Saturday, 27 March 2010 11:00–13:00

KEYNOTE SYMPOSIUM

Best and practice changing abstracts

1N Invited

Evaluation of the breast cancer screening programme in Southwest Netherlands: a case–control study

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Background: Previously, we demonstrated, by means of trend analyses, a downward trend in the Dutch breast cancer mortality rates until 2001, which started immediately after the initiation of mammography screening. Recently we started a case–control study for the evaluation of the Dutch breast cancer screening program. The results of the Southwest region are presented for the period 1990–2003.

Methods: Data of the screening organization of Southwest region (where screening was implemented in the period 1990–1996) on date of birth, invitations, screening visits, and death, and screening status was used. Eligible women were those aged 49−75 years at first invitation, who were ever invited for mammography screening between 1990–2003 and gave permission for exchange of their data with the cancer registry, GP or for linkage for statistical purposes. The attendance rate at the initial screenings among the eligible women varied between 59% and 88%. Data on date of diagnosis, TNM-stage and therapy of all women diagnosed with breast cancer were obtained from the Comprehensive Cancer Registry Rotterdam. Cases were women diagnosed with breast cancer after the first invitation and died of breast cancer. Five controls were matched to each case based on age at the case's last invitation (index), year of birth, year of first invitation and number of invitations before and up to the index invitation. All controls were alive at the time of death of the matched case and breast cancer free at case's diagnosis. Screening was defined as attending the mammography unit after receipt of a screening invitation. The odds ratios, ORs, and respective 95% confidence interval, CI, of the matched case–control sets were calculated by conditional logistic regression.

Results: There were 755 cases and 3,739 matched controls, aged 49−75 at first invitation: 36% of the cases were never screened (29.9% were screen-detected and 34.6% were interval cancers) compared to 18% of the controls. Among the cases, the proportion of localized tumors (stage 0−I) was considerably higher in women with screen-detected tumors (34.1% versus 10.7% detected between intervals and 10.4% never-screened). The OR of the association between breast cancer mortality and attending screening during the 4 years preceding the index was 0.44 (95% CI 0.37–0.53) and 0.48 (95% CI 0.41–0.58) for attending the last (index) invitation. Correcting for the method of Duffy et al., using their published data, yielded ORs of 0.66 (95% CI 0.47–0.92) and 0.72 (95% CI 0.52–1.00), respectively.

Conclusion: The results of the present case–control study suggest reductions of 52−56% (28−34% after correction for selection bias) in breast cancer mortality among women who were invited and attended the mammography screening program in the Southwest region of the Netherlands between 1990–2003.

2N Invited

Model based predictions show higher mortality reduction for the UK Breast Screening Frequency Trial: no definitive answer on the optimal screening frequency

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Background: The UK breast screening frequency trial did not show a significant difference in breast cancer mortality between screening every year (study group) and screening every three years (control group). In the present study, the UK frequency trial is simulated using a micro simulation model in order to clarify the results of the trial and predict the effect on breast cancer mortality of screening every year vs. once every three years.

Material and Methods: The MISCAN breast cancer model was used to simulate the trial. Age specific breast cancer incidence rates for the years 1975–1988 (before the implementation of a nationwide screening program in the UK) were used to estimate age specific disease onset parameters for the simulation model. The predicted number of invasive cancers in each group by size and the number of breast cancer deaths in each group from cancers diagnosed in the trial up to the year 2006 were compared with the results of the trial.

Results: The total numbers of invasive cancers detected was predicted accurately for the study group and somewhat too high for the control group. Although the predicted difference in size distribution between the control and study group was larger than observed, the predicted numbers of deaths in both groups were close to the observed numbers. The predicted difference between the number of deaths in the control group and the study group was larger than the observed difference, corresponding to a predicted relative risk of 0.84, which is within the confidence interval of the reported relative risk (0.63–1.37).

	Observed				Predicted			
	Study		Control		Study		Control	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Tumour size (mm)								
1−20	170	(73)	134	(66)	194	(82)	153	(65)
21−50	59	(25)	64	(32)	40	(17)	72	(31)
50+	4	(2)	5	(2)	3	(1)	9	(4)
unknown	2		5		0		0	
Total number of invasive cancers	235		208		238		234	
Deaths	50		55		45		54	
RR	0.93 (0.63–1.37)				0.84			

Conclusions: Although limited data was available to estimate parameters for the micro simulation model, the predicted relative risk is within the reported confidence intervals. The predicted relative risk of 0.84 indicates that the actual mortality reduction resulting from shortening the screening interval might be larger than currently reported. The UK frequency trial seems to have a lack of power to detect a difference in breast cancer mortality between the two groups and therefore does not provide a definitive answer on the optimal screening frequency.

