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Radiation dose-effect relation in breast cancer

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Radiation therapy has a major role in the treatment of breast cancer. Its effect on local control is remarkable, as a sufficient radiation dose decreases the risk of local recurrence by three-fold. This effect has been demonstrated in randomised trials including more than 20,000 patients, independently of the type of surgery. For a long time the effect of radiotherapy on overall survival has been debated, however recent worldwide randomised evidence show that the treatment significantly decreases breast-cancer mortality and that the effect on overall survival has been jeopardised by long-term toxic effects mainly related to old-fashioned radiation techniques.

One of the main parameters of radiation therapy is the total radiation dose. We will assume that most centres use a conventional fraction size of 1.8 or 2 Gy. Our considerations will apply to all treatment settings such as adjuvant radiotherapy, after breast-conserving surgery or mastectomy, and radiotherapy alone for locally advanced disease.

The most common adjuvant total radiation dose used is 45 to 50 Gy. The role of an additional dose on the tumour bed after breast-conserving surgery has also been much debated. In 1985, in a study that involved 463 patients [Int J Radiat Oncol Biol Phys 1985, 11: 1751–7], we showed by multivariate analysis that there was a linear relation between dose and tumour control. The dose effect was described by the following equation: $RR = 18.36 \times \exp[-0.04746 \times D\,(Gy)]$,

where RR is the relative risk of local recurrence and D the total radiation dose comprised between 35 to 85 Gy. With this dose relation, we predicted that and additional dose of 15 Gy would halve the risk of local recurrence in a population of patients with subclinical disease (RR = 0.5). The EORTC randomised trial [N Engl J Med 2001, 345: 1378–87] evaluating the role of a boost dose included 5,318 patients with complete breast-conserving surgery. The results corroborated the previous hypothesis with an estimated hazard ratio reduction of 0.59 and 0.51 in univariate and multivariate analyses, respectively.

We will discuss related issues to these findings: 1) is the linear dose-effect independent of other factors, such as tumour size, heterogeneity and oxygenation? 2) Is it possible to improve local control in younger women treated with breast-conserving surgery and with a recognised higher risk of local recurrence? 3) Is the linear dose-effect also valid for long-term iatrogenic effects?

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Update of the Danish trials of postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy

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Aim: To evaluate the role of postmastectomy radiotherapy in the presence of adjuvant systemic therapy the Danish Breast Cancer Cooperative Group (DBCG) conducted a randomized trial in high-risk pre- and postmenopausal (<70 years) breast cancer patients between 1982 and 1990.

Methods: A total of 3,083 patients with pathological stage II and stage III breast cancer were after mastectomy randomly assigned to receive adjuvant systemic therapy and postoperative irradiation to the chestwall and regional lymph nodes (1,538 pts), or adjuvant systemic therapy alone (1,545 pts). Pre- and menopausal patients received 8–9 cycles of CMF with an interval of 4 weeks, whereas postmenopausal patients received tamoxifen 30 mg daily for one year. The median potential follow-up time was >18 years. The endpoints were loco-regional control, distant metastases, freedom from any recurrence and overall survival.

Results: Overall the 20-year actuarial probability of loco-regional recurrence was 8% in irradiated patients versus 41% in patients who received adjuvant systemic therapy alone ($p < 0.0001$), (Relative Risk (RR): 0.13 (95% [cfl 0.10–0.17]. Recurrence-free probability at 20 years was 30% in irradiated patients compared to 19% in non-irradiated ($p < 0.0001$), RR: 0.54 [0.46–0.64]. These figures were also reflected in a superior survival of the irradiated patients (34% versus 25% at 20 years ($p < 0.0001$), RR: 0.65 [0.56–0.76]. A multivariate analysis demonstrated that postmastectomy irradiation resulted in a significant improvement in freedom from any recurrence and overall survival, irrespective of menopausal status, tumor size, number of positive nodes and histopathologic grading. Radiotherapy did not result in excess cardiac morbidity or death, and other radiation related side-effects were minor.

