trials, there were indications that high-risk patents with a full rectum in the planning CT scan had less biochemical control compared with patients with a relatively empty rectum. These results indicated that image guidance techniques are of paramount importance in combination with intensity modulated radiotherapy (IMRT).
Several image guidance techniques are currently in clinical use: ultrasound, implanted markers and Cone Beam CT on the treatment machine. The advantages and disadvantages of these techniques will be discussed in detail.

155 INVITED

Laparascopic surgery

T. Piechaud. *France*

Abstract not received.

156 INVITED

Comparison of laparoscopic prostatectomy with open radical prostatectomy for early stage PCA. Is there a real benefit for the patient?

M. Wirth. *Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik fü Urologie, Dresden, Germany*

Open retropubic radical prostatectomy is the standard treatment of localized prostate cancer in men with an adequate life expectancy. It was superior to watchful waiting in clinically diagnosed disease in a randomized trial concerning tumor control and overall mortality. New surgical approaches like conventional laparoscopic and robotic radical prostatectomy have not been investigated in a prospective randomized trial in comparison with open surgery yet. In experienced hands, the results of the different surgical approaches seemed to be comparable. Recent non-randomized comparative studies, however, suggest that conventional laparoscopy has an increased risk of postoperative urinary incontinence. Furthermore, there is a long learning curve in conventional laparoscopy which is associated with an increased risk of positive margins and rectal injuries that may cause fistulas. Until now, there is no conclusive evidence that laparoscopic approach has any clinically meaningful advantages compared with open surgery. Robot-assisted radical prostatectomy is an advancement of laparoscopic surgery. Centers with a high case load report excellent outcome concerning potency and uninary continence as well as tumor control in properly selected patients. The number of centers offering robot-assisted radical prostatectomy is fastly growing despite the currently still very high costs of this procedure. The development in the years to come will show whether robot-assisted radical prostatectomy wil establish a new standard of care of localized prostate cancer.

157 INVITED

Chemotherapy developments in hormone refractory prostate cancer, ongoing trials in early and advanced disease

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

In the late 1990s, phase I and II studies using docetaxel demonstrated substantial activity in terms of pain responses and median survival figures of 16−20 months, that warranted the initiation of two randomized phase III 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 mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone. 1,006 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). In an updated survival analysis (ASCO prostate 2007) the survival benefit has sustained (19.2 vs 16.3 months, HR 0.87).
SWOG 99−16 was built on the prejuidice that the combination of docetaxel plus estramustine had the greatest therapeutical potential and was the comparator against mitoxantrone plus prednisone. 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).
These study results have 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).
In the setting of 2nd line chemotherapy, the recently completed SPARC trial has identified the oral platinum compound satraplatin as effective therapy. In the SPARC trial, 950 patients failing one line of chemotherapy were randomized to receive satraplatin plus prednisone, or placebo plus prednisone. Satraplatin provided significantly superior PFS and Time To Pain Progression. Results have been presented at ASCO 2007 and will also be available at ECCO 14.

Symposium (Wed, 26 Sep, 14:45−16:50)
Development of early markers of response

158 INVITED

Introductory talk (broad overview multiple approaches)

G.B. Mills. *USA*

Abstract not received.

159 INVITED

Targeting MEK in tumors with BRAF and RAS mutations

D. Solit. *Memorial Sloan-Kettering Cancer Center, Medicine, New York, USA*

Constitutive ERK activation is a common finding in human cancer and is often the result of activating mutations of BRAF and RAS. BRAF missense mutations occur in approximately 8% of human tumors, most frequently in melanoma, papillary thyroid cancer and colon cancer. Mutations in BRAF have been found predominantly in tumors in which RAS is commonly mutated but concurrent mutations of both BRAF and RAS are extremely rare. Though over 40 different kinase domain mutations in BRAF have been identified, a single base-pair substitution in exon 15 at codon 600 (V600E) is found in over 80% of cases. The majority of mutations identified cause constitutive kinase activation with the V600E mutation demonstrating approximately 500-fold greater kinase activity than wild-type BRAF. Supporting its classification as an oncogene, V600E BRAF stimulates ERK signaling, induces proliferation and is capable in model systems of promoting transformation. However, BRAF mutations are common in nevi and colon polyps suggesting that BRAF mutation alone is insufficient for tumorigenesis and additional mutations are required for cancer development. Though such data suggest that BRAF mutation is likely an early initiating event in tumors such as melanoma and colon cancer, preclinical studies suggest that tumors with V600E BRAF mutation remain dependent upon BRAF for proliferation and survival. Given its frequent occurrence in human cancer and the continued requirement for BRAF activity in tumors with BRAF mutation, efforts are underway to develop targeted inhibitors of BRAF and its downstream effectors. The first generation of RAF inhibitors, including sorafenib, were notable for their lack of specificity and potency for RAF and these agents have shown limited efficacy in tumors with a high incidence of BRAF mutation such as melanoma. Novel inhibitors of the pathway with greater selectivity for BRAF and MEK are now in Phase 1 and 2 clinical trials with promising early results. To maximize the likelihood of success with these agents, clinical trials enriched with patients whose tumors possess BRAF and RAS mutations have been proposed.

160 INVITED

Biopsy-driven biomarker development: pharmacodynamic studies in early clinical trials

J. Tabernero, T. Macarulla, J. Capdevila, A. Prat, F.J. Ramos, E. Elez, J. Baselga. *Vall d'Hebron University Hospital, Medical Oncology Department, Barcelona, Spain*

The selection of a therapeutic effective dose with conventional cytotoxic agents has been usually based on the consecution of the maximally tolerated dose. This principle does not apply for targeted agents, where the definition of the optimal biologic dose (OBD) would be preferred instead. The definition of OBD may be established based on pharmacokinetic endpoints or, preferably, by demonstrating the desired effect on the target molecule in normal or tumor host tissues. Normal tissues such as peripheral blood mononuclear cells, skin, mucosa or hair may be good surrogates for evaluating the exposure of a selected drug and kinetics of the target