Breast-conserving surgery followed by whole-breast irradiation offers survival benefits over mastectomy without irradiation

J. de Boniface1,2, J. Frisell1,3, L. Bergkvist4,5 and Y. Andersson4,5

1Department of Molecular Medicine and Surgery, Karolinska Institutet, 2Department of Surgery, Breast Centre, Capio St Göran’s Hospital, and 3Department of Breast and Endocrine Surgery, Karolinska University Hospital, Stockholm, and 4Centre for Clinical Research Uppsala University, Västmanland County Hospital, and 5Department of Surgery, Västmanland County Hospital, Västerås, Sweden

Correspondence to: Dr J. de Boniface, Department of Surgery, Breast Centre, Capio St Göran’s Hospital, Sankt Göransplan 1, SE-11281 Stockholm, Sweden (e-mail: jana.de-boniface@ki.se)

Background: The prognostic equivalence between mastectomy and breast-conserving surgery (BCS) followed by radiotherapy was shown in pivotal trials conducted decades ago. Since then, detection and treatment of breast cancer have improved substantially and recent retrospective analyses point towards a survival benefit for less extensive breast surgery. Evidence for the association of such survival data with locoregional recurrence rates is largely lacking.

Methods: The Swedish Multicentre Cohort Study prospectively included clinically node-negative patients with breast cancer who had planned sentinel node biopsy between 2000 and 2004. Axillary lymph node dissection was undertaken only in patients with sentinel node metastases. For the present investigation, adjusted survival analyses were used to compare patients who underwent BCS and postoperative radiotherapy with those who received mastectomy without radiotherapy.

Results: Of 3518 patients in the Swedish Multicentre Cohort Study, 2767 were included in the present analysis; 2338 had BCS with postoperative radiotherapy and 429 had mastectomy without radiotherapy. Median follow-up was 156 months. BCS followed by whole-breast irradiation was superior to mastectomy without irradiation in terms of both overall survival (79.5 versus 64.3 per cent respectively at 13 years; \( P < 0.001 \)) and breast cancer-specific survival (90.5 versus 84.0 per cent at 13 years; \( P < 0.001 \)). The local recurrence rate did not differ between the two groups. The axillary recurrence-free survival rate at 13 years was significantly lower after mastectomy without irradiation (98.3 versus 96.2 per cent; \( P < 0.001 \)).

Conclusion: The present data support the superiority of BCS with postoperative radiotherapy over mastectomy without radiotherapy. The axillary recurrence rate differed significantly, and could be one contributing factor in a complex explanatory model.

Paper accepted 8 April 2018
Published online 21 June 2018 in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.10889

Introduction

The pivotal trials showing equivalent oncological outcomes after breast-conserving surgery (BCS) with adjuvant whole-breast radiotherapy (RT) and after mastectomy were conducted decades ago1,2. Data from these trials have been crucial to change in the understanding of local treatment of breast cancer, but since then the scenario has changed substantially. Survival rates are increasing, probably owing to a combination of decreasing tumour size and fewer patients presenting with node-positive disease at diagnosis. At the same time, the use of adjuvant treatment has increased markedly, and is currently based more on tumour biology than disease stage.

In recent years, several large retrospective analyses of contemporary data3–5 have suggested the stage-adjusted superiority of BCS over mastectomy in early breast cancer in terms of breast cancer-specific survival and overall survival. Other publications have focused on young women6–8 or triple-negative breast cancer9, with the results indicating that BCS is at least as good as mastectomy in terms of survival outcomes. This interesting finding has led some authors to question whether mastectomy without RT should be offered at all as a treatment alternative for early breast cancer10, or whether it is time to abandon the ‘mastectomy myth’11. A convincing explanation for these observations is still lacking, and there might be explanatory factors that were not adjusted for...
in the mostly retrospective, non-randomized published studies.

Locoregional recurrence rates have reportedly been higher after BCS than mastectomy\(^2,12\), and especially so in triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer\(^13\), although contradictory results were reported by Zumsteg and colleagues\(^9\). Unfortunately, locoregional recurrence rates were rarely available in the abovementioned retrospective studies, as few registries provided reliable data on these events. Therefore, it has not been clearly shown whether locoregional recurrence is truly a more common event after BCS than mastectomy. Likewise, it could not be elucidated whether locoregional recurrences may explain the observed differences in survival after BCS and mastectomy.

Despite their impressive population sizes, retrospective observational analyses are not only prone to selection effects, but frequently also lack data on recurrence and oncological treatments administered. Therefore, the present analysis was performed using data from the Swedish Multicentre Cohort Study, in which patients were enrolled prospectively and followed up regularly, with the aim of comparing survival and locoregional recurrence rates following BCS with RT and mastectomy without RT.

