portfolio. The growth of the specialty of palliative medicine represents both an opportunity and a challenge. Cancer as a progressive chronic disease requires management by a multidisciplinary team – the members of which may have different perspectives. The challenge is to provide patient-centered care, using all the interventions available to us.

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Pain control for bone metastases

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Purpose: to improve palliative care of patients with painful bone metastases by reducing the number of visits to the radiotherapy department. The effect on palliation of a single fraction of 8 Gy was compared to that of a total dose of 24 Gy in 6 fractions.

Patients: 1171 patients were randomized. The primary tumour was in the breast in 39%, in the prostate in 23%, in the lung in 25% and in other locations in 13% of the patients. Bone metastases were located in the spine (30%), the pelvis (36%), femur (10%), ribs (8%), humerus (6%) and other sites (10%).

Method: questionnaires were used to collect information on pain, analgesic consumption, side effects during treatment, quality of life and costs. Questionnaires were sent out every week up to 3 months, thereafter every 4 weeks up to 2 years. Pain was measured on a pain scale from 0 (no pain) to 10 (worst imaginable pain).

Results: on average patients participated in the study for 4 months. The median survival was 7 months. Different techniques were used to analyse the pain data. Overall no differences between the two treatment schedules were found. On average patients lowered their pain score from 7 to 4 and it was shown that this reduction occurred mainly in the first 4–6 weeks. The response rate was 89% defined as a decrease of at least 2 points as compared to the initial pain score. With regard to quality adjusted life years similar results were found. The number of retreatments was 188 (16%). This number was higher in the 1 × 8 irradiation group, namely 147 (25%) versus 41 (8%) in the 6 × 4 group. More pathological fractures occurred in the single dose group. The actual percentage however, was still below the percentages mentioned in other studies.

Conclusion: given the quality in the effects on palliation, we had to conclude that a single fraction is preferred in patients with painful bone metastases, even at the expense of a higher chance of retreatment. The results of the Dutch trial will be discussed with reference to other studies on this subject.

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Abstract not received.

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Radiation treatment for bone metastases from prostrate cancer

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Bone pain affects the majority of patients with metastatic prostate cancer. Following relapse from first-line hormonal treatment, palliation of such pain may include analgesia, further hormonal treatment, chemotherapy and bisphosphonates, but external beam radiotherapy (EBRT) or radio-isotope treatment is often the best option.

In randomised trials of palliative local EBRT, although in patients with a variety of cancers, not specifically prostate, a single radiation treatment of 8 Gy is comparable to fractionated regimens. Pain relief should be achieved in 70% to 80% of patients. Fractionated EBRT may still be appropriate where there is a low metastatic burden, for weight-bearing bones, and where there is a risk of impending pathological fracture or spinal cord compression. Hemibody radiotherapy has the attraction of treating multiple sites of metastases at one time provided they are confined to one "half" of the body, but while the response is rapid (50% within 48 hours, 80% within 7 days) many patients will experience nausea and vomiting, and diarrhoea is not uncommon in patients who receive "lower hemibody" treatment. Bone marrow suppression for a variable length of time may occur.

Early clinical trials with Sr89 demonstrated efficiency in end-stage patients, and two randomised controlled trials, from Canada and the UK, subsequently confirmed its benefit. In the Canadian trial, Sr89 showed a clear improvement in outcome when added to local EBRT, in terms of response rate, duration of effect, reduction in new sites of pain, and cost effectiveness. In the UK trial, two groups of patients were enrolled, one where painful metastases were felt suitable for local radiotherapy, and another where hemibody radiotherapy was more appropriate, and within each of these two groups patients were randomised to receive EBRT or Sr89. Sr89 was equivalent to EBRT in terms of response rate and duration, but Sr89 reduced the frequency with which new metastases developed. In both of these trials no survival benefit could be shown, and the main toxicities were an increase in bone pain for two or three days after the injection, and a reduction in platelets. Other isotopes, including Re186 and Sam153, have been less extensively researched, but appear to produce an earlier response than Sr89, but with a shorter duration of action. Sr89 has subsequently been combined with chemotherapy in an attempt to improve the response rates further, and currently the UK group is examining the role of Sr89 in patients with evidence of biochemical relapse from first line hormonal treatment.

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Brain metastases – Radiosurgery or whole brain irradiation?

