Plenary Lecture

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Monotoring cancer occurrence and outcome in Europe in the 21st century

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Monitoring cancer occurrence implies measurement of the number of new cases of cancer, as an indicator of need for services or care, or to calculate incidence rates, for comparisons of risk in different populations, or over time. These data come from population-based cancer registries. Mortality rates have traditionally been used for the same purpose, but ratios of mortality rates are only valid indicators of differences in risk if case fatality rates are constant. Available survival data suggest that, except for cancers with very poor prognosis, this is rarely the case. Mortality data are, however, available for almost all countries of Europe, although the degree of detail and quality of information is variable.

Cancer registration has developed progressively in Europe since the first registries (Hamburg and Denmark) were set up, more than 50 years ago. Some standardization of methodology was provided *via*international organizations (IARC and IACR), but new impetus was given to the process by the establishment of the European Network of Cancer Registries (ENCR) in 1989, which also provided opportunities for a wide variety of collaborative actions. These include the cancer database EUROCIM, to which all European registries are invited to contribute, receiving in return a copy for their own purposes. EUROCIM is primarily a research tool, but the data are used to prepare comprehensive sets of estimates of incidence, mortality and prevalence at national level, annually for the 15 member states of the EU itself (the EUCAN estimates), and five-yearly for all countries of Europe. In 1999, there were 1.57 million new cancer cases in the EU countries, and 930,000 deaths. The most common cancers were lung (in men), breast (in women), and cancers of the large bowel (in both sexes combined). The "Europe-95" estimate is for all 38 countries of Europe, where there were an estimated 2.6 million new cases and 1.6 million deaths. A systematic review of the time trends shows rather uniform patterns for certain cancers (breast, stomach, lymphoma), while trends for lung cancers are quite different according to the maturity of the smoking epidemic.

European registries have also collaborated in comparative studies of survival (EUROCARE), the third cycle of which concerns cases diagnosed in 1990-1994. These data, together with incidence, are used to estimate prevalence of different cancers in Europe.

In June 2003, the future of cancer registration in Europe is well established, although future financial support available *via* the European Union is less sure. One may predict a gradual extension of registry work, beyond the 31.5% of the European population covered, and including at least regional coverage of most countries. The future of collaborative projects, and the extension of the current EUCAN project to a true European Cancer Database, as has been done for childhood cancers with the ACCIS project, is less certain.

Proffered Papers

Breast cancer I

16 ORAL

A combined analysis of three European audits of primary breast cancer management.

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Background: Retrospective audits of adjuvant chemotherapy in breast cancer management have been undertaken in several European countries. Results of a combined analysis of three datasets from Belgium (Chemodose 99), Spain (OSQAR) and the UK (Audit of Primary Breast Cancer Patients) are reported.

Materials and methods: Variables available in all three datasets were identified, their definitions compared and formats edited. They were merged into a single dataset of individual observations. Analysis addressed the incidence of neutropenic events and chemotherapy dose intensity. Multivariate adjusted odds ratios (ORs) of low average relative dose intensity (ARDI) were calculated by robust multiple logistic regression allowing for clustering by audit.

Results: The Belgian audit contributed 661 breast cancer patients, the Spanish audit 1168, and the UK audit 422. Mean age at diagnosis ± SD was 51.5 ± 11.4 years. (Inter-audit range: 48.5 ± 10.9 to 53.1 ± 11.8 years.) Patients were post-menopausal in 51% of cases and 59% had oestrogen receptors. The diagnostic spread was stage I 17%, II 63%, III 15% and IV 5%. Prior or concomitant radiotherapy was reported in 36%. Fifty-four percent received CMF-based regimens, 42% anthracycline-based, and 3% other regimens. One or more neutropenic events were observed in 27% of patients. Repeated neutropenic events were observed in 12%. Age-adjusted incidence of neutropenic events by cycle is shown in Figure 1. Mean ARDI ± SD was 93.2% ± 10.3%. ARDI was d 85% in 17% of patients. Independent associations with ARDI d 85% were confirmed for occurrence of neutropenic events (OR 3.5, 95% CI 2.6-4.7); use of a non-anthracycline-based regimen (OR 1.6, CI 1.1-2.4); prior or concomitant radiotherapy (OR 1.5, CI 1.5-1.6);

postmenopausal status (OR 1.3, CI 1.2-1.3); and stage of disease. ORs for stages II to IV, compared to stage I, were 1.4 (CI 1.0-1.8), 1.9 (CI 1.5-2.5) and 2.0 (CI 1.3-3.0). Use of colony-stimulating factors (CSFs) was reported in 14% of patients. (Inter-audit range: 5% to 17%.) In 18% of patients with one or more neutropenic events, use of CSF started after the first event.

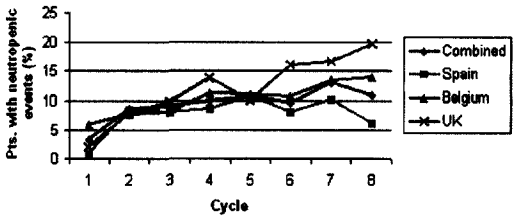

Fig. 1. Incidence of neutropenic events by cycle, adjusted for age (N combined = 251

Conclusions: Low ARDI was associated with the occurrence of neutropenic events, use of a non-anthracycline-based regimen, prior or concomitant radiotherapy, postmenopausal status, and higher stage of disease. Prospective studies should be performed to confirm these findings and to identify additional risk and protective factors.