**Methods**

Between September 2000 and January 2004, the prospective Swedish Multicentre Cohort Study enrolled patients with breast cancer from 26 Swedish hospitals. Level I and II completion axillary lymph node dissection (ALND) was undertaken only in patients with sentinel node-positive disease. Completion ALND was carried out if no sentinel lymph node could be identified. Inclusion criteria were: primary unifocal, clinically node-negative invasive breast cancer smaller than 30 mm in diameter at preoperative staging. Preoperative imaging comprised mammography and/or ultrasonography; MRI was not part of the study protocol. Patients whose tumours exceeded 30 mm in size on final histopathological examination no longer fulfilled the inclusion criteria and were excluded. Exclusion criteria were: neoadjuvant chemotherapy and/or RT, pregnancy, previous allergic reaction to blue dye or isotope, previous ipsilateral breast surgery and suspected tumour multifocality. The injection techniques used for sentinel node biopsy have been described in detail elsewhere\(^14,15\). Written informed consent was obtained from all patients before enrolment. The study was approved by the central ethics committee in Stockholm and the individual regional ethics committees before study initiation (no. 00-053; updated in 2015, no. 2015/979-32).

Follow-up was scheduled as annual mammography and clinical examination; however, telephone interviews by trained nurses were performed instead by a few centres. The recently updated database includes follow-up reports from each participating hospital submitted in autumn 2016 (last visit, incidence of breast cancer relapse, tumour location, contralateral breast cancer and death).

For the present analysis, patients were selected from the above cohort who met following additional criteria: they had to have follow-up within Sweden and have a confirmed invasive breast cancer on histopathology. Surgical axillary staging had to have been performed. Patients with previous or synchronous breast cancer were excluded. To restrict the selection of patients to those with early breast cancer, patients with a pathological tumour size larger than 30 mm or more than nine positive lymph nodes on ALND were also excluded, as were a few patients with distant metastases diagnosed within 2 months of study inclusion. To compare patients treated by BCS followed by whole-breast RT with patients undergoing mastectomy without RT, all other local treatment strategies were excluded (Fig. 1).

Breast cancer death was defined as death from breast cancer, and patients were censored either at the date of death or last date of follow-up if no breast cancer death had occurred. Data on breast cancer as a cause of death were received both from participating centres and from the national cause of death database. Isolated axillary recurrence was defined as an axillary nodal recurrence, without a concurrent ipsilateral in-breast recurrence diagnosed within 3 months before or after the axillary recurrence. Patients without any breast cancer event were censored at the date of last follow-up.
Table 1  Patient and tumour characteristics according to local treatment combination

