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Active surveillance activities in Europe for prostate cancer

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The incidence of early prostate cancer (PC) in Europe increases due to growing screening activities. Up to 30% of the cancers detected are of low risk, and indicated as harmless indolent tumours that are extremely unlikely to become symptomatic during life. In the European Randomised Study for Screening of Prostate Cancer, men that underwent surveillance for indolent tumours showed an almost 0% 10-year disease specific mortality, while 1 out of 4 men of those analysed died in the same period due to other causes than their PC. Expectant management is a generally accepted treatment option, as the outcome of localized PC may only partly be altered by radical surgery or radiotherapy. In the Scandinavian Prostate Cancer Group study 4, radical prostatectomy accomplished a decrease in PC specific mortality and metastasis compared to expectant management with delayed hormonal therapy of 18% to 13% and of 26% to 19%, respectively. This favourable effect was limited only to men aged <65 at diagnosis.
Active surveillance (AS) may provide a partial solution to the current overtreatment dilemma due to screening. In general, patients diagnosed with PC are selected for AS based on a number of well accepted inclusion criteria (like T1c/T2 PCa, PSA $\leqslant$ 10.0, PSA-density <0.2, Gleason score $\leqslant$3+3=6, and $\leqslant$2 positive prostate biopsy cores), and monitored till signs of tumour progression occur that initiate delayed invasive therapy with curative intent. While AS is offered in various non-validated schemes, a number of multicenter studies has been initiated in the EU that provide information and access for participation of patients with indolent tumours with the aim of validating and improving current AS protocols. Individual pre-treatment risk assessment for the presence of indolent cancers has been made feasible with validated nomograms.
The multicenter observational PRIAS study (www.prias-project.org) has recruited over 900 European and North American men from 2006 onwards. The follow-up protocol consists of PSA measurements, digital rectal examinations, and standard repeat biopsies. In the first 500 participants men baseline patient characteristics, PSA doubling time (PSA-DT) distributions, findings in repeat biopsies, clinical stage progression, treatment-free survival, compliance with the protocol, reasons for stopping AS, and outcomes after radical prostatectomy (RP) were studied. Also Quality of Life assessments at various time points were performed. After 2 years 27% of patients had shifted to invasive therapy. After Radical Prostatectomy, 13% showed T3 disease and 48% Gleason score >6; re-biopsies indicated these adverse findings in all cases.
In the UK, an AS study is coordinated from Royal Marsden Hospital for over 7 years, recruiting over 400 men. Analyses of biopsy related histologic markers, serum PSA isoforms, and diffusion weighted MRI all illustrate that extra value might be obtained from additional markers to predict the biological aggressiveness of these tumours.
Various analyses suggest that repeat biopsies seem essential in monitoring these patients. However, other monitoring parameters as well as inclusion criteria are under discussion. Compared to immediate therapy, the delayed treatment has not been associated with a higher risk of unfavourable outcomes. Analysis of surrogate clinical endpoints and evaluation of candidate biomarkers and imaging modalities may provide further guidance in AS.

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Watchful waiting in patients with prostate cancer – US

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Background: The majority of men (over 90%) diagnosed with low risk prostate cancer today in the United States undergo some form of intervention, despite high levels of evidence that older men with low risk, screen detected prostate cancers are unlikely to benefit from treatment. Active surveillance is an alternative approach to immediate intervention for the management of low risk prostate cancer in selected individuals thought to harbor low grade, low volume cancer.
Materials and Methods: Literature review of surveillance programs in the United States with published criteria for patient selection and triggers for intervention.
Results: Active surveillance or careful monitoring of individuals with the intention to cure should disease progression occur, has been described in multiple centers in North America that are gaining experience with this approach to management of low risk prostate cancer. Criteria for selection of men for surveillance, and appropriate triggers for intervention that will insure high rates of cure are being investigated.
Conclusions: Active surveillance as an option for management of low risk prostate cancer is underutilized in the United States, and barriers to acceptance of this approach should be addressed to reduce the over treatment of prostate cancer in an era of intense screening.