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Brain metastases is an important cause of morbidity and mortality in cancer patients. The median survival for patients with symptomatic metastases to the brain is about 1 month if they remain untreated and about 3 to 6 months if they undergo conventional whole brain irradiation (WBRT). Patients treated with surgery and postoperative radiotherapy have a significantly longer survival, improved quality of life compared to those treated with WBRT alone. Following complete surgical resection no significant difference in overall length of survival or the time of functional independence has been noted. However, the frequency of recurrences and morality due to neurological cause is lower. A number of reports have shown that stereotactic, radiosurgery (SRS) is an effective, noninvasive therapeutic, approach that can produce substantial functional survival, especially in patients with good performance status and without extracranial metastasis when used alone or in combination with WBRT. The results of SRS are comparable to the aforementioned recent randomised trials of resection and WBRT. There is evidence that the efficacy of SRS is not increased by adding WBRT and there is a trend to withhold WBRT in as many cases as possible to avoid both the short- and long-term morbidity of that treatment. Furthermore the advantages of SRS over surgery in terms of cost, hospitalisation, morbidity, and wider applicability strongly suggest that a randomised trial to compare SRS with surgery in combination with and without WBRT is warranted. This would help to clarify should SRS be used instead of surgery and followed by WBRT, adjuvantly with WBRT, or on tumour progression or recurrence after WBRT.

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Retreatment in head and neck squamous cell carcinoma

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Our experience of full dose re-irradiation (re-RT) in head and neck carcinoma (HNC) was reviewed in a series of 169 patients who presented with an inoperable HNC in a previously irradiated area (>50 Gy). The treatment consisted of a combination of radiotherapy (60 Gy) and chemotherapy (CT) (mainly 5FU-Hydroxyurea). Toxicity was markedly increased compared to the toxicity due to the first RT, but still remained acceptable. A 37% complete remission was observed at 6 months and the overall survival rate were 21 and 9% at 2 and 5 years, respectively. The median survival was 10 months which is higher that that usually reported in comparable studies using palliative CT. These findings are in agreement with few other studies showing that full-dose re-RT combined with CT is feasible in inoperable HNSCC and could lead to a small proportion of patients long-term free of disease.

These findings strongly suggest that re-RT + CT might constitute a standard in the difficult and frequent situation of HNSCC inoperable relapse in a previously irradiated area. However, in spite of the encouraging results, it remains to be proved that the combination of re-RT and CT is superior to palliative CT alone. It that aim, we have started a randomized trial within the GORTEC (French Group for Head and Neck Oncology), comparing re-RT + CT to CT alone. In addition, since there is strong evidence of added toxicity due to the re-RT, it is necessary to attempt to minimize this toxicity, which could be further tested by optimizing the re-irradiated volumes (3D conformal

therapy, IMRT) or by using radioprotectors (amifostine?). Finally it remains to be tested in further studies what could be the optimal re-RT/CTschedule which would offer the best balance between tolerance and efficacy.

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The estrogen receptor as a target for breast cancer prevention

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The estrogen receptor (ER) is an important target for the modulation of estrogen action. Tamoxifen a non steroidal antiestrogen is the endocrine treatment of choice for all stages of breast cancer and the first drug available that reduces the incidence of breast cancer in high risk women. The advance was possible because tamoxifen selectively modulates ER action at different target sites i.e., it is estrogen-like in bone but antiestrogenic in breast. Additionally, tamoxifen causes a small increase in endometrial cancer incidence in postmenopausal women. Raloxifene, also an antiestrogen, has been developed for the prevention of osteoporosis but with anticipated breast and endometrial safety. It is currently being tested for the prevention of breast cancer and coronary heart disease. We have compared and contrasted the interaction of tamoxifen and raloxifene at ER alpha and found that whereas tamoxifen only silences activating function 2 (AF-2) raloxifene silences AF-1 and 2. data could explain the reduced estrogenity of raloxifene in uterus but other mechanisms need to be found to explain the estrogen-like effects of raloxifene on bone.

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Coactivators and hormone action

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Activation of transcription by nuclear receptors is potentiated by coactivator proteins which are recruited to the receptor in the presence of hormone. Hormone binding results in a conformational change in the receptor forming a novel surface to which coactivators may directly bind by means of leucine rich (LXXLL) motifs. Mutagenesis experiments on the oestrogen receptor (ER) have defined the major interaction site on the ligand binding domain consists of a hydrophobic groove flanked by conserved glutamic acid and lysine residues. Peptide competition studies demonstrate that residues N-terminal to the leucine motif are also involved in high affinity binding to the ER. In contrast, recruitment of the p160 protein SRC-1 to the androgen receptor occurs primarily by means of interactions between the N-terminal AF1 domain of the receptor and a glutamine-rich region in the. The role of the nuclear receptor interacting protein RIP140, which contains multiple LXXLL motifs, is being analysed in vivo following deletion of the gene in mice by homologous recombination. RIP140 is widely expressed in both embryonic and adult tissues and shows specific patterns of expression at different developmental stages. RIP140 (−/−) animals are viable and occur in a normal Mendelian ratio although show a reduction in growth compared to wild type and heterozygous controls. Female (−/−) mice are infertile while males, although fertile, die prematurely. The basis of these phenotypic changes is currently under investigation.

