Implementation of the Breast Cancer workflow solution

Version 1.2

KN » 2015.05.12

This document

This document is aimed at professionals who want to evaluate the depth and correctness of the knowledge embedded in the workflow for breast cancer diagnosis and treatment.

We imagine that the key target group for this is the doctors and specialists in oncology and breast cancer, therefore we have done no effort to explain the concepts in this document, which we assume are known to the reader.

It shows how the workflow has been constructed from the guideline and other knowledge sources, and it contains the guideline in its full text.

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## Sources of knowledge

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<th>Explanation</th>
</tr>
</thead>
</table>
| 1  | UK NICE Guideline “Early and locally advanced breast cancer: Diagnosis and treatment” | The guideline is referred in this document  
- How it is translated into workflow by means of examples in the section “Text-to-Workflow Conversion”  
- A copy of the guideline text is available in the section “Guideline text” |
| 2  | DBCG Guidelines | Guidelines from the Danish Breast Cancer Group (DBCG) |
| 3  | Family Risk assessment, NICE | See the section “List of Value Expressions” |
| 4  | A range of inputs | For example the calculations of  
- Bloom Richardson grading  
- Staging information  
- Medicine information (in particular for dosage of chemotherapy) |
Overview

The solution guides the users through the following workflow (depicted as a high level phase diagram, with the green boxes showing the main variant conditions):

Figure 1: Overview of the solution. Green boxes show the main variant conditions

Figure 2: Two screen captures of the proposed solution as it appears in a browser
Guideline text

This is the text as it appears on the following link. All of the business rules embedded in this text are implemented

http://www.nice.org.uk/guidance/cg80/chapter/1-guidance

When you click on the link you get the following:

![Figure 3: Screen print of the site (when activating the link above) 2015.04.12](image-url)

1.1 Referral, diagnosis and preoperative assessment

Patients with symptoms that could be caused by breast cancer are referred by their GP or another health professional to local breast clinics. Local breast clinics refer patients to the breast cancer centre.
The important details are in the text, despite NICE has tried to provide a flow overview using a Flow Chart.

Figur 1: NICE trying to provide an overview usign a Flow Chart.

This text is the main source of the logic of the solution. We have taken the text in case it gets removed from the site:

1.1 Referral, diagnosis and preoperative assessment

Patients with symptoms that could be caused by breast cancer are referred by their GP to designated breast clinics in local hospitals (see NICE clinical guideline 27, ‘Referral guidelines for suspected cancer’). In addition, women aged between 50 and 70 are invited for screening mammography every 3 years through the NHS Breast Screening Programme (NHSBSP) in England or the Breast Test Wales Screening Programme (BTWSP) in Wales. For most patients, whether they are referred following breast screening or after presentation to a GP, diagnosis in the breast clinic is made by triple assessment (clinical assessment, mammography and/or ultrasound imaging, and core biopsy and/or fine needle aspiration cytology). It is best practice to carry out these assessments at the same visit (see NICE cancer service guidance ‘Improving outcomes in breast cancer – Manual update’).

Preoperative assessment of the breast and axilla

1.1.1 The routine use of magnetic resonance imaging (MRI) of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS).
1.1.2 Offer MRI of the breast to patients with invasive breast cancer:

- if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
- if breast density precludes accurate mammographic assessment
- to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.

Preoperative staging of the axilla

1.1.3 Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered.

1.2 Providing information and psychological support

1.2.1 All members of the breast cancer clinical team should have completed an accredited communication skills training programme.

1.2.2 All patients with breast cancer should be assigned to a named breast care nurse specialist who will support them throughout diagnosis, treatment and follow-up.

1.2.3 All patients with breast cancer should be offered prompt access to specialist psychological support, and, where appropriate, psychiatric services.

1.3 Surgery to the breast

Ductal carcinoma in situ

1.3.1 For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination to NHSBSP reporting standards. Re-excision should be considered if the margin is less than 2 mm, after discussion of the risks and benefits with the patient.