3N Invited

Stage migration after introduction of sentinel lymph node dissection in breast cancer treatment in Denmark: a nationwide study

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Background: Sentinel lymph node dissection (SLND) was introduced in breast cancer treatment in Denmark between 1997 and 2004. It has made more extensive lymph node examinations possible. As a result more metastases are found. This phenomenon is called stage migration. The purpose of the present study was, based on a large and nationwide data material, to estimate the magnitude of stage migration and its therapeutic consequences after introduction of SLND in breast cancer treatment in Denmark.

Materials and Methods: We retrieved information on nodal status, tumour size, age at diagnosis, type, grade and hormone receptor status from the Danish Breast Cancer Corporative Group database. The distribution of lymph node metastases and its consequences on risk-allocation was compared between 1993–1996 and 2005–2008 in a univariate and a multivariate analysis.

Results: We included a total of 24051 patients in the study; 10231 patients from the first period and 13820 patients from the second period. The proportion of patients having macrometastases was not significantly different in the 1993–1996 and the 2005–2008 cohorts, 40.5% and 40.7% respectively. However, patients having only micrometastases increased from 5.1% to 9.0% ($P < 0.0001$). The results did not vary significantly between the different Danish departments of pathology. According to the risk-allocation of today only a minor increase, from 7.8% to 8.8%, was seen in patients offered adjuvant treatment due to positive nodal status as the only high risk factor. In addition, the multivariate analysis showed that negative hormone receptor status was significantly associated to negative nodal status.

Conclusions: Introduction of SLND in breast cancer treatment in Denmark has resulted in a 4% increase in the proportion of node positive patients. This increase is exclusively caused by identification of more micrometastases. However, the stage migration has only minor therapeutic consequences according to adjuvant treatment because nodal status is losing its significance in risk-allocation due to introduction of other high risk factors. Furthermore, we showed that hormone receptor negative patients have a lower risk of lymph node metastases compared to hormone receptor positive patients when adjusted for confounders, despite the fact that these patients are generally considered having more aggressive disease. This

could indicate that hormone receptor negative cancers are less likely to spread lymphogenously.

4N Invited

Disease-free survival in breast cancer patients with minimal lymph node involvement: results in 241 isolated tumour cells or micrometastases in the sentinel lymph node with negative complementary axillary dissection

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Background: Sentinel lymph node (SLN) biopsy has led to an increase in the detection of minimal lymph node involvement (micrometastases-pN1mi and isolated tumor cells-pN0i+). The outcome may be different between patients with minimal lymph node involvement (MLNI) in the SLN with negative complementary axillary dissection (CAD) and those with negative SLN without CAD. The aim of this study was to determine the disease free survival (DFS) of breast cancer patients with MLNI in SLNs.

Patients and Methods: The Institut Curie SLN Database was used to identify all patients who underwent a SLNB for invasive breast cancer between January 2000 and December 2006 and had MLNI (pN0i+ and pN1mi) with a negative CAD or negative SLN (pN0) without CAD. The primary endpoint, DFS, was estimated using Kaplan-Meier method. The log-rank test was used to determine differences in DFS of patients from different groups.

Results: The whole series of 1701 patients was divided into three groups according to axillary status, pN0i+ with a negative CAD (n = 104), pN1mi with a negative CAD (n = 137) and pN0 without CAD (n = 1460). With a median follow-up of 52 months (range 1–110 months), there was no statistical difference in axillary recurrence rates between pN0, pN1mi and pN0i+, respectively 0.48%, 0%, and 0% (p = 0.753). MLNI in SLN was not associated with a significantly shorter DFS, compared with negative SLN without CAD, respectively 94.1% for pN0, 92.5% for pN1mi and 96.3% for pN0i+ (p = 0.599).

Conclusions: In this series, MLNI with negative CAD was not associated with a worse DFS compared to negative SLN. It seems therefore important to distinguish MLNI followed by a negative CAD, from MLNI without CAD performed. However, longer follow-up is needed to confirm these results, as well as the impact of MLNI on overall survival.

5N Invited

Elective irradiation of Internal Mammary Chain (IMC) after mastectomy has no impact on 10y overall survival in breast cancer − results of a randomized phase III study in France

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Background: Post operative radiotherapy after mastectomy for breast cancer includes the supraclavicular area and usually the chest wall. In some institutions, the target volume is extended to the internal mammary chain (IMC). There was however no proof that this elective irradiation was efficacious. Moreover, this irradiation could be responsible of some of fatal coronary events occurring after irradiation. The objective of this randomized trial was to evaluate the impact of internal mammary chain irradiation (IMC-RT) on 10y overall survival in breast cancer patients treated with mastectomy.

