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**Prognosis after treatment for loco-regional recurrence in 535 high-risk breast cancer patients from the DBCG 82 b&c randomization studies**

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**Background and aim:** In the DBCG 82 b&c trials 3083 patients with stage II and III breast cancer were randomized to ± postmastectomy RT. The aim of the present study was to investigate the prognosis after loco-regional recurrence (LRR) and to compare different types of salvage treatment.
**Material and methods:** A total of 535 patients from the DBCG 82 b&c trials experienced a LRR a first and only site of failure. LRR was defined as recurrence on the chest wall, axillary or supra/infraclavicular regions without concomitant distant metastases (DM). Follow-up data were selected from medical records and general practitioners. Endpoints were overall survival and DM. The different type of salvage treatments were compared in terms of their ability of achieving complete remission and persistent loco-regional control of the LRR.
**Results:** Complete remission of the LRR depended on type of salvage treatment and was 96% among patients having surgery+RT (176/183), 93% among patients having surgery alone (139/149), 81% among patients having RT alone (88/109) and 46% among patients having systemic treatment alone (37/80). Persistent loco-regional control was 58% among patients having surgery+RT (107/183), 32% among patients having surgery alone (47/149), 49% among patients having RT alone (53/109) and finally 25% among patients having systemic treatment alone (20/80).
The 5-, 10- and 15-year survival after LRR was 36%, 20% and 14%, respectively. The 5-, 10- and 15-year actuarial probability of DM was 73%, 81% and 84%, respectively. In univariate analysis, original randomization group was not important for survival ($p = 0.15$), whereas site of LRR ($p < 0.001$), time interval to LRR ($p < 0.001$) and the following original tumor variables: tumor size ($p = 0.001$), malignancy grade ($p = 0.002$), invasion of the skin ($p = 0.02$), invasion of the fascia ($p = 0.01$), number of positive nodes ($p < 0.001$) and extracapsular invasion ($p = 0.001$) were prognostic factors for survival. In multivariate analysis small primary tumor size ($p = 0.01$), chest wall or axillary failure alone ($p < 0.001$) and long interval to LRR > 2 years ($p < 0.001$) were independent good prognostic factors for survival.
**Conclusion:** Persistent loco-regional control was increased among patients having surgery and RT as salvage treatment after LRR. Survival after treatment for LRR was poor, but with independent good prognostic factors for survival being small primary tumor, location of the LRR at the chest wall or in the axilla and a long time interval from mastectomy to LRR of more than 2 years.
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**Long-term risk of cardiovascular disease in 10-year survivors of breast cancer**

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**Purpose:** To assess cardiac risk according to radiation field in breast cancer patients, accounting for cardiac risk factors.
**Patients and methods:** We studied incidence of cardiovascular disease (CVD) in a group of 10-year survivors (n = 4368) who were treated in the NKI and the DDHK for early breast cancer between 1970 and 1987. Follow-up was for 98% complete until January 2000. Treatment-specific incidence of CVD was evaluated by calculating standardized incidence ratios (SIRs) based on comparison with general population rates and by using Cox proportional hazards regression.
**Results:** After a median follow-up of 18 years 942 cardiovascular events (acute myocardial infarction (MI), angina pectoris and congestive heart failure) were observed resulting in a SIR of 1.3 (95%CI: 1.2–1.4) and an absolute excess risk of 63/10,000 person-years. For the treatment period 1970–79, radiotherapy (RT) on the internal mammary chain (IMC) was associated with an increased risk of MI both for patients wit left- and right-sided tumors in comparison with non-irradiated patients; hazard ratio (HR), 2.2; 95%CI: 1.3–3.7, and 2.9; 95%CI: 1.7–5.1, respectively, while for the treatment period 1980–86, these risks had declined to 0.8 (0.4–1.6) and 0.9 (0.5–1.7), respectively. Patients irradiated on the left chest wall experienced a significantly increased risk of MI as compared to those treated with surgery only in both treatment periods (HR, 2.8; 95%CI: 1.4–5.5, and 3.7; 95%CI: 1.2–11.5, respectively). RT on the right chest wall showed a non-significantly 1.5-fold increased risk of MI for the period 1970–79, while from 1980 on, no MIs occurred in this treatment group. RT on the breast only, applied from 1980 on, was not associated with an increased risk of MI, with HRs of 0.7 (95%CI: 0.3–1.6) for left-sided, and 0.9 (95%CI: 0.4–2.2) for right-sided tumors. Hypertension, smoking, diabetes mellitus and hypercholesterolemia acted as independent risk factors for MI, with HRs of 2.0 (1.5–2.7), 2.1 (1.5–2.7), 1.3 (0.9–1.8) and 3.0 (2.2–4.1), respectively. Analysis on the combined effects of smoking and RT revealed a more than additive effect on MI, with a HR of 3.0; 95%CI: 2.0–4.5 (HR for irradiated non-smokers, 1.3; HR for non-irradiated smokers, 1.4).
**Conclusions:** Radiotherapy after 1979 is not associated with increased MI risk, with the only exception for radiation to the left chest wall. The combination of smoking and RT appears to exert a greater than additive effect on MI risk.