1.3.2 Enter patients with screen-detected DCIS into the Sloane Project (UK DCIS audit)\(^5\).

1.3.3 All breast units should audit their recurrence rates after treatment for DCIS.

Paget's disease

1.3.4 Offer breast conserving surgery with removal of the nipple-areolar complex as an alternative to mastectomy for patients with Paget's disease of the nipple that has been assessed as localised. Offer oncoplastic repair techniques to maximise cosmesis.

1.4 Surgery to the axilla

Invasive breast cancer
1.4.1 Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy (SLNB) is the preferred technique.

1.4.2 SLNB should only be performed by a team that is validated in the use of the technique, as identified in the New Start training programme.\[^6\]

1.4.3 Perform SLNB using the dual technique with isotope and blue dye.

1.4.4 Breast units should audit their axillary recurrence rates.

**Ductal carcinoma in situ**

1.4.5 Do not perform SLNB routinely in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease.\[^7\]

1.4.6 Offer SLNB to all patients who are having a mastectomy for DCIS.

**Evaluation and management of a positive sentinel lymph node**

1.4.7 Offer further axillary treatment to patients with early invasive breast cancer who:

- have macrometastases or micrometastases shown in a sentinel lymph node
- have a preoperative ultrasound-guided needle biopsy with histologically proven metastatic cancer.

The preferred technique is axillary lymph node dissection (ALND) because it gives additional staging information.

1.4.8 Do not offer further axillary treatment to patients found to have only isolated tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative.

**1.5 Breast reconstruction**

1.5.1 Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.

**1.6 Postoperative assessment and adjuvant therapy planning**

**Predictive factors**
1.6.1 Assess oestrogen receptor (ER) status of all invasive breast cancers, using immunohistochemistry with a standardised and qualitatively assured methodology, and report the results quantitatively.

1.6.2 Do not routinely assess progesterone receptor status of tumours in patients with invasive breast cancer.

1.6.3 Test human epidermal growth receptor 2 (HER2) status of all invasive breast cancers, using a standardised and qualitatively assured methodology.

1.6.4 Ensure that the results of ER and HER2 assessments are available and recorded at the multidisciplinary team meeting when guidance about systemic treatment is made.

**Adjuvant therapy planning**

1.6.5 Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded.

1.6.6 Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient.

1.6.7 Consider using Adjuvant! Online to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer.

1.6.8 Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments.

**1.7 Endocrine therapy**

**Ovarian suppression/ablation for early invasive breast cancer**

1.7.1 Do not offer adjuvant ovarian ablation/suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy.

1.7.2 Offer adjuvant ovarian ablation/suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.

**Aromatase inhibitors for early invasive breast cancer**

1.7.3 Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.
1.7.4 Offer an aromatase inhibitor, either exemestane or anastrozole, instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low risk\textsuperscript{10} and who have been treated with tamoxifen for 2–3 years.

1.7.5 Offer additional treatment with the aromatase inhibitor letrozole for 2–3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years.

1.7.6 The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women\textsuperscript{11}.

1.7.7 The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence\textsuperscript{11}.

**Tamoxifen for ductal carcinoma in situ**

1.7.8 Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS.

**1.8 Chemotherapy**

1.8.1 Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen.

1.8.2 Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.

**1.9 Biological therapy**

1.9.1 Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.

1.9.2 Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following:

- a left ventricular ejection fraction (LVEF) of 55% or less
- a history of documented congestive heart failure
- high-risk uncontrolled arrhythmias
- angina pectoris requiring medication
- clinically significant valvular disease
• evidence of transmural infarction on electrocardiograph (ECG)

• poorly controlled hypertension.

1.9.3 Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.

1.10 Assessment and treatment of bone loss

1.10.1 Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:

• are starting adjuvant aromatase inhibitor treatment

• have treatment-induced menopause

• are starting ovarian ablation/suppression therapy.

1.10.2 Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status.

1.10.3 Offer bisphosphonates to patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (2008) [12] (see appendix 2 of the full guideline).

