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INVITED EDITORIAL

Second Acta Oncologia Symposium on Prostate Cancer Controversies

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An overview of the current and future status in the diagnosis and treatment of prostate cancer was presented during the Second Acta Oncologica symposium held on the Faeroe Islands. The specific areas covered included Etiology-Biology-Pathology; Screening-Staging; Radiobiology; Curative Treatments of Localized Prostate Cancer; Endocrine Therapy, Chemotherapy, Bisphosphonates therapy and Gene and Immunotherapy. In addition to the presented invited papers a significant number of poster presentations were also given.

This and a previous issue of "Acta Oncologica" include some of the information presented at this most interesting, informative, and in some sense provocative meeting.

The current status of methods for detecting prostate cancer was discussed. The increase in the number of ultrasound guided core biopsies was noted. The reason for this increase is that the cancer detection rate is increased by up to 35% as compared to the detection rate with the standard number of biopsies. The prognosis of the individual cancer can be adequately predicted when pathological information concerning any extra-prostatic extension, margin status, tumor volume, number of positive cores, presence of vesicular invasion, and of most importance, Gleason Score is available. Unfortunately much of this data is only available on prostatectomy specimens.

A major problem is determining the volume of the prostate. This is not easily done with present radiological techniques. However the development of newer approaches will be of great importance.

A new target for evaluation of prostate cancer treatment and the significance and management of prostatic intraepithelial neoplasia (PIN) is under investigation. Estrogen receptor beta (ER-ß) signalling in the prostate is under intensive investigation. A pro-differentiative role for ER-β in the prostatic epithelium of mice was demonstrated. The results indicated that ER-ß might be a novel target for pharmacological intervention.

Diet, life style, and the risk of prostate cancer was discussed by Alicja Wolk [1]. She noted that despite the fact that prostate cancer has become a major health problem worldwide, very little is known about the etiology. Dietary factors, dietary supplements and physical activity seem to have an impact in the causation and prevention of the disease. Greater risk is associated a high consumption of meats and dairy products. Some protection seems to be related to a diet including fatty fish and tomato products. Another factor related to an increased risk is high levels of circulating insulin like growth factor, IGF-1. Additionally it was noted that increased intake of vitamin E and selenium, and increased physical activity have a positive effect on decreasing the risk of prostate cancer [1].

Current controversies surrounding prostate cancer were discussed by Peter Albertsen [2]. He noted that the current primary curative treatments of prostate cancer, surgery and irradiation have few, if any, randomized trials that demonstrate their relative effectiveness, compared to "watchful waiting". In addition each treatment carries a significant incidence of treatment related disabilities. He noted the recent Swedish trial comparing surgery and watchful

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waiting, which at the time of the meeting had failed to show a survival difference after 8 years of follow-up [3], but with a longer follow-up did so [4]. One should note that this is the first randomized primary treatment trial of either radiation or surgery published, thus, increasing the scientific evidence of a benefit in the early tumors from surgery [5]. This does not mean that surgery is a better treatment than radiation therapy; we simply do not know. Indeed, no trials have been published comparing radiation to surgery or to watchful waiting, although one large trial in the UK is ongoing. It is most assuredly an important area to explore.

Albertsen [2] further challenged the advocates of PSA screening, noting that despite the decrease in mortality, the incidence of discovered disease has increased. Thus Albertsen questions the concept of PSA screening, despite the apparent benefits of early detection. He notes the criticism of screening including the identification of sub-clinical possibly benign disease, the morbidity related to treatment, and the associated public health and social costs.

The role of lymph node staging in prostate cancer was also discussed [6]. It was noted that the data justifying lymph node dissection for patients with low Gleason Scores, and PSA less than 7 were based on studies utilizing limited dissections. Results from studies utilizing more extensive dissection reveal a higher rate of metastases. The question is whether limited dissection is of value even in favourable candidates, indeed whether more extensive dissection would be of any benefit. Some newer approaches include "sentinel node testing, high resolution MRI studies with nanoparticles and PET studies using acetate or choline as tracers [6]. In another report on 95 patients who were potential candidates for radical prostatectomy, and who were examined with pre-diagnostic and pre-operative staging by phased array MRI reported that, these examinations were not accurate enough to utilize for pre-operative staging.

