate of regional failure:** • Brachytherapy = 1% • External beam RT = 1% p = 0.54 **5-year actuarial rate of distant metastasis:** • Brachytherapy = 3% • External beam RT = 5% p = 0.17 **5-year actuarial rate of disease-free survival:** • Brachytherapy = 87% • External beam RT = 91% p = 0.30 **5-year actuarial rate of overall survival:** • Brachytherapy = 87% • External beam RT = 93% p = 0.23 **5-year actuarial rate of cause-specific survival:** • Brachytherapy = 97% • External beam RT = 97% p = 0.34 **Contralateral breast failure:** • Brachytherapy = 1% • External beam RT = 4% p = 0.03 **Excellent/good cosmetic outcome for patients observed 5 or more years:** • Brachytherapy = 99% (78/79)	Adverse events in patients treated with brachytherapy: • Asymptomatic fat necrosis = 4% (8/199) • Grade II fibrosis = 4% (8/199) • Grade I/II persistent oedema = 6% (12/199)	Each brachytherapy patient was matched with an external beam RT patient treated at the study centre between 1980 and 1997. Patients were matched for age, tumour size, nodal status, oestrogen receptor status, and use of adjuvant tamoxifen. There were no statistically significant differences between the two groups in terms of age, tumour size, margins of excision, nodal status, oestrogen receptor status, use of adjuvant tamoxifen, and use of systemic chemotherapy. 41 patients who did not meet all eligibility criteria for the brachytherapy protocols were also included in the analysis. The authors noted that the reasons for ineligibility were minor and were unlikely to affect recurrence rate. The authors note that selection criteria were highly restrictive. The controls were treated during an earlier period than the cases. Patients with whole breast radiation had statistically significant longer follow-up than those with partial breast irradiation. The authors note that the rate of contralateral breast failure should be viewed with caution as the study did not control for all potential variables that might affect it.

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
King TA et al. (2000)[5] **Non-randomised controlled trial** USA Study period: 1992–1993 **n = 144 patients** Population: breast cancer patients suitable for breast-conserving therapy • Brachytherapy = 35% (50/144) • External beam RT = 65% (94/144) Mean age (years): • Brachytherapy = 63.0 • External beam RT = 56.9, p = 0.002 Inclusion criteria: intraductal or invasive tumours ≤ 4 cm, negative surgical margins, three or fewer positive axillary nodes. Exclusion criteria: clinical or radiographic evidence of multicentricity. Technique: for external beam RT, decisions regarding the total dose and administration of boost dose were made on an individual patient basis. Brachytherapy patients were assigned to receive either LDR or HDR brachytherapy. Implant was performed during segmental mastectomy or re-excision when possible. Catheters were loaded 3 – 5 days postoperatively. **Median follow-up (months): 75 (brachytherapy patients)** Disclosure of interest: none stated	**Total number of local-regional recurrences:** • Brachytherapy = 7.8% (4/51) • External beam RT = 5.3% (5/94), p = 0.23 **Breast recurrences:** • Brachytherapy = 2.0% (1/51) • External beam RT = 5.3% (5/94), p = 0.24 **Regional node recurrences:** • Brachytherapy = 5.9% (3/51) • External beam RT = 0% (0/94), p = 0.04 **Disease-free survival at last follow-up:** • Brachytherapy = 88% • External beam RT = 92% **Excellent or good cosmetic result at median follow-up of 20 months (as judged by a blinded panel):** • Brachytherapy = 75% • External beam RT = 84%, p = not significant	**Grade I and II treatment complications:** • Brachytherapy = 21.6% (11/51) • External beam RT = 79.8% (75/94) p < 0.001 For brachytherapy, these included skin erythema, moist desquamation, telangiectasia, pain and fibrosis. For external beam RT, they included skin erythema, desquamation, discolouration, hyperpigmentation, dimpling, breast pain, tenderness, shrinkage and fibrosis. **Grade III treatment complications requiring surgical intervention:** • Brachytherapy = 7.8% (4/51) • External beam RT = 5.3% (5/94), p = not significant In the brachytherapy group, these included one wound haematoma, one infected seroma and two cases of fat necrosis. In the external beam RT group, these included three wound abscesses, one wound haematoma, and one wound dehiscence.	Controls were identified from retrospective chart review. A subset of controls was matched for pathological stage, tumour size and breast size with patients in the brachytherapy group. The controls were treated during the same study period. One patient in the brachytherapy group had two breast cancers included in the study. To evaluate cosmesis, a blinded panel of healthcare professionals reviewed photographic slides. Patients in the brachytherapy group were older and included more patients with invasive cancer than the control group. The groups were similar in terms of tumour size, nodal involvement, histological grade, and percentage with a component of extensive intraductal carcinoma.

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Shah NM et al. (2004)[6] **Case series** USA Study period: 1997–2003 **n = 103 patients** Population: patients with stage 1 and 2 breast carcinomas • Interstitial brachytherapy = 72.8% (75/103) • Balloon brachytherapy = 27.2% (28/103) Mean age (years): • Interstitial brachytherapy = 63.5 • Balloon brachytherapy = 62.0 Inclusion criteria: unicentric primary tumours with invasive ductal histological features; T1, T2, N0 and N1 disease; negative microscopic assessment of surgical margins; no collagen-vascular disease or concurrent pregnancy; no known unresected residual carcinoma and no diffuse microcalcifications; no prior malignancy except non-melanoma skin carcinoma < 5 years before enrolment or continuously disease free ≥ 5 years. For patients with balloon brachytherapy, these criteria were modified to exclude patients with positive lymph node status. Tumours were required to be ≤ 2 cm and the volume had to be consistent with manufacturer's recommendation with respect to size of balloon selected. A distance of ≥ 5 mm was required between the balloon surface and the skin.	**Procedure aborted for device-related issue:** • Interstitial brachytherapy = 6.7% (5/75) • Balloon brachytherapy = 25% (7/28) p = 0.04 (In five patients, the balloon ruptured prior to treatment, one patient developed haemorrhage in treatment cavity, one patient's treatment was aborted because of suboptimal placement of the balloon. The majority of such problems occurred early in the series). **Good/excellent cosmesis (scored by radiation oncologist, surgeon and clinic nurse):** • Interstitial brachytherapy = 89.3% • Balloon brachytherapy = 92.8% p = 0.72 **Cosmesis < excellent:** • Interstitial brachytherapy = 34.7% • Balloon brachytherapy = 32.1% p = 1.00	**Skin erythema (grade 1):** • Interstitial brachytherapy = 17.3% • Balloon brachytherapy = 42.9% p = 0.01 **Skin erythema (> grade 1):** • Interstitial brachytherapy = 5.3% • Balloon brachytherapy = 0.0% p = 0.06 **Subcutaneous fibrosis (> grade 1):** • Interstitial brachytherapy = 32.0% • Balloon brachytherapy = 10.7% p = 0.04 **Symptomatic fat necrosis:** • Interstitial brachytherapy = 12.0% • Balloon brachytherapy = 7.1% p = 0.73	An additional 12 patients were enrolled in the study but were not eligible for treatment. The first 75 consecutive eligible patients received interstitial brachytherapy. The most recent 28 patients received balloon brachytherapy. Patients who were treated early in the study were more likely to have negative oestrogen receptor status or positive axillary lymph nodes. All patients in the balloon brachytherapy group had positive oestrogen receptor status whereas 15% of patients in the interstitial group had negative oestrogen receptor status. The authors note that there were less balloon device-related issues later on the series, which likely relates to increasing familiarity with the limitations of the device and greater utilisation of the smaller balloon size.