1.11 Radiotherapy

Radiotherapy after breast conserving surgery

1.11.1 Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.

1.11.2 Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery and discuss with them the potential benefits and risks (see recommendation in section 1.3.1)

Radiotherapy after mastectomy

1.11.3 Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins.

1.11.4 Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence into the current UK trial (SUPREMO)
assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40.

1.11.5 Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).

**Dose fractionation**

1.11.6 Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.

**Breast boost**

1.11.7 Offer an external beam boost to the site of local excision to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy.

1.11.8 If an external beam boost to the site of local excision following breast conserving surgery is being considered in patients with early invasive breast cancer, inform the patient of the side effects associated with this intervention, including poor cosmesis, particularly in women with larger breasts.

**Radiotherapy to nodal areas**

1.11.9 Do not offer adjuvant radiotherapy to the axilla or supraclavicular fossa to patients with early breast cancer who have been shown to be histologically lymph node-negative.

1.11.10 Do not offer adjuvant radiotherapy to the axilla after ALND for early breast cancer.

1.11.11 If ALND is not possible following a positive axillary SLNB or four-node sample, offer adjuvant radiotherapy to the axilla to patients with early breast cancer (see recommendations in sections 1.4.1 and 1.4.7).

1.11.12 Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and four or more involved axillary lymph nodes.

1.11.13 Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status.

1.11.14 Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery.
1.12 Primary systemic therapy

Early breast cancer

1.12.1 Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery.

1.12.2 Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. However, the increased risk of local recurrence with breast conserving surgery and radiotherapy rather than mastectomy after systemic therapy should be discussed with the patient.

Locally advanced or inflammatory breast cancer

1.12.3 Offer local treatment by mastectomy (or, in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy.

1.13 Complications of local treatment and menopausal symptoms

Lymphoedema

1.13.1 Inform all patients with early breast cancer about the risk of developing lymphoedema and give them relevant written information before treatment with surgery and radiotherapy.

1.13.2 Give advice on how to prevent infection or trauma that may cause or exacerbate lymphoedema to patients treated for early breast cancer.

1.13.3 Ensure that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.

Arm mobility

1.13.4 All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy regimens.

1.13.5 Identify breast cancer patients with pre-existing shoulder conditions preoperatively as this may inform further decisions on treatment.

1.13.6 Give instructions on functional exercises, which should start the day after surgery, to all breast cancer patients undergoing axillary surgery. This should include relevant written information from a member of the breast or physiotherapy team.

1.13.7 Refer patients to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment.
Menopausal symptoms

1.13.8 Discontinue hormone replacement therapy (HRT) in women who are diagnosed with breast cancer.

1.13.9 Do not offer HRT (including oestrogen/progestogen combination) routinely to women with menopausal symptoms and a history of breast cancer. HRT may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed.

1.13.10 Offer information and counselling for all women about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment.

1.13.11 Tibolone or progestogens are not recommended for women with menopausal symptoms who have breast cancer.

1.13.12 The selective serotonin re-uptake inhibitor antidepressants paroxetine and fluoxetine may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen.

1.13.13 Clonidine, venlafaxine and gabapentin should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects.

1.13.14 Soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended for the treatment of menopausal symptoms in women with breast cancer.

1.14 Follow-up

Follow-up imaging

1.14.1 Offer annual mammography to all patients with early breast cancer, including DCIS, until they enter the NHSBSP/BTWSP. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.

1.14.2 On reaching the NHSBSP/BTWSP screening age or after 5 years of annual mammography follow-up we recommend the NHSBSP/BTWSP stratify screening frequency in line with patient risk category.

1.14.3 Do not offer mammography of the ipsilateral soft tissues after mastectomy.

1.14.4 Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.
1.14.5 After completion of adjuvant treatment (including chemotherapy, and/or radiotherapy where indicated) for early breast cancer, discuss with patients where they would like follow-up to be undertaken. They may choose to receive follow-up care in primary, secondary, or shared care.

