Introduction

Cora N. Sternberg

Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy

Prostate cancer is a leading cause of morbidity and mortality worldwide. In more developed countries it is the most common cancer in men and the 4th most common cause of cancer mortality. Its incidence varies geographically due to environmental factors, and has increased since the introduction of widespread PSA screening.

Patients are more frequently diagnosed at an earlier stage due to increased public awareness and PSA testing. Due to this stage migration, 80% are M0 at presentation. For patients with localized disease, most get local treatment with curative radiation therapy or surgery. However, watchful waiting (expectant therapy), radical prostatectomy, external beam radiation with or without hormone therapy, and brachytherapy (seed implantation) are all utilized. There are no published reports of randomized studies in which these different treatments have been compared.

David P. Dearnaley discusses the considerable advances that have been made in radiotherapy technology. High dose radiation volume can be shaped much more precisely around the prostate and surrounding structures using conformal radiotherapy methods (CFRT) or intensity modulated techniques (IMRT) and different fractionation schedules. Several randomized trials have shown that hormonal therapy as an adjuvant to radiation appears to have a synergistic positive effect.

Nonetheless, many fail local therapy and early identification of patients at high-risk for recurrence after prostatectomy and radiation therapy has become increasingly relevant.

Hein Van Poppel discusses the place of surgery in patients with advanced prostate cancer, and proposes to use the terminology of early prostate cancer for patients with T1–T2 tumors and to consider T3–4 tumors locally advanced as they clinically extend outside the prostate capsule for which local treatment could still be an option. Advanced prostate cancer is then used for the Tx N+M+ patients where cure cannot be obtained by local treatment. Based on several randomized trials, most clinicians recommend a combination of radiotherapy and hormonal therapy for stage T3 prostate cancer. However, this combination has not been proven superior to surgery alone or surgery in combination with either early or late radiotherapy and/or hormonal therapy. There have been limited reports on radical prostatectomy in clinical T3 prostate cancer patients. The European Association of Urology guidelines for the treatment of prostate cancer recommends radical prostatectomy for locally advanced prostate cancer for selected patients with unilateral and limited T3, a PSA <20 ng/ml, a Gleason score <8 and a life expectancy of at least 10 years. Neoadjuvant hormonal treatment prior to radical prostatectomy has been shown in numerous randomized trials to reduce the positive margin rate, but to have no influence on the PSA failure rate or on overall survival.

Fritz Schröder, addresses the question of what to do in patients with a rising PSA during follow-up, which varies according to the stage of prostate cancer. The rate of rise has been shown to be indicative of clinical progression at various rates and times in the different clinical situations. Therapeutic options vary markedly as to whether a rise of PSA occurs in locally confined prostate cancer managed by potentially curative options such as radical prostatectomy or watchful waiting and, as a sign of progression under endocrine treatment of advanced disease. The Scandinavian randomized study of watchful waiting compared with radical prostatectomy is the only information available on clinical progression of locally confined prostate cancer. Radical prostatectomy produced a modest but significant advantage of 5.3% and 5% in prostate cancer specific and overall mortality.

PSA kinetics such as PSA-velocity (PSAV), the increase of PSA in ng/mL/year or PSA doubling time (PSADT), the reciprocal value of PSA slope. Both options have been used alone or together with molecular subforms such as free-PSA (FPSA), or as the ratio of PSA divided by prostatic volume (PSA density, PSAD) to design predictive nomograms. Prediction of bone metastases in men with locally confined disease and low PSA levels is difficult. Studies have attempted to evaluate this problem, which

may have a significant impact with respect to the care of patients with locally confined cancer.