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Exclusion criteria: invasive or in situ lobular carcinoma or pure ductal carcinoma in situ, skin involvement, breast unsatisfactory for brachytherapy, last breast surgery > 8 weeks before planned brachytherapy. Technique: all patients were treated with HDR brachytherapy. Implants were placed either perioperatively (at the time of re-excision) or within 8 weeks postoperatively. HDR afterloader was used. MammoSite balloon brachytherapy catheter (Proxima Therapeutics Inc) was used for balloon brachytherapy. **Mean follow-up (months):** • **Interstitial brachytherapy = 61 (range 29–106)** • **Balloon brachytherapy = 19 (range 8–40)** **p < 0.0001** Disclosure of interest: none stated			

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Ott OJ (2007)[7] **Case series** Germany, Austria Study period: 2000–2005 **n = 274** Population: patients with early breast cancer Median age (years) = 61 (range 39–85) Histology: • Invasive ductal = 66% (181/274) • Invasive lobular = 16% (45/274) • Tubular = 10% (26/274) • Other histologies = 8% (22/274) Inclusion criteria: tumour diameter ≤ 3 cm, complete resection with clear margins ≥ 2 cm, post-surgical negative axillary lymph nodes (pN0) or singular nodal micro-metastasis (pN1 mi), no distant metastasis or contralateral breast cancer, oestrogen and/or progesterone receptor-positive tumours, age 35 years or older. Exclusion criteria: multifocal invasive growth pattern, poorly differentiated tumours, postoperative residual micro-calicifications, extensive intraductal component, vessel invasion, involved or unknown margins, pregnancy. Technique: interstitial brachytherapy catheters were usually implanted as closed cavity surgery, approximately 57 days after breast conserving surgery. Total treatment time was 5 days, given on an inpatient basis. **Median follow-up (months) = 32 (range 8–68)** Disclosure of interest: none stated	**In-breast recurrence at follow-up = 0.7% (2/274)** (relapses at 13 and 56 months respectively) **Local recurrence-free survival probability at 3 years** **Distant metastasis-free rate = 99.3% (272/274** **Overall survival rate (median follow-up of 32 months)= 98.5% (270/274)** (Four patients died, all of them free of breast cancer disease). **Cosmetic result at follow-up (according to physician):** • Excellent = 57.7% (158/274) • Good = 36.1% (99/274) • Fair = 5.8% (16/274) • Poor = 0.4% (1/274) **Cosmetic result at follow-up (according to patient):** • Excellent = 60.2% (165/274) • Good = 31.4% (86/274) • Fair = 6.9% (19/274) • Poor = 1.5% (4/274)	**Peri-operative complications** • Brachytherapy implant infection (mostly superficial and restricted to the insertion points) = 3.3% (9/274) • Haematoma = 2.2% (6/274) **Acute toxicity (within 90 days)** • Radio-dermatitis (grade 1/2) = 6.6% (18/274) **Late side effects** • Subjective breast pain = 7.3% (20/274) • Hyperpigmentation = 6.6% (18/274) • Breast tissue fibrosis = 19.3% (53/274) (grade 1 = 32, grade 2 = 20, grade 3 = 1) • Telangiectasia = 12.8% (35/274) (grade 1 = 22, grade 2 = 10, grade 3 = 3) • Asymptomatic fat necrosis = 4.7% (13/274)	7% (20/274) of patients in the trial were not compliant with inclusion and exclusion criteria. The violations were regarded as 'minor' and these patients were included in the analysis. As for Polgar et al (above), the reported survival rates may suggest a potentially low risk population.

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Vicini FA (2007)[8] **Case series** USA Study period: 1993–2001 **n = 199** Population: patients with stage 1-2 breast cancer Median age (years) = 65 (range 40–90) Inclusion criteria: infiltrating ductal carcinoma < 3 cm in greatest dimension, negative surgical margins ≥ 2 mm, older than age 40 years, surgically staged axilla with ≤ 3 positive lymph nodes (in 1997, changed to negative lymph nodes). Exclusion criteria: extensive intraductal component, infiltrating lobular histology, ductal carcinoma in situ, clinically significant areas of lobular carcinoma in situ. Technique: interstitial brachytherapy – 79 patients were treated as outpatients with a HDR implant and 120 patients were treated as inpatients with LDR implant. 70% (139/199) patients received adjuvant therapy after completion of brachytherapy. Implant placement was done with either an open or closed cavity. **Median follow-up (years) = 8.0 (8.6 for surviving patients)** Disclosure of interest: none stated	**Ipsilateral breast tumour recurrence** • 5-year actuarial rate = 1.6% • 10-year actuarial rate = 3.8% **Contralateral breast tumour recurrence** • 5-year actuarial rate = 2.2% • 10-year actuarial rate = 5.2% **Disease-free survival** • 5-year actuarial rate = 96.7% • 10-year actuarial rate = 93.7% **Overall survival** • 5-year actuarial rate = 87.3% • 10-year actuarial rate = 72.9% **Cause-specific survival** • 5-year actuarial rate = 97.2% • 10-year actuarial rate = 94.6% Excellent cosmetic result = 15.7% (30/191) Good cosmetic result = 83% (159/191)	Not reported	The study population is the same as the one reported in the non-randomised comparative study by the same author (Vicini et al, 2003). This study reports a longer follow-up. 41 patients who did not meet all the eligibility criteria were included in the analysis. The authors noted that the reasons for ineligibility were minor and were unlikely to affect recurrence rate. 3% (6/199) patients were lost to follow-up.

