Symposia

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Early breast cancer – the randomised evidence

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The current cycle of the 5-yearly worldwide meta-analyses in early breast cancer has brought together information on 130,000 randomised women, with a median follow-up of about 10 years. 40,000 were in trials of adjuvant hormonal therapies (3000 ovarian ablation; 37,000 tamoxifen), 50,000 were in trials of chemotherapy (10,000 monochemotherapy; 20,000 polychemotherapy vs not; 20,000 one polychemotherapy versus another), and over 30,000 were in trials of local therapy (including 20,000 in trials of radiotherapy). Most trials did not involve women with good-prognosis screen-detected tumours, for whom any benefits might well be smaller.

For women with receptor-positive disease, or for women whose receptor status has not been determined, tamoxifen is of substantial benefit both in those aged under 50 and in older women: 5 years of adjuvant tamoxifen appears better that 2 years, but there is as yet inadequate evidence as to whether 10 years of tamoxifen is better than 5. In such women tamoxifen produces a decrease in breast cancer mortality that is about 50 times the increase it produces in endometrial cancer mortality, and, in more than 200,000 woman-years of randomised experience, tamoxifen had no apparent effect on mortality from causes other than breast or endometrial cancer. In terms of the 10-year incidence of new tumours, the extra number of endometrial cancers that it caused is smaller than the number of new cancers it prevented in the opposite breast. Polychemotherapy (e.g. with some months of CMF or of an anthracycline-based regimen) is of substantial value for women aged under 50 and is of some value for women aged 50-69, but has hardly been tested in older women.

Overall, radiotherapy had no net effect on 20-year survival. But, all radiotherapy trials involved regimens that were effective at controlling local recurrence, producing about a threefold reduction (e.g. from 30% down to 10% local recurrence). This yielded a moderate but definite reduction (e.g. from 50% down to 46%) in the 20-year risk of death from breast cancer. But, many of the radiotherapy regimens in these trials involved substantial doses to the heart and other intrathoracic sites, and, overall, there was a moderate but definite increase of a few per cent in the 20-year risk of death from vascular causes. In women with a low local recurrence risk the hazards of the types of radiotherapy used in many of these trials would outweigh the 20-year survival benefits, but in premenopausal women with a low 20-year risk of death from other causes and a high risk of local recurrence such radiotherapy produces an absolute improvement of a few per cent in 20-year survival. If some type of radiotherapy that involves much less intrathoracic irradiation than was usual in these trials can avoid most of the vascular hazard while retaining most of the benefit, then from such radiotherapy a wider range of breast cancer patients can expect an improvement of a few per cent in long-term survival.

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Improving outlook for ovarian cancer – Fact or fiction?

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National and international cancer registry data indicate a definite improvement in outlook for ovarian cancer over the past 10–20 years, with a widening gap between incidence and mortality. This has been most marked in women aged <65 years. Because of the nature of the disease, screening and earlier diagnosis are unlikely to be contributory factors, and registration errors (e.g. inclusion of "borderline" malignancy) have been excluded in several studies. Thus the improvement is likely to be treatment-related, and the timing (since the mid 1970s) suggests that the increasing use of chemotherapy (particularly cisplatin an carboplatin) is probably pivotal. This is borne out by national audit studies in Scotland, which have also shown that other important factors include an integrated approach to therapy in specialist clinics, involving both initial treatment and treatment at relapse. Expert surgery is particularly crucial in this respect. Further improvements may already be underway, following the introduction of taxoids, with a potential survival benefit, comparable to that seen as a result of platinum itself, of approximately 12 months. In the future, new drugs aimed at novel targets offer further hope for an improving outlook, particularly as the mechanisms underlying drug resistance are better understood.

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Adjuvant and palliative therapy for colorectal cancer

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Ten years ago, there was no evidence in the scientific literature that adjuvant chemotherapy for colorectal cancer or pre- or postoperative radiotherapy for rectal cancer could reduce recurrences and improve survival. Palliative chemotherapy was not known to improve survival and there was no documented evidence of any other patient benefit.

Today there is convincing evidence that postoperative chemotherapy for about six months improves five years survival from about 50% to about 60% in colon cancer Dukes' stage C. Uncertainties still exist in stage B and in rectal cancer. There is also evidence that preoperative radiotherapy substantially decreases local failure rates and slightly improve survival. Postoperative radiochemotherapy may achieve the same benefits, although with greater morbidity even if treatment techniques are optimized. Long term consequences are still not known in detail. However, the surgical technique has, at last, also improved in many centres, and the value of additional radio(chemo)therapy must be revisited. Palliative chemotherapy, using biochemically modulated 5-FU prolongs median survival by about six months and improves the well-being of a substantial proportion of the patients. Several peroral drugs may achieve the same benefits with greater convenience. Most recently, several other drugs have also shown promising activity in colorectal cancer. When properly timed with 5-FU, they may result in even greater benefits.

Conclusions: The improvements seen during the latest 10-year period in treatment results are not large. Yet, they are of definite clinical value since they have established that radiotherapy should be an integrated part of the initial treatment for many patients with rectal cancer and chemotherapy for subgroups of patients with coloncancer. Palliative chemotherapy provides survival and quality of life gains telling that such treatment should be provided within routine care at most places world-wide.

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Palliative treatments for metastatic cancer, and use of quality of life endpoints to assess them

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For most solid tumours of adults available treatments have limited ability to influence survival in the face of metastatic disease. The major goal of treatment is therefore palliation, as measured by improvement in symptoms and quality of life (QL). Tumour response is at best a surrogate measure for palliation, and may not be correlated with palliative endpoints if the treatment induces new symptoms due to toxicity. Use of a measure of QL as a primary endpoint in clinical trials will be illustrated from Canadian studies of chemotherapy for hormone-resistant prostate cancer (HRPC). Principles include: (i) the definition of a single measure of QL, recorded by the patient, as the primary endpoint; this should be validated and might be a global scale or a dominant symptom such as pain or fatigue. (ii) A priori definition of a clinically meaningful change in this endpoint, as compared to baseline, to determine a criterion for palliative response; in general a change of 10 units on a scale from 0 to 100 units correlates reproducibly with other measures of clinical change. (iii) Supportive use of