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Erβ – New development

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Estrogen signalling is complex and it has always been difficult to reconcile this fact with the textbook dogma that there only exists one estrogen receptor. (ER). Following our discovery of a second ER (Erβ), reported in 1996, views on estrogen mechanism of action have changed dramatically. Erα and Erβ appear to be quite distinct biologically and it may even be appropriate to describe their relationship as a yin-yang situation. Data from Erβ −/− mice show the following phenotypical characteristics: prostate hyperplasia; polycystic ovaries with follicular arrest (fertility is reduced by 80% in the females); lipodystrophy; defeminization of pubertal bone growth in females (i.e. -/- female mice are indistinguishable from wt and -/- male mice in that they do not show the usual slowing down of cortical bone growth typical of wt females during puberty); feminization (i.e. elimination of imprinting) of liver metabolism in -/- mice, indicating that these animals are not neonatally imprinted by estrogen at birth.

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Genetic dissection of glucocorticoid receptor function in mice

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Glucocorticoids are involved in numerous physiological processes. Most of the effects are thought to be mediated by the glucocorticoid receptor (GR) via activation and repression of gene expression. Activation requires binding of a receptor dimer while repression is mediated in many cases by protein-protein interaction of GR monomers with other transcription factors. To analyse glucocorticoid receptor function in vivo several mutations were generated in the mouse. Mice with a disrupted GR gene (null mutation) die shortly after birth due to respiratory failure indicating an important role of GR in lung function. To separate activating from repressing functions of the GR a point mutation in the D-loop of the receptor, which is required for receptor dimerization, was generated with a Cre-loxP based strategy. Mice carrying this point mutation (GR^{dim}) survive and allow to distinguish between GR functions dependent on DNA binding and those mediated by protein-protein interaction. Using cells from this mutant the molecular mechanism of cross-talk of GR with AP1 and NFkB was analyzed. Effects of glucocorticoids on AP1-controlled functions are not altered in GR^{dim} mice, suggesting that effects of GR on AP1 activity do not require DNA-binding. Further, DNA-binding-independent activity of the receptor is sufficient for immunosuppression in vivo. Since mice with a disrupted GR gene die after birth, cell-specific mutations have been generated with the Cre-loxP system. The GR gene was inactivated in liver, thymus and brain, respectively. Absence of GR in brain leads to alterations in control via the hypothalamic-pituitary-adrenal axis. The mutant mice appear to be less anxious revealing an involvement of GR in emotional behaviour and are impaired in learning and memory as shown in water maze studies. Mice deficient in GR function in liver and thymus are presently studied.

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New antioestrogens for breast cancer

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Considerable progress has been made in antioestrogen development recently. In the past most agents were based on the tamoxifen-like triphenylethylene structure and include toremifene, droloxifene, TAT-59 and idoxifene. The new or newly developed antioestrogens have novel structures and include the benzothiophenes, raloxifene and SERM III (Lilly), the benzpyran, 57050 (Schering) and the oestrogen analogue Faslodex (ICI 182780, Zeneca). It is likely that the new compounds will be more potent than the triphenylethylenes since preliminary evidence indicates that they are more efficient inhibitors of the oestrogen receptor (ER) in the breast and uterus. Whereas the triphenylethylenes block only one ER activating factor (AF2) at least two of the newer antioestrogens have been shown to block a second activating factor (AF1) thus inhibiting growth factor activation of ER. All four of the newer antioestrogens are in phase II or III clinical trial development: a summary of their activities will be presented.

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How to respond to complementary medicine: Introduction

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The use of complimentary medicine is increasing throughout Europe. This is partly a response to the wider availability of alternatives to conventional medicine, and partly due to disillusionment with the end results and morbidities associated with the use of conventional treatment.

This symposium will review the use of complimentary medicine in Europe, focusing on the availability of different types of complimentary medicine, the patient populations that use or seek advice about the use of complimentary medicine, and most particularly the attitude of the medical and nursing profession towards the use of complimentary therapies. There is only a small literature reporting attempts to scientifically validate the use of complimentary medicine, and the issues of whether or not it is possible to conduct unbiased clinical research in the field of complimentary medicine will be discussed.