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Vicini FA (2005)[9] **Case series** USA Study period: 2002–2004 **n = 1419** Population: patients with stage 0, 1 or 2 breast cancer Median age (years) = 65 (range 35–93) Ductal carcinoma in situ = 14% 'Recommended' inclusion criteria: age older than 45 years, tumour ≥ 2 cm in greatest dimension, invasive ductal histology, negative lymph node status, negative marginal status, applicator placement within 10 weeks of final lumpectomy procedure, cavity with dimension at least 3.0 cm. 'Recommended' exclusion criteria: extensive intraductal component, collagen vascular disease. Patients with inadequate balloon-to-skin distances, excessive cavity size or poor balloon-cavity conformance were also excluded. Technique: balloon brachytherapy using MammoSite™ device. Patients could be enrolled prior to final lumpectomy to allow device placement in an open fashion during that procedure (n = 488), or they could be enrolled postlumpectomy and undergo implantation using a closed technique (n = 586). **Median follow-up (months) = 5 (range 1–25)** Disclosure of interest: none stated	88% (1237/1403) of implanted patients were treated with accelerated partial breast irradiation and constitute the study population. **The device was explanted in 123 patients**. The reasons for explantation included inadequate balloon-to-skin distance (n = 43), poor cavity-balloon conformance (n = 35), inadequate margins (n = 13), balloon deflation (n = 11), positive lymph node status (n = 9), balloon symmetry problem (n = 4), lobular histology (n = 3), adverse event (n = 2), large tumour size (n = 1), vascular involvement (n = 1). **Excellent/good cosmesis**: • All visits = 95.0% (1030/1084) • 3 months = 95.0% (717/755) • 9 months = 94.0% (346/368) • 12 months = 92.3% (229/248) • 18 months = 90.0% (63/70) • 24 months = 94.7% (18/19) Factors associated with good/excellent cosmetic result: skin spacing (≥ 7 mm versus < 7 mm, p = 0.0001), larger bra size (C and D cup size versus A and B cup size, p = 0.0074), absence of infection (p = 0.0349). **To date, one local recurrence has been reported (0.1%).**	**Breast infection = 8.1% (92/1140)** **Device-related infection = 5.3% (60/1140)** (no variable was associated with an increased risk of developing infection, including open vs closed cavity, systemic chemotherapy, length of implantation, time of enrollment onto trial [before or after treatment]). **Radiation recall reaction** (skin reaction occurring when chemotherapy is administered shortly after radiation treatment) = 3.4% (15/442) (described as minimal for one patient, moderate for eight patients, severe for two patients and unknown in four patients).	Mammosite registry trial. The study involved 223 different investigators at 87 sites. The trial was initially sponsored by the manufacturer and then the American Society of Breast Surgeons assumed management in 2003. Patients were enrolled at various times (before, during and after treatment). 98.9% (1403/1419) of patients enrolled in the study were implanted with the balloon device. Reasons for not implanting the device include positive lymph node status, patient request, lobular histology. 43 patients were treated with boost therapy and were not included in the analysis. Patients were not enrolled prospectively and there may have been some selection bias (subset analysis of 56 patients enrolled prior to treatment demonstrated no statistically significant differences in measures of efficacy).

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Benitez PR (2007)[10] **Case series (prospective)** USA Study period: 2000–2001 **n = 70** Population: patients with early-stage invasive ductal breast cancer Inclusion criteria: age ≥ 45 years, unifocal invasive ductal carcinoma, tumour size ≤ 2 cm, absence of extensive intraductal component, cavity size ≥ 3 cm in one dimension, node-negative, final margins negative. Placement of the balloon catheter had to be within 10 weeks of final lumpectomy procedure. Exclusion criteria: pure intraductal carcinoma, lobular histology, collagen vascular disease. Technique: balloon brachytherapy using MammoSite™ device (RTS Cytyc Corp). Balloon placement could be done either by open cavity or closed cavity technique. CT imaging was used after device placement to determine conformance and final eligibility for treatment. HDR source was used and treatment continued for 5 days. **Mean follow-up for 36 patients with long-term follow-up (months) = 60.6 (range 28–74)** Disclosure of interest: none stated	**The catheter could not be placed in 22.9% (16/70) of patients** (due to cavity size not amenable to balloon placement in 10, ineligible by criteria in 4, skin spacing in 2). **Of the patients implanted, 79.6% (43/54) were successfully treated.** Reasons for catheter explantation in 11 patients: poor cavity conformance (n =7), inadequate skin spacing (n = 2), positive node (n = 1), age < 45 years (n = 1). **No local or regional recurrences have occurred.** **No patient has developed a contralateral breast cancer.** **Good/excellent cosmetic outcome at last follow-up (median follow-up 62.8 months, mean 58 months) = 81.3%** In the 36 patients with longer follow-up, cosmetic outcomes were stable or improved with good/excellent results in 83.3% of patients (median follow-up = 62.4 months, mean 60.6 months). Increased skin spacing improved cosmetic outcomes, with statistical significance as a continuous variable (p = 0.0248). **100% of patients rated their satisfaction as good or excellent.**	**Toxicities in all treated patients** • Infection = 9.3% (4/43) (including severe mastitis in one patient and one abscess) • Seroma formation = 32.6% (14/43) (50% with open and 17.4% with closed placement, all resolved by 36 months) 'Only a small number were symptomatic and required aspiration'. • Asymptomatic fat necrosis = 9.3% (4/43) (none requiring surgical correction) • Telangiectasia = 39.5% (17/43) • Retraction of the breast or nipple = 20.9% (9/43) Both telangiectasia and retraction occurred more frequently in patients with skin spacing < 7 mm vs ≥ 7 mm (p = 0.0422 and 0.0458 respectively). The authors note that the only serious adverse events related to the device were mastitis and abscess (one case each).	Prospective enrolment. Same study centre as Vicini FA et al, 2005. The patients were, however, recruited during an earlier period. Multi-institution study. Of the 43 treated patients, seven have been discontinued from follow-up (three deceased, two have been placed in hospice and two lost to follow-up).

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Chao KK (2007)[11] **Case series (prospective)** USA Study period: 2000–2006 **n = 80** Population: patients with stage 0–II breast cancer Inclusion criteria: stage 0–II breast cancer, recommended minimal clear margin of ≥ 2 mm, age > 40 years, final tumour size ≤ 3.0 cm, metastatic involvement of ≤ 3 axillary lymph nodes. Technique: Balloon brachytherapy using MammoSite™ device (RTS Cytyc Corp). Balloon placement could be done either by open cavity or closed cavity technique (postoperatively). CT imaging was used after device placement to determine conformance and final eligibility for treatment. HDR source was used and treatment continued for 5 days. **Mean follow-up (months) = 25.8 (range 3–72)** Disclosure of interest: none stated	**Ipsilateral breast tumour recurrence = 2.5% (2/80)** (median time to recurrence = 9.6 months) **3-year actuarial rate of ipsilateral breast tumour recurrence = 2.9%** **No patients developed any regional nodal failure.** **3-year actuarial rate of distant metastasis = 95.8%** **3-year actuarial rate of disease-free survival = 95.8%** **3-year actuarial rate of overall survival = 91.3%** **3-year actuarial rate of overall survival for patients with invasive breast cancer = 88.1%** **3-year actuarial rate of overall survival for patients with noninvasive breast cancer = 100%** **Good/excellent cosmesis** • 6 months = 98.5% (64/65) • 12 months = 96.9% (62/64) • 24 months = 97.2 % (35/36) • 36 months = 88.2% (15/17) • 48 months = 100% (8/8)	Complications in all patients • Seroma = 45% (36/80) • Symptomatic seroma = 10% (8/80) • Fat necrosis = 8.8% (7/80) • Infection during radiotherapy = 11.3% (9/80) • Late infection = 3.8% (3/80) • Pain requiring analgesia = 55.7% • Chronic pain (> 1-year follow-up) = 5% (4/80) Complications in open-cavity placements • Seroma = 61.1% (22/36) • Symptomatic seroma = 13.9% (5/36) • Fat necrosis = 8.3% (3/36) Complications in closed-cavity placements • Seroma = 31.8% (14/44) • Symptomatic seroma = 6.8% (3/44) • Fat necrosis = 9.1% (4/36) The development of a breast infection was associated with the development of a symptomatic seroma.	Same study centre as Vicini FA et al, 2005. There may be some patient overlap, but this study has longer follow-up. Multi-institution study. 3.8% (3/80) of patients were lost to follow-up.