The role of irradiation in the treatment of prostate cancer continues to expand [7]. Although there have not been any reported randomized studies comparing the two curative agents, retrospective studies comparing them show equivalence in overall survival and Biologically No Evidence of Disease (BNED). The question of choice for the patients who have favourable disease, is one of the differing evaluation of quality of life factors. Complications such as potency, rectal function and urinary functions are related to these treatments. The question as to the treatment of patients with less favourable disease is not so difficult, and the choice should be for the most part radiation if the aim is long-term cure [7].

Quality of life issues following irradiation treatment for carcinoma of the prostate were addressed in the review of self reported symptoms from patients treated with neo-adjuvant androgen deprivation therapy external beam irradiation, and high dose rate (HDR) brachytherapy boost at the Karolinska University Hospital, Stockholm [8]. During the years 2000–2003 patients were questioned before and after treatment, using a questionnaire based on the EORTC LENT/SOMA toxicity scale [9]. Some 525 patients responded to one or more questionnaires. Significant findings included statistically significant worsening of sexual, urinary and bowel function. These problems developed during the treatment and increased for up to 34 months, after which they diminished. The symptoms reported seemed to be less pronounced than those reported in external beam dose escalation studies. Further follow-up is necessary. A presentation on the biology of prostate cancer treated by radiation made the point that the total radiation dose is not a reliable measure of the biological effect when dose per fraction or dose-rate is changed. Large differences in biological effectiveness per-gray (Gy) are noted between the 2 Gy doses of external beam radiation therapy and the large boost doses given by high dose rate irradiation (HDR) using after-loading sources [10]. These effects commonly are more profound in rapidly dividing tissues such as the usual cancer, than in normal tissue. However, prostate cancer presents a different picture due to the fact that unlike most tumors, prostate cancer divides more slowly than the normal surrounding tissues so that higher doses to the prostate are tolerated with fewer chronic complications in the normal surrounding tissue than would be normally expected. These differences were explained using the Linear Quadratic formula. The unusually slow growth rate of prostate cancer is associated with high sensitivity to increased fraction size, thus explaining why a large number of small fractions are not an optimum treatment for prostate carcinoma. Theoretical calculations using Linear Quadratic equation modelling demonstrate a stronger enhancement of tumor effect than of late normal tissue complications.

As part of the program on curative disease, a presentation related to second opinion among patients in the Swedish Prostate Cancer Support Organization was presented. This was followed by a mini symposium on the importance of second opinion as part of the curative treatment of localized

prostate cancer. Controversial and economic aspects and problems were discussed.

New aspects of endocrine treatment were discussed [11]. Also of importance was a discussion of the rationale for the design of nuclear hormone receptor modulators, and implications for the treatment of prostate cancer.

Androgen independent prostate cancer presents a serious problem for the patient and physician. Information concerning the experimental use of docetaxel and new generation biphosphonates was also presented at the symposium. Interesting data was presented about the experimental use of zoledronic acid and docetaxel, that leads to additive and/or synergistic cytostatic effects on prostate cancer cells [12]. The optimal use of Somatostatin (sms) in the treatment of hormone refractory prostate cancer was also discussed. The discussion related to the optimal use of sms and the useage, in experimental cell studies, of a new sms derivative, smsdx. Proteomic analysis was performed to determine the effect of smsdx incubation on cell protein expression. The findings demonstrated that smsdx may be useful in the treatment of hormone refractory disease.

At the time of the meeting, the survival benefit from docetaxel in hormone refractory prostate cancer was not known, but was reported at a later date [13,14].

Data was presented on thrombospondin, a potent inhibitor of angiogenesis [15]. The findings indicated that thrombospondin is expressed in normal prostate tissue, but not in tumors in a rat model.

The research focusing on viral vectors was also discussed. The use of oncolytic viruses and the expansion and adoptive transfer of antigen-specific T lymphocytes for treatment were reported and discussed [16].

This symposium presented a complete spectrum of interest in the present and future prevention, diagnoses and treatment of prostate cancer. The publication of this material will be of major interest to researchers, epidemiologists and clinicians.

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