|                          | BCS with RT (n = 2338) | Mastectomy without RT (n = 429) | P†  |
|--------------------------|------------------------|---------------------------------|-----|
| Patient age (years)‡     | 58 (23–88)             | 63 (28–94)                      | < 0·001‡ |
|  41                      | 86 (3–7)               | 22 (5–1)                        | < 0·001 |
| 41–50                    | 413 (17–7)             | 58 (13–5)                       |       |
| 51–65                    | 1276 (54–6)            | 165 (38–5)                      |       |
| > 65                     | 563 (24–1)             | 184 (42–9)                      |       |
| Invasive tumour size (mm) | 14 (1–30)              | 16 (2–30)                       | < 0·001‡ |
|  1–5                     | 82 (3–5)               | 15 (3–5)                        | < 0·001 |
| 6–10                     | 497 (21–3)             | 58 (13–5)                       |       |
| 11–20                    | 1413 (60–4)            | 245 (57–1)                      |       |
| 21–30                    | 346 (14–8)             | 111 (25–9)                      |       |
| Histological subtype     |                        |                                 | < 0·001 |
| Ductal                   | 1627 (69–6)            | 256 (59–7)                      |       |
| Lobular                  | 233 (10–0)             | 76 (17–7)                       |       |
| Other                    | 145 (6–2)              | 31 (7–2)                        |       |
| Ductal and lobular       | 17 (0–7)               | 5 (1–2)                         |       |
| Missing                  | 316 (13–5)             | 61 (14–2)                       |       |
| Multifocal tumour        |                        |                                 | < 0·001§ |
| Yes                      | 88 (3–8)               | 64 (14–9)                       |       |
| No                       | 2250 (96–2)            | 365 (85–1)                      |       |
| Nottingham Histological Grade |                  |                                 | 0·030 |
| 1                        | 661 (28–3)             | 95 (22–1)                       |       |
| 2                        | 1136 (48–6)            | 225 (52–4)                      |       |
| 3                        | 469 (20–1)             | 96 (22–4)                       |       |
| Missing                  | 72 (3–1)               | 13 (3–0)                        |       |
| Oestrogen receptor status|                        |                                 | 0·433§ |
| Positive                 | 1983 (84–8)            | 369 (86–0)                      |       |
| Negative                 | 309 (13–2)             | 50 (11–7)                       |       |
| Missing                  | 46 (2–0)               | 10 (2–3)                        |       |
| Progesterone receptor status |                    |                                 | 0·905§ |
| Positive                 | 1639 (70–1)            | 298 (69–5)                      |       |
| Negative                 | 630 (26–9)             | 116 (27–0)                      |       |
| Missing                  | 69 (3–0)               | 15 (3–5)                        |       |
| Pathological node category |                      |                                 | 0·024 |
| pN0                      | 1779 (76–1)            | 348 (81–1)                      |       |
| pN1                      | 489 (20–9)             | 76 (17–7)                       |       |
| pN2                      | 70 (3–0)               | 5 (1–2)                         |       |
| Adjuvant treatment       |                        |                                 | 0·207§ |
| Endocrine therapy        |                      |                                 |       |
| Yes                      | 1576 (67–4)            | 303 (70–6)                      |       |
| No                       | 722 (30–9)             | 119 (27–7)                      |       |
| Missing                  | 40 (1–7)               | 7 (1–6)                         |       |
| Chemotherapy             |                        |                                 |       |
| Yes                      | 489 (20–9)             | 52 (12–1)                       |       |
| No                       | 1779 (76–1)            | 372 (86–7)                      |       |
| Missing                  | 70 (3–0)               | 5 (1–2)                         |       |

Values in parentheses are percentages unless indicated otherwise; ‡values are median (range). BCS, breast-conserving surgery; RT, radiotherapy. †χ² test, except ‡Mann–Whitney U test and §Fisher’s exact test.

Statistical analysis

The initial power calculation has been described elsewhere; in the main trial, the primary endpoint was axillary recurrence. In the present study, breast cancer-specific survival was calculated from the date of operation to the date of breast cancer death or the date of last clinical follow-up, if death did not occur. Overall survival was calculated from the date of surgery to the date of death from any cause, or the date of last follow-up noted in the electronic patient charts, which are automatically linked to the population register containing information on death and date of death.

Descriptive data are presented as numbers with percentages and median (range). The Mann–Whitney U test was used for comparison of continuous variables in the two local treatment groups. The χ² test or Fisher’s exact test, as appropriate, was used for analysis of the distribution of categorical variables between the groups.
Table 2  Univariable and multivariable Cox regression analyses for overall survival