Table 2b Summary of key efficacy and safety findings on brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision (study identified after consultation period)

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**

Abbreviations used: CI, confidence interval; HDR, high dose rate; LDR, low dose rate; RT, radiotherapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Vicini FA (2008)[13] **Case series** USA Study period: 2002–2004 **n = 1440 patients (1449 cases)** Population: patients with early stage breast cancer Median age (years) = 65.5 (range 32–94) Ductal carcinoma in situ = 13% Inclusion/exclusion criteria not stated. Technique: balloon brachytherapy using MammoSite™ device. **Median follow-up (months) = 30.1 (range 0–58.6)** Disclosure of interest: MammoSite Breast Brachytherapy Registry trial was supported in part by a grant from Cytyc Corporation to the American Society of Breast Surgeons and BioStat International Inc.	**Ipsilateral breast tumour recurrence = 1.6% (23/1449)** **2-year actuarial rate of ipsilateral breast tumour recurrence = 1.04%** **2-year actuarial rate of disease-free survival = 95.8%** **2-year actuarial rate of overall survival = 97.3%** **2-year actuarial rate of overall survival for patients with invasive breast cancer = 97.1%** **2-year actuarial rate of overall survival for patients with noninvasive breast cancer = 98.7%** **Good/excellent cosmesis** • 12 months = 94.6% (927/980) • 24 months = 94.1 % (708/752) • 36 months = 93.1% (375/403) • 48 months = 92.5% (62/67) *Analysis of first 400 cases* **3-year actuarial rate of disease-free survival = 93.4%** **3-year actuarial rate of overall survival = 95.8%** **3-year actuarial rate of overall survival for patients with invasive breast cancer = 95.2%** **3-year actuarial rate of overall survival for patients with noninvasive breast cancer = 100%**	**Breast seromas = 23.9% (346/1449)** **Symptomatic breast seromas = 10.6% (153/1449)** **Fat necrosis = 1.5%**	Mammosite registry trial. Patients were enrolled at various times (before, during and after treatment). Patients were not enrolled prospectively and there may have been some selection bias (subset analysis of 51% of patients enrolled prior to treatment demonstrated no statistically significant differences in measures of efficacy). A lot of data were collected retrospectively and there may have been under-reporting of some toxicities.

Validity and generalisability of the studies

- All of the studies included highly selected subgroups of patients.
- Most of the studies only included patients above 35 years old.
- Five studies included only interstitial brachytherapy, three studies included only balloon brachytherapy and one included both.
- There were no randomised controlled trials of balloon brachytherapy.
- In one case series, patients were not recruited prospectively and they were not consecutive so there may have been some selection bias[9].
- In one non-randomised controlled trial, the control patients were treated during an earlier period than the accelerated partial brachytherapy patients. Survival in breast cancer patients is likely to have improved over this period[4].
- The authors of one paper have noted that there were less balloon-device related issues later on in the series as the investigators became more familiar with the technology[6].
- Three studies included patients with ductal carcinoma in-situ[5,9,11].

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.
Professor D Dodwell, Dr D Lee, Professor J Yarnold (Royal College of Radiologists)

Professor S Heys, Mr S Nicholson (British Association of Surgical Oncology)

Mrs A Snee (Society of Radiographers)

- Four Specialist Advisers consider the procedure to be definitely novel and of uncertain safety and efficacy. One Adviser considered it to be the first in a new class of procedure. One Specialist Adviser considered the procedure to be established practice and no longer new.
- An appropriate comparator would be whole breast external beam radiotherapy, with or without a local boost.
- Patient selection is important. One adviser suggested the following inclusion criteria: age>50 years old, invasive ductal carcinoma (?DCIS), less or equal to

2-3cm in size, no extensive DCIS associated with main tumour mass, negative microscopic margins ≥ 2mm, lymph node negative or 0-3 nodes involved.

- The multicatheter technique has been studied the most. Long-term data on toxicity and local control are limited for other methods of accelerated partial breast irradiation. The best modality of delivery is not yet defined.
- The key efficacy outcomes include local and regional recurrence rates, cancer specific mortality, cosmetic outcome, quality-of-life outcomes.
- Adverse events include erythema, infections, seroma formation, breast fibrosis, fat necrosis, skin telangiectasias, breast pain, breast oedema, hyperpigmentation and catheter failure.
- Two Advisers stated that the potential impact on the NHS is moderate and two stated that it was major, in terms of numbers of patients eligible for treatment and use of resources.

Issues for consideration by IPAC

- The literature search for this procedure returned over 900 results, a large proportion of which appeared relevant to this overview.
- This procedure was notified as accelerated partial breast irradiation, which is a more general term, including external beam radiation, brachytherapy and intraoperative radiation. NICE's Interventional Procedure Programme informal policy is that novel radiotherapy techniques are not currently in remit unless they are brachytherapy techniques (i.e. including implantation or insertion of radiotherapy implants).
- A pilot study on Mammosite® has been completed at Clatterbridge Centre for Oncology and a further five UK sites are currently participating in a phase II trial (FORUM – Feasibility of Breast Radiotherapy using Mammosite®). The trial will include 100 patients and recruitment is expected to be complete by the end of 2009.
- A large prospective randomised controlled trial is underway in the USA (National Surgical Adjuvant Breast Project [NSABP] B-39/Radiation Therapy Oncology Group [RTOG] 0413). The trial was begun in March 2005 and is

expected to recruit 4300 patients over 4.6 years. The trial will compare accelerated partial breast irradiation (interstitial brachytherapy, MammoSite or three-dimensional conformal external beam radiotherapy) with whole breast external beam radiation with or without a boost. The study will include patients aged ≥ 18 years with stage 0, 1, or 2 breast cancer resected by lumpectomy, tumour size ≤ 3.0 cm and no more than three histologically positive nodes. On histological examination, the tumour must be ductal carcinoma in situ or invasive adenocarcinoma of the breast.

