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Radiation dose-effect relation in breast cancer

R. Arriagada[1,2]. [1]*Karolinska Institutet, Radiumhemmet, Stockholm, Sweden;* [2]*Institut Gustave-Roussy, Villejuif, France*

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

M. Overgaard. *On behalf of the DBCG Radiotherapy Group. Department of Oncology, Aarhus University Hospital, Aarhus, Denmark*

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

J.R. Yarnold. *The Institute of Cancer Research Royal Marsden NHS Trust, Academic Unit of Radiotherapy, Sutton, United Kingdom*

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

C. Cordon-Cardo. *Memorial Sloan-Kettering Cancer Center, New York, USA*

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

important not only for causing prostate cancer, but also for permitting or inhibiting prostate tumor cells to respond to therapeutic interventions. Clinical trials have shown different responses to various therapies that correlate with molecular alterations. Biological determinants related to treatment response and markers aimed at individualized therapies are being defined and implemented. It is expected that the newly developed high-throughput methods, such as expression profiling by microchip technology, will complement our armamentarium of predictive tools needed to address the molecular complexity that characterizes prostate cancer.
In addition to molecular genetics, a new "systems pathology" approach is being developed. Systems pathology can be defined as a discipline that integrates clinical variables with histological and cellular features, as well as molecular profiles. This is achieved through the application of novel technologies in the areas of object-oriented image analysis, pattern recognition, and quantitative biomarker multiplexing. The obtained complex data-sets are analyzed by distinctive supervised mathematical approaches, including machine learning algorithms and neural networks. Our working hypothesis is that by using this approach we could significantly improve the accuracy of predictive tools, such as individualized nomograms already developed for the management of prostate cancer.
The practice of conventional histopathology based on light microscopy changed and was in part complemented in the second half of the twentieth century by three technological advances: ultrastructure, immunohistochemistry, and molecular diagnostics. The first two represented incremental gains in diagnostic power and efficiency, but did not force substantial changes in the practice of morphological studies. However, "molecular medicine" is profoundly changing the approach to tissue analyses. Perhaps more importantly, molecular medicine is altering the pathway for advancement. In the recent years the elucidation of the molecular pathogenesis of neoplastic diseases and the multistep nature of cancer progression has directly led to the discovery and application of molecular tumor markers. The diagnosis and prognosis have in many cases been enhanced by the use of the marker(s), and finally the marker may constitute a therapeutic target (e.g. Her-2/neu and Herceptin, Bcr-Abl and Gleevec). With the advances in biotechnology and bioinformatics, the integration of these approaches made sense. More over, the preceding sequence of events can be predicted to accelerate. Rather than elucidating a molecular pathway, we will have a complete view of the molecular genetics and protein profile of a given tumor. This comprehensive understanding will lead to the development of specific therapies and to the rational selection of therapeutic modalities for a specific patient. Integrated tests will allow an accurate assessment of the response and modification of therapy when required. The detailed morphologic and molecular knowledge of the natural history of tumors will yield markers for inherited and acquired risks, tumorigenesis and tumor progression. These will in turn make early diagnosis and cancer monitoring a reality.

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The evolving role of chemotherapy in prostate cancer

