# A report on
# radiotherapy following breast-conserving surgery in women with early invasive breast cancer for Universitätsklinikum Schleswig-Holstein/Campus Kiel

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| APBI | Accelerated partial breast irradiation |
| AEs | Adverse events |
| ASCO | American Society of Clinical Oncology |
| BCS | Breast conservation surgery |
| BSC | Best supportive care |
| CI | Confidence interval |
| CR | Complete response |
| CRD | Centre for Reviews and Dissemination |
| DARE | Database of Abstracts of Reviews of Effects |
| GIN | Guidelines International Network |
| Gy | Gray |
| HR-WBI | Hypofractionation of the Whole Breast |
| HRQoL | Health-related quality of life |
| HR | Hazard ratio |
| hrs | hours |
| HTA | Health technology assessment |
| IMRT | Intensity Modulated Radiotherapy |
| KSR Ltd | Kleijnen Systematic Reviews Ltd |
| mths | months |
| NA | Not applicable |
| NCCN | National Comprehensive Cancer Network |
| NHS | National Health Service |
| NHS EED | National Health Service Economic Evaluation Database |
| NICE | National Institute for Health and Care Excellence (UK) |
| NR | Not reported |
| OS | Overall survival |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| PICOS | Population, Intervention, Comparator, Outcome, and Study design |
| PB | Partial breast |
| RCT | Randomised controlled trial |
| RD | Reduced dose |
| SDM | Shared Decision Making |
| SRT | Standard-course Radiotherapy |
| UCLA | University of California, Los Angeles |
| UK | United Kingdom |
| WB | Whole breast |
| WHO | World Health Organization |
| wks | weeks |
| yrs | years |

# 1. PROJECT OBJECTIVES

## 1.1. GLOBAL AIM

A key aim of the research project “Making SDM a reality” is to create interactive websites to inform patients as part of shared decision making (SDM).

## 1.2. SPECIFIC OBJECTIVES

To describe the interventions available to patients aged 60 and over with invasive breast cancer who have undergone breast conserving surgery.

To present evidence on the effectiveness and efficacy of whole breast (WB) radiation, reduced dose (RD) radiation of the whole breast and partial breast (PB) radiation as well as treatment without radiation therapy.

# 2. METHODS

## 2.1. INCLUSION CRITERIA

The specific objectives underpinning the literature searches for this topic were developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. No needs assessment was provided for this review. Inclusion and exclusion criteria for this review are set out in Table 1.

Table 1: Radiotherapy following breast-conserving surgery: PICOS

| Item | Included | Excluded |
|---|---|---|
| **Populations** | Patients with invasive breast cancer<br>• >60 years of age<br>• pT1-2 (< 3 cm) cN0/pN0*<br>• ER pos./PR positive<br>• HER2negative<br>• G1-2**<br>• No further risk factors<br>• After breast conserving surgery<br>• Endocrine therapy is planned | • Radiation is contraindicated<br>• Adjuvant chemotherapy |
| **Interventions** | • **Whole breast (WB)** moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)<br>• **Reduced dose (RD)** moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/tumour bed: 40.05 Gy in 15 fractions for 3 weeks)<br>• **Partial breast (PB)** partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | |
| **Comparators** | • As above<br>• **No radiation** (more for patients >75 years of age) | |
| **Outcomes** | • Frequency of dosing; frequency/duration of radiotherapy sessions etc.<br>• Appropriateness<br>• All-cause mortality<br>• Cause-specific mortality<br>• Local recurrence (ipsilateral breast tumour recurrence)<br>• Time to return to usual activity<br>• Time off work/return to work<br>• Feelings/satisfaction<br>• Risks/side effects | |
| **Study designs** | • Systematic reviews<br>• Guidelines<br>• Other Shared Decision Making (SDM) tools<br>• Large single studies (where evidence gaps exist | Pre Jan 2015 |

| Item | Included | Excluded |
|---|---|---|
| | from other studies) | |
| **Subgroup** | Women more suitable to undergo partial breast radiation: free resection margin ≥ 2mm | |

*The TNM system is the most widely used cancer staging system. In the TNM system: The T refers to the size and extent of the main tumour. The main tumour is usually called the primary tumour. The N refers to the number of nearby lymph nodes that have cancer. The M refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumour to other parts of the body.

**Grading systems differ depending on the type of cancer. In general, tumours are graded as 1, 2, 3, or 4, depending on the amount of abnormality. In Grade 1 tumours, the tumour cells and the organization of the tumour tissue appear close to normal. Grade 2 tumours are moderately differentiated (intermediate grade)

## 2.2. FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

1. What does the treatment involve?
2. When is radiation appropriate?
3. Will I live longer?
4. Will my cancer come back?
5. How time-consuming will the treatment be?
6. How will I feel after radiation?
7. What are the risks/side effects?

## 2.3. LITERATURE SEARCHES

Literature searches were conducted on 8 and 9 October 2020 to identify systematic reviews and evidence-based guidelines about radiotherapy following breast conserving surgery in women with early invasive breast cancer. In addition to the formal searches, a targeted search was conducted to identify studies specifically about shared decision making in this population.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range to 2015-2020. Searches were not limited by language or publication status.

### *2.3.1. Systematic reviews and guidelines*

The following systematic review specific databases were searched from 2015:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 10 of 12, October 2020
- Database of Abstracts of Reviews of Effects (DARE) (CRD): 2015 to 31 Mar 2015
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): 2015 to 31 Mar 2018
- KSR Evidence (Internet) (https://ksrevidence.com/): 2015-8/10/2020
- Epistemonikos (Internet) (www.epistemonikos.org): 2015-8/10/2020

- INAHTA (internet) (https://database.inahta.org/): 2015-8/10/2020

The following guidelines resources were searched from 2015:

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 8 October 2020
- NICE Evidence (www.evidence.nhs.uk): 2015-8/10/2020
- NICE Guidance (www.nice.org.uk): 2015-8/10/2020
- ECRI Guidelines Trust (https://guidelines.ecri.org/): 2015-8/10/2020

The following sources were searched for SDM specific publications in this population:

- Embase (Ovid): 1974-2020/10/08
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid): 1946 to October 02, 2020
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 10 of 12, October 2020

Full details of all search strategies are presented in Appendix 1.

#### *2.3.2. Handling of citations*

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

#### *2.3.3. Supplementary searches*

For this evidence report, searches for systematic reviews and guidelines were supplemented by targeted web searches to find information for the more narrative aspects of FAQs. The bibliographies of included studies and review articles were also checked for additional relevant articles.

### 2.4. STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Two reviewers independently screened the title and abstract of each record identified by the searches and determined the potential relevance of each record. For potentially relevant records, the full paper was obtained, independently checked, and inclusion criteria applied. Any disagreements were resolved through discussion.

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence tables. Where more than one study could provide evidence, the most relevant studies were selected using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations which are representative of the target population or sub population preferred). Where there were gaps in the evidence (no systematic review or guideline available), as described in the study design section of the PICOS, relevant randomised controlled trials (RCTs) were searched for and extracted.

### 2.5. DATA SYNTHESIS

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus. Where necessary, primary studies reported in systematic reviews were checked to determine if they reported any additional evidence for

outcomes that were not reported in secondary sources (i.e. evidence gaps). Where data permitted, risk ratios were calculated (when not available in the source document).

Where data were only reported as a pictorial figure (e.g. Figure 2 in this report), the figure was extracted to Microsoft Paint ensuring that exactly 50 'arrow keys' of movement were required to move from one line to another. This enabled calibration of the data which were then converted to the number of patients, from which relative risks were calculated using Review Manager 5.4.1 and presented as a three-way analysis (see Table 15 of this report).

# 3. RESULTS

## 3.1. LITERATURE SEARCHES AND INCLUSION ASSESSMENT

A total of 840 records were retrieved from literature searches. After de-duplication, 618 titles and abstracts were screened by two reviewers. Thirty-four full papers, including one record provided by the commissioner and three records retrieved through reference checking, were identified as potentially relevant. After further review, 29 records were excluded. A total of five studies (one systematic review, one guideline and three randomised controlled trials (RCTs)) were included. A summary of the study selection process according to a modified PRISMA flow chart is reported in Figure 1.

## 3.2. OVERVIEW OF INCLUDED STUDIES

Seven frequently asked questions (FAQs, see section 2.2) of most relevance were compiled and inclusion/exclusion criteria drawn up, through consultations with the commissioner, and scoping of available evidence, to develop a comprehensive body of evidence to answer the FAQs. Through subsequent searching and screening, five papers were identified as key sources of evidence. Systematic reviews, guidelines, RCTs and their associated interventions, are summarised in Table 2. Table 3 provides details of excluded and de-prioritised studies, respectively. The three studies which were deprioritised included results from the IMPORT LOW trial but did not include any relevant information not already reported by Coles 2017[1] or Bhattacharya 2019[2].