1.14.6 Patients treated for breast cancer should have an agreed, written care plan, which should be recorded by a named healthcare professional (or professionals), a copy sent to the GP and a personal copy given to the patient. This plan should include:

- designated named healthcare professionals
- dates for review of any adjuvant therapy
- details of surveillance mammography
- signs and symptoms to look for and seek advice on
- contact details for immediate referral to specialist care, and
- contact details for support services, for example support for patients with lymphoedema.

[5] The Sloane Project


[7] Patients considered at high risk of invasive disease include those with a palpable mass or extensive microcalcifications.

[8] See Adjuvant! Online


[10] Low-risk patients are those in the EPG or GPG (excellent prognostic group or good prognostic group) in the Nottingham Prognostic Index (NPI), who have 10-year predictive survivals of 96% and 93%, respectively. They would have a similar prediction using Adjuvant! Online.


The summaries of product characteristics state that HRT is contraindicated in women with known, past or suspected breast cancer. Informed consent should be obtained and documented.

These drugs are not licensed for the stated use. Informed consent should be obtained and documented.
Text-to-Workflow Conversion

The following figures explain – by their examples – how the text is converted into workflow instructions. The initial paragraphs of the guideline are shown.

- In the top of each figure the text of the guideline is shown
- Below it the corresponding part(s) of the matrix is shown

They show only the black and the green area of the matrix, which together contain all the workflow decisions.

The elements used in the examples shown are the following:

- **State variables** and relevance rules:
  - A state variable has a column in the green part of the matrix. It can only be true (Yes) or false (No). Its default value from the start is denoted underneath its name.
  - An “S” denotes a step where the value is “Set” to true or false, and the “Y” (or “N”) denotes that the step is only relevant, if the value is true (or “Yes”) (or false, if “N” or “No”).
    - Assuming and AND rule
    - You can have OR rules or any Boolean combination rules as well

The number of state variables is approximately 300. And the number of steps is approximately 250.

![Flow chart diagram showing decision and action complexity](image)

**Figure 4:** Diagram showing the decision complexity (the number of decision points) and the action complexity (number of activities). The usual “Flow Chart” model cannot handle clinical processes like cancer. Our proposed model can.

- **Value Expressions:**
  - The value of a state variable is determined by other data in the matrix
  - Examples:
    - Whether the excision target is met (a threshold on the excision margin being at least 2mm)
    - Whether there is a high risk of invasive cancer – depending on whether there is EITHER extensive micro calcifications OR a palpable mass
  - Value expressions are used extensively to calculate suggested decisions, whenever data is available to suggest a decision (and whenever data is changed, and the decision should be re-taken based on the new knowledge)

The list of main value expressions can be seen in the section “Value Expressions”.
Other elements frequently used (but not in the following examples) include

- **Predecessors:**
  - Sequence: If A → B, then A must be completed, before B can start. You know this from project plans
  - Logical: If A → B, then B must be redone if any of the information on step A is changed. Logical predecessors are also sequence predecessors

- **Role** and **access rights** (the blue area in the matrix):
  - A user has a particular role (or a collection of roles)
  - You can determine which roles are allowed to carry out a step (or to see it, if they don’t carry it out)

Furthermore the key data necessary in the flow to document and serve as input to the decisions is shown in the red area of the matrix.

![Figure 5: Conversion of text to workflow example (1)](image-url)
**Figure 6: Conversion of text to workflow example (2)**

**Figure 7: Conversion of text to workflow example (3)**
Figure 8: Conversion of text to workflow example (4)

```java
if(MarginMmNumber < 2.0; true; false)
```

Figure 9: Conversion of text to workflow example (5)
Figure 10: Conversion of text to workflow example (6)

Surgery to the Axilla
Invasive Breast Cancer

Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy (SLNB) is the preferred technique.

- SLNB should only be performed by a team that is validated in the use of the technique, as identified in the New Start training programme.¹
- Perform SLNB using the dual technique with isotope and blue dye.
- Breast units should audit their axillary recurrence rates.