Conclusion: Adjuvant systemic therapy in high-risk breast cancer patients treated with modified radical mastectomy can not sufficiently prevent loco-regional recurrences. The study definitely indicates that optimal treatment of high-risk breast cancer can only be achieved if both loco-regional and systemic tumor control are aimed for. Therefore radiotherapy has an important role in the multidisciplinary treatment of breast cancer.

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Hypofractionation in breast cancer radiotherapy

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There is evidence that the average fractionation sensitivity of breast cancer is greater than has been assumed in the past, and comparable with that of dose-limiting late normal tissue adverse effects. If true, the implication is that hypofractionation (fraction sizes >2 Gy) should be evaluated for the treatment of primary breast cancer. Recently, a direct estimate of 4.1 Gy (95%CI: 1.0–9.7) was reported for the fractionation sensitivity of breast cancer in the Royal Marsden Hospital/Gloucestershire Oncology Centre Breast Fractionation Trial (N = 1,410). Meanwhile, a randomised comparison of 50 Gy in 25 fractions of 2.0 Gy and 42.5 Gy in 16 fractions of 2.67 Gy (N = 1,234) in Ontario reported no significant differences in local tumour recurrence between arms. If the two Ontario schedules are truly iso-effective with respect to tumour control, this result is consistent with a higher fractionation sensitivity than previously thought, assuming tumour repopoulation is unimportant. Hypofractionation lends itself to acceleration, taking advantage of the relative sparing of early skin reactions as fraction size increases and the absence of a significant time dependency for late adverse effects. The implications of advanced radiotherapy techniques for delivering the biological advantages of hypofractionation are also worth considering. Rather than increase dose intensity by increasing the number of 2.0 Gy fractions, it creates opportunities for escalating dose intensity by modulating fraction size (this argument does not hold for the lymphatic pathways). The implications of dose escalated intensity modulated radiotherapy are under test in forthcoming UK trials. The hypothesis is that higher doses per fraction to high-risk areas and lower fraction sizes to low-risk areas of the breast will offer a clinically superior and cost-effective approach of matching dose intensity to tumour recurrence risk compared to standard sequential boost techniques. In conclusion, future prospects for exploiting the biology of hypofractionation in breast cancer using advanced radiotherapy technologies look bright, with prospects for testing the limits of accelerated hypofractionation and dose escalated intensity modulated radiotherapy by the end of the decade.

Scientific Symposium
Prostate cancer innovations

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Molecular pathology in prostate cancer

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The etiopathogenesis of neoplastic diseases is characterized by its multiple nature. Biological, chemical, and physical agents have been identified as initiating or promoting neoplastic mechanisms. However, they all appear to a have common molecular basis, granting genetic instability and causing somatic derangements to pre-neoplastic and tumor cells. In addition to these somatic mutations, which are the most frequent abnormalities identified in human cancer, germ-line mutations associated with specific familial cancer syndromes have been also characterized. Epidemiologic and molecular genetic studies have unveiled the underlying mutations of specific genes predisposing patients to distinct cancers, such as certain colorectal and breast tumors. It is therefore conceivable to view cancer as fundamentally a genetic disease entailing germ-line and somatic mutations. However, epigenetic events and altered patterns of protein expression have been also identified in neoplastic lesions, and their identification has become as important in the context of certain tumor classification schemes, as well as in the predicting course of disease.

Alterations in proto-oncogenes and tumor suppressor genes seem equally prevalent among human cancers. Multiple mutations appear to be required to conform the malignant phenotype. Genetic instability leads to a sequence of events that creates phenotypic alterations, granting a selective advantage to specific tumor cells. Metastasis is the ultimate outcome of tumor progression in this selective process. It appears that it is the accumulation rather than the order of these pleiotropic events that confers neoplastic cells the ability for tumor progression.

Prostate cancer diagnosis and assessment is entering an era in which immunopathology and molecular genetics could play important roles, as they do in the context of other solid tumors. During the past years a tremendous amount of information has been generated regarding the principles that govern cell growth, cell senescence, and cell death ("apoptosis") itself. Combinations of abnormalities in these processes are