Figure 1: PRISMA flow diagram for radiotherapy after breast surgery

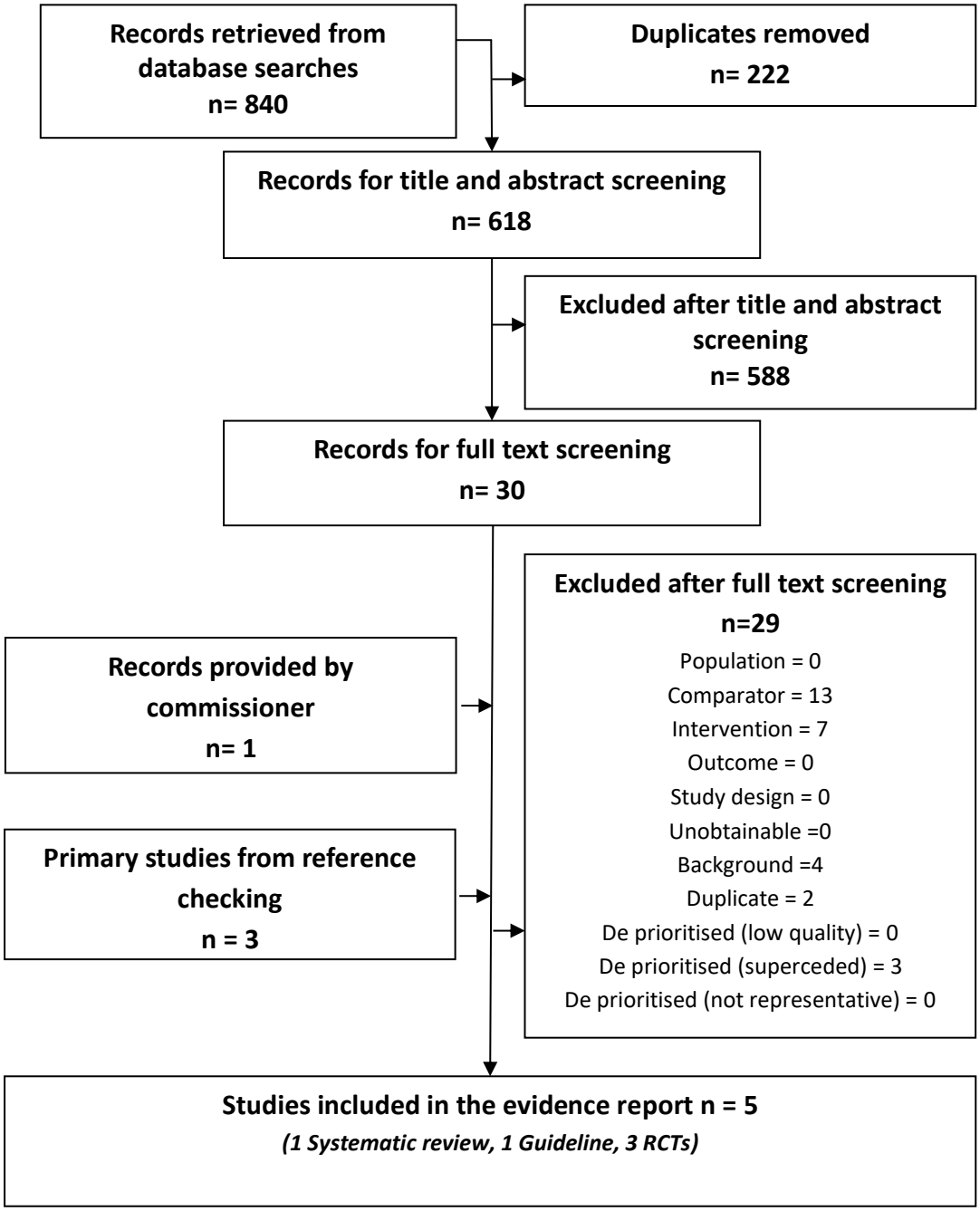


Table 2: Included studies

| Trial Name | Main paper | Other Paper | Source Type | WB | RD | PB | No radiation | FAQs |
|---|---|---|---|---|---|---|---|---|
| NA | Hickey 2016[3, 4] | | Systematic Review | Yes | No | Yes | No | 1,5 |
| NA | Leitlinienprogramm Onkologie 2020[5] | | Guideline | Yes | Yes | Yes | Yes | 2 |
| IMPORT LOW | Coles 2017[1] | Bhattacharya 2019[2] | RCT | Yes | Yes | Yes | No | 1,3,4,7 |
| PRIME II | Kunkler 2015[6] | | RCT | Yes | No | No | Yes | 1,3,4,7 |
| RAPID† | Whelan 2019[7] | Hickey 2016[3, 4] | RCT | Yes | No | Yes | No | 1,3,4,7 |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**RCT** Randomised Control Trial
**NA** Not Applicable
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

### *3.2.1 Trials*

The trials which contributed evidence to this review are summarised below. It should be noted that none of the trials matched the age criterion (i.e.>60 years of age) as set out in Table 1 of this review. Additionally, PRIME II included 3% of patients with Grade 3 or unknown Grade. Nevertheless, the evidence from these trials is the most relevant that could be identified.

**IMPORT LOW**

IMPORT LOW is a multicentre, randomised controlled, phase 3, non-inferiority trial done in 30 radiotherapy centres in the UK. Women aged 50 years or older who had undergone breast conserving surgery for unifocal invasive ductal adenocarcinoma of grade 1–3 were randomly assigned (1:1:1) to receive 40 Gy whole breast radiotherapy (control), 36 Gy whole breast radiotherapy and 40 Gy to the partial breast (reduced dose group), or 40 Gy to the partial breast only (partial breast group) in 15 daily treatment fractions.[1]

**PRIME II**

PRIME II is a multicentre, randomised controlled, phase 3 trial undertaken in 76 radiotherapy centres in four countries. Women aged 65 and over with grade 1 and 2 tumour plus those with grade 3 tumour histology or lymphovascular invasion (but not both) were recruited. Eligible patients were randomly assigned to either whole breast radiotherapy (40–50 Gy in 15–25 fractions) or no radiotherapy.[6]

**RAPID**

RAPID is a multicentre, randomised controlled, phase 3, non-inferiority trial done in 33 cancer centres in Canada, Australia and New Zealand. Women aged 40 years or older with

ductal carcinoma in situ or node-negative breast cancer treated by breast conserving surgery were randomly assigned (1:1) to receive either external beam Accelerated partial breast irradiation (APBI) (38·5 Gy in 10 fractions delivered twice per day over five to eight days) or whole breast irradiation (42·5 Gy in 16 fractions once per day over 21 days, or 50 Gy in 25 fractions once per day over 35 days).[7]

Table 3: Excluded studies

| Study | Main exclusion reason |
|---|---|
| Huang 2017[8] | Intervention/Comparator- Did not include the specified comparison between two or more of:<br>• **Whole breast (WB)** moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)<br>• **Reduced dose (RD)** moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks.<br>• **Partial breast (PB)** partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)<br>• **No radiation** |
| Nilsson 2015[9] | |
| Valle 2017[10] | |
| Liu 2017[11] | |
| Andrade 2019[12] | |
| Budach 2015[13] | |
| Marta 2015[14] | |
| Smith BD 2018[15] | |
| Sardar 2017[16] | |
| Koukourakis 2015[17] | |
| Kindts 2017[18, 19] | |
| Hickey. B. 2016[20, 21] | |
| Vicini 2019[22] | |
| Garg 2018[23] | |
| Harness 2018[24] | |
| Jayasekera 2018[25] | |
| Kanda 2020[26] | |
| Henson 2016[27] | |
| Matuschek 2016[28] | |
| Matuschek 2017[29] | |
| Nicholas Zdenkowski 2016[30] | Background- Information did not meet the PICOS criteria and was utilised for background information only. |
| Royal College of Radiologists 2017[31] | |
| Royal College of Radiologists 2019[32] | |
| Yang 2017[33] | |
| Smith 2018[34] | Duplicate |
| Bhattacharya 2019[2] | |
| Korzets 2019[35] | Deprioritised - superseded |
| Marta 2019[36] | |
| Haussmann 2020[37] | |

### 3.3. FAQ1: What does the treatment involve?

Breast cancer is the most common form of cancer in women, with approximately 69,000 new cases diagnosed each year within Germany.[38] Advanced breast cancer usually requires a combination of treatments, which may include surgery (mastectomy), chemotherapy, radiotherapy, hormone therapy and/or targeted immunotherapies. In patients with early stage breast cancer, trials have demonstrated equivalent survival when comparing

mastectomy to breast conserving surgery (lumpectomy) plus adjuvant radiotherapy.[7, 39] As a result, this approach has become the preferred method of treatment in patients with early stage breast cancer.[40] That being said, radiotherapy treatment is not suitable for all patients. For example, consensus has yet to be reached regarding whether radiotherapy should be used in older patients following breast conservation surgery (BCS) due to uncertainty around the mortality benefit in this population.[41]

BCS involves excision of the tumour along with a small margin of surrounding normal tissue (Tailby 2017[39]). To maximise the probability of success, several criteria should be met prior to undertaking BCS, such as the tumour being of small size (T1-2, preferably <3 cm diameter), localised (no signs of spread to lymph nodes or presence of isolated tumour cells (cN0/pN0)), and either well differentiated or moderately differentiated (G1-2).[1]

Whole breast external radiation is commonly administered following BCS, in which two opposing tangential fields apply radiation directly to the breast, which may or may not include irradiation of the underlying chest wall and lower axilla. The patient first undergoes a chest CT scan in order to define the area on which the radiation will be focused. The patient is then required to lay still on a table while radiation is beamed directly at the target area.[42] Generally this process occurs daily (except for weekends) over a period of three or more weeks.

In conventional fractionated radiation, doses of 45 to 50 Gy are delivered in 25 fractions of 1.8 to 2.0 Gy per fraction over the course of five to six weeks.[7] This may be followed by boost irradiation, in which an additional dose of 10 to 16 Gy are applied in five to eight fractions directly to the tumour bed.[7]

More recently, hypofractionated methods of irradiation have demonstrated equivalent success to conventional fractionated radiation with the benefit of reducing associated radiation induced toxicities, such as oedema, skin desquamation and pain.[1, 43] Although several variations exist, all methods of hypofractionated radiation involve the delivery of large doses of radiation in fewer yet larger daily fractions. This results in both significant reductions in treatment schedule and an improved therapeutic index by improving tumour control while decreasing normal tissue damage. [44]

Standard hypofractionation of the whole breast (HF-WBI) involves the administration of a total dose of 40-42 Gy delivered in 15 or 16 fractions over a period of three weeks.[40] This is referred to as **whole breast (WB)** in this review. An alternative method, hypofractionation of the partial breast, has been facilitated through the development of advanced imaging technologies.[45] Various methods can be used to deliver partial breast irradiation, including 3D conformal radiotherapy, intensity modulated radiotherapy (IMRT) or truncated opposing tangential fields.[1] This is referred to as **partial breast (PB)** in this review. This differs from WB in that the tangential fields are shortened, focussing the energy directly to the tumour bed and immediately adjacent tissue. Because PB results in a lower exposure of surrounding organs and tissue, a higher dose can be delivered in each fraction; for example, treatment

schedules may consist of a total dose of 38-40 Gy being administered in only 10 fractions over a period of two weeks.[1]

Another variation of hypofractionated irradiation involves the administration of lower dose radiation to the whole breast of 36 Gy with an additional 40 Gy administered directly to the tumour bed in 15 fractions[1] and studies involving schedules of even greater intensification with higher dose fractions are presently underway.[46] This is referred to as **reduced dose (RD)** in this review. Although adjunctive hypofractionated irradiation is generally the preferred treatment following breast conservation surgery, the benefits and harms of different doses and schedules may vary.[46]

### 3.4. FAQ2: When is radiation appropriate?

According to the German guideline, Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, radiation therapy of the affected breast should be done after BCS due to invasive tumour.[5] For some patients (a) life expectancy <10 years, b) with small tumours (pT1), c) without affected lymph nodes (pN0), d) hormone receptor positive and HER2 negative undergoing endocrine adjuvant therapy, e) clear merging around the tumour) a decision against radiation therapy could be made following individual consultation and accepting a higher risk of local recurrence.[5]

### 3.5. FAQ3: Will I live longer?

Data were compiled from three trials to provide evidence of survival following treatment after reconstructive breast surgery. No difference was observed at five year follow-up for patients treated with WB, RD or PB in the IMPORT LOW trial.[1] Similarly , no differences were observed between WB and no radiation in the PRIME II trial [6] or WB and PB in the RAPID trial [7] See Table 4 for details.

Mortality from breast cancer was noticeably higher for patients not treated with radiation compared to those treated with WB in the PRIME II trial.[6] No difference was observed in breast cancer mortality between WB and PB in the RAPID trial[7] See Table 5 for details. However, for other cancers WB was associated with notably fewer deaths (1.6%) than PB (3.0%) in the same study.[7] See Table 6 for details.

Death from cardiac disease was reported in the PRIME II and RAPID trials but no differences were observed between WB and no radiation in PRIME II[6] or WB and PB in RAPID[7]. See Table 7 for details.