- A European multicentre Phase III trial using interstitial brachytherapy started in May 2004 and is intending to recruit 1170 patients. The aim of the trial is to assess the role of brachytherapy alone compared to whole breast irradiation in a defined low-risk group of invasive breast cancer or ductal carcinoma in situ concerning local failure (all ipsilateral local recurrences) to affirm the hypothesis that local control rates in each arm are equivalent. Participating countries are Austria, Czech Republic, Germany, Hungary, Poland, Spain and Switzerland.
- There are a number of delivery systems available for brachytherapy and new devices are being developed.

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Appendix A: Additional papers on brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Arthur DW, Koo D, Zwicker RD et al. (2003) Partial breast brachytherapy after lumpectomy: low-dose-rate and high-dose-rate experience. International Journal of Oncology, Biology, Physics. 56: 681–9.	Case series 44 patients Median follow-up = 42 months Interstitial brachytherapy	All patients remained locally controlled. Overall rate of good/excellent cosmesis = 79.6% Good/excellent cosmesis with HDR = 90% LDR and adriamycin were significant predictors for late unfavourable cosmetic changes.	Larger studies are included.
Baglan KL, Martinez AA, Frazier RC et al. (2001) The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast-conserving therapy. International Journal of Oncology, Biology, Physics. 50: 1003–11.	Case series 37 patients Median follow-up = 31 months Interstitial brachytherapy	One ipsilateral breast recurrence (crude failure rate = 2.6%) No regional or distant failures. Three minor breast infections, all resolved with antibiotics. Good/excellent cosmesis = 100%	Larger studies are included.
Benitez PR, Chen PY, Vicini FA et al. (2004) Partial breast irradiation in breast-conserving therapy by way of interstitial brachytherapy. American Journal of Surgery 188: 355–64.	Case series 199 patients Median follow-up = 5.7 years Interstitial brachytherapy	Infection = 11% (22/199) (five required operative intervention). Fat necrosis at 5 years = 11% (22/199) The incidence of fat necrosis increased with time (most were asymptomatic). Five ipsilateral failures. 5-year actuarial local recurrence rate = 1.2% 5-year actuarial cause-specific survival rate = 99%	A more recent report from the same centre is included (Vicini et al, 2007).
Benitez PR, Streeter O, Vicini F et al. (2006) Preliminary results and evaluation of MammoSite balloon brachytherapy for partial breast irradiation for pure ductal carcinoma in situ: a phase II clinical study. American Journal of Surgery 192: 427–33.	Case series 100 patients Median follow-up = 9.5 months Balloon brachytherapy	Inadequate skin distance and poor cavity conformance were the main factors limiting the use of the balloon device. Good/excellent cosmesis = 98% Two ipsilateral breast recurrences. No serious adverse events were reported. Infection rate = 4%	Same study as Vicini et al, 2005.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Chao KK, Vicini FA, Wallace M et al. (2007) Analysis of treatment efficacy, cosmesis, and toxicity using the MammoSite breast brachytherapy catheter to deliver accelerated partial-breast irradiation: the William Beaumont Hospital experience. International Journal of Oncology, Biology, Physics. 69: 32–40.	Case series 80 patients Median follow-up = 22 months Balloon brachytherapy	3-year actuarial rate of ipsilateral breast tumour recurrences = 2.9%.	Same study centre as Benitez P et al, 2007 and Vicini F et al, 2005, which are included in table 2.
Chen PY, Vicini FA, Benitez P et al. (2006) Long-term cosmetic results and toxicity after accelerated partial breast irradiation: a method of radiation delivery by interstitial brachytherapy for the treatment of early-stage breast carcinoma. Cancer 106: 991–9.	Case series 199 patients Median follow-up = 6.4 years Interstitial brachytherapy	Breast pain, oedema, erythema and hyperpigmentation diminished over time. Breast fibrosis and hypopigmentation increased until the 2-year mark and then stabilised. Fat necrosis rate at 5 years = 11% Infection = 11% Good/excellent cosmesis = 95–99%	A more recent report from the same centre is included (Vicini et al, 2007).
Chen S, Dickler A, Kirk M et al. (2007) Patterns of failure after MammoSite brachytherapy partial breast irradiation: a detailed analysis. International Journal of Oncology, Biology, Physics. 69: 25–31.	Case series 78 patients Median follow-up = 26 months Balloon brachytherapy	Treatment failures in patients with > 6 month follow-up = 7% (5/70) Crude local failure rate = 5.7% (4/70) Estimated progression-free survival at 48 months = 89.8% Of 5 patients who failed, 2 would not have met standard criteria for partial breast irradiation treatment.	Study focuses on case reports of treatment failures.
Cuttino LW, Todor D, Arthur FW. (2005) CT-guided multi-catheter insertion technique for partial breast brachytherapy: reliable target coverage and dose homogeneity. Brachytherapy 4: 10–17.	Case series 77 patients Interstitial brachytherapy	CT guidance improved the percentage of patients satisfying all dosimetric goals from 42% to 93%.	Larger studies are included.
DeBiose DA, Horwitz EM, Martinez AA et al. (1997) The use of ultrasonography in the localization of the lumpectomy cavity for interstitial brachytherapy of the breast. International Journal of Oncology, Biology, Physics. 38: 755–9.	Case series 38 patients Interstitial brachytherapy	The authors conclude that ultrasonography appears to be a more accurate means of identifying the full extent of the lumpectomy cavity when compared to clinical estimates.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Dickler A, Kirk MC, Choo J et al. (2005) Cosmetic outcome and incidence of infection with the MammoSite breast brachytherapy applicator. The Breast Journal 11: 306–10.	Case series 30 patients Median follow-up = 13 months Balloon brachytherapy	Good/excellent cosmesis = 93.3% Infection rate = 13.3%	Larger studies are included.
DiFronzo LA, Tsai PI, Hwang JM et al. (2005) Breast conserving surgery and accelerated partial breast irradiation using the MammoSite system. Archives of Surgery 140: 787–94.	Case series 40 patients Mean follow-up = 13.3 months Balloon brachytherapy	Good/excellent cosmesis = 97% (39/40) Infection rate = 8% (3/40) 12% (5/40) devices were explanted because of unfavourable final pathological findings or infection.	Larger studies are included.
Dowlatshahi K, Snider HC, Gittleman MA et al. (2004) Early experience with balloon brachytherapy for breast cancer. Archives of Surgery 139: 603–8.	Case series 112 patients Follow-up = 1 to 6 months Balloon brachytherapy	Transient skin erythema = 25% (28/112) Localized oedema = 3% (3/112) Infection = 6% (7/112) In 4 patients, punctured or ruptured balloons had to be replaced.	Larger studies with longer follow-up are included.
