

and borderline lesions, Atypical Hyperplasia, Micro Invasion had marked interobserver variations. During the eighties with the increase in detection of D.C.I.S., several trials were activated in Europe and United States. In order to find the optimal management mainly to develop like in invasive cancer conservative surgical procedures and to appreciate the role of radiotherapy. 3 trials activated separately in Germany, Denmark and Norway end up by lack of accrual. A Swedish one is still on the way. 2 others trials evaluate the worth of radiotherapy and also Tamoxifen: The U.K. D.C.I.S. trial still open and the N.S.A.B.P. B24 closed. E.O.R.T.C. in Europe and N.S.A.B.P. in the United States performed two identical trials: Wide complete excision with or without Radiotherapy (50 Gy). The N.S.A.B.P. B17 has been closed in December 1990 with 818 patients. Results have been published at 5 and 8 years of Follow Up. Disease Free Survival: Surgery = 72% and 62% - Surgery + Radiotherapy = 83% and 75% (P: 0.00003). But overall survival at 8 years is 94% and 95% (N.S.). At 8 years the cumulative incidence of local invasive recurrence decrease from 13.4% to 3.9% and for non-invasive from 13.4% to 8.2%. The E.O.R.T.C. is closed since 7/96 with 1010 cases. No data by treatment arm are yet available but the whole population D.F.S at five years is 79% and invasive D.F.S survival is 90%. In both trials, the average incidence rate of local recurrence during the first five years is about 4%.

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### Genes and the development of prostate cancer

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Human prostate cancer is a complex disease whose clinical outcome is frequently difficult to predict by traditional histopathological and clinical diagnostic techniques such as serum PSA testing. In particular, the degree and severity of metastatic spread has posed problems in terms of management of disease. It is clear that there is a genetic component in prostate cancer with possibly significant differences between the familial form, which is relatively rare and affects younger patients in the 40-60 age group, and the sporadic form which affects most elderly patients. The advent of the "new genetics" and high throughput screening of patients can narrow down and identify first of all gene loci and then genes themselves and should bring untold benefits to the