17 ORAL

Can Danish breast cancer patients by early diagnosis achieve the same survival as observed in Sweden? A study in screened and non-screened Danish and Swedish populations.

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Background: A 9% difference in 5-year survival in breast cancer patients diagnosed in 1983-89 has been reported in comparisons between the Danish and the Swedish Cancer Registry. Our study aim was to analyse, whether previous observed differences in terms of survival and extent of disease still exists or if the Danish figures for breast cancer patients approach the Swedish.

Methods: Population based cohorts of patients with primary invasive breast cancer in 1996-1997 in selected geographical areas in Denmark and Sweden were compared with respect to stage of disease and outcome. The regions under study were selected as a Danish (Funen) and a Swedish (Malmö) county with mammography screening together with two Danish counties with no screenings programme. Median follow-up time was 6.4 years [5.6 to 7.6].

Results: No difference in extent of disease or survival was observed in areas with screening programmes regardless of country. However, there were significant differences in stage distribution and survival between the screening populations in Sweden and Denmark and two Danish non-screening populations, all in benefit to the populations provided mammography screening. Tumour size was 17 / 18 vs. 20 mm ($p<0.001$). The 5 year over-all survival was in Malmö 77% [72-82], in Funen 75% [71-78] and in the Danish non-screening counties 71% [68-73]. Corresponding disease-specific survival was 84% [79-78] and 83% [80-86] vs. 77% [74-79]. In the multivariate regression analysis increasing age, tumour size and extent of disease decreased survival and explained the observed differences in survival between patient populations. After adjusting for extent of disease there were no difference in survival according to county of residence.

Conclusion: The observed differences in survival could be attributed to early diagnosis and more favourable stage distribution in populations offered mammography screening programmes and was not related to country of residence (Sweden/Denmark). The study suggests that non-screening counties by focus on early detection may approach the same beneficial stage distribution and survival as observed in Sweden.

18 ORAL

Impact of early start of adjuvant chemotherapy in breast cancer in Denmark.

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Background: Evidence on the impact of early start of adjuvant chemotherapy is sparse as randomised trials have not been performed. The topic is of interest due to pressure from patients and politicians to start treatment as early as possible and to avoid waiting lists for chemotherapy.

Material and methods: In the database of the Danish Breast Cancer Co-operative Group information was available on date of breast surgery and date of starting chemotherapy for 7772 patients receiving adjuvant chemotherapy during 1977-1999. The majority (80%) had received i.v. CMF and 6% classical CMF. The remaining 14% received CEF. The time period between surgery and start of chemotherapy was examined in multivariate Cox-proportional hazard analyses including age, tumour diameter, number of removed lymph nodes, number of tumour involved lymph nodes, receptor status, histological type (+/- ductal), malignancy grade, +/- radiotherapy and type of chemotherapy.

Results: The analyses showed that timing of chemotherapy had no independent significant effect on survival, implying that patients who started chemotherapy soon after surgery had a similar prognosis to those starting chemotherapy later, which in the present material was up to 3 months after surgery. We cannot rule out that there may be an impact restricted to certain subgroups of patients (premenopausal with tumours not expressing oestrogen receptors, Colleoni et al JCO, 18(3), 2000: 584-90).

19 ORAL

Fractionation sensitivity of breast cancer. Results of a randomised trial

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Aim: To test the long-term normal tissue and tumour effects of fraction sizes larger than 2.0 Gy in patients undergoing breast radiotherapy.

Methods: Between January 1986 and March 1998, 1410 patients were enrolled in a three-arm randomised controlled clinical trial testing non-standard fractionation to the whole breast after breast conservation surgery for T1-3 N0-1 M0 breast cancer. Patients were randomised to 50 Gy in 25 fractions (control arm) versus 2 dose levels of an experimental schedule delivering 13 fractions of 3.0 Gy or 3.3 Gy over 5 weeks (treating five times per fortnight). Electron boost allocation (14 Gy in 7 fractions) was determined independently of this randomisation. Frontal photographs were taken after surgery under standard conditions and repeated annually to 5 years. Patients were reviewed clinically 3-monthly to 3 years, 6-monthly to 5 years and annually to 10 years. Change in photographic breast appearance was the primary endpoint. Local tumour control was a secondary endpoint.

Results: The normal tissue changes have been previously presented: The estimate of a/b for any change in breast appearance was 4.2.Gy (95% C.I. 2.5 – 7.3). 152 ipsilateral breast recurrences occurred during follow up. There was no statistically significant difference in tumour control probability at 10 years between the three arms of the trial, all ranging between 86% and 88%. The increase in 10-year tumour control rate in the breast after 42.9 Gy in 13 fractions compared to 50 Gy in 25 fractions was estimated at 1% with 95% confidence limits –2% and +3%. The point estimate of a/b for tumour control was 4 Gy.

Conclusion: It is possible that the fractionation sensitivity of breast cancer may be comparable with that of dose-limiting normal tissues, but low statistical power limits the precision of the point estimate of a/b for tumour control. Nevertheless, the current trial has sufficient power to generate a useful width of the confidence interval for equivalence of the 25 and 13 F schedules.