Table 4: All-cause mortality

| Source | Median follow-up time (years) | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|---|
| IMPORT LOW _Coles 2017[1] | 5 | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 674 | 40 (6%) | Hazard ratio | 1 | No diff |
| | | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 673 | 39 (6%) | | 0.97 (0.62, 1.50) | |
| | | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 669 | 37 (6%) | | 0.91 (0.58, 1.42) | |
| PRIME II_Kunkler 2015[6] | 5 | WB | 40–50 Gy in 15–25 fractions | 658 | 40 (6.1%) | P value | 0.34 | No diff |
| | | No radiation | NA | 668 | 49 (7.3%) | | | |
| RAPID[†]_Whelan 2019[7] | 5 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 64 (6.0%) | Hazard ratio | 1 | No diff |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 76 (7.1%) | | 1.18 (0.84, 1.64) | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NA** Not applicable, **CI** = confidence interval, **No diff** = no statistical difference.
[†] Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

Table 5: Cause-specific mortality, breast cancer

| Source | Median follow up time (years) | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|---|
| PRIME II_Kunkler 2015[6] | 5 | WB | 40–50 Gy in 15–25 fractions | 658 | 4 (0.6%) | Risk ratio | RR* 0.51 (0.15, 1.68) | No diff |
| | | No radiation | NA | 668 | 8 (1.2%) | | | |
| RAPID† _Whelan 2019[7] | 5 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 16 (1.5%) | Risk ratio | RR* 0.89 (0.46, 1.74) | No diff |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 18 (1.7%) | | | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NA** Not applicable, **NR** Not reported, **CI** = confidence interval, **No diff** = no statistical difference.
**RR*** Calculated from data in the paper
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

Table 6: Cause-specific mortality, other cancer

| Source | Median follow-up time (years) | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|---|
| RAPID† _Whelan 2019[7] | 5 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 17 (1.6%) | Risk ratio | RR* 0.53(0.30, 0.96) | Favours WB |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 32 (3.0%) | | | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NR** Not reported, **CI** = confidence interval, **No diff** = no statistical difference.
**RR*** Risk ratio calculated from data in the paper
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

Table 7: Cause-specific mortality, cardiac disease

| Source | Median follow-up time (years) | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|---|
| PRIME II_Kunkler 2015[6] | 5 | WB | 40–50 Gy in 15–25 fractions | 658 | 6 (0.9%) | Risk ratio | RR* 2.0 (30.51, 8.08) | No diff |
| | | No radiation | NA | 668 | 3 (0.4%) | | | |
| RAPID[†]_Whelan 2019[7] | 5 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 9 (0.8%) | Risk ratio | RR* 1.51 (0.54, 4.22) | No diff |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 6 (0.5%) | | | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NA** Not applicable, **NR** Not reported, **CI** = confidence interval, **No diff** = no statistical difference.
**RR*** Risk ratio calculated from data in the paper
[†] Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

### 3.6. FAQ4: WILL MY CANCER COME BACK?

Data were compiled from three trials to provide evidence of relapse and recurrence following treatment after reconstructive breast surgery. No difference was observed for local relapse at five year follow-up for patients treated with WB, RD or PB in the IMPORT LOW trial.[1] Similarly, no differences in ipsilateral breast tumour (same side) recurrence were observed between WB and PB in the RAPID trial[7]. However, WB was associated with a reduced recurrence of ipsilateral breast tumour than no radiation in the PRIME II trial HR 5.19 [95% CI 1.99 – 13.52], Kunkler 2015.[6] Small numbers of patients were associated with regional recurrence (as reported in PRIME II and RAPID). [6 7] See Table 8 for details.

Data from the same three trials provided evidence on distant relapse/recurrence at five years. Whilst no statistical differences were reported between any of the treatments, a numerical advantage for distant recurrence at five years was observed for WB (0.5% of patients) compared to no radiation (1.0% of patients).[6] There is considerable uncertainty as to whether this constitutes a genuine difference in effect. See Table 9 for details.

Contralateral breast cancer events at five years were reported in PRIME II_Kunkler 2015[6] and RAPID_Whelan 2019.[7] Whilst no statistical differences were reported, WB was associated with more events (1.5% of patients) than no radiation (0.7% of patients) in PRIME II but more events (3.6% of patients) than PB (2.7% of patients) in RAPID. See Table 10 for details. There is considerable uncertainty as to whether these results constitute genuine differences in effect. IMPORT LOW reported on a composite of any breast cancer events at five years and found no difference between WB, RD and PB.[1] See Table 10 for details.

Non breast cancer events at five years were reported in PRIME II and RAPID. PRIME II_Kunkler 2015[6] reported 4.3% of patients in the WB arm having non breast cancer within five years compared to 3.7% of patients in the no radiation arm. There is considerable uncertainty as to whether this constitutes a genuine difference in effect. In RAPID,_Whelan 2019[7] reported 5.4% of patients in the WB arm having non breast cancer within five years compared to 7.9% of patients in the PB arm. This is a statistically significant difference. See Table 11 for details.

Table 8: Local relapse/recurrence

| Source | Median follow-up time (years) | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|---|
| **Local relapse** | | | | | | | | |
| IMPORT LOW _Coles 2017[1] | 5 | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 674 | 9 (1.3%) | Hazard ratio | 1 | No diff |
| | | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 673 | 3 (0.4%) | | 0.33 (0.09, 1.20) | |
| | | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 669 | 6 (0.9%) | | 0.65 (0.23, 1.84) | |
| **Ipsilateral breast tumour recurrence** | | | | | | | | |
| PRIME II_Kunkler 2015[6] | 5 | WB | 40–50 Gy in 15–25 fractions | 658 | 9 (1.3%) | Univariate Hazard ratio | 1 | WB |
| | | No radiation | NA | 668 | 27 (4.1%) | | 5.19 (1.99, 13.52) | |
| RAPID_Whelan 2019[7] | 8* | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 28 (2.6%) as first event | Hazard ratio* | 1 | No diff at 90% CI |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 37 (3.5%) as first event | | 1.27 (90% CI, 0.84, 1.91) | |
| **Regional recurrence** | | | | | | | | |
| PRIME II_Kunkler 2015[6] | 5 | WB | 40–50 Gy in 15–25 fractions | 658 | 3 (0.5%) | Risk ratio | RR* 0.38 (0.10, 1.43) | No diff |
| | | No radiation | NA | 668 | 8 (1.5%) | | | |
| RAPID[+]_Whelan 2019[7] | 5 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) | 1065 | 2 (0.2%) as first event | Risk ratio | RR* 0.50 (0.09, 2.74) | No diff |

| Source | Median follow-up time (years) | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|---|
| | | | based on criteria such as young age or close margins, pre-specified by centre | | | | | |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 4 (0.4%) as first event | | | |

* Hazard rate calculated on 8 years of data

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NA** Not applicable, **NR** Not reported, **CI** = confidence intervals, **No diff** = no statistical difference.
**RR*** Risk ratio calculated from data in the paper
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

Table 9: Distant relapse/recurrence

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| **Distant relapse at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 674 | 13 (1.9%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 673 | 10 (1.5%) | | 0.77 (0.34, 1.75) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 669 | 12 (1.8%) | | 0.92 (0.42, 2.03) | |
| **Distant recurrence at 5 years** | | | | | | | |
| PRIME II_Kunkler 2015[6] | WB | 40–50 Gy in 15–25 fractions | 658 | 3 (0.5%) | Kaplan-Meier estimates of survival | RR* 0.44 (0.11, 1.68) | No diff |
| | No radiation | NA | 668 | 7 (1.0%) | | | |
| RAPID† _Whelan 2019[7] | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 18 (1.7%) as first event | Risk ratio | RR* 0.90 (0.48, 1.70) | No diff |
| | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 20 (1.9%) as first event | | | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NR** Not reported, **CI** = confidence intervals, **No diff** = no statistical difference.
**RR*** Risk ratio calculated from data in the paper
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

Table 10: Other breast cancer events

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| **Contralateral breast cancer at 5 years** | | | | | | | |
| PRIME II_Kunkler 2015[6] | WB | 40–50 Gy in 15–25 fractions | 658 | 10 (1.5%) | Kaplan-Meier estimates of survival | RR* 2.03 (0.70, 5.91) | No diff but no radiation numerical advantage |
| | No radiation | NA | 668 | 5 (0.7%) | | | |
| RAPID† _Whelan 2019[7] | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 38 (3.6%) | Risk ratio | RR* 1.32 (0.82, 2.12) | No diff |
| | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 29 (2.7%) | | | |
| **Any breast cancer related event at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 674 | 33 (4.9%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 673 | 24 (3.6%) | | 0.72 (0.43, 1.22) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 669 | 33 (4.9%) | | 1.00 (0.62, 1.62) | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NR** Not reported, **CI** = confidence intervals, **No diff** = no statistical difference
**RR*** Risk ratio calculated from data in the paper
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

Table 11: Non breast second cancer

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| **Non-breast second cancer at 5 years** | | | | | | | |
| PRIME II_Kunkler 2015[6] | WB | 40–50 Gy in 15–25 fractions | 658 | 25 (3.7%) | Kaplan-Meier estimates of survival | RR* 0.91 (0.53, 1.54) | No diff |
| | No radiation | NA | 668 | 28 (4.3%) | | | |
| RAPID[†]_Whelan 2019[7] | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre | 1065 | 57 (5.4%) as first event | Risk ratio | RR* 0.68 (0.49, 0.94) | WB |
| | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1070 | 84 (7.9%) as first event | | | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NR** Not reported, **CI** = confidence intervals, **No diff** = no statistical difference
**RR*** Risk ratio calculated from data in the paper
[†] Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

### 3.7. FAQ5: How time-consuming will the treatment be?

Standard course radiotherapy (SRT) involves five to six weeks of daily radiation.[10] This can be a substantial investment of time and can create a logistical burden on the patients.[10] WB treatment is directly compared to PB, RD, and no radiation.[1, 6, 7] WB can comprise of doses between 40-50 Gy, which are delivered over the course of 15-25 daily fractions.[1, 6, 7] WB treatment is delivered once per day over the course of three to five weeks.[1, 6, 7] This may vary slightly due to the consideration of additional criteria such as the age of the patient, close margins, and other pre-specifications defined by the treatment centre.[7]

RD treatment is typically comprised of 40-42.5 Gy in 15 fractions.[1] This treatment is similar to WB treatment in that it can be delivered over a similar course of time of three weeks.[1] However, the RD treatment dose is noticeably lower than WB treatment.

PB can be delivered between 38-40 Gy at 10-15 fractions, which is a lower dose when compared to WB treatment. PB treatment can be administered twice per day between five to eight days.[7] However, it is noted that PB treatment doses are delivered with six hour gaps in between, which can create a longer daily treatment time for the patient.[7] Alternatively, PB treatment can be delivered over two weeks.[1]

Treatment times, as reported in the trials, are set out in Table 12 below. Of regimes involving radiation, PB requires less days than both WB and RD but with more treatment time within a day.