Figure 11: Conversion of text to workflow example (7)
Figure 12: Conversion of text to workflow example (8)

Evaluation and Management of a Positive Sentinel Lymph Node

- Offer further axillary treatment to patients with only invasive breast cancer who:
  - Have macrometastases or micrometastases shown in a sentinel lymph node.
  - Have a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease.
  - Offer SLNB to all patients who are having a mastectomy for DCIS.

1. New START Sentinel Lymph Node Biopsy Training Programmes. The Royal College of Surgeons of England (www.rcsurgeons.ac.uk/education/courses/new_start.html). (f)

Patients considered at high risk of invasive disease include those with a palpable mass or extensive microcalcifications.

Figure 13: Conversion of text to workflow example (9)
Figure 14: Conversion of text to workflow example (10)

Figure 15: Conversion of text to workflow example (11)
Value Expressions

Use of Value Expressions
The Value Expressions are used to dynamically calculate the values of variables, as soon as the input is available. This includes:

- Proposed decisions
- Derived calculations such as BMI from height and weight
- Thresholds and categorizations such as
  - Staging of the cancer
  - Risk assessments of the patient
  - Age groups
  - And many more

Figure 16: Example of the use of value expressions

List of Value Expressions
The list of main Value Expressions used in the solution comprises the following. It is unordered and the intention of showing the list is that the reader can assure himself / herself of the depth of the knowledge lying behind the solution:
<table>
<thead>
<tr>
<th>Ref</th>
<th>Value expression</th>
<th>Input, based on</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age group</td>
<td>The date of birth</td>
</tr>
<tr>
<td>2</td>
<td>Menopausal</td>
<td>Whether periods have disappeared</td>
</tr>
<tr>
<td>3</td>
<td>Comorbidity threshold passed</td>
<td>A list of comorbidities declared to be present</td>
</tr>
<tr>
<td>4</td>
<td>Diagnosis of cancer</td>
<td>The triple test (3 inputs, the outcomes of each test)</td>
</tr>
</tbody>
</table>
| 5   | Whether MRI is proposed to be conducted | Whether  
- suspected to be invasive,  
- biopsy,  
- breast density, and whether  
- the individual tests in the triple test have discrepancy on the extent |
| 6   | Whether ultrasound to the axilla is recommended | Whether suspicion that it is invasive |
| 7   | Whether SLNB is recommended | Risk of invasive cancer and whether a DCIS is removed by mastectomy |
| 8   | Risk of invasive cancer | Whether  
- Palpable mass OR  
- Extensive microcalcifications |
| 9   | Lymph node involvement (positive or negative, if positive whether more than 4 are involved) | The lymph node involvement and the thresholds for counting a lymph node to be involved |
| 10  | Grade  
- Grade 1  
- Grade 2  
- Grade 3 | Derived from the BR score (Bloom Richardson Grade) |
| 11  | Family induced risk | Risk score (see below) or gene test |
12 Family risk score

A complex calculation involving this table (Source: http://www.nice.org.uk/guidance/cg164/ifp/chapter/first-steps-finding-out-about-your-family-history):

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Relatives affected</th>
<th>Age at diagnosis</th>
<th>Referral for estimation of breast cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer only</td>
<td>1 first-degree relative</td>
<td>Under 40</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2 first-degree relatives</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 first- and 1 second-degree relative</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>3 first-degree relatives</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2 second-degree relatives</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>1 first-degree male relative</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td>Bilateral breast cancer</td>
<td>1 first-degree relative</td>
<td>Under 50 for diagnosis of first cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>Breast and ovarian cancer</td>
<td>1 first-degree relative with breast cancer and 1 first-degree relative with ovarian cancer</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 first-degree relative with breast cancer and 1 second-degree relative with ovarian cancer</td>
<td>Any age</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 second-degree relative with breast cancer and 1 first-degree relative with ovarian cancer</td>
<td>Any age</td>
<td>Yes</td>
</tr>
</tbody>
</table>

13 Stage information

From
- Type of cancer,
- Size of tumor,
- Spread / metastases,
- Lymph node involvement

With a complex set of rules for combining the data. See the next info box (Source: http://www.cancer.gov/cancertopics/pdq/treatment/breast/Patient/page2#_153)

See section “Stage calculation – in one of the Value Expressions” below.