|                      | Univariable analysis |         |          |                      | Multivariable analysis |         |          |
|----------------------|----------------------|---------|----------|----------------------|------------------------|---------|----------|
|                      | Hazard ratio         | P       | Hazard ratio | P                   |                        | Hazard ratio | P       |
| Age (years)          |                      |         |            |                      |                        |                      |         |
| < 41                 | 0.20 (0.11, 0.37)    | < 0.001 | 0.16 (0.80, 0.34) | < 0.001             |                        |                      |         |
| 41–50                | 0.22 (0.17, 0.30)    | < 0.001 | 0.21 (0.15, 0.30) | < 0.001             |                        |                      |         |
| 51–65                | 0.40 (0.34, 0.47)    | < 0.001 | 0.41 (0.34, 0.49) | < 0.001             |                        |                      |         |
| > 65                 | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Invasive tumour size (mm) |                  |         |            |                      |                        |                      |         |
| 1–5                  | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| 6–10                 | 0.98 (0.58, 1.67)    | 0.951   | 1.19 (0.59, 2.40) | 0.625              |                        |                      |         |
| 11–20                | 1.47 (0.89, 2.42)    | 0.133   | 1.63 (0.83, 3.18) | 0.154              |                        |                      |         |
| 21–30                | 2.26 (1.35, 3.79)    | 0.002   | 2.09 (1.05, 4.15) | 0.036              |                        |                      |         |
| Histological subtype |                      |         |            |                      |                        |                      |         |
| Ductal               | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Lobular              | 1.02 (0.80, 1.31)    | 0.850   | 0.79 (0.61, 1.03) | 0.088              |                        |                      |         |
| Other                | 0.85 (0.61, 1.18)    | 0.332   | 0.82 (0.57, 1.20) | 0.317              |                        |                      |         |
| Ductal and lobular   | 0.35 (0.09, 1.41)    | 0.141   | 0.38 (0.09, 1.53) | 0.172              |                        |                      |         |
| Multifocal tumour    |                      |         |            |                      |                        |                      |         |
| Yes                  | 1.04 (0.75, 1.45)    | 0.812   | 0.94 (0.65, 1.37) | 0.756              |                        |                      |         |
| No                   | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Pathological node category |            |         |            |                      |                        |                      |         |
| pN0                  | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| pN1                  | 1.37 (1.15, 1.64)    | 0.001   | 1.58 (1.27, 1.96) | < 0.001             |                        |                      |         |
| pN2                  | 2.00 (1.36, 2.92)    | < 0.001 | 2.75 (1.77, 4.28) | < 0.001             |                        |                      |         |
| Nottingham Histological Grade |    |         |            |                      |                        |                      |         |
| 1                    | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| 2                    | 1.77 (1.44, 2.18)    | < 0.001 | 1.80 (1.39, 2.31) | < 0.001             |                        |                      |         |
| 3                    | 2.09 (1.65, 2.64)    | < 0.001 | 2.23 (1.64, 3.02) | < 0.001             |                        |                      |         |
| Oestrogen receptor status |             |         |            |                      |                        |                      |         |
| Positive             | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Negative             | 1.35 (1.09, 1.66)    | 0.005   | 1.45 (1.02, 2.05) | 0.037              |                        |                      |         |
| Progesterone receptor status |             |         |            |                      |                        |                      |         |
| Positive             | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Negative             | 1.29 (1.09, 1.52)    | 0.003   | 0.98 (0.77, 1.23) | 0.838              |                        |                      |         |
| Adjuvant chemotherapy |                      |         |            |                      |                        |                      |         |
| Yes                  | 1.17 (0.96, 1.44)    | 0.122   | 1.22 (0.92, 1.62) | 0.174              |                        |                      |         |
| No                   | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Adjuvant endocrine therapy |             |         |            |                      |                        |                      |         |
| Yes                  | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| No                   | 0.90 (0.75, 1.05)    | 0.176   | 1.00 (0.78, 1.29) | 0.999              |                        |                      |         |
| Local treatment      |                      |         |            |                      |                        |                      |         |
| BCS with RT          | 1.00 (reference)     |         | 1.00 (reference) |                      |                        |                      |         |
| Mastectomy without RT | 1.87 (1.56, 2.24)    | < 0.001 | 1.70 (1.38, 2.10) | < 0.001             |                        |                      |         |

Values in parentheses are 95 per cent confidence intervals. BCS, breast-conserving surgery; RT, radiotherapy.

Survival analysis was first performed by the Kaplan–Meier method, with comparison of survival curves by means of the log rank test. Cox proportional hazards regression analysis was then added to adjust the results for tumour and patient characteristics. All variables listed in Table 1 were included in the multivariable regression analysis, regardless of their significance on univariable regression. Surrogate tumour subtypes were not included to avoid confounding with the underlying factors already included in the analysis. Results are presented as hazard ratios (HRs) with 95 per cent confidence intervals.

All data analysis was performed using SPSS® version 22 (IBM, Armonk, New York, USA). Statistical significance was set at a level of 5 per cent for all analyses.

**Results**

**Overall and breast cancer-specific survival according to local treatment**

Of 3518 patients enrolled in the Swedish Multicentre Cohort Study, 2767 remained in the analysis after applying the selection criteria (Fig. 1); 429 patients underwent...
Table 3 Univariable and multivariable Cox regression analyses breast cancer-specific survival

| Age (years)          | Univariable analysis | Multivariable analysis |
|----------------------|----------------------|------------------------|
|                      | Hazard ratio | P   | Hazard ratio | P   |
| < 41                 | 0.66 (0.34, 1.27)  | 0.216 | 0.43 (0.19, 0.96) | 0.041 |
| 41–50                | 0.68 (0.48, 0.98)  | 0.039 | 0.63 (0.41, 0.97) | 0.035 |
| 51–65                | 0.68 (0.52, 0.89)  | 0.005 | 0.72 (0.53, 0.99) | 0.044 |
| > 65                 | 1.00 (reference)   |       | 1.00 (reference) |       |