Table 12: Treatment times

| Source | Intervention | Dose | Treatment time |
|---|---|---|---|
| IMPORT LOW _Coles 2017[1] | WB | 40-42.5 Gy in 15-16 fractions for 3 weeks | 3 weeks |
| RAPID† _Whelan 2019[7] | | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) | Once per day over 3-5 weeks |
| PRIME II_Kunkler 2015[6] | | 40–50 Gy in 15–25 fractions | Over 3-5 weeks |
| IMPORT LOW _Coles 2017[1] | PB | 38-40 Gy in 10 fractions for 2 weeks | 2 weeks |
| RAPID† _Whelan 2019[7] | | 38.5 Gy/10 fractions bd (with 6 hour gap) | Twice per day over 5-8 days |
| | | | |
| IMPORT LOW _Coles 2017[1] | RD | 36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks | 3 weeks |
| PRIME II_Kunkler 2015[6] | No radiation | NA | NA |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NA** Not applicable
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

### 3.8. FAQ6: How will I feel after radiation?

According to the University of California Health Department of Radiation Oncology, fatigue is commonly experienced after radiation. Cancer treatment of any kind will generally require mental and physical effort.[47] However, continuation of normal daily activities can generally be expected with appropriate rest. The UCLA Health Department also note that feeling anxious, depressed, hopeless, or afraid is common and expressing these feelings with a friend, family member, psychologist, or support group is recommended.[47]

Patients were self-assessed to determine if an excellent or good cosmetic result was experienced in the RAPID trial.[7] Cosmetic results were derived from the Cancer Breast Cancer Cosmetic Rating System.[48] Characteristics (in terms of the size and shape of the breast, location of the areola and nipple, presence of telangiectasia (spider veins), appearance of the surgical scar) were graded on a four-point scale: 0=excellent or no difference, 1=good or small difference, 2=fair or moderate difference and 3=poor or large difference. Cosmetic results were reported as a composite of these elements. At baseline, 78% of the WB patients experienced an excellent or good cosmetic result, whereas this result was experienced in 76% of the PB patients. While no difference was identified at baseline or at the three year follow-up period, a more discernible difference was noted at the five and seven year follow-up period. At the five year follow-up point, 82% of WB patients experienced an excellent or good cosmetic result, whereas among the PB patients, 70% experienced this result. By the seven year follow-up point, 85% of WB patients experienced an excellent or good cosmetic result, while 69% of the PB patients experienced an excellent or good cosmetic result. Results are set out in Table 13.

According to the IMPORT LOW trial, patients reported experiencing shoulder stiffness, arm or shoulder pain, swollen arms or hands, and difficulties raising their arms.[1] Patients who received WB, RD, or PB reported similar experiences of shoulder stiffness between 13-14%.[1] Similar experiences of arm or shoulder pain were reported among patients who received WB, RD, or PB, which were between 23-24%.[1] Of the patients who received PB treatment, 4% reported experiencing swollen arms or hands.[1] Whereas, 5% and 6% of WB and RD treatment patients experienced swollen arms or hands.[1] WB and PB patients reported experiencing difficulty in arm raising between 10-11%.[1] However, only 6% of RD treatment patients reported difficulty in arm raising.[1] Depending on the level of severity, these experiences can impact when patients feel able to return to work or other daily activities. These findings are presented in more detail in section 3.9.

Table 13: Self-assessed feelings after radiation

| Source | Median follow-up time (years) | Intervention | Dose | N | No events (% of N) | > 10% between groups |
|---|---|---|---|---|---|---|
| **Excellent or good cosmetic result (patient self-assessment)** | | | | | | |
| RAPID† _Whelan 2019[7] | Baseline | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) | 1028 | 807 (78%) | No diff |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 1034 | 789 (76%) | |
| | 3 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) | 910 | 748 (82%) | No diff |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 963 | 711 (73%) | |
| | 5 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) | 816 | 702 (82%) | Favours WB |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 873 | 618 (70%) | |
| | 7 | WB | 50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) | 621 | 529 (85%) | Favours WB |
| | | PB | 38.5 Gy/10 fractions bd (with 6 hour gap) | 690 | 476 (69%) | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**No diff** = no statistical difference
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

### 3.9. FAQ7: WHAT ARE THE RISKS/SIDE EFFECTS?

Two studies reported data pertaining to the side effects of hypofractionated radiotherapy following breast conservation surgery. One study compared WB with PB.[7] The second study compared all three interventions (hypofractionation of the whole breast (WB), reduced dose hypofractionation of the whole breast + tumour bed boost (RD), and hypofractionated partial breast irradiation (PB)) and reported results across two publications.[1 2]

The study by Coles 2017[1] compared the results of all three treatments arms with regards to pain, swelling and sensitivity, stiffness and mobility impairment, and appearance (Table 14).

Results demonstrate a statistically significant improvement in patients treated with reduced dose (RD) and partial breast (PB) irradiation with regards to change in breast appearance (irradiated breast compared to the other side) at five years (HR 0.74 [95% CI 0.54 – 1] and HR 0.64 [95% CI 0.46 - 0.89], respectively) and breast hardness/firmness at five years (HR 0.53 [95% CI 0.36 – 0/79] and HR 0.47 [95% CI 0.32 – 0.71], respectively). Similar results were detected for adverse events at 5 years.

A statistically significant improvement was demonstrated when using PB compared to WB with regards to breast swelling at five years (HR 0.49 [95% CI 0.27 – 0.89]) and skin problems in breast at five years (HR 0.64 [95% CI 0.42 – 0.99]). No difference was observed for the RD group compared to WB or PB groups for these outcomes. No difference was detected for adverse events at 5 years for breast swelling and numbers affected were low at n=1,4 and 1 for WB, RD and PB respectively.

There were no differences between the three treatment groups with regards to breast size, shoulder stiffness, skin appearance, arm or shoulder stiffness, swelling of the hands or arms, difficulty in raising of arm, breast pain, or oversensitivity of breast at five years (Table 13).

The study by Bhattacharya 2019[2] pooled total adverse events reported within three assessment tools to provide a single composite outcome (see Figure 2 and Table 15). At six months after treatment, fewer patients in the RD group experienced one or more adverse events than patients within the WB group (RR 1.18 [95% CI 1.00, 1.38]), however due to potential imprecision in data calibration this is regarded as an insignificant difference. There were no differences between RD and PB groups.

At one year post-treatment, both RD and PB groups demonstrated statistically significant reductions in the number of patients experiencing one or more adverse events compared to WB (RR 1.20 [95% CI 1.02, 1.42] and RR 1.23 [95% CI 1.04, 1.45], respectively).

At five years post-treatment, PB demonstrated fewer patients experiencing one or more adverse events compared to WB (RR 1.20 [95% CI 1.00, 1.44]), however, this is regarded as an insignificant difference. In contrast to results at one year, RD did not show any statistically significant improvement over WB at five years.

The study by Whelan 2019[7] compared the incidence of adverse events between WB and PB patients during the acute post-treatment period (one to three months) and the late post-

treatment period (≥3 months) - see Table 16. During the acute period, patients treated with PB experienced significantly lower rates of radiation dermatitis, breast swelling and any acute toxicity; however these patients experienced significantly higher rates of all reported adverse events during the late period compared to patients who received WB (induration or fibrosis (hardening), telangiectasia (spider veins), breast pain, chest wall pain, fatty necrosis (lumpiness) and any late toxicity (side effects that occur more than 3 months after irradiation)).

Table 14: Risks and side effects as reported in Coles et al 2017

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| **Breast appearance changed cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 158 (38%) | Hazard ratio | 1 | Favours PB and RD |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 123 (28%) | | 0.74 (0.54, 1.00) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 113 (27%) | | 0.64 (0.46, 0.89) | |
| **Breast smaller cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 119 (29%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 110 (25%) | | 0.83 (0.59, 1.16) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 104 (25%) | | 0.78 (0.54, 1.11) | |
| **Breast harder or firmer cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 115 (28%) | Hazard ratio | 1 | Favours PB and RD |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 74 (17%) | | 0.53 (0.36, 0.79) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 58 (14%) | | 0.47 (0.32, 0.71) | |
| **Shoulder stiffness cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 56 (14%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy | 433 | 56 (13%) | | 0.93 (0.64, 1.35) | |

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| | | in 15 fractions for 3 weeks) | | | | | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 58 (14%) | | 1.06 (0.73, 1.54) | |
| **Skin appearance changed cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 63 (15%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 59 (14%) | | 1.07 (0.68, 1.68) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 49 (12%) | | 0.87 (0.54, 1.40) | |
| **Arm or shoulder pain cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 98 (24%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 104 (24%) | | 0.94 (0.71, 1.25) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 97 (23%) | | 0.97 (0.73, 1.28) | |
| **Swollen arm or hand cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 21 (5%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 26 (6%) | | 1.19 (0.67, 2.11) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 16 (4%) | | 0.59 (0.30, 1.15) | |
| **Difficulty raising arm cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 42 (10%) | Hazard ratio | 1 | No diff |

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 45 (10%) | | 0.98 (0.64, 1.50) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 47 (11%) | | 1.08 (0.71, 1.64) | |
| **Breast pain cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 67 (16%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 59 (14%) | | 0.96 (0.68, 1.35) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 54 (13%) | | 0.96 (0.68, 1.36) | |
| **Breast swollen cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 31 (8%) | Hazard ratio | 1 | Favours PB over WB |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 26 (6%) | | 0.84 (0.49, 1.41) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 17 (4%) | | 0.49 (0.27, 0.89) | |
| **Breast over sensitive cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 64 (16%) | Hazard ratio | 1 | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 59 (14%) | | 0.89 (0.62, 1.27) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 54 (13%) | | 0.80 (0.55, 1.14) | |

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| **Skin problems in breast cumulative at 5 years** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 411 | 50 (12%) | Hazard ratio | 1 | Favours PB over WB |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 433 | 42 (10%) | | 0.78 (0.52, 1.18) | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 421 | 35 (8%) | | 0.64 (0.42, 0.99) | |
| **Adverse events at 5 years: Breast appearance changed** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 295 | 80 (27%) | P value | NA | Favours PB and RD |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 325 | 66 (19%) | | 0·047 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 331 | 49 (15%) | | <0·0001 | |
| **Adverse events at 5 years: Breast smaller** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 294 | 66 (22%) | P value | NA | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 326 | 63 (19%) | | 0.373 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 331 | 56 (17%) | | 0.086 | |
| **Adverse events at 5 years: Breast harder or firmer** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 292 | 27 (9%) | | NA | Favours PB over WB |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 325 | 23 (7%) | | 0.376 | |