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**Lymph node ratio as prognostic factor in node-positive breast cancer**

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**Background:** The latest AJCC/TNM Cancer Staging 6th edition introduced over previous editions major changes in the pathologic nodal (pN) staging that more accurately reflect breast cancer disease continuum. However, concerns have been expressed regarding stage migration, i.e. decreased separation between prognostic groups due to reclassification. Some authors have suggested the lymph node ratio (LNR), defined as the proportion of involved nodes among excised nodes, as a potential alternative. But, before the LNR can be considered for staging, many issues must be settled. Studies of the LNR have been based on relatively homogeneous single institution data, or on large population data but with restrictive selection and using complex multivariate models. The present study will address how the LNR performs, without adjustment, in heterogeneous cases.
**Material and Methods:** Data for women diagnosed in 1988–97 with primary invasive node-positive breast carcinoma were abstracted from the Surveillance, Epidemiology, and End Results 9-registries (SEER 2004). Other than required histology confirmation (pathologic staging), there were no restrictions based on tumour size, age, or treatment. Cases with biopsy only and as few as one node examined were eligible. Three LNR groups were defined: low LNR ($\leqslant 0.25$), intermediate LNR (0.25–0.75), and high LNR ($> 0.75$). Classification performance was evaluated by the survival separation between prognostic groups, as compared with the TNM pN categories. The LNR and the TNM pN were examined within cases previously staged according to the AJCC 3rd edition. Survival estimates used the Kaplan-Meier method. Event was death from any-cause. Significance testing used the logrank test, larger values of $Chi^2$ indicating better separation.

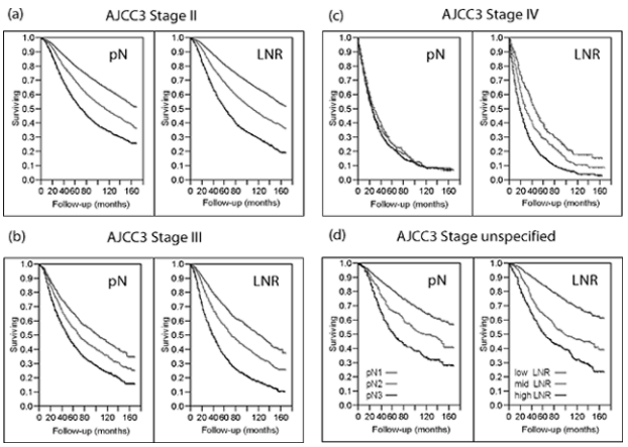


Fig. 1: Overall survival in node-positive breast cancer. Nodal classification based on the 6th TNM (pN) compared with classification based on Lymph node ratio (LNR), applied to cases already previously staged according to the 3th AJCC TNM system (AJCC3).