| Invasive tumour size (mm) | Univariable analysis | Multivariable analysis |
|---------------------------|----------------------|------------------------|
| 1–5                       | 1.00 (reference)     | 1.00 (reference)       |
| 6–10                      | 0.80 (0.30, 2.11)    | 0.653                  | 0.88 (0.26, 3.02) | 0.840 |
| 11–20                     | 2.00 (0.82, 4.87)    | 0.127                  | 1.80 (0.57, 5.70) | 0.319 |
| 21–30                     | 3.90 (1.58, 9.63)    | 0.003                  | 2.39 (0.74, 7.71) | 0.146 |

| Histological subtype      | Univariable analysis | Multivariable analysis |
|---------------------------|----------------------|------------------------|
| Ductal                    | 1.00 (reference)     | 1.00 (reference)       |
| Lobular                   | 0.99 (0.68, 1.44)    | 0.974                  | 0.91 (0.60, 1.37) | 0.648 |
| Other                     | 0.80 (0.47, 1.35)    | 0.400                  | 0.96 (0.54, 1.70) | 0.885 |
| Ductal and lobular        | 0.41 (0.06, 2.93)    | 0.375                  | 0.38 (0.05, 2.79) | 0.345 |

| Multifocal tumour         | Univariable analysis | Multivariable analysis |
|---------------------------|----------------------|------------------------|
| Yes                       | 0.93 (0.54, 1.59)    | 0.783                  | 0.84 (0.47, 1.50) | 0.566 |
| No                        | 1.00 (reference)     | 1.00 (reference)       |

| Pathological node category| Univariable analysis | Multivariable analysis |
|---------------------------|----------------------|------------------------|
| pN0                       | 1.00 (reference)     | 1.00 (reference)       |
| pN1                       | 2.20 (1.70, 2.83)    | < 0.001               | 2.77 (1.63, 4.72) | < 0.001 |
| pN2                       | 3.74 (2.33, 6.02)    | < 0.001               | 2.64 (1.93, 3.60) | < 0.001 |

| Nottingham Histological Grade | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
| 1                             | 1.00 (reference)     | 1.00 (reference)       |
| 2                             | 2.82 (1.89, 4.21)    | < 0.001               | 2.33 (1.48, 3.67) | < 0.001 |
| 3                             | 5.30 (3.51, 8.00)    | < 0.001               | 3.88 (2.26, 6.37) | < 0.001 |

| Oestrogen receptor status    | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
| Positive                     | 1.00 (reference)     | 1.00 (reference)       |
| Negative                     | 2.12 (1.60, 2.80)    | < 0.001               | 1.76 (1.05, 2.97) | 0.033 |

| Progesterone receptor status | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
| Positive                     | 1.00 (reference)     | 1.00 (reference)       |
| Negative                     | 1.80 (1.41, 2.30)    | < 0.001               | 1.21 (0.85, 1.71) | 0.288 |

| Adjuvant chemotherapy        | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
| Yes                           | 0.65 (0.50, 0.85)    | 0.001                  | 1.13 (0.94, 2.02) | 0.101 |
| No                            | 1.00 (reference)     | 1.00 (reference)       |

| Adjuvant endocrine therapy   | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
| Yes                           | 1.00 (reference)     | 1.00 (reference)       |
| No                            | 0.93 (0.72, 1.21)    | 0.593                  | 0.89 (0.58, 1.37) | 0.603 |

| Local treatment              | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
| BCS with RT                   | 1.00 (reference)     | 1.00 (reference)       |
| Mastectomy without RT         | 1.76 (1.33, 2.33)    | < 0.001               | 1.69 (1.22, 2.33) | 0.001 |

Values in parentheses are 95 per cent confidence intervals. BCS, breast-conserving surgery; RT, radiotherapy.

mastectomy without RT and 2338 had BCS followed by whole-breast RT.

Median follow-up was 156 (range 0–189) months; there was one postoperative death from cardiac failure. Overall, there were 653 deaths, translating into a 13-year overall survival rate of 77·2 per cent for the entire cohort (79·5 per cent for BCS with RT and 64·3 per cent for mastectomy without RT; P < 0·001) (Fig. 2). A total of 277 patients died from breast cancer, with a 13-year breast cancer-specific survival rate of 89·6 per cent for the entire cohort (90·5 per cent for BCS with RT and 84·0 per cent for mastectomy without RT; P < 0·001) (Fig. 3).