Methods: Multicentric randomized phase III trial comparing chest wall, axillary and supra-clavicular irradiation with or without IMC-RT in newly diagnosed stage I and II breast cancers. Inclusion criteria: Patients under 76-years-old with positive axillary nodes or internal/central tumor location, whatever pN. Stratification was done by center, nodal status and tumor location (internal/central vs. external). IMC-RT consisted in a combination of photons (12.5 Gy in five fractions) and electrons (32.5 Gy in 13 fractions) over 5 weeks. The target field included the first five intercostal spaces. Adjuvant chemotherapy or hormonal treatment was at the discretion of the physician. We planned to include 1200 pts that allowed us to detect 10% difference in survival (observed arm: 40% versus 50% RT-arm).

Results: A total of 1334 patients (in 12 centers) have been randomized. Mean age was 56.5 yrs, 1003 (75%) pts had positive lymph no, 1147 (86%) received chemotherapy or/and hormonotherapy. With a median follow-up of 10 yrs, we observed 535 deaths. 10-yr survival was 62.57% in case of IMC-RT and 59.55% without IMC-RT (p = 0.8762 by log-rank test). No difference was obtained in the different subgroups: positive or negative axillary nodes, external vs central/internal tumors, or according the adjuvant chemotherapy or hormonotherapy. Causes of death are known in 422 Pts: most of these deaths were due to breast cancer (371); no increase in cardiac toxicity was observed in the IMC-RT group with a median FU of 5y. The late toxicity will be update at the time of the meeting.

Conclusion: There are no clear beneficial effects of the IMC specific irradiation on the overall survival most probably because the scarcity of the invasion and several other factors such as chemotherapy and hormonotherapy.

6N Invited

Irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer: state of the day of EORTC phase III trial 22922/10925 with 4004 patients

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Background: Postmastectomy locoregional radiotherapy is known to improve disease free and overall survival in patients with involved axillary lymph nodes. Our trial was designed to investigate the contribution of IM-MS lymph node irradiation to this effect.

Material and Methods: Eligible patients had involved axillary lymph nodes and/or a medially located primary tumour. Based on randomisation, half received IM-MS radiotherapy to a dose of 50 Gy in 25 fractions. The original trial design aimed at detecting a 5% increase in 10-year overall survival (from 50 to 55%, HR = 0.86). After reviewing the patient characteristics and in view of new data in the literature, the objectives of the trial were updated in April 2003 to target a 10-y overall survival benefit from 75% to 79% (HR = 0.82). Three analyses are planned, at respectively 10, 15 and 20 years median follow-up, each at the 0.022 significance level. The first analysis will be done after 1000 deaths have been observed. At each annual visit, data on survival, recurrences, second tumours, toxicity and performance score are recorded. At 5 and at 10 years, an additional late toxicity evaluation form is completed for cardiac, pulmonary and other diseases.

Results: Between July 1996 and January 2004, a total of 4004 patients entered this study. Of all patients, 59% were postmenopausal; 33.8%, 52.1% and 14.1% had stage I, stage II and stage III respectively. A majority of the patients (76.1%) was treated with breast conserving therapy of which 85.1% received a boost. After mastectomy, 73.2% of the patients in both randomisation arms received chest wall irradiation. 6.8% in the no IM-MS and 7.8% in the IM-MS group received axillary radiotherapy. Nearly all node-positive and over 2/3 of node-negative patients received adjuvant systemic treatment. The evaluation of the dummy run and the individual case review confirmed a positive influence of the quality assurance program on protocol compliance. At 3 years of follow-up, an additional 57 cases of lung toxicity in the IM-MS arm were recorded, translating into a significant higher rate of “any lung” toxicities after IM-MS treatment (4.3% vs. 1.3%; p < 0.0001). Other toxicity was the same in both treatment arms and no significant worsening of the performance score was observed, suggesting that treatment-related toxicity did not impair patient’s daily activities.

Currently, median follow-up is 7.3 years and 558 patients have died, giving an estimated overall 10-y OS within 79.1%-82.5% (95% confidence interval), close to the anticipations. Data maturity for the first analysis is expected to be reached in 3 to 4 years.

Conclusions: Toxicity at 3 years was limited, obviating the need for early disclosure of the results. For the evaluation of the primary endpoint at 10 years, we need to wait for 2012. As IM-MS irradiation seems well tolerated with limited toxicity and no impairment on performance score at 3 years, it can in the meantime still be considered as a treatment option, especially in high-risk patients.