**Results:** 37,015 cases were available. Median follow-up was 94 months (range 0–167), age 58 years (21–100), tumour size 24 mm (0–930), number involved nodes 3 (1–75), nodes examined 15 (1–90). Ten-year overall survival (OS) was 51.9% (95% confidence interval 51.3–52.5). By TNM, OS ranged from 61.0% (60.2–61.8) in pN1, to 28.5% (28.5–29.9) in pN3, with $Chi^2 = 2777.7$. By LNR, OS ranged from 62.9% (62.1–63.6) in low-LNR to 22.5% (21.1–23.9) in high-LNR, $Chi^2 = 4499.9$. Table 1 shows OS when TNM and LNR were applied to cases previously staged with AJCC3. Figure 1 displays wider prognostic separation by LNR.

Table 1: AJCC3

| | No. of | pN*i* 10yOS | | | TNM | LNR 10yOS | | | LNR |
|---|---|---|---|---|---|---|---|---|---|
| | cases | pN1 | pN2 | pN3 | $Chi^2$ | Low | Mid | High | $Chi^2$ |
| Stage II | 27,525 | 63.6% | 48.5% | 34.5% | 1328.4 | 64.3% | 47.4% | 29.5% | 1783.3 |
| Stage III | 6,128 | 45.5% | 36.0% | 24.2% | 238.7 | 50.9% | 35.4% | 17.8% | 615.6 |
| Stage IV | 1,301 | 9.4% | 9.1% | 8.9% | 0.4 | 18.0% | 10.7% | 4.8% | 83.4 |
| Unstaged | 2,061 | 64.9% | 50.4% | 33.9% | 132.1 | 69.3% | 47.2% | 32.3% | 221.9% |

**Conclusion:** LNR consistently improved nodal classification. Further investigations on its role for staging are warranted.

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**Tumour positive sentinel node findings in patients with DCIS**

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**Introduction:** Ductal carcinoma in situ (DCIS) is nowadays a common finding in patients with screen detected breast cancer. There are no axillary metastases in DCIS, by definition. However, even the most meticulous histological examination of the mastectomy or breast resection specimen may fail to reveal invasion. Our aim was to evaluate the prevalence of sentinel node metastases in patients with DCIS.
**Methods:** Altogether 1470 patients underwent sentinel node biopsy between April 2004 andMarch 2005 in the Breast Surgery Unit of Helsinki University Central Hospital. 93 of them had DCIS, with or without microinvasion in the in the breast resection or mastectomy specimen. These 93 patients were included in the study. A prospectively collected database was used.
**Results:** Tumour positive sentinel node findings were detected in 6 (6%) patients. One patient had a 7 mm metastasis and another a 1, 95 mm micrometastasis. The remaining four patients had isolated tumour cells only. Four patients had tumour positive sentinel findings in the intraoperative diagnosis. They underwent axillary clearance without further metastatic findings. Axillary clearance as a second operation was omitted in two patients with false negative intraoperative findings. Both of them had isolated tumour cells in a single sentinel node in the postoperative diagnosis.
**Conclusions:** The majority of the tumour positive sentinel node findings in patients with DCIS are micrometastases or isolated tumour cells only, without further metastases in the axillary clearance specimen. Apart from signs of missed invasion, these findings may represent tumour cells transported to the nodes by passive mechanisms due to preoperative breast manipulation. When micrometastases or isolated tumour cells are encountered in patients with pure DCIS in the breast resection or mastectomy specimen, axillary clearance is not warranted.