Patient and tumour characteristics are presented in Table 1. Notably, patients in the mastectomy group differed from those in the BCS group in terms of a higher percentage of lobular and multifocal tumours of a higher histological grade and larger size in an older population. In the BCS group, more patients had positive lymph nodes and had received chemotherapy. To allow for these group differences, survival outcomes were adjusted for all factors listed in Table 1 in multivariable Cox regression analyses. These analyses showed that treatment with mastectomy without RT was an independent negative factor for overall survival (HR 1·70, 95 per cent c.i. 1·38
to 2-10), together with oestrogen receptor (ER) negativity, higher tumour grade, higher nodal category, tumour size above 20 mm and older age (Table 2). Findings were similar for breast cancer-specific survival (Table 3); being treated by mastectomy without adjuvant RT was an independent negative factor (HR 1.69, 1.22 to 2.33), as were ER negativity, older age, higher tumour grade and higher nodal category.

**Locoregional recurrence rates according to local treatment and impact on survival**

As the isolated axillary recurrence rate was the primary endpoint of the prospective cohort study, this outcome was compared between the two treatment groups. Overall, 41 isolated axillary recurrences were found (1.5 per cent): 26 (1.1 per cent) after BCS with RT and 15 (3.5 per cent) after mastectomy without RT ($P = 0.001$). The resulting 13-year isolated axillary recurrence-free survival rates were 98.3 and 96.2 per cent respectively ($P < 0.001$). Median time to isolated axillary recurrence was 39 (range 4–157) months overall: 39.5 (10–157) months for BCS with RT and 39 (4–117) months for mastectomy without RT ($P = 0.357$). Of 41 isolated axillary recurrences, 31 occurred in patients with node-negative disease.

Overall, 139 recurrences within the ipsilateral breast or chest wall were recorded, with 13-year local recurrence-free survival rates of 90.5 and 95.1 per cent in the BCS with RT and mastectomy without RT groups respectively ($P = 0.428$).

Both local recurrence and isolated axillary recurrence were strong independent predictors of breast cancer death, with HRs of 3.04 (95 per cent c.i. 2.05 to 4.50) and 4.28 (2.55 to 7.17) respectively when these events were added separately into the multivariable regression analysis performed previously. The same was true for overall survival as an endpoint in the case of isolated axillary recurrence, with a HR of 2.64 (1.66 to 4.19); local recurrence showed a near-significant association with worse overall survival (HR 1.40, 1.00 to 1.96).

Independent risk factors for developing an isolated axillary recurrence on multivariable Cox regression analysis were undergoing mastectomy without adjuvant RT (HR 2.98, 1.44 to 6.17) and high histological grade (HR 3.94, 1.28 to 12.16). Even adjusting for the number of excised axillary lymph nodes did not change the HR for mastectomy without RT compared with BCS with RT; 12 of 15 cases of isolated axillary recurrence after mastectomy without RT were classified as node-negative and the patients underwent sentinel node biopsy only.

**Discussion**

This large prospective cohort study of early breast cancer with long follow-up has confirmed the superiority of BCS with postoperative RT over mastectomy without RT in terms of breast cancer-specific survival and overall survival. Although a number of explanatory factors, such as selection bias owing to co-morbidity and socioeconomic factors, remain unknown, an increased axillary recurrence rate after mastectomy without RT may be one of several factors contributing to this finding. It is possible that tangential RT fields originating from whole-breast RT after BCS exert some protective effect on axillary recurrence by controlling minimal residual disease, although this could not fully explain the survival advantage in patients treated with BCS with RT over those who underwent mastectomy without RT.

False-negative rates in sentinel node biopsy range between 0 and 40 per cent, with a median of 7 per cent. Despite this, axillary recurrences after a negative sentinel node biopsy are rare, which may be attributed to improved systemic therapies, unintended RT to the lower axilla by tangential fields in whole-breast irradiation, and immunological processes. In the present cohort, the 10-year axillary recurrence rate among node-negative individuals was only 1.6 per cent. Interestingly, most reports and reviews on axillary recurrence rates after a negative sentinel node biopsy without completion axillary dissection did not elaborate on differences between BCS and mastectomy.

One exception is the report from Milan by Galimberti and colleagues on a cohort of 5262 patients with a median follow-up of 7 years. In this study, both external-beam RT and BCS were shown to be significantly protective of axillary recurrence as a first event; however, both lost statistical significance on multivariable analysis. From the same institution, Gentilini and co-workers recently published data on an interesting comparison of axillary recurrence rates in patients operated by BCS and irradiated by external-beam whole-breast RT or by intraoperative partial breast irradiation. The 10-year cumulative incidence of axillary recurrence was significantly lower for those receiving whole-breast RT (1.3 versus 4.0 per cent), clearly demonstrating an effect of unintentional RT to the lower axilla resulting from tangential fields in whole-breast irradiation.