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(Bio) Imaging guided selection and application of personalized radiotherapy

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The radiotherapeutic management of prostate cancer relies heavily on optimizing its treatment based on the clinical parameters of disease that currently only include the prostate specific antigen (PSA) level at clinical presentation, histopathological Gleason score and the TNM staging system. In turn, the TNM system relies mainly on morphological staging using magnetic resonance (MR) imaging and bone scanning. Recent advances and developments in imaging methods and hardware such as MR particle imaging, dynamic contrast enhanced MR, diffusion weighted MR, MR spectroscopy, and positron emission tomography (PET) with CT using newer tracers such as choline are being investigated to assess its utility for improved staging of the disease extent, selecting patients with localized or local regional disease for radiotherapy, and optimizing tumour target volume delineation for personalized prostate radiotherapy. Herein lies the opportunity to define parameters of prostate cancer disease activity distinct from simple morphological size criteria such as regions of tumour density, proliferation, angiogenesis and hypoxia. This functional and biological information may substantially aid selection of patients for differing prostate treatment strategies. Therapy opportunities in prostate radiotherapy could include combined modality therapy with radiation using agents such as hormonal therapy, radiosensitizing agents, agents to limit angiogenesis and agents that affect growth factors associated with signal transduction and proliferation. In addition, there will be radiotherapeutic opportunities to improve local control by utilizing bio-imaging for selective targeting of regions of potential radioresistance such as hypoxia within the prostate gland. This may involve optimizing radiobiological rationale for dose escalation with hypofractionation. This may be achieved with intensity modulated radiotherapy (IMRT) with integrated simultaneous boosting of these biologically selected regions within the prostate gland or seminal vesicles. In addition, IMRT may permit tolerable irradiation of the pelvic nodal region where appropriate. The use of image guided methods will be needed to ensure accurate and reliable treatment delivery as well as targeting of any biologically relevant boost regions. Another important aspect of bio-imaging is the opportunity to assess disease response potentially during treatment to initiate alternate treatment options for poor responders. The rationale for integration of functional and biological targeting in prostate cancer needs careful study and its true utility and impact for clinical outcomes in prostate radiotherapy will need to be defined in clinical trials.

Scientific Symposium (Wed, 23 Sep, 09:00−11:00)
Is cytotoxic treatment outdated in advanced or early breast cancer

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Newer cytotoxics in breast cancer – are there any and are they still needed?

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The advent of targeted therapies has revolutionized the field of oncology and we now are in a much better position to understand and fight the scrounge called cancer. And as has been the habit of humankind, we now question the gold standard “old” chemotherapy with the glittering “new” targeted therapy.
Important part of early breast cancer patients treated only with surgery relapse. The introduction of chemotherapy and radiation therapy changed this dreadful scenario to give us cure rates of up to 70% in early stage breast cancer. The history is proof of this with the advent of CMF (Cyclophosphamide + Methotraxate + 5-FU) based treatment and then the introduction of anthracyclines followed by taxanes.
Anthracyclines and taxanes have now become an integral part of the chemotherapy regimes in the treatment of adjuvant and metastatic breast cancer. Both agents have been shown to provide better survival and clinical benefit to patients. But both, anthracyclines and taxanes, have some important side effects. Cardiotoxicity with anthracylines and neuropathy with taxanes are a reality. Newer agents are being required so as to mitigate the side effects and increase the therapeutic efficacy of these molecules. And newer agents which serve this purpose to increase the therapeutic

index are being developed. Pegylated doxorubicin and Nab paclitaxel are just two examples of such development. In addition newer molecules targeting microtubules like Eribulin and Epothilones have demonstrated increased efficacy and different safety profile.
Targeted therapies are an addition to the armamentarium of agents to fight breast cancer. But when used as monotherapy without chemotherapy have led to modest responses and benefits to patients. Overall, the results of trials with chemotherapy in combination with molecular-targeted therapies have been superior than targeted agents administrated alone.
Chemotherapy is an integral and irreplaceable part of the treatment of breast cancer. But there is a need for agents with better therapeutic index and agents overcoming the resistance to existing chemotherapeutic drugs. Targeted therapies do play an important role in a subgroup of patients in combination with to chemotherapy.