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**French National Survey on DCIS; analysis of clinico-pathological features and treatments in 1289 patients.**

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**Introduction:** DCIS represents 10–15% of all breast cancers (BC), but its treatment has changed over the past 20 years.
**Material and methods:** A prospective, nationwide survey on pure DCIS was conducted in 77 centres in France from March 2003 to April 2004, to assess epidemiological, radiological, pathological features and treatment options. 1289 patients were evaluable: 53% were treated in cancer centres, 28% in private clinics and 19% in University hospitals. Median age was 56 years.
**Results:** Conservative surgery alone (CS), CS with radiotherapy (CS+RT) and mastectomy (M) were performed in 99 (7.7%), 797 (61.8%) and 393 (30.5%) patients, respectively. 385 (30.2%) patients had BC family history. Among 816 menopausal women, 417 (52.3%) underwent hormonal replacement therapy (HRT). Radiological and pathological features are detailed in the table according to treatment groups. In the CS+RT group, a 50-Gy median dose was delivered to the breast, with a 10-Gy boost in 49% of the cases. 170 patients underwent endocrine therapy, 138 by Tamoxifen, 25 by Aromatase Inhibitors and 7 by LHRH agonists. Important inter-regional variations in mastectomy rates (from 22.6% to 39%), RT use after CS (from 81% to 96%) and endocrine therapy (from 6% to 34%) were observed. CS alone was used only in selected cases, with small and low grade tumours, and no comedo subtype.

| | CS (%) | CS+RT (%) | M (%) | Total (%) |
|---|---|---|---|---|
| Mammographically detected | 87 | 90 | 83 | 88 |
| Median tumor size | 6 mm | 11 mm | 35 mm | 15 mm |
| Grade | | | | |
| 1 | 57 | 22 | 10 | 21 |
| 2 | 31 | 41 | 36 | 38 |
| 3 | 12 | 37 | 54 | 41 |
| Comedo subtype | 5 | 22 | 33 | 24 |
| ER+ | 81 | 74 | 61 | 70 |
| PgR+ | 50 | 65 | 50 | 60 |
| Previous biopsy | 72 | 59 | 65 | 62 |
| Surgery | | | | |
| 1 time | 94 | 81 | 40 | 70 |
| 2–3 times | 6 | 19 | 60 | 30 |
| Sentinel node biopsy | 7 | 13 | 42 | 21 |
| Axillary dissection | 4 | 5 | 22 | 10 |

**Conclusion:** These results are globally in accordance with the French DCIS guidelines recently published (www.fnclcc.fr).

## *Oral presentations* (Mon, 31 Oct, 9.15–11.15)
## Management of advanced breast cancer

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**First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: a randomized, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100)**

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**Purpose:** Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), inhibits tumour angiogenesis, which is essential for tumour growth. Bevacizumab has been shown to have activity in late-stage metastatic breast cancer (MBC) (Cobleigh et al. Semin Oncol 2003; 30(Suppl 16):117–24; Miller et al. J Clin Oncol 2005;23:792–99). We designed a randomized phase III trial to compare the efficacy and safety of paclitaxel with or without bevacizumab as first-line therapy in patients with locally advanced or metastatic breast cancer.
**Methods:** Patients were randomly assigned to receive paclitaxel 90 mg/m$^2$ on days 1, 8 and 15 of a 4-week cycle, either alone or in combination with bevacizumab 10 mg/kg on days 1 and 15. The primary endpoint was progression-free survival (PFS); response was assessed by RECIST criteria every 3 cycles. The study provided 85% power to detect a 33% improvement in PFS assuming a one-sided type one error of 2.5%, requiring that 650 patients be recruited.
**Results:** A total of 722 patients were enrolled between December 2001 and May 2004. Treatment arms were well balanced for median age (55 vs 56 years), disease-free interval ($\leqslant$24 months in 41% of patients in each arm), ER status (63% and 64%), number of disease sites (29% and 28%) and exposure to adjuvant chemotherapy (64% and 65%). Hypertension requiring treatment (13.5% vs 0; $p < 0.0001$), grade 3/4 proteinuria (2.5% vs 0; $p = 0.0004$) and grade 3/4 neuropathy (20.5% vs 14.2%; $p = 0.01$) were more frequent in patients receiving combination therapy. Thromboembolic events and serious bleeding episodes were infrequent (<1.5%) in both groups. Combination therapy significantly increased response rates in all patients (28.2% vs 14.2%; $p < 0.0001$) and in the subset of patients with