The proportion of axillary levels I–II receiving 95 per cent of the isodose by standard tangential fields varies between 23 and 87 per cent (average 55 per cent); likewise, it was shown that between 5 and 80 (mean 48.7) per cent of the 50-Gy RT dose intended for the breast reached the lower axilla. It is therefore agreed that whole-breast RT does not achieve adequate axillary coverage if high...
tangents are not used, as in the present study. Despite this, there is mounting clinical evidence that even standard tangential fields provide a degree of regional control. A 2011 review reported that external-beam whole-breast irradiation decreased the rate of axillary recurrence after a negative sentinel node biopsy. Likewise, the watershed randomized trials on sentinel node-positive patients not undergoing completion axillary dissection demonstrated much lower axillary recurrence rates than expected, only enrolling patients treated by BCS with mandatory whole-breast irradiation. Although it could be argued that systemic treatment effects must play a major part in these results in node-positive populations, this is likely to have less impact in the present analysis as only a minority of patients received adjuvant chemotherapy.

An important drawback of the present analysis is that socioeconomic differences and co-morbidities were not registered prospectively at the time of study, precluding the analysis of these potentially significant confounders. Furthermore, detailed information on irradiation doses and target volumes was not recorded, but high tangents were not in use in whole-breast or chest-wall irradiation. A major composite impact of these factors is certainly to be expected because the increased axillary recurrence rate, although significant, cannot explain the observed differences in survival rates. In addition, there were several significant baseline differences between the two groups, which in large part can be explained by the underlying selection mechanisms for the surgical methods studied. Multifocality, for example, is known as an independent predictor of the surgical choice of mastectomy, but may at the same time represent both a risk factor for a false-negative sentinel node biopsy and for worse prognosis. This factor, however, was not identified as an independent predictor in the adjusted analyses, which is in line with publications reporting that the type of surgery might not influence the association between multifocality and worse tumour characteristics and outcome. The observed group differences do pose a substantial problem, but as randomized prospective trials in this area are unlikely to be undertaken in the near future, this large prospective cohort comes as close to a controlled setting as possible.

This large prospective cohort study has provided further support for the survival benefits resulting from BCS followed by whole-breast irradiation in patients with early breast cancer. The data indicate a contributory role of partial RT coverage of the lower axillary levels in the avoidance of axillary recurrences; however, the improvements in breast cancer-specific survival and overall survival call for further explanatory factors, and socioeconomic variables and co-morbidity should receive closer scrutiny.

The present data do not support the historical claim that there is a higher risk of local recurrence after BCS followed by RT.

Acknowledgements

The authors thank all responsible surgeons and staff at participating centres for enrolling and following patients, and the Centre for Clinical Research Västerås of Uppsala University for data management. The study received funding from the Swedish Society for Medical Research, the Swedish Breast Cancer Association, the Swedish Cancer Society and the Centre for Clinical Research, Uppsala University. No preregistration exists for the studies reported in this article. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Disclosure: The authors declare no conflict of interest.