14 DBCG stages – which are slightly different in Denmark

A modified Grade calculation, e.g. Stage 0 does not exist

15 Whether examinations should be performed for the following

- Estrogen receptor positive
- Progesteron receptor positive
- HER2 positive

Based on
- The nature of the cancer and on
- Which set of rules are applied

16 The threshold applied for ER and PR

Different depending on which set of rules are applied. The appropriate threshold is applied and positivity is determined accordingly

17 Whether the tumor is triple negative

The above mentioned tests
<table>
<thead>
<tr>
<th>Ref</th>
<th>Value expression</th>
<th>Input, based on</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>DBCG (Danish) risk factors</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• age,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• menopausal state,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• tumor size,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• lymph node involvement,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ductal or lobular</td>
</tr>
<tr>
<td>19</td>
<td>Prognosis group</td>
<td>(DBCG version and and Global version)</td>
</tr>
<tr>
<td>20</td>
<td>DBCG treatment group</td>
<td>Based on a range of input factors, including</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Estrogen receptor positivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HER2 positivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Menopausal state</td>
</tr>
<tr>
<td>21</td>
<td>Input factors for whether patient has a strong enough heart to stand Herceptin / Trastuzumab treatment</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LVEF evolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Congestive heart failures</td>
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<tr>
<td></td>
<td></td>
<td>• Arrytmias</td>
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<tr>
<td></td>
<td></td>
<td>• Angina pectoris</td>
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<tr>
<td></td>
<td></td>
<td>• Valcular disease</td>
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<tr>
<td></td>
<td></td>
<td>• Transmural infarcts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood pressure in control</td>
</tr>
<tr>
<td>22</td>
<td>Risk of recurrence</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• lymph node involvement,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• tumor grade,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• age,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• if lumpectomy: whether clear margins, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• whether ER positive</td>
</tr>
<tr>
<td>23</td>
<td>Breast surgery recommended at all</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>24</td>
<td>Breast surgery at first or wait for initial adjuvant treatment</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inflamatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fixed to lymph nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spread to lymph nodes above shoulder region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Skin or muscle involved in tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Size (more than 5 cm)</td>
</tr>
<tr>
<td>25</td>
<td>Axilla surgery recommended</td>
<td>Lymph node involvement</td>
</tr>
<tr>
<td>26</td>
<td>Whether lumpectomy can be chosen</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• How localized the tumor is</td>
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<tr>
<td></td>
<td></td>
<td>• Family history and risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Whether previous radiation has been received</td>
</tr>
<tr>
<td>Ref</td>
<td>Value expression</td>
<td>Input, based on</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>27</td>
<td>Whether breast reconstruction after mastectomy can be advised</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Comorbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Whether adjuvant treatment needs preclude it</td>
</tr>
<tr>
<td>28</td>
<td>Whether excision margin targets are met</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Whether adjuvant treatment should be offered</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Whether cancer is invasive or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Always (in e.g. Denmark)</td>
</tr>
<tr>
<td>30</td>
<td>Whether chemo therapy should be offered</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Type of chemo therapy medicine based on regimen chosen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dosis based on the correct input</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Weight</td>
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<tr>
<td></td>
<td></td>
<td>o Body Surface Area</td>
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<tr>
<td></td>
<td></td>
<td>• How to administer the medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Initial and continuous dosage differences</td>
</tr>
<tr>
<td>31</td>
<td>Whether radiation therapy should be offered</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lumpectomy or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mastectomy combined with some situations where the tumor was large and the lymph nodes involved</td>
</tr>
<tr>
<td>32</td>
<td>Whether biological therapy should be offered (Trastuzumab / Herceptin)</td>
<td>Based on whether</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HER2 positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Heart is strong enough (cf. above)</td>
</tr>
<tr>
<td>33</td>
<td>Whether hormone therapy should be offered</td>
<td>Based on whether hormone receptor (ER or PR) positive</td>
</tr>
<tr>
<td>34</td>
<td>Which kind of hormone treatment should be offered</td>
<td>Options are in overview:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ovarian ablation based on menopausal state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Surgical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tamoxifen based on menopausal state AND whether Tamoxifen has been used before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aromatase inhibitor based on menopausal state OR whether Tamoxifen has been used before</td>
</tr>
<tr>
<td>35</td>
<td>Whether Hormone Replacement Therapy should be discontinued</td>
<td>Based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Whether HRT was undertaken before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Except a few rare cases – and then particular medication is devised</td>
</tr>
<tr>
<td>Ref</td>
<td>Value expression</td>
<td>Input, based on</td>
</tr>
<tr>
<td>-----</td>
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</tr>
</tbody>
</table>
| 36  | Prognosis (Nottingham Prognostic Index) group | Based on  
   - Tumor size  
   - Lymph node involvement  
   - Histological grade (based on Bloom Richardson scale) |
| 37  | Body Surface Area calculation | Based on  
   - height and  
   - weigh  
   - and the selected formula  
     - DuBois  
     - Mosteller |
| 38  | Pregnancy Group | Number of pregnancies |
| 39  | Localization code | Distance and direction from center |
| 40  | Bloom Richardson scale evaluation (used in grading cf. above) | How the tumor appears in a microscope |
| 41  | Radiation dosage | |
The following is one of the value expressions, number 13 in the list above.