R. De Wit. *Erasmus University Medical Center, Department of Medical Oncology, Rotterdam, The Netherlands*

Clinical results of chemotherapy in androgen independent prostate cancer have been disappointing for many years. Objective responses reported in single agent chemotherapy studies conducted in the 1980s were scarce. In the 1990s, changes in prostate-specific antigen (PSA) levels were demonstrated to correlate with response, and these levels have served as a surrogate endpoint for evaluable disease. Also, "palliative measurement scales" were developed by Canadian investigators, which measure pain and analgesic consumption. By using these criteria, randomized studies have shown mitoxantrone plus either prednisone or hydrocortisone to provide symptom improvement, but there was no impact on survival.
In parallel, phase I and II studies were conducted to test new agents, including the taxanes, paclitaxel and docetaxel. The studies used weekly and 3-weekly schedules, with and without concomitant estramustine. Substantial activity in terms of pain responses, PSA decreases and median survivals of 16–24 months were demonstrated, that warranted the initiation of two randomized phase 3 studies; TAX 327 and study SWOG 99-16.
TAX 327 investigated the regimen of docetaxel 75 mg/m^2 every 3 weeks plus prednisone (10 mg daily), and the weekly regimen of docetaxel 30 mg/m^2 (5 of 6 weeks) plus prednisone, versus the accepted regimen of mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone [1]. The primary endpoint was overall survival. Secondary endpoints were pain, PSA levels and QL. From March 2000 through June 2002, 1006 patients were randomized. The docetaxel every 3 weeks regimen resulted in significantly superior survival and higher PSA and pain response rates compared with mitoxantrone. The survival was 18.9 vs 16.5 months, the reduction in the HR of death was 0.76 (0.62–0.92). Also, during the course of chemotherapy improvements in quality of life were significantly more frequently obtained in patients on docetaxel as compared with mitoxantrone (22% vs 13%, P = 0.009). Docetaxel every 3 weeks was well tolerated, with few cases of neutropenic fever (3%). There were no treatment-related deaths. Grade 3/4 non-hemotologic toxicities were rare.
SWOG 99–16 was built on the prejuidice that the combination of docetaxel plus estramustine had the greatest therapeutical potential and was the compator against mitoxantrone plus prednisone [2]. Also in this study the median overall survival was superior in the group receiving the docetaxel regimen, 17.5 vs 15.6 months, HR 0.80 (0.67–0.97). The incorporation of estramustine in the docetaxel regimen, however, was characterized by increased gastrointestinal and cardiovascular toxicity (mostly thromboembolic complications).
In view of this increased toxicity profile on the one hand and the apparent lack of improved effectiveness as compared with the similar survival benefit as obtained with docetaxel every 3 weeks plus prednisone in TAX 327 on the other, there appears no further role for the use of estramustine as an add-on to docetaxel [3].
These study results have also prompted studies to test the use of chemotherapy earlier in the course of the disease, such as the International trial TAX 3501, investigating immediate adjuvant hormonal treatment plus docetaxel vs hormonal treatment alone vs deferred therapy by the same therapeutical options in patients prostate cancer at high risk of relapse after radical prostatectomy. In the setting of androgen independent disease, studies will be aimed to investigate the addition of new active agents to docetaxel. Ongoing and planned randomised studies are employing the addition of high-dose calcitriol, DN-101 (International Industry sponsored trial), the addition of bevacuzimab (CALGB/ECOG/NCIC), astrasentan (SW0G) and the bisphosphonate risedronic acid (Netherlands).

References

[1] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502–12.
[2] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513–20.
[3] De Wit R. Shifting paradigms in prostate cancer; docetaxel plus low-dose prednisone – finally an effective chemotherapy. Eur J Cancer. 2005; 41:502–7.

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Targeted therapy in androgen-independent prostate cancer

C.N. Sternberg. *San Camillo and Forlanini Hospitals, Department of Medical Oncology/Pavilion Cesalpino II, Rome, Italy*

Most currently available hormonal therapies, interfering with the androgen receptor axis are considered to be palliative, since hormone unresponsiveness eventually develops. Hormonal resistance occurs as cells become self sufficient, insensitive to anti-growth signals, invade and metastasize with limitless replicative potential. There is sustained angiogenesis and they are able to evade apoptosis and programmed cell death. Understanding of the biology of prostate cancer and hormonal resistance has grown. Strategic information as to how prostate cancers arise and progress has led to identification of novel therapeutic targets.
The combination of docetaxel chemotherapy and prednisone has been shown to be effective in improving survival in two large phase III randomized trials. Can one improve upon the results with docetaxel chemotherapy in hormone refractory prostate cancer (HRPC)? How much is an incremental gain in survival worth in terms of quality of life? What is the role of investigational treatments such as tyrosine kinase growth factor inhibitors, antisense oligonucleotides, endothelin antagonists, anti-angiogenesis agents in lieu of or in addition to traditional hormones and chemotherapy? And, what makes an ideal therapeutic target?
An ideal therapeutic target should theoretically be present in the majority of patients and have a causative relationship to tumor genesis. It should have an essential function in tumor cells, but not be essential for normal cellular function.
Growth Factor Receptor Inhibition: A number of tyrosine kinase growth factor receptors have been cloned which transmit an intracellular signal. This signal can be increased by overexpression of the receptors or by increased ligands or ligand binding (which increases signal transduction). All of the tyrosine kinase receptors have differences in their extracellular ligand binding domain and differences at the level of the tyrosine kinases. There is an increasing knowledge of the intracellular domain and knowledge that mutations in these domains may determine whether or not a signal is important and whether or not an inhibitor may function. Overexpression of the extracellular receptors can also produce amplification in the intracellular signal transduction.