References

1 Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1989; 320: 822–828.
2 Veronesi U, Cugini M, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347: 1227–1232.
3 van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol 2016; 17: 1158–1170.
4 Hofvind S, Holen A, Aas T, Roman M, Sebuodegård S, Akslen LA. Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumor characteristics. Eur J Surg Oncol 2015; 41: 1417–1422.
5 Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 2014; 149: 267–274.
6 Bantema-Joppe EJ, de Munck L, Visser O, Willemsen PH, Langendijk JA, Siesling S et al. Early-stage young breast cancer patients: impact of local treatment on survival. Int J Radiat Oncol Biol Phys 2011; 81: e553–e559.
7 Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (≤ 40 years) early breast cancer patients: a systematic meta-analysis comparing...
breast-conserving surgery versus mastectomy. *Breast* 2015; 24: 175–181.
8 Ye JC, Yan W, Christos PJ, Nori D, Ravi A. Equivalent survival with mastectomy or breast-conserving surgery plus radiation in young women aged < 40 years with early-stage breast cancer: a national registry-based stage-by-stage comparison. *Clin Breast Cancer* 2015; 15: 390–397.
9 Zumsteg ZS, Morrow M, Arnold B, Zheng J, Zhang Z, Robson M et al. Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1–2 N0 triple-negative breast cancer. *Ann Surg Oncol* 2013; 20: 3469–3476.
10 Johns N, Dixon JM. Should patients with early breast cancer still be offered the choice of breast conserving surgery or mastectomy? *Eur J Surg Oncol* 2016; 42: 1636–1641.
11 McCormick B. The mastectomy myth. *Lancet Oncol* 2016; 17: 1033–1037.
12 Jatoi I, Proschan MA. Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: a pooled analysis of updated results. *Am J Clin Oncol* 2005; 28: 289–294.
13 Millar EK, Graham PH, O’Toole SA, McNeil CM, Browne L, Morey Al. et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. *J Clin Oncol* 2009; 27: 4701–4708.
14 Andersson Y, de Boniface J, Jönsson PE, Ingvar C, Liljegren G, Bergkvist L et al.; Swedish Breast Cancer Group; Swedish Society of Breast Surgeons. Axillary recurrence rate 5 years after negative sentinel node biopsy for breast cancer. *Br J Surg* 2012; 99: 226–231.
15 Bergkvist L, de Boniface J, Jönsson PE, Ingvar C, Liljegren G, Frisell J; Swedish Society of Breast Surgeons. Axillary recurrence rate after negative sentinel node biopsy in breast cancer: three-year follow-up of the Swedish Multicenter Cohort Study. *Ann Surg Oncol* 2008; 247: 150–156.
16 Nieweg OE, Jansen L, Valdes Olmos RA, Rutgers EJ, Peterse JL, Hoefnagel KA et al. Lymphatic mapping and sentinel lymph node biopsy in breast cancer. *Eur J Nucl Med Mol Imaging* 1999; 26(Suppl): S11–S16.
17 de Boniface J, Frisell J, Bergkvist L, Andersson Y; Swedish Breast Cancer Group and the Swedish Society of Breast Surgery. Ten-year report on axillary recurrence after negative sentinel node biopsy for breast cancer from the Swedish Multicentre Cohort Study. *Br J Surg* 2017; 104: 238–247.
18 van der Ploeg IM, Nieweg OE, van Rijk MC, Valdés Olmos RA, Kroon BB. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: a systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008; 34: 1277–1284.
19 Pepels MJ, Vestjens JH, de Boer M, Smidt M, van Diest PJ, Borm GF et al. Safety of avoiding routine use of axillary dissection in early stage breast cancer: a systematic review. *Breast Cancer Res Treat* 2011; 125: 301–313.
20 Galimberti V, Manika A, Maisonneuve P, Corso G, Salazar Moltrasio L, Intra M et al. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. *Eur J Surg Oncol* 2014; 40: 1201–1208.
21 Gentilini O, Botteri E, Leonardi MC, Rotmensz N, Vila J, Peradze N et al. Ipsilateral axillary recurrence after breast conservative surgery: the protective effect of whole breast radiotherapy. *Radiother Oncol* 2017; 122: 37–44.
22 Reed DR, Lindsley SK, Mann GN, Austin-Seymour M, Korsjoen T, Anderson BO et al. Axillary lymph node dose with tangential breast irradiation. *Int J Radiat Oncol Biol Phys* 2005; 61: 358–364.
23 Orcetti R, Hatcher A, Leonardi MC, Gennari R, Galimberti V, Garibaldi C et al. Irradiation with standard tangential breast fields in patients treated with conservative surgery and sentinel node biopsy: using a three-dimensional tool to evaluate the first level coverage of the axillary nodes. *Br J Radiol* 2005; 78: 51–54.
24 van Wely BJ, Teerenstra S, Schinagl DA, Aufenacker TJ, de Wilt JHI, Strobbe LJ. Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy. *Br J Surg* 2011; 98: 326–333.
25 Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencrzan P, Leitch AM et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010; 252: 426–432.
26 Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P et al.; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013; 14: 297–305.
27 Andersson Y, Frisell J, Sylvan M, de Boniface J, Bergkvist L. Causes of false-negative sentinel node biopsy in patients with breast cancer. *Br J Surg* 2013; 100: 775–783.
28 Schiule J, Frisell J, Ingvar C, Bergkvist L. Sentinel node biopsy for breast cancer larger than 3 cm in diameter. *Br J Surg* 2007; 94: 948–951.
29 Weissenbacher TM, Zschage M, Janni W, Jeschke U, Dimpf T, Mayr D et al. Multicentric and multifocal versus unifocal breast cancer: is the tumor-node-metastasis classification justified? *Breast Cancer Res Treat* 2010; 122: 27–34.
30 Lynch SP, Lei X, Hsu L, Meric-Bernstam F, Buchholz TA, Zhang H et al. Breast cancer multifocality and multicentricity and locoregional recurrence. *Oncologist* 2013; 18: 1167–1173.
31 Shaikh T, Tam TY, Li T, Hayes SB, Goldstein L, Bleicher R et al. Multifocal and multicentric breast cancer is associated with increased local recurrence regardless of surgery type. *Breast* 2015; 21: 121–126.