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Targeted regimes without cytotoxics – are they ready for prime time?

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Current context/presentation goal: Chemotherapy has been shown to improve outcome both in early and advanced breast cancer. Nevertheless, chemotherapy is associated with a broad array of side effects that significantly alter the quality of life. One of the research goals in the next years will be to decrease the number of patients treated with cytotoxic agents. There are two ways to decrease indications of chemotherapy: i. to identify patients who do not get benefit from such treatment, ii. to substitute cytotoxic treatment by targeted agents, that do not exhibit toxicity.
In the presentation, we will focus only on Her2-overexpressing breast cancer, and will discuss whether targeted approaches without cytotoxics could improve outcome.
Her2 signalling in breast cancer: Her2 overexpression occurs in around 10% of early breast cancer. Overexpression is related to gene amplification, and leads to the activation of intracellular kinase pathways. Her2 is though to mediate oncogenesis of such cancers. Interestingly, several additional molecular events are sometimes observed in this subset of cancers. These events could mediate resistance to Her2-inhibitors. These molecular events include PI3KCA mutations (Stemke-Hale et al, Cancer Res. 2008 Aug 1;68(15):6084−91), IGF1R overexpression (Nahta et al, Breast Cancer Res. 2006; 8(6): 215.), PTEN loss (Nagata et al, Cancer Cell. 2004 Aug;6(2):117−27). These data suggest that Her2-overexpressing breast cancer is an umbrella that includes several molecular entities, some of them being highly sensitive to Her2-inhibitors, while other ones are resisting to this kind of approach.
Efficacy of Her2 inhibitors as single agents: Two Her2 inhibitors (Trastuzumab, Lapatinib) have been developed until now. When used in the first line metastatic setting, the two agents exhibit the same range of efficacy. In the phase II reported by Vogel et al (JCO 2002 Feb 1;20(3):719−26), trastuzumab was associated with a 35% objective response rate in patients with Her2-overexpressing breast cancer. Interestingly, 7 out of 85 patients with Her2+++ breast cancer have presented a complete clinical response. In the phase II reported by Gomez et al (JCO 2008 Jun 20;26(18):2999–3005), lapatinib was associated with a 24% response rates.
New generation of HER inhibitors are being developed. In phase II trials performed in patients previously treated with trastuzumab, neratinib/trastuzumab (ASCO 09) and trastuzumab-DM1 (ASCO 09) were associated with 28 and 32% response rates respectively. Interesting, the neratinib/trastuzumab combination was associates with 7% complete response. Altogether, the phase II trials performed with targeted therapy alone suggest that a subset of patients with Her2-overexpressing breast cancer is highly sensitive to Her2-inhibition alone. Adding other targeted agents, including pertuzumab (Baselga et al, ASCO 07, Abstract No:1004) or everolimus (Andre, ASCO 08, Abstract No:1003) could increase efficacy in biomarker-selected population.
Unfortunately, there is no data about whether such high level of efficacy translates into long term PFS in the metastatic setting.
Looking at pCR rates in patients treated with targeted agents in the preoperative setting could be a possible way to get information about whether targeted agent could substitute chemotherapy. Unfortunately, there are only a few studies that evaluated Her2-inhibitors without chemotherapy in the preoperative setting. The NeoALTTO program will provide some relevant information regarding this question. In this trial, Her2-inhibitors are being provided for 6 weeks before combining them with chemotherapy. Since biopsies are being done at day 14, and radiological assessment at week 6, this trial will provide informations about whether some patients are highly sensitive to Her2 inhibition and whether these patients could be characterized in terms of biological profile.
Combining Her2 inhibitors with chemotherapy: Lessons from randomized trials: Five trials (Piccart-Gebhart et al, NEJM 2005 Oct 20;353(16):1659−72; Romond et al, NEJM 2005 Oct 20;353(16):1673−84; Joensuu et al, NEJM2006 Feb 23;354(8):809−20, Spielmann SABCS 2007, Slamon SABCS 2007) have evaluated the efficacy of trastuzumab in the adjuvant setting. All these trials included adjuvant chemotherapy. Although there is some debate about whether combined arm could be more effective than sequential arm, there is no doubt that using trastuzumab alone after chemotherapy is effective in a subset of patients. Such data reinforce the concept that a subset of patients could be treated with Her2-inhibitor alone.
Chemotherapy-free regimen in the metastatic setting: Lessons from randomized trials: Two randomized trials (Kaufman et al. Ann. Oncol 2006;17(suppl. 9): abstract LBA2; Johnson, SABCS 2008) have evaluated whether a combination between Her2 inhibitor and endocrine therapy is more effective than endocrine therapy alone. The two trials reported a benefit of using Her2 inhibitor. Interestingly, in the EGF30008 trial, the lapatinib/letrozole arm was associated with a median PFS at 8 months, a number in range with PFS observed in trials combining taxanes + Her2-inhibitors.
Conclusion: The current data suggest that a subset of patients with Her2-overexpressing breast cancer is highly sensitive to targeted approach, and could be spared from chemotherapy. This subset of patients should be identified soon using biomarker studies from preoperative trials. In the daily practice, it is not yet recommended to use targeted agents without chemotherapy. One potential exception could be elderly patients with Her2-overexpressing/ER-positive cases without visceral involvement. The discussion about how to provide evidence for equivalency between targeted approaches and cytotoxic regimen will be done during presentation.