Dragun AE, Harper JL, Jenrette JM et al. (2007) Predictors of cosmetic outcome following MammoSite breast brachytherapy: a single-institution experience of 100 patients with two years of follow-up. International Journal of Oncology, Biology, Physics. 68: 354–8.	Case series 100 patients Median follow-up = 24 months Balloon brachytherapy	Excellent cosmesis = 69% (62/90) Good cosmesis = 21% (19/90) 'Acceptable acute and late-term toxicity profiles.'	Larger studies are included.
Esserman LE, Da Costa D, d'Almeida M et al. (2006) Imaging findings after breast brachytherapy. American Journal of Roentgenology 187: 57–64.	Case series (retrospective review) 43 patients 27 interstitial, 16 balloon brachytherapy.	Mild to moderate skin thickening = 60% (26/43) Diffuse increased density = 2% (1/43) 35% (15/43) of patients had seroma or mass at first follow-up. Calcification = 19% (8/43)	Larger studies are included.
Evans SB, Kaufmann SA, Price LL et al. (2006) Persistent seroma after intraoperative placement of MammoSite for accelerated partial breast irradiation: incidence, pathologic anatomy, and contributing factors. International Journal of Oncology, Biology, Physics. 65: 333–9.	Case series 38 patients Median follow-up = 17 months Balloon brachytherapy	Overall rate of detectable seroma = 76% Persistent seroma (> 6 months) = 68.4% (26/38) (46% of these patients experienced at least modest discomfort at some point during follow-up) 3 patients required biopsy or complete cavity excision. Seroma was associated with a suboptimal cosmetic outcome.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Fentimann IS, Deshmane V, Tong D et al. (2004) Caesium^{137} implant as sole radiation therapy for operable breast cancer: a phase II trial. Radiotherapy and Oncology 71: 281–5.	Case series 50 patients Median follow-up = 6.3 years Interstitial brachytherapy	Patients alive without relapse = 80% Site of recurrence was in the index quadrant in 78% (7/9) cases of relapse. Good/excellent cosmesis = 81% (21/26)	Larger studies are included.
Hannoun-Levi JM, Houvenaeghel G, Ellis S et al. (2004) Partial breast irradiation as second conservative treatment for local breast cancer recurrence. International Journal of Oncology, Biology, Physics. 60: 1385–92.	Case series 69 patients Median follow-up = 50.2 months Interstitial brachytherapy	Patients with local breast recurrence were treated with lumpectomy and interstitial brachytherapy. Overall 5-year survival = 91.8% The authors concluded that the results were comparable to standard mastectomy.	Larger studies are included.
Harper JL, Jenrette JM, Vanek KN et al. (2005) Acute complications of MammoSite brachytherapy: a single institution's initial clinical experience. International Journal of Oncology, Biology, Physics. 61: 169–74.	Case series 37 patients Mean follow-up = 7 months Balloon brachytherapy	Operative wound complications = 8% (3/37) Wound infections = 16% (6/37) Seromas = 32% (12/37) Catheter failure due to leak = 5% (2/37) Balloon rupture = 8% (3/37) The authors note that there is a steep learning curve for this procedure.	Larger studies are included.
Jeruss JS, Vicini FA, Beitsch PD et al. (2006) Initial outcomes for patients treated on the American Society of Breast Surgeons MammoSite clinical trial for ductal carcinoma-in-situ of the breast. Annals of Surgical Oncology 13: 967–76.	Case series 169 patients Mean follow-up = 7.4 months Balloon brachytherapy	Patients with device-to-skin distance of ≥7 mm had the best cosmetic outcomes. Breast infections = 3% (5/169)	Same study as Vicini et al, 2005.
Kaufman SA, DiPetrillo TA, Price LL et al. (2007) Long-term outcome and toxicity in a phase I/II trial using high-dose-rate multicatheter interstitial brachytherapy for T1/T2 breast cancer. Brachytherapy 6: 286–92.	Case series 32 patients (33 breast cancers) Median follow-up = 83.9 months Interstitial brachytherapy	Actuarial local recurrence at 5 years = 6.1% Fat necrosis = 53% (17/32) Fat necrosis, pain and cosmesis appeared to improve with longer follow-up, whereas subcutaneous toxicity worsened.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Keisch M, Vicini F, Kuske R et al. (2003) Initial clinical experience with the MammoSite breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy. International Journal of Oncology, Biology, Physics. 55: 289–93.	Case series 43 patients Follow-up = 1 months Balloon brachytherapy	Two patients were explanted because of inadequate skin spacing and seven because of suboptimal conformance of the surgical cavity to the balloon. Good/excellent cosmesis at 1 month = 88%	Larger studies with longer follow-up are included.
Kuske RR, Winter K, Arthur DW et al. (2006) Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: toxicity analysis of RTOG 95-17. International Journal of Oncology, Biology, Physics. 65: 45–51.	Case series 99 patients Median follow-up = 2.7 years Interstitial brachytherapy	Grade 3 or 4 toxicity = 3% for HDR and 9% for LDR 'Acute and late toxicity was modest and acceptable.'	Larger studies are included.
Lawenda BD, Taghian AG, Kachnic LA et al. (2003) Dose-volume analysis of radiotherapy for T1N0 invasive breast cancer treated by local excision and partial breast irradiation by low-dose-rate interstitial implant. International Journal of Oncology, Biology, Physics. 56: 671–80.	Case series 48 patients Median follow-up = 23.1 months Interstitial brachytherapy (LDR)	Excellent/very good cosmesis = 91.8% 92% of patients were satisfied with cosmetic outcome. Perioperative complications: 2 bleeding, 2 abscesses, 1 haematoma, 1 non-healing sinus tract requiring surgical intervention. Significant fibrosis = 8% (4/48)	Larger studies are included
Lopchinsky, Giles KA. (2004) Recurrent abscess after MammoSite brachytherapy. The Breast Journal 10: 536–8.	Case report. Balloon brachytherapy.	Recurrent abscess developed after balloon brachytherapy. Almost 7 months elapsed before healing occurred.	Complication is mentioned in one of the included case series.
Lovey K, Fodor J, Major T et al (2007) Fat necrosis after partial-breast irradiation with brachytherapy or electron irradiation versus standard whole-breast radiotherapy – 4-year results of a randomized trial. International Journal of Oncology, Biology, Physics. 69: 724–31.	Randomised controlled trial.	4-year actuarial rate of fat necrosis: • all patients = 31.1% • whole breast irradiation = 31.9% • HDR brachytherapy = 36.5% • Partial breast electron irradiation = 17.7% Symptomatic fat necrosis: • whole breast irradiation = 8.5% • HDR brachytherapy = 11.4% • Partial breast electron irradiation = 7.5% Symptomatic fat necrosis was associated with a worse cosmetic outcome but asymptomatic fat necrosis was not.	A paper with a more comprehensive set of results from the same RCT centre is included (Polgar et al, 2007).