Rising PSA of 0.1 or 0.2 from previously non-measurable levels is defined as PSA progression after radical prostatectomy. The natural history of a PSA rise after radical prostatectomy is well understood. On average it takes as long as 8 years to the occurrence of metastatic disease and 3 years to death of prostate cancer, which will only occur in a fraction of men. Unfortunately, randomized studies establishing either radiotherapy or endocrine treatment in this setting are unavailable. PSA doubling time, Gleason score and time to PSA recurrence are significant prognostic factors. The extremely long natural history from a PSA rise to metastatic disease and potential death as well as the low rate of events in untreated men should encourage delayed treatment. However, the issue of early versus delayed treatment is unresolved. Men with a rising PSA are very often treated with radiation or hormonal manipulations. Occasional impressive responses to radiotherapy have been observed. However, patients with a Gleason score of 7 or higher, PSA recurrence earlier than 2 years after radical prostatectomy or a short post-operative PSA doubling time may, however be candidates for early endocrine management.

For those in whom such treatment is unsuccessful or who present with metastatic disease, androgen deprivation therapy is often used to improve disease-free and overall survival. Metastatic prostate cancer is primarily characterized by osseous metastases and is ultimately considered incurable. Helen Boyle and Jean-Pierre Droz describe mechanisms of hormone sensitivity and normal biology of the androgen receptor. Hormonal treatment of prostate cancer is composed of a wide variety of techniques with different mechanisms of action. Sexual changes, osteoporosis and cognitive changes are long-term consequences of this therapy. Meta-analyses have failed to demonstrate significant survival advantages with the use of complete androgen blockade (usually an LHRH agonist and an anti-androgen). Intermittent hormonal deprivation to decrease the side effects of hormone suppression and particularly the long-term effects is under investigation.

Cora N. Sternberg discusses how to treat hormone-refractory prostate cancer (HRPC) patients. Most patients eventually develop hormone resistance and require other forms of treatment. The median time to hormonal resistance in patients with metastatic disease is 24 months. Discontinuing the anti-androgen, while castration is maintained, may lead to a benefit in up to 30% of patients. Other secondary hormonal manipulations may also be effective in patients who develop androgen resistance. Mechanisms of androgen resistance are those that involve the androgen receptor and those that bypass the receptor completely. Pathways involving androgen-receptor–mediated survival of prostate-cancer cells include amplification or mutations of the receptor, deregulation of growth factors or cytokines, and alteration of co-activators. One pathway, which bypasses the androgen receptor is related to the neuro-endocrine differentiation of prostate cancer cells. Another important pathway involves deregulation of apoptotic genes. The tumor suppressor gene PTEN (phosphatase and tensin homologue) and the anti-apoptotic gene Bcl-2 play important roles in HRPC.

In patients who develop HRPC, two large randomized phase III trials have demonstrated a 20–24% decrease in mortality with the combination of docetaxel and prednisone therapy. Large-scale clinical trials are seeking to build upon these results by adding anti-sense anti-apoptototic oligonucleotides such as anti-BCL-2 therapy (Oblimersen Sodium, Genasense), anti-angiogenic agents such as monoclonal antibody therapy against the vascular endothelial growth factor (VEGF) (Bevacizumab, Avastin), anti-endothelin receptor antagonists (Atrasentan), vitamin D analogues (Calcitriol) and tyrosine kinase inhibitors. Other strategies, which have shown promising results include immunotherapy with dendritic cell vaccines. (APC8015, Provenge).

Newer generation bisphosphonates may be able to relieve pain caused by bone metastases, prevent treatment-related loss of bone mineral density, and possibly slow the growth of metastases. The use of bisphosphonates is based on evidence that in prostate cancer, the metastatic process is associated with increased bone resorption.

Second-line chemotherapeutic strategies include phase III trials of new agents such as oral bis-(acetato)-ammine-dichloro-(cyclohexylamine) platinum IV (Satraplatin) and Epothilone-B analogue (Ixapepilone).

There is an urgent need to find surrogate endpoints for locally confined prostate cancer in order to facilitate future studies. In addition, strategic and rational therapeutic approaches require an understanding of molecular mechanisms driving disease development and progression.