Cancer may spread from where it began to other parts of the body.

When cancer spreads to another part of the body, it is called metastasis. Cancer cells break away from where they began (the primary tumor) and travel through the lymph system or blood.

Lymph system. The cancer gets into the lymph system, travels through the lymph vessels, and forms a tumor (metastatic tumor) in another part of the body.

Blood. The cancer gets into the blood, travels through the blood vessels, and forms a tumor (metastatic tumor) in another part of the body.

The metastatic tumor is the same type of cancer as the primary tumor. For example, if breast cancer spreads to the bone, the cancer cells in the bone are actually breast cancer cells. The disease is metastatic breast cancer, not bone cancer.

The following stages are used for breast cancer:

This section describes the stages of breast cancer. The breast cancer stage is based on the results of testing that is done on the tumor and lymph nodes removed during surgery and other tests.

**Stage 0** (carcinoma in situ)

There are 3 types of breast carcinoma in situ:

**Ductal carcinoma in situ (DCIS)** is a noninvasive condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, DCIS may become invasive cancer and spread to other tissues. At this time, there is no way to know which lesions could become invasive. Enlarge

**Lobular carcinoma in situ** (LCIS) is a condition in which abnormal cells are found in the lobules of the breast. This condition seldom becomes invasive cancer. Information about LCIS is not included in this summary.
Lobular carcinoma in situ (LCIS). Abnormal cells are found in the lobules of the breast. Paget disease of the nipple is a condition in which abnormal cells are found in the nipple only.

Stage I

Stage I breast cancer. In stage IA, the tumor is 2 centimeters or smaller and has not spread outside the breast. In stage IB, no tumor is found in the breast or the tumor is 2 centimeters or smaller. Small clusters of cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes.

In stage I, cancer has formed. Stage I is divided into stages IA and IB.

In stage IA, the tumor is 2 centimeters or smaller. Cancer has not spread outside the breast.

In stage IB, small clusters of breast cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes and either:

- no tumor is found in the breast; or
- the tumor is 2 centimeters or smaller.

Stage II

Stage II is divided into stages IIA and IIB.

In stage IIA:
no tumor is found in the breast or the tumor is 2 centimeters or smaller. Cancer (larger than 2 millimeters) is found in 1 to 3 axillary lymph nodes or in the lymph nodes near the breastbone (found during a sentinel lymph node biopsy); or the tumor is larger than 2 centimeters but not larger than 5 centimeters. Cancer has not spread to the lymph nodes.