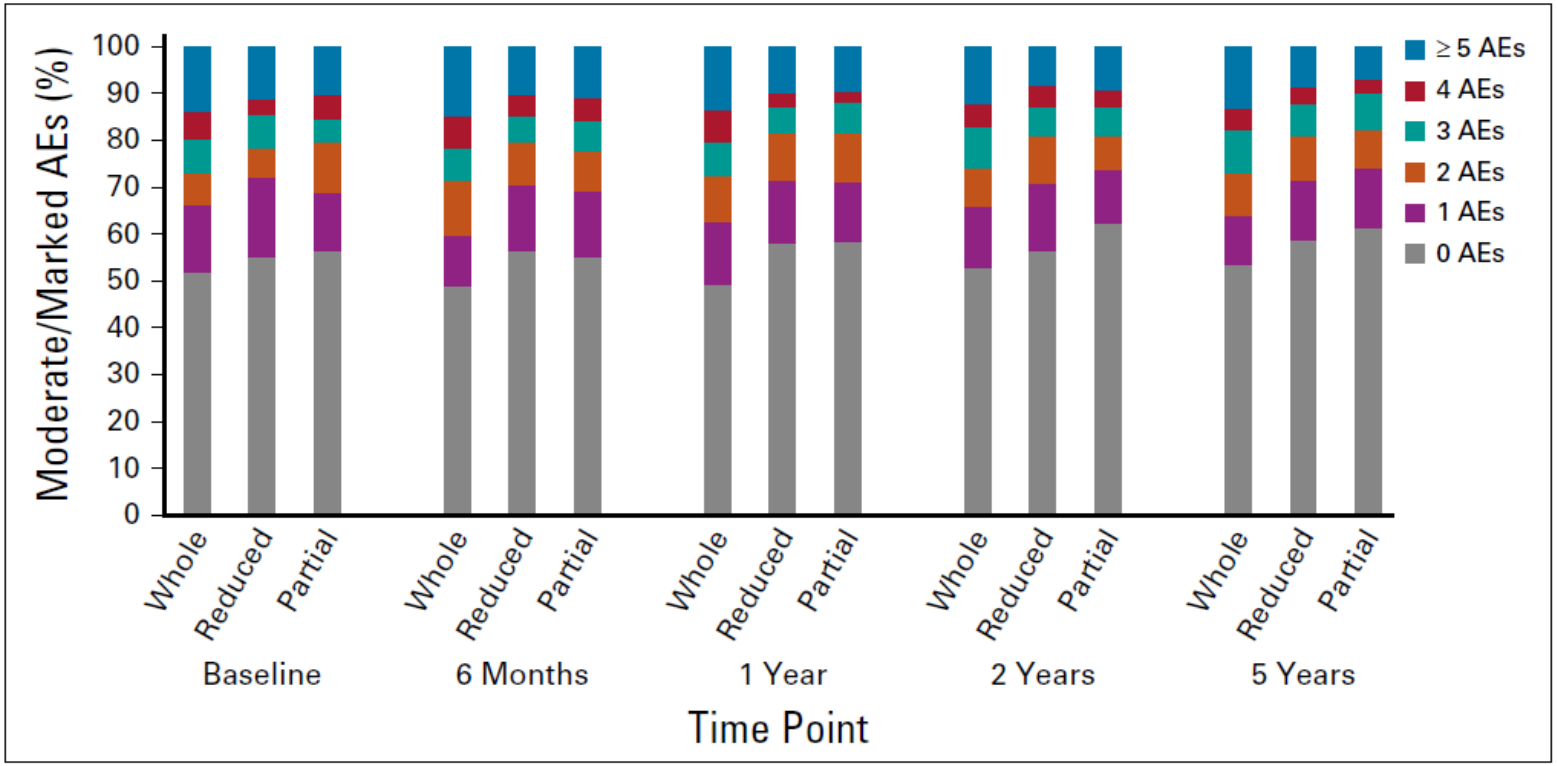
| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 330 | 15 (5%) | | 0.024 | |
| **Adverse events at 5 years: Shoulder stiffness** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 296 | 12 (4%) | P value | NA | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 328 | 23 (7%) | | 0.161 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 331 | 13 (4%) | | 0.999 | |
| **Adverse events at 5 years: Skin appearance changed** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 294 | 22 (7%) | P value | NA | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 325 | 23 (7%) | | 0.878 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 330 | 22 (4%) | | 0.051 | |
| **Adverse events at 5 years: Arm or shoulder pain** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 297 | 33 (11%) | P value | NA | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 329 | 43 (13%) | | 0.465 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 331 | 24 (7%) | | 0.097 | |
| **Adverse events at 5 years: Swollen arm or hand** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 295 | 5 (2%) | P value | NA | No diff |
| | RD | Moderate hypofractionated dose-reduced radiation of the | 330 | 15 (5%) | | 0.066 | |

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| | | whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | | | | | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 330 | 2 (1%) | | 0.264 | |
| **Adverse events at 5 years: Difficulty raising arm** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 297 | 10 (3%) | | NA | |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 328 | 17 (5%) | P value | 0.326 | No diff |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 331 | 15 (5%) | | 0.542 | |
| **Adverse events at 5 years: Breast pain** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 295 | 13 (4%) | | NA | |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 330 | 18 (5%) | P value | 0.584 | No diff |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 328 | 13 (4%) | | 0.842 | |
| **Adverse events at 5 years: Breast swollen** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 295 | 1 (<1%) | | NA | |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 329 | 4 (1%) | P value | 0.377 | No diff |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 328 | 1 (<1%) | | 0.999 | |
| **Adverse events at 5 years: Breast over sensitive** | | | | | | | |
| IMPORT LOW | WB | Moderate hypofractionated radiation of the whole breast | 296 | 9 (3%) | P value | NA | |

| Source | Intervention | Dose | N | No events (% of N) | Measure of Effect | Effect Size (95% CI) | Favoured |
|---|---|---|---|---|---|---|---|
| _Coles 2017[1] | | (40-42.5 Gy in 15-16 fractions for 3 weeks) | | | | | |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 330 | 16 (5%) | | 0.308 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 330 | 13 (4%) | | 0.665 | |
| **Adverse events at 5 years: Skin problems in breast** | | | | | | | |
| IMPORT LOW _Coles 2017[1] | WB | Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks) | 296 | 7 (2%) | | NA | |
| | RD | Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks) | 328 | 10 (3%) | P value | 0.632 | |
| | PB | Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) | 330 | 9 (3%) | | 0.806 | |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**NR** Not reported, **CI** = confidence intervals, **No diff** = no statistical difference

Figure 2: Summary of adverse events by grade




*Source: Bhattacharya 2019*[2]

Table 15: Patients experiencing one or more adverse events

| Outcome | Author | Follow-up | Estimates for WB | Estimates for RD | Estimates for PB | Outcome measure | Favoured |
|---|---|---|---|---|---|---|---|
| **No. of patients experiencing one or more Adverse events (composite)*** | IMPORT LOW _Bhattacharya 2019[2] | 6 months | 166/321 (51.6%) | 148/337 (43.8%) | | RR 1.18 (95% CI 1.00, 1.38) | No diff |
| | | | | | 155/342 (45.2%) | RR 1.14 (95% CI 0.98, 1.34) | No diff |
| | | | | 148/337 (43.8%) | | RR 0.97 (95% CI 0.82, 1.15) | No diff |
| | | 1 year | 156/307 (50.8%) | 141/333 (42.4%) | | RR 1.20 (95% CI 1.02, 1.42) | Favours RD |
| | | | | | 139/336 (41.4%) | RR 1.23 (95% CI 1.04, 1.45) | Favours PB |
| | | | | 141/333 (42.4%) | | RR 1.02 (95% CI 0.86, 1.22) | No diff |
| | | 5 years | 140/298 (47%) | 139/332 (41.8%) | | RR 1.12 (95% CI 0.94, 1.34) | No diff |
| | | | | | 130/333 (39%) | RR 1.20 (95% CI 1.00, 1.44) | No diff |
| | | | | 139/332 (41.8%) | | RR 1.07 (95% CI 0.89, 1.29) | No diff |

Source: Extracted and calibrated from Figure 3 of Bhattacharya 2019[2] (Figure 2 in this review)

* The composite outcome includes adverse events reported within the following assessments: Body Image Scale (BIS) assessment (self-conscious about appearance; less physically attractive as a result of disease/treatment; dissatisfied with appearance when dressed; less feminine as a result of disease/treatment; difficult looking at yourself naked; less sexually attractive; avoid people because of way you felt about appearance; disease/treatment has left body feeling less whole; have you been dissatisfied with your body?; dissatisfied with appearance of your scar), Protocol-specific (PS) item (appearance of skin in breast changed; overall appearance of breast changed; breast smaller; breast harder/firmer to touch; nipple position affected; problem getting bra to fit; shoulder stiffness), and Quality of Life Questionnaire Breast Cancer-Specific (QLQ-BR23) Module (pain in arm or shoulder; swollen arm or hand; difficulty raising arm or moving it sideways; breast pain; breast swollen; breast oversensitive; skin problems on breast).

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)

**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)

**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)

**RR** = risk ratio; **CI** = confidence intervals; **No diff** = no statistical difference.

Table 16: Risks and short-term effects in patients treated with whole breast or partial breast radiotherapy from Whelan 2019†

| Outcome | Author | Follow-up | Estimates for WB | Estimates for PB | Outcome measure | Favoured |
|---|---|---|---|---|---|---|
| **Radiation dermatitis** | Whelan 2019[7] | 1-3 months | 328/1065 (30.8%) | 102/1070 (9.5%) | RR 3.23 (95% CI 2.63, 3.97) | Favours PB |
| **Fatigue** | | | 151/1065 (14%) | 139/1070 (13%) | RR 1.09 (95% CI 0.88, 1.35) | No diff |
| **Breast swelling** | | | 91/1065 (8.5%) | 64/1070 (6%) | RR 1.43 (95% CI 1.05, 1.94) | Favours PB |
| **Breast pain** | | | 82/1065 (7.7%) | 71/1070 (6.6%) | RR 1.16 (95% CI 0.85, 1.58) | No diff |
| **Pneumonitis** | | | 8/1065 (0.8%) | 2/1070 (<0.5%) | RR 4.02 (95% CI 0.86, 18.9) | No diff |
| **Any acute toxicity side effects < 3 mths** | | | 484/1065 (45.4%) | 300/1070 (28%) | RR 1.62 (95% CI 1.44, 1.82) | Favours PB |
| **Induration or fibrosis (hardening)** | | ≥ 3 months | 49/1065 (4.6%) | 245/1070 (22.9%) | RR 0.20 (95% CI 0.15, 0.27) | Favours WB |
| **Telangiectasia (spider veins)** | | | 39/1065 (3.7%) | 99/1070 (9.3%) | RR 0.40 (95% CI 0.28, 0.58) | Favours WB |
| **Breast pain** | | | 20/1065 (1.9%) | 51/1070 (4.8%) | RR 0.39 (95% CI 0.24, 0.66) | Favours WB |
| **Chest wall pain** | | | 3/1065 (<0.5%) | 30/1070 (2.8%) | RR 0.10 (95% CI 0.03, 0.33) | Favours WB |
| **Fatty necrosis (lumpiness)** | | | 4/1065 (<0.5%) | 29/1070 (2.7%) | RR 0.14 (95% CI 0.05, 0.39) | Favours WB |
| **Any late toxicity side effects ≥ 3 mths** | | | 142/1065 (13.3%) | 346/1070 (32.3%) | RR 0.41 (95% CI 0.35, 0.49) | Favours WB |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks)
**RR** = risk ratio; **CI** = confidence intervals; **No diff** = no statistical difference; **mths** Months
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

# 4. DISCUSSION

## 4.1. SUMMARY OF MAIN FINDINGS

This review describes the interventions available to patients aged 60 years and over with invasive breast cancer who have undergone breast conserving surgery. It also presents evidence on the effectiveness and efficacy of Whole Breast (WB) radiation, Reduced Dose (RD) radiation of the whole breast and Partial Breast (PB) radiation as well as treatment without radiation therapy.

The key findings of this review are summarised in the summary of evidence table (Table 17). There are relative advantages and disadvantages associated with each of the strategies.

In general terms radiation therapy is recommended for most patients in that it offers advantages in terms of mortality and relapse/remission (except possibly contralateral breast cancer at five years). The choice of which type of radiation is less clear cut although PB offers some advantages in terms of treatment time commitments and short term adverse events. However, WB appears to be associated with less adverse events in the long term when compared to PB.