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Niehoff P, Polgar C, Ostertag H et al. (2006) Clinical experience with the Mammosite® radiation therapy system for brachytherapy of breast cancer: results from an international trial. Radiotherapy and Oncology 79: 316–200.	Case series 32 patients Mean follow-up = 20 months Balloon brachytherapy	72% (23/32) of patients were eligible for intracavitary brachytherapy. 3 cases of balloon rupture. 2 abscesses within 3 months of implantation, 10 cases of serious seroma formation. Erythema = 91% (21/23)	Larger studies are included.
Niehoff P, Ballardini B, Polgar C et al. (2006) Early European experience with the MammoSite radiation therapy system for partial breast brachytherapy following breast conservation operation in low-risk breast cancer. The Breast 15: 319–25.	Case series 54 patients Mean follow-up = 14 months Balloon brachytherapy	Seroma = 36% (16/44) Abscess = 4.5% (2/44) Skin discolouration/inflammation = 82% (36/44) Teleangiectasia = 18% (8/44)	Larger studies are included.
Ott OJ, Schulz-Wendtland R, Uter W et al. (2005) Fat necrosis after conserving surgery and interstitial brachytherapy and/or external beam irradiation in women with breast cancer. Strahlentherapie und Onkologie 181: 638–44.	Non-randomised comparative study 85 patients	Incidence of fat necrosis: • all patients = 15% • accelerated partial breast irradiation = 15% • whole breast external-beam = 20% • external beam combined with interstitial boost = 9% Interstitial brachytherapy does not lead to higher rates of fat necrosis, fibrosis or pain.	Study focuses on rates of fat necrosis.
Perera F, Yu E, Engel J et al. (2003) Patterns of breast recurrence in a pilot study of brachytherapy confined to the lumpectomy site for early breast cancer with six years' minimum follow-up. International Journal of Oncology, Biology, Physics. 57: 1239–46.	Case series 39 patients Median follow-up = 91 months Interstitial brachytherapy	5-year actuarial rate of ipsilateral breast recurrence = 16.2% Interval to recurrence ranged from 20 months to 58 months. Two contralateral breast recurrences (at 34 and 36 months).	Larger studies are included.
Polgar C, Major T, Somogyi A et al (1999) Sole brachytherapy of the tumor bed after breast conserving surgery: a new radiotherapeutic strategy for patients at low risk of local relapse. Neoplasma 46: 182–189.	Case series 44 patients Median follow-up = 20 months Interstitial brachytherapy	Excellent cosmesis = 100% 2.3% (1/44) local failure 2.3% (1/44) regional failure No distant metastasis Grade 2 radiation effects = 4.5% (2/44)	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Polgar C, Major T, Fodor J et al (2004) High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. International Journal of Oncology, Biology, Physics. 60: 1173–81.	Non-randomised controlled study 125 patients Median follow-up = 81 months (partial breast irradiation) and 83 months (whole breast RT)	Total ipsilateral breast failure: • interstitial brachytherapy = 6.7% (3/45) • whole breast RT = 11.4% (5/44) • whole breast RT + boost = 8.3% (3/36) The differences in 5-year and 7-year actuarial rates of ipsilateral breast recurrence were not statistically significant. There were no significant differences in relapse-free survival or cancer-specific survival. Excellent/good cosmesis: • interstitial brachytherapy = 84.4% • whole breast RT = 68.3%, p = 0.04	A RCT from the same study centre is included (Polgar et al, 2007).
Poti Z, Nemeskeri C, Fekeshazy A et al. (2004) Partial breast irradiation with interstitial ^{60}CO brachytherapy results in frequent grade 3 or 4 toxicity. Evidence based in a 12-year follow-up of 70 patients. International Journal of Oncology, Biology, Physics. 58: 1022–33.	Case series 70 patients Median follow-up = 12 years Interstitial brachytherapy	Study period = 1987–1992. Final study population = 34 patients Grade ≥ 2 radiation-induced toxicity = 97% (33/34) Grade ≥ 2 telangiectasia = 85% Fibrosis = 88% Fat necrosis = 41% Poor cosmetic results = 50% (17/34)	Larger studies are included with more recent study periods.
Richards GM, Berson AM, Rescigno J et al. (2004) Acute toxicity of high-dose-rate intracavitary brachytherapy with the MammoSite applicator in patients with early-stage breast cancer. Annals of Surgical Oncology 11: 739–46.	Case series 31 patients (32 breast cancers) Median follow-up = 11 months Balloon brachytherapy	25% bright erythema and patchy moist desquamation. Infection rate = 16% (5/32) Good/excellent cosmesis = 86%	Larger studies are included.
Soran A, Evrensel T, Beriwal S et al. (2007) Placement technique and the early complications of balloon breast brachytherapy. American Journal of Clinical Oncology 30: 152–5.	Case series 125 patients Median follow-up = 11 months (open technique and 5 months (percutaneous technique) Balloon brachytherapy	Catheter removed without the patient completing treatment = 13.6% (17/125) Complications with open technique: • Delayed abscess = 3% (2/74) • Persistent seroma = 30% (22/74) • Skin infection = 3% (2/74) • Balloon rupture = 6% (4/74) Complications with percutaneous technique: • Skin infection = 3% (1/34) • Balloon rupture = 3% (1/34) Good or excellent cosmesis = 95%	A larger study and one with longer follow-up are included.
Strnad V, Ott O, Potter R et al. (2004) Interstitial brachytherapy alone after breast conserving surgery: interim results of a German-Austrian multicenter phase II trial. Brachytherapy 3: 115–9.	Case series 176 patients Follow-up = 12 months Interstitial brachytherapy	All patients were disease free at follow-up. Perioperative breast infection = 0.6% (1/176) Grade 2 fibrosis = 7.0% (12/172) Grade 2/3 teleangiectasia = 1.2% (2/172) Good/excellent cosmesis = 92–95%	Same study centre as Ott OJ et al, 2007.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Tsai PI, Ryan M, Meek K et al. (2006) Accelerated partial breast irradiation using the MammoSite device: early technical experience and short-term clinical follow-up. The American Surgeon 72: 929–34.	Case series 51 patients Mean follow-up = 16 months Balloon brachytherapy	No ipsilateral breast recurrences. Two patients developed brain metastases and died. 9.8% (5/51) devices were explanted because of unfavourable final pathological findings or infection. Good/excellent cosmesis = 86% (44/51)	Larger studies are included.
Wazer DE, Berle L, Graham R et al. (2002) Preliminary results of a phase I/II study of HDR brachytherapy alone for T1/T2 breast cancer. International Journal of Oncology, Biology, Physics. 53: 889–97.	Case series 32 patients (33 breast cancers) Median follow-up = 33 months Interstitial brachytherapy	No peri- or postoperative infections. Clinically evident fat necrosis = 24% (8/33) Good/excellent cosmesis = 88% (29/33) One case of ipsilateral breast tumour recurrence 23 months after brachytherapy. 4-year actuarial recurrence rate = 3%.	Larger studies are included.
Wazer DE, Kaufman S, Cuttino L et al. (2006) Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. International Journal of Oncology, Biology, Physics. 64: 489–95.	Case series 75 patients Median follow-up = 73 months Interstitial brachytherapy	Good/excellent cosmesis = 91% The use of adriamycin-based chemotherapy after accelerated partial breast irradiation was found to be associated with a significant increase in the incidence of higher-grade skin toxicity, higher risk of fat necrosis and suboptimal cosmetic outcome.	Larger studies are included.
Zannis V, Beitsch P, Vicini F et al. (2005) Descriptions and outcomes of insertion techniques of a breast brachytherapy balloon catheter in 1403 patients enrolled in the American Society of Breast Surgeons MammoSite breast brachytherapy registry trial. American Journal of Surgery 190: 530–8.	Case series 1403 patients Balloon brachytherapy	Postoperative placement, after the final pathology report is issued, decreases the incidence of premature removal of the catheter because of disqualifying pathology. Good/excellent cosmesis = 95% One local recurrence (0.1%).	Same study as Vicini et al, 2005.