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Role of maintenance chemotherapy in advanced breast cancer

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Advanced/Metastatic Breast Cancer (MBC) is considered an incurable disease. First line chemotherapy in patients with MBC is associated with a median disease free survival between 5−12 months, and a median overall survival (OS) between 24−36 months. In general, it can be said, that patients who respond to chemotherapy present a better OS than non-responders. However, treatment duration remains controversial. Should we continue treatment until disease progression or should we stop it once a positive response or stabilization of the disease has been achieved? Different strategies of maintenance chemotherapy have been used in randomized clinical trials to answer this question. A good inclusion criteria for maintenance chemotherapy would be patients with HER-2 (−) tumors, negative hormone receptor tumors or hormone refractory patients. In HER-2 (+) patients the use of trastuzumab until progression appears to be clinically justified, as well as the use of endocrine therapy in hormone receptor (+) tumors following chemotherapy. Over the last 20 years, ten randomized clinical trials have been published comparing short vs. long duration treatment in MBC patients. Seven of these studies did not use new agents such as taxanes or pegilated liposomal adriamycin (PLA). Overall, these trials have shown a consistent benefit in terms of better time to progression (TTP) for the maintenance arm, but only one has shown an improvement in OS and, in one data on this parameter are still pending. In conclusion, maintenance chemotherapy may be a reasonable approach to obtain better TTP but a modest benefit in OS according to a recent meta-analysis. Further trials with current agents/regimens are required in order to obtain evaluable-relevant clinical new data to help us in decision making to justify a change in clinical practice. Any clinical trial should have quality of life as a secondary end-point since added extra toxicity is a major concern in any form of maintenance treatment

Scientific Symposium (Wed, 23 Sep, 09:00−11:00)
New targets for ovarian cancer

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Biology of tumor angiogenesis and potential biomarkers of angiogenesis

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In 2004 Avastin was approved as the first anti-angiogenic drug for human use. Additional anti-angiogenic compounds were approved since, and clinical use has demonstrated that they provide survival advantage to metastatic renal cancer and, in combination with chemotherapy, to advanced colorectal, breast, and non-small lung cancers. Many clinical