Potentially contradictory results were found in respect of longer term cosmetic / appearance issues relating to WB versus PB, which might be a result of differing adverse outcomes of radiation. One potential reason for this is different dosing regimens deployed in the RAPID and IMPORT LOW trials. In RAPID, the prescribed dose was 38.5 Gy in 10 fractions administered twice per day, separated 6-8 hours over 5-8 days. Reporting on the trial, Whelan concluded that, as a result of increased late toxicity and adverse cosmesis, a twice per day regimen could not be recommended.[7] By contrast, the dose received by those assigned to the partial breast group in Import Low was 40 Gy in 15 fractions. This difference in regimen might explain the seemingly contradictory results. It is worth noting that the dosing regimen used at Universitätsklinikum Schleswig-Holstein/Campus Kiel is different to both RAPID and IMPORT LOW, namely 38-40 Gy in 10 fractions for 2 weeks.

Additionally, a question asked of patients in RAPID was a composite of the size and shape of the breast, location of the areola and nipple, presence of telangiectasia (spider veins) and appearance of the surgical scar. Results are categorical (split into excellent, good, fair and poor results) but have been reported as dichotomous “Excellent or good result” and suggested that WB was favoured over PB at 5 and 7 years. A related question was asked in IMPORT LOW i.e. “Has the overall appearance of your breast changed, compared with the other side? Results for this were dichotomous (i.e. yes/no). In this instance, results at 5 years favoured PB over WB. Further research is required to understand these slightly contradictory results, although it should be recognised that the questions and answer possibilities were very different between studies.

## 4.2. ONGOING AND FUTURE STUDIES

Two of the three RCTs are the subject of continuing research. The PRIME II and the IMPORT LOW studies note that follow-up is ongoing and will be finished on the 10th anniversary of the last randomised patient in each study. [1 6]

## 4.3. COMPARISON WITH OTHER REVIEWS

The review of partial breast irradiation undertaken by Hickey 2016[3, 4] identified six studies of potential relevance. However, on reviewing these studies, it was clear that only one RCT, RAPID (as reported in Whelan 2019[7]) met the precise inclusion criteria for this report. The other two RCTs identified in this review, namely PRIME II and IMPORT LOW were identified as ongoing studies and accordingly not evaluated. No other systematic reviews were identified that met the inclusion criteria for this review (notably the precise dosing requirements of the treatment regimens under review).

As previously stated, neither RAPID nor IMPORT LOW exactly match the treatment regimen used in Universitätsklinikum Schleswig-Holstein/Campus Kiel. Partial breast irradiation is a relatively new intervention and it is unclear which dosing / frequency schedule is most effective. It was decided to explore implications of this by examining other single arm studies. Whilst not fitting our study inclusion criteria, but to fill in the gap on outcomes of the PB radiation schedule used in our study, we also investigated four recently reported single arm studies involving PB which provided evidence for effectiveness, complication rates and cosmetic outcomes. An earlier study, the NSABP B-17 trial was not examined since patients were accrued over 30 years ago, between October 1985 to December 1990.[49]

The lack of comparator(s) in these studies make it impossible to infer relative advantages/disadvantages of the procedure but they do provide information as to possible outcomes associated with PB.

A single arm study, reporting outcomes for 247 patients in receipt of 40 Gy in 10 Gy daily fractions, found that, at a median follow-up time of 3.9 years, 97.2% of patients were recurrence free with only four patients experiencing ipsilateral in breast recurrence and one experiencing regional recurrence in an axillary lymph node.[50]

Another study of 106 patients, using the same radiotherapy regime, reported 16 (15%) experiencing grade ≥ 2 toxicity (the most common being erythema (skin redness) in 2 patients (1.8%) and skin colour changes in 4 patients (3.8%), both at 4 to 9 weeks after radiation therapy). Only two instances of grade 3 toxicity were reported, including one patient with acute moist desquamation (thinning/weeping skin) after radiation therapy and another with fibrosis at 2 years. Overall, there were 3 breast cancer recurrences.[51]

Long-term outcomes of once accelerated partial breast irradiation (38.5 Gy in 10 once daily fractions) were reported for 242 suitable patients. With a median follow-up of 76 months, two patients (0.6%) had an invasive ipsilateral breast tumour recurrence and two patients (0.6%) had an axillary ipsilateral failure. 99.4% of patients were local recurrence-free. Progression-free survival was 98.4% at 5 years and 92% at 10 years. Acute and late skin

toxicity were 7.7% (grade 1), 0.6% (grade 2), and 4.4% (grade 1), 1.1% (grade 2), respectively. There were no grade 3/4 toxicities. Very few patients (2%) or physicians (2%) assessed cosmetic outcome as fair or poor at the 2-year follow-up.[52]

Finally, a German phase II trial of patients receiving 38 Gy in 3.80 Gy daily fractions, five times a week was identified. Strictly speaking, this study did not meet our criteria for PB because the study protocol allowed only one fraction/day to avoid additional toxicity at the early part of the study. However, it is discussed here because it relates to experience in a German setting and might reflect a more cautious variant of PBA worthy of further consideration. With a median follow-up of 25.5 months, early toxicity and late side effects were reported as mild. At the last follow-up visit, 19.4% of the patients (14/72) experienced grade 1 hypersensation/mild pain related to the tumour bed. One patient (1/72; 1.4%) reported pain corresponding to grade 2. Treatment-associated grade 1 dyspigmentation was found in 2/72 patients (2.8%). Grades 1 and 2 breast tissue fibrosis were reported in 5.6% (4/72) and 12.5% (9/72), respectively. Grade 1 telangiectasia (spider veins) occurred in one out of 72 patients (1.4%). Asymptomatic grade 1 lipoid necrosis was found in 2/72 patients (2.8%). There were no late toxicities ≥ grade 3. Patients subjectively judged the cosmetic outcome as excellent in 42.6% (26/61), good in 50.8% (31/61), fair in 3.3% (2/61), and poor in 3.3% (2/61). In summary, patients subjectively rated the cosmetic results as good to excellent in 93.4% (57/61) of the evaluated cases.[53] This compares to 76% of patients at baseline and 73% of patients at 3 years in the PB arm of the RAPID trial (see Table 13) and hence suggests a more favourable result. Comparable data were not available in the IMPORT LOW trial although results, at 5 years, in relation to changes in overall appearance favour PB over WB in that trial.

## 4.4. STRENGTH, LIMITATIONS AND UNCERTAINTIES

We can be reasonably confident all relevant primary studies which met the precise dosing requirements as set out in the inclusion criteria have been identified. We have also been able to synthesise results from three RCTs which have not been assessed in other systematic reviews. Nevertheless, a full systematic review of all primary studies might yield other evidence not found in this review of systematic reviews/guidelines. None of the three RCTs matched the age criterion specified for this review (as mentioned in Section 3.2.1), nevertheless they provide the best available evidence to address the FAQs in the review. Considerable treatment-specific evidence gaps exist, notably in terms of comparative cause-specific mortality estimates and certain categories of relapse/recurrence for RD and treatment without radiation. More general evidence gaps exist in regard of quality of life and impact on daily living following treatment with different strategies.

## 4.5. RECOMMENDATIONS FOR FURTHER RESEARCH

Ongoing work on PRIME II and IMPORT LOW with longer follow-up periods will undoubtedly inform the relative effectiveness of different strategies. Further work might also be helpful to identify patients who might not be eligible for any form of radiation therapy.

Table 17: Summary of Evidence

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| **FAQ2: When is radiation appropriate?** | | | | | | | |
| Appropriateness | Leitlinienprogramm Onkologie[5] | Radiation therapy recommended for most patients (see section 3.4) Certainty of evidence: high (based on strong consensus informed by systematic review (with homogeneity) of RCTs) | | | | Strong | ⇗ WB/RD/PB over no radiation |
| **FAQ3: Will I live longer?** | | | | | | | |
| All-cause mortality | IMPORT LOW _Coles 2017[1]; PRIME II_Kunkler 2015[6]; RAPID† _Whelan 2019[7] | No difference observed between interventions | | | | Moderate / Low | ⇔ |
| Cause-specific mortality, Breast Cancer | PRIME II_Kunkler 2015[6]; RAPID† _Whelan 2019[7] | No difference compared to PB / no radiation | No evidence | No difference compared to WB | No difference compared to WB | Low | ⇔ ● RD |
| Cause-specific mortality, Other Cancer | RAPID† _Whelan 2019[7] | No difference compared to PB | No evidence | No difference compared to WB | No evidence | Low | ⇔ ● RD / No radiation |
| Cause-specific mortality, Cardiac disease | PRIME II_Kunkler 2015[6]; RAPID† _Whelan 2019[7] | No difference observed between interventions | | | | Low | ⇔ |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| **FAQ4: Will my cancer come back?** | | | | | | | |
| Local relapse | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Ipsilateral breast tumour recurrence | PRIME II_Kunkler 2015[6], RAPID† _Whelan 2019[7] | HR = 1, 5.19 (1.99 – 13.52) no radiation, no difference compared to PB | No evidence | No difference compared to WB | HR = 5.19 (1.99 – 13.52), 1.0 WB | Low | ⇗ WB over no radiation ⇔ No difference WB and PB ● RD |
| Regional recurrence | PRIME II_Kunkler 2015[6], RAPID† _Whelan 2019[7] | No difference compared to PB or no radiation Numerically superior to no radiation | No evidence | No difference compared to WB | No difference compared to WB | Low | ⇔ ● RD |
| Distant relapse at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Distant recurrence at 5 years | PRIME II_Kunkler 2015[6], RAPID† _Whelan 2019[7] | No difference compared to PBor no radiation | No difference compared to WB or PB | No difference compared to WB or RD | No difference compared to WB | Low | ⇔ ● RD |
| Contralateral breast cancer at 5 years | PRIME II_Kunkler 2015[6], RAPID† _Whelan | More events within 5 years (1.5%) than no | No evidence | No difference compared to WB | Less events within 5 years (0.7%) than | Low | ⇗ No radiation |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| | 2019[7] | radiation (0.7%) , no difference compared to PB | | | WB (1.5%) | | (numerical) ⇔ No difference WB and PB ● RD |
| Any breast cancer related event at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Non-breast second cancer at 5 years | PRIME II_Kunkler 2015[6], RAPID† _Whelan 2019[7] | Lower events within 5 years (5.4%) than PB (7.9%) , no difference compared to no radiation | No evidence | Higher events within 5 years (7.9%) than WB (5.4%) | No difference compared to WB | Low | ⇗ WB over PB ⇔ No difference WB and no radiation ● RD |
| **FAQ5: How time-consuming will the treatment be?** | | | | | | | |
| Treatment time | IMPORT LOW _Coles 2017[1]; PRIME II_Kunkler 2015[6]; RAPID† _Whelan 2019[7] | Once per day for 3 to 5 weeks | 3 weeks | Twice per day for between 5 days and 2 weeks | NA | Medium / High | ⇗ PB over WB / RD ⇔ No difference WB and RD |
| **FAQ6: How will I feel after radiation?** | | | | | | | |
| Excellent or good cosmetic result - baseline | RAPID† _Whelan 2019[7] | No difference compared to PB | No evidence | No difference compared to WB | No evidence | Low | ⇔ ● RD / No |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| | | | | | | | radiation |
| Excellent or good cosmetic result – at 3 years | RAPID† _Whelan 2019[7] | No difference compared to PB | No evidence | No difference compared to WB | No evidence | Low | ⇔ ● RD / No radiation |
| Excellent or good cosmetic result – at 5 years | RAPID† _Whelan 2019[7] | Favoured over PB (82% v 70% satisfaction) | No evidence | Inferior to WB (70% v 82% satisfaction) | No evidence | Low | ⇗ WB over PB ● RD / No radiation |
| Excellent or good cosmetic result – at 7 years | RAPID† _Whelan 2019[7] | Favoured over PB (85% v 69% satisfaction) | No evidence | Inferior to WB (69% v 85% satisfaction) | No evidence | Low | ⇗ WB over PB ● RD / No radiation |
| **FAQ7: What are the risks/side effects?** | | | | | | | |
| Breast appearance changed at 5 years | IMPORT LOW _Coles 2017[1] | HR = 1, 0.74 (0.54 – 1.0) RD, 0.64 (0.46 – 0.89) PB | HR = 0.74 (0.54 – 1.0), 0.64 (0.46 – 0.89) PB, 1.0 WB | HR = 0.64 (0.46 – 0.89), 0.74 (0.54 – 1.0) RD, 1.0 WB | No evidence | Low | ⇗ PB and RD over WB ● No radiation |
| Breast smaller at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Breast harder or firmer at 5 years | IMPORT LOW _Coles 2017[1] | HR = 1, 0.53 (0.36 – 0.79) RD, 0.47 (0.32 – 0.71) PB | HR = 0.53 (0.36 – 0.79), 0.47 (0.32 – 0.71 PB, 1.0 WB | HR = 0.47 (0.32 – 0.71) PB, 0.53 (0.36 – 0.79) RD, 1.0 | No evidence | Low | ⇗ PB and RD over WB |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| | | | | WB | | | ● No radiation |
| Shoulder stiffness at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Skin appearance changed at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Arm or shoulder pain at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Swollen arm or hand at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Difficulty raising arm at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Breast pain at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Breast swollen at 5 years | IMPORT LOW _Coles 2017[1] | HR = 1, 0.49 (0.27 – 0.89) PB | No difference compared to WB or PB | HR = 0.49 (0.27 – 0.89) , 1.0 WB | No evidence | Low | ⇗ PB over WB ● No radiation |
| Breast over sensitive at 5 years | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| Skin problems in breast at 5 years | IMPORT LOW _Coles 2017[1] | HR = 1, 0.64 (0.42 – 0.99) PB | No difference compared to WB or PB | HR = 0.64 (0.42 – 0.99) , 1.0 WB | No evidence | Low | ⇗ PB over WB ● No radiation |
| AE at 5 years: Breast appearance | IMPORT LOW _Coles 2017[1] | P = 0.047 RD, <0.0001 PB) | P = 0.047 WB | P <0.0001 | No evidence | Low | ⇗ PB and RD over WB ● No radiation |
| AE at 5 years: Breast smaller | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Breast harder or firmer | IMPORT LOW _Coles 2017[1] | P = 0.376 RD, =0.024 PB) | P = 0.376 WB | P = 0.024 | No evidence | Low | ⇗ PB over WB ⇔ RD and WB ● No radiation |
| AE at 5 years: Shoulder stiffness | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Skin appearance changed | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Arm or shoulder pain | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| | | | | | | | ● No radiation |
| AE at 5 years: Swollen arm or hand | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Difficulty raising arm | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Breast pain | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Breast swollen | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Breast over sensitive | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| AE at 5 years: Skin problems in breast | IMPORT LOW _Coles 2017[1] | No difference compared to PB or RD | No difference compared to WB | No difference compared to WB | No evidence | Low | ⇔ ● No radiation |
| Moderate/marked AEs (any grade) at baseline | IMPORT LOW _ Bhattacharya 2019[2] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Moderate/marked AEs (any grade) at 6 months | IMPORT LOW _ Bhattacharya 2019[2] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| Moderate/marked AEs (any grade) at1 year | IMPORT LOW _ Bhattacharya 2019[2] | RR 1.23 (95% CI 1.04, 1.45), 1.0 RD; RR 1.23 (95% CI 1.04, 1.45), 1.0 PB | RR 1.23 (95% CI 1.04, 1.45), 1.0 RD; No difference compared to PB | RR 1.23 (95% CI 1.04, 1.45), 1.0 PB; No difference compared to RD | No evidence | Low | ⇗ RD/PB over WB ● No radiation |
| Moderate/marked AEs (any grade) at 2 years | IMPORT LOW _ Bhattacharya 2019[2] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Moderate/marked AEs (any grade) at 5 years | IMPORT LOW _ Bhattacharya 2019[2] | No difference compared to PB or RD | No difference compared to WB or PB | No difference compared to WB or RD | No evidence | Low | ⇔ ● No radiation |
| Radiation dermatitis | Whelan† 2019[7] | RR 3.23 (95% CI 2.63, 3.97) | No evidence | RR 1.0 | No evidence | Low | ⇗ PB over WB |
| Fatigue (1-3 months) | Whelan† 2019[7] | No diff compared to PB | No evidence | No diff compared to WB | No evidence | Low | ⇔ ● No radiation / RD |
| Breast swelling (1-3 months) | Whelan† 2019[7] | RR 1.43 (95% CI 1.05, 1.94) | No evidence | RR 1.0 | No evidence | Low | ⇗ PB over WB |
| Breast pain (1-3 months) | Whelan† 2019[7] | No diff compared to PB | No evidence | No diff compared to WB | No evidence | Low | ⇔ ● No radiation / RD |
| Pneumonitis (1-3 months) | Whelan† 2019[7] | No diff compared to PB | No evidence | No diff compared to WB | No evidence | Low | ⇔ |

| Outcome | Source | WB | RD | PB | No radiation | Certainty – quality of evidence | Assessment for use in DA |
|---|---|---|---|---|---|---|---|
| | | | | | | | ● No radiation/ RD |
| Any acute toxicity (1-3 months) | Whelan† 2019[7] | RR 1.62 (95% CI 1.44, 1.82) | No evidence | RR 1.0 | No evidence | Low | ⇗ PB over WB |
| Induration or fibrosis (≥3 months) | Whelan† 2019[7] | RR 0.20 (95% CI 0.15, 0.27) | No evidence | RR 1.0 | No evidence | Low | ⇗ WB over PB |
| Telangiectasia (≥3 months) | Whelan† 2019[7] | RR 0.40 (95% CI 0.28, 0.58) | No evidence | RR 1.0 | No evidence | Low | ⇗ WB over PB |
| Breast pain (≥3 months) | Whelan† 2019[7] | RR 0.39 (95% CI 0.24, 0.66) | No evidence | RR 1.0 | No evidence | Low | ⇗ WB over PB |
| Chest wall pain(≥3 months) | Whelan† 2019[7] | RR 0.10 (95% CI 0.03, 0.33) | No evidence | RR 1.0 | No evidence | Low | ⇗ WB over PB |
| Fatty necrosis (≥3 months) | Whelan† 2019[7] | RR 0.14 (95% CI 0.05, 0.39) | No evidence | RR 1.0 | No evidence | Low | ⇗ WB over PB |
| Any late toxicity(≥3 months) | Whelan† 2019[7] | RR 0.41 (95% CI 0.35, 0.49) | No evidence | RR 1.0 | No evidence | Low | ⇗ WB over PB |

**WB** Moderate hypofractionated radiation of the whole breast (40-42.5 Gy in 15-16 fractions for 3 weeks)
**RD** Moderate hypofractionated dose-reduced radiation of the whole breast (36 Gy in 15 fractions/ tumour bed: 40.05 Gy in 15 fractions for 3 weeks)
**PB** Partial breast radiation (38-40 Gy in 10 fractions for 2 weeks) **AE** Adverse events, **HR** Hazard ratio, **NA** Not applicable
† Results from RAPID should be interpreted with caution as radiotherapy dosage/frequency is different to that used in Universitätsklinikum Schleswig-Holstein/Campus Kiel (see discussion section)

| Type of Arrow | Assessment for use in decision aid |
|---|---|
| ⇧ | **"Proof or strong indication of effect"**<br>**Difference in favour of group A versus B based on high to moderate quality data***<br>**The effect estimate ideally should be significant, but may sometimes be only borderline significant but from several studies indicating a trend (that according to KSR should be mentioned)** |
| ⇗ | **"Indication or hint of effect"**<br>**Difference in favour of group A versus B based on low quality data that appears reportable in the DA (e.g., large effect on survival based on registry data, consistently very convincing effects from observational studies supported by one small RCT with same direction of effect)** |
| ⇔ | **"No Proof/Indication of effect or a hint of effect that is too weak to report"**<br>**No difference shown among groups based on moderate to high quality data**<br>**or difference shown but does not seem reliable enough to be reported based on low or very low quality data** |
| ● | **No data to report: no difference shown from low/very low quality studies or no studies** |

*The term "Data Quality" includes assessment of evidence (level of evidence, risk of bias assessment) as well as transferability of study results to our target population. This should be either taken from original reviews/meta-analyses or provided by KSR for studies where no external evidence assessment exists.
In this review the quality of evidence was judged to be low where findings were generated from single RCTs. If all three RCTs reported the same finding then the certainty of evidence was judged to be moderate/low. An assessment of medium/ high reflects findings from all RCTs as well as the systematic review. An assessment of Strong is based on evidence from systematic review of RCTs with homogeneity

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## APPENDIX 1: SEARCH STRATEGIES

| Database | Dates | Results |
|---|---|---|
| CDSR | 2015 - Iss 10, Oct 2020 | 41 |
| DARE | 2012 - 31 Mar 2015 | 0 |
| HTA | 2012 to 31 Mar 2018 | 11 |
| NICE Evidence | 01/01/2015 – 8/10/2020 | 61 |
| NICE Guidance | 2015-2020 | 3 |
| KSR Evidence | 2015-2020 | 208 |
| Epistemonikos | 2015-2020 | 175 |
| GIN | 2015-2020 | 1 |
| INAHTA | 2015-2021 | 7 |
| ECRI | 2015-2020 | 17 |
| **Total** | | **524** |
| **Total after de-duplication** | | **362** |

Cochrane Database of Systematic Reviews (CDSR): Issue 10/12 Oct 2020
Searched 8.10.20

| | | |
|---|---|---|
| #1 | MeSH descriptor: [Breast Neoplasms] explode all trees | 13009 |
| #2 | MeSH descriptor: [Breast] explode all trees | 745 |
| #3 | MeSH descriptor: [Neoplasms] explode all trees | 78890 |