Appendix B: Related NICE guidance for brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision

Guidance	Recommendation
Interventional procedures	**High dose rate brachytherapy for carcinoma of the cervix. NICE interventional procedures guidance 160 (2006).** 1.1 Current evidence on the safety and efficacy of high dose rate brachytherapy for carcinoma of the cervix appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians should ensure that patients have appropriate counselling and pain management. In addition, use of the Institute's *Information for the public* is recommended (available from www.nice.org.uk/IPG160publicinfo). **High dose rate brachytherapy for prostate cancer. NICE interventional procedures guidance 174 (2006).** 1.1 Current evidence on the safety and efficacy of high dose rate (HDR) brachytherapy in combination with external-beam radiotherapy for localised prostate cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 A multidisciplinary team should be involved in the planning and use of this procedure. **Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedures guidance 201 (2006).** 1.1 Current evidence on the short-term safety of preoperative high dose rate brachytherapy for rectal cancer and its efficacy in reducing tumour bulk appears adequate. However, evidence about the advantages of the procedure as an adjunct to surgery and its effect on long-term survival is not adequate to support the use of this procedure without special arrangements for consent, audit and clinical governance. 1.2 Clinicians wishing to undertake preoperative high dose rate brachytherapy for rectal cancer should take the following actions. • Inform the clinical governance leads in their Trusts. • Inform patients, as part of the consent process, about the uncertainty of the procedure influencing their long-term survival, and provide them with clear written information. Use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG201publicinfo). • Audit and review clinical outcomes of all patients having preoperative high dose rate brachytherapy for rectal cancer (see section 3.1). 1.3 Further research will be useful, and clinicians are encouraged to

	enter patients into well-designed trials and to collect longer-term follow-up data. The Institute may review the procedure upon publication of further evidence. **Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedures guidance 132 (2005).** 1.1 Current evidence on the safety and short- to medium-term efficacy of low dose rate brachytherapy for localised prostate cancer appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Most of the evidence on the efficacy of low dose rate brachytherapy for localised prostate cancer relates to the reduction of prostate-specific antigen (PSA) levels and to biopsy findings. The effects on quality of life and long-term survival remain uncertain. Clinicians should ensure that patients understand these uncertainties and the alternative treatment options. Use of the Institute's *Information for the public* is recommended. 1.3 A multidisciplinary team should be involved in the planning and use of this procedure. The Institute has issued a cancer service guideline on *Improving Outcomes in Urological Cancers* (www.nice.org.uk/csguc). 1.4 Further research and audit should address quality of life, clinical outcomes and long-term survival. **Interstitial laser therapy for breast cancer. NICE interventional procedures guidance 089 (2004).** 1.1 Current evidence on the safety and efficacy of interstitial laser therapy for breast cancer does not appear adequate to support the routine use of this procedure. It is suitable for use only within good-quality research studies approved by a research ethics committee and with explicit patient consent. 1.2 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.

Technology appraisals	None
Clinical guidelines	A Clinical Guideline on early breast cancer is in development (final scope August 2006) – the scope includes radiotherapy (external beam and brachytherapy). The guideline is due to be published in January 2009.
Cancer service guidance	**Improving outcomes in breast cancer – manual update. Cancer service guidance (2002)**. **Radiotherapy** *Recommendations* Breast cancer site-specific groups should produce network-wide guidelines on the appropriate use of radiotherapy for patients with invasive or in-situ disease. Radiotherapy should be regarded as standard therapy for all women who have undergone breast conserving surgery, and should also be discussed with women who have had mastectomy. An additional boost dose of radiation to the tumour bed should be considered for younger women, particularly those below the age of 40. Radiotherapy may be given as adjuvant or neo-adjuvant treatment, or it may be used as the sole local treatment modality when surgery is inappropriate. The optimum fractionation level is currently unknown but the ongoing START trial is designed to answer this question.
Public health	None

Appendix C: Literature search for brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision

Database	Date searched	Version searched
Cochrane Library	30/11/2007	Issue 4, 2007
CRD databases (DARE & HTA)	26/11/2007	October, 2007
Embase	30/11/2007	1980 to 2007 Week 47
Medline	30/11/2007	1950 to November Week 2 2007
Premedline	30/11/2007	November 29, 2007
CINAHL	30/11/2007	1982 to November Week 4 2007
British Library Inside Conferences	30/11/2007	-
NRR	26/11/2007	Issue 4, 2007
Controlled Trials Registry	30/11/2007	-

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1.	Brachytherapy/
2.	brachytherap$.tw.
3.	(internal radiotherap$ or internal radiation therap$).tw.
4.	(intracavit$ radiotherap$ or intracavit$ radiation therap$).tw.
5.	(implant therap$ or implant radiation therap$).tw.
6.	(interstitial radiotherap$ or interstitial radiation therap$).tw.
7.	accelerated partial breast irradiation.tw.
8.	APBI.tw.
9.	or/1-8
10.	Breast Neoplasms/
11.	(breast$ adj3 (cancer$ or carcinoma$ or adenocarcinom$ or neoplasm$ or malignan$ or tumo?r$ or metasta$)).tw.
12.	Carcinoma, Ductal, Breast/
13.	Carcinoma, Intraductal, Noninfiltrating/
14.	((ductal or intraductal) adj3 (cancer$ or carcinoma$ or adenocarcinom$ or neoplasm$ or malignan$ or tumo?r$ or metasta$)).tw.
15.	DCI.tw.
16.	DCIS.tw.
17.	or/10-16

18.	9 and 17