Stage IIA breast cancer. No tumor is found in the breast and cancer is found in 1 to 3 axillary lymph nodes or lymph nodes near the breastbone (left panel); OR the tumor is 2 centimeters or smaller and cancer is found in 1 to 3 axillary lymph nodes or lymph nodes near the breastbone (middle panel); OR the tumor is larger than 2 centimeters but not larger than 5 centimeters and has not spread to the lymph nodes (right panel).

In stage IIB, the tumor is:

larger than 2 centimeters but not larger than 5 centimeters. Small clusters of breast cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes; or

larger than 2 centimeters but not larger than 5 centimeters. Cancer has spread to 1 to 3 axillary lymph nodes or to the lymph nodes near the breastbone (found during a sentinel lymph node biopsy); or

larger than 5 centimeters. Cancer has not spread to the lymph nodes.

Stage IIB breast cancer. The tumor is larger than 2 centimeters but not larger than 5 centimeters and small clusters of cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes (left panel); OR the tumor is larger than 2 centimeters but not larger than 5 centimeters and cancer is found in 1 to 3 axillary...
Stage IIIA breast cancer. No tumor is found in the breast or the tumor may be any size and cancer is found in 4 to 9 axillary lymph nodes or lymph nodes near the breastbone (left panel); OR the tumor is larger than 5 centimeters and small clusters of cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes (middle panel); OR the tumor is larger than 5 centimeters and cancer is found in 1 to 3 axillary lymph nodes or lymph nodes near the breastbone (right panel).

In stage IIIA:

- no tumor is found in the breast or the tumor may be any size. Cancer is found in 4 to 9 axillary lymph nodes or in the lymph nodes near the breastbone (found during imaging tests or a physical exam); or
- the tumor is larger than 5 centimeters. Small clusters of breast cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes; or
- the tumor is larger than 5 centimeters. Cancer has spread to 1 to 3 axillary lymph nodes or to the lymph nodes near the breastbone (found during a sentinel lymph node biopsy).

Stage IIIB
Stage IIIB breast cancer. The tumor may be any size and cancer has spread to the chest wall and/or to the skin of the breast and caused swelling or an ulcer. Cancer may have spread to up to 9 axillary lymph nodes or the lymph nodes near the breastbone. Cancer that has spread to the skin of the breast may be inflammatory breast cancer.

In stage IIIB, the tumor may be any size and cancer has spread to the chest wall and/or to the skin of the breast and caused swelling or an ulcer. Also, cancer may have spread to:

- up to 9 axillary lymph nodes; or
- the lymph nodes near the breastbone.

Cancer that has spread to the skin of the breast may also be inflammatory breast cancer. See the section on Inflammatory Breast Cancer for more information.

Stage IIIC breast cancer. No tumor is found in the breast or the tumor may be any size and may have spread to the chest wall and/or to the skin of the breast and caused swelling or an ulcer. Also, cancer has spread to 10 or more axillary lymph nodes (left panel); OR to lymph nodes above or below the collarbone (middle panel); OR to axillary lymph nodes and lymph nodes near the breastbone (right panel). Cancer that has spread to the skin of the breast may be inflammatory breast cancer.

In stage IIIC, no tumor is found in the breast or the tumor may be any size. Cancer may have spread to the skin of the breast and caused swelling or an ulcer and/or has spread to the chest wall. Also, cancer has spread to:
10 or more axillary lymph nodes; or
lymph nodes above or below the collarbone; or
axillary lymph nodes and lymph nodes near the breastbone.

Cancer that has spread to the skin of the breast may also be inflammatory breast cancer. See the section on Inflammatory Breast Cancer for more information.

For treatment, stage IIIIC breast cancer is divided into operable and inoperable stage IIIIC.

Stage IV

Stage IV breast cancer. The cancer has spread to other parts of the body, most often the bones, lungs, liver, or brain.

In stage IV, cancer has spread to other organs of the body, most often the bones, lungs, liver, or brain.