#4 #2 AND #3 344
#5 ((breast) near/5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)):ti,ab,kw 36987
#6 ((mammar*) near/5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)):ti,ab,kw 254
#7 #1 OR #4 OR #5 OR #637077
#8 MeSH descriptor: [Radiotherapy] explode all trees 6076
#9 (radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion*) 52217
#10 ((Radio or radiation or roentgen or rontgen) NEAR (treatment* or therap*)) 15368
#11 #8 OR #9 OR #10 52629
#12 #7 AND #11 6084
#13 MeSH descriptor: [General Surgery] explode all trees 351
#14 MeSH descriptor: [Mastectomy, Segmental] explode all trees 485
#15 (surger* OR resect* OR lumpectom* or Local* Excis* or quadrectom* or segmentectom*) 246632
#16 (breast* NEAR/2 conserv*) 1802
#17 ((partial or segment*) NEAR/2 (mammectom* or mastectom*)) 1249
#18 #13 or #15 or #16 or #17 246904
#19 #12 AND #18 with Cochrane Library publication date Between Jan 2015 and Dec 2020 2177

**CDSR 41**

Database of Abstracts of Reviews of Effects (DARE) (CRD): 2015 to 31 March 2015
Health Technology Assessment Database (HTA) (CRD): 2015 to 31 March 2018
https://www.crd.york.ac.uk/CRDWeb/
Searched: 08.10.20

1 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES 1798
2 (((breast) near5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) IN DARE, HTA FROM 2015 TO 2020 81
3 (((mammar*) near5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) IN DARE, HTA FROM 2015 TO 2020 2
4 #1 OR #2 OR #3 1814
5 MeSH DESCRIPTOR Radiotherapy EXPLODE ALL TREES 907
6 ((radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion*)) IN DARE, HTA FROM 2015 TO 2020 83
7 (((Radio or radiation or roentgen or rontgen) NEAR (treatment* or therap*))) IN DARE, HTA FROM 2015 TO 2020 29
8 #5 OR #6 OR #7 970
9 MeSH DESCRIPTOR General Surgery EXPLODE ALL TREES 61
10 MeSH DESCRIPTOR Mastectomy, Segmental EXPLODE ALL TREES 73

11 ((surger* OR resect* OR lumpectom* or Local* Excis* or quadrectom* or segmentectom*)) IN DARE, HTA FROM 2015 TO 2020 264
12 ((breast* NEAR2 conserv*)) IN DARE, HTA FROM 2015 TO 2020 6
13 (((partial or segment*) NEAR2 (mammectom* or mastectom*))) IN DARE, HTA FROM 2015 TO 2020 0
14 #9 OR #10 OR #11 OR #12 OR #13 393
15 #4 AND #8 AND #14 29
16 * IN DARE FROM 2015 TO 2020 411
**17 #15 AND #16 0**
18 * IN HTA FROM 2015 TO 2020 2176
**19 #15 AND #18 11**

**ECRI Institute Guidelines Trust (Internet): up to 2020/10/8**
**https://guidelines.ecri.org/**
**Searched: 8.10.20**

**2015+**

**Search terms Results**

**'breast cancer radiotherapy' 17**

2015+

| **Search terms** | **Results** |
|---|---|
| 'breast cancer radiotherapy' | 17 |

**Epistemonikos (www.epistemonkos.org/): up to 8.10.20**
**Searched: 8.10.20**
(title:((title:(breast* OR mammar*) OR abstract:(breast* OR mammar*))) OR abstract:((title:(breast* OR mammar*) OR abstract:(breast* OR mammar*)))) AND (title:(neoplasm* OR cancer* OR tumo?r* OR metasta* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR dcis OR ductal OR infiltrat* OR intraductal* OR lobular OR medullary) OR abstract:(neoplasm* OR cancer* OR tumo?r* OR metasta* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR dcis OR ductal OR infiltrat* OR intraductal* OR lobular OR medullary)) AND (title:(radiat* OR radiotherap* OR irradiat* OR radiotreatment* OR radio-treatment* OR brachytherap* OR EBRT OR IMRT OR hyperfraction* OR hypofraktion*) OR abstract:(radiat* OR radiotherap* OR irradiat* OR radiotreatment* OR radio-treatment* OR brachytherap* OR EBRT OR IMRT OR hyperfraction* OR hypofraktion*)) AND (title:(surger* OR resect* OR lumpectom* OR Local* Excis* OR quadrectom* OR segmentectom*) OR abstract:(surger* OR resect* OR lumpectom* OR Local* Excis* OR quadrectom* OR segmentectom*))

Filtered: 2015-2020, Systematic Review

175 results

**Guidelines International Network (G-I-N) (https://g-i-n.net/): up to 8.10.20**
**Searched: 8.10.20**

**2015 to current**

| Search term | Hits |
|---|---|
| Breast Cancer radiotherapy | 0 |
| Breast conserv* | 1 |
| Total | 1 |

**Database: INAHTA up to 2020/10/8**
https://database.inahta.org/
**Searched: 18.8.20**
((((breast* or mammar*)))) AND (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary ) AND (radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion* ) AND (surger* OR resect* OR lumpectom* or Local* Excis* or quadrectom* or segmentectom*)
FROM 2015 TO 2021
29 hits – 7 after sifted for relevance

FROM 2015 TO 2020
Search retrieved 53 records

**Database: KSR Evidence up to 8/10/20**
https://www.ksrevidence.com/
**Searched: 8.10.20**

# Query Results
1 breast* or mammar* in All text 4365 results
2 neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary in All text 23632 results
3 #1 and #2 in All text 3217 results
4 radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion* in All text 3544 results
5 surger* OR resect* OR lumpectom* or Local* Excis* or quadrectom* or segmentectom* in All text 24131 results
6 #3 and #4 and #5 in All text 208 results

Search run Thu Oct 08 2020

**NICE Evidence Search (Internet): up to 2020/10/8**
https://www.evidence.nhs.uk/
**Searched: 8.10.20**

| **Search terms** | **Results (Guidance or SR): 01/01/2015-8/10/2020** |
|---|---|
| **Breast cancer radiotherapy** | 61 (249 before JR sifted for relevance) |

**National Institute for Health and Care Excellence (NICE): Guidelines**
https://www.nice.org.uk/
**Searched 8.10.20**

| **Keywords** | **Hits** |
|---|---|
| Breast cancer in Conditions - Guidance | 41 (2 after sifting) |
| Breast cancer radiotherapy | 18 (1 additional after sifting) |
| **Total** | **3** |

**SDM topic searches**

**SDM facet: SDM Terms only**

| **Database** | **Dates** | **Results** |
|---|---|---|
| Embase | 1974-2020/week 33 | 185 |
| MEDLINE, IP, DU & Epub | 1946 to Oct 02 2020 | 108 |
| CENTRAL | 2015 - Issue 9, Sept 2020 | 23 |
| Other searches | | |
| **Total** | | **316** |
| **Total after de-duplication** | | **256** |

**Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 10 of 12, October 2020**
**Searched: 9.10.20**

ID Search Hits
#1 MeSH descriptor: [Breast Neoplasms] explode all trees 13009
#2 MeSH descriptor: [Breast] explode all trees 745
#3 MeSH descriptor: [Neoplasms] explode all trees 78890
#4 #2 AND #3 344
#5 ((breast) near/5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)):ti,ab,kw 36987
#6 ((mammar*) near/5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)):ti,ab,kw 254
#7 #1 OR #4 OR #5 OR #637077
#8 MeSH descriptor: [Radiotherapy] explode all trees 6076
#9 (radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion*) 52217
#10 ((Radio or radiation or roentgen or rontgen) NEAR (treatment* or therap*)) 15368
#11 #8 OR #9 OR #10 52629
#12 #7 AND #11 6084
#13 MeSH descriptor: [General Surgery] explode all trees 351
#14 MeSH descriptor: [Mastectomy, Segmental] explode all trees 485
#15 (surger* OR resect* OR lumpectom* or Local* Excis* or quadrectom* or segmentectom*) 246632
#16 (breast* NEAR/2 conserv*) 1802
#17 ((partial or segment*) NEAR/2 (mammectom* or mastectom*)) 1249
#18 #13 or #15 or #16 or #17 246904
#19 #12 AND #18 with Cochrane Library publication date Between Jan 2015 and Dec 2020 2177
#20 MeSH descriptor: [Decision Making] explode all trees 3889
#21 ((share* or sharing* or inform*) near/3 (decision* or deciding* or choice*)) 5410
#22 sdm 467
#23 #20 or #21 or #22 8920
**#24 #19 and #23 with Publication Year from 2015 to 2020, with Cochrane Library publication date Between Jan 2015 and Dec 2020, in Trials 23**

**Embase (Ovid): 1974-2020/10/08**
**Searched: 8.10.20**

1 exp breast tumour/ (541482)
2 (breast$ adj5 (neoplas$ or cancer$ or tumo?r$ or metasta$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullary)).ti,ab,ot,hw. (624849)

3 (mammar$ adj5 (neoplas$ or cancer$ or tumo?r$ or metasta$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullary)).ti,ab,ot,hw. (41126)
4 or/1-3 (639710)
5 exp breast radiotherapy/ (2477)
6 exp radiotherapy/ (538158)
7 (radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion*).ti,ab,ot,hw. (1250807)
8 ((Radio or radiation or roentgen or rontgen) adj (treatment* or therap*)).ti,ab,ot,hw. (159116)
9 or/5-8 (1279926)
10 exp breast surgery/ (81510)
11 partial mastectomy/ (16958)
12 lumpectomy/ (2808)
13 (surger* or resect* or lumpectom* or Local* Excis* or quadrectom* or segmentectom*).ti,ab,ot,hw. (2749930)
14 (breast* adj2 conserv*).ti,ab,ot,hw. (17227)
15 ((partial or segment*) adj2 (mammectom* or mastectom*)).ti,ab,ot,hw. (19460)
16 or/10-15 (2783880)
17 4 and 9 and 16 (42416)
18 shared decision making/ (7386)
19 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (51930)
20 sdm.ti,ab. (3451)
21 or/18-20 (56058)
22 17 and 21 (310)
**23 limit 22 to yr="2015 -Current" (185)**

**MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid): 1946 to October 02, 2020**
**Searched: 8.10.20**
1 exp Breast Neoplasms/ (294238)
2 (breast adj5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti,ab,kw. (349308)
3 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or metasta* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti,ab,kw. (33821)
4 or/1-3 (429877)
5 exp Radiotherapy/ (186350)
6 (radiat* or radiotherap* or irradiat* or radiotreatment* or radio-treatment* or brachytherap* or EBRT or IMRT or hyperfraction* or hypofraktion*).ti,ab,kw. (707910)
7 ((Radio or radiation or roentgen or rontgen) adj (treatment* or therap*)).ti,ab,kw. (87967)
8 or/5-7 (755720)
9 exp General Surgery/ (38985)
10 exp Mastectomy, Segmental/ (8669)

11 (surger* or resect* or lumpectomy* or Local* Excis* or quadrectom* or segmentectom*).ti,ab,kw. (1475569)
12 (breast* adj2 conserv*).ti,ab,kw. (10549)
13 ((partial or segment*) adj2 (mammectom* or mastectomy*)).ti,ab,kw. (894)
14 or/9-13 (1501907)
15 4 and 8 and 14 (15077)
16 exp Decision Making/ (203982)
17 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (38552)
18 sdm.ti,ab. (2722)
19 or/16-18 (234983)
20 15 and 19 (282)
21 limit 20 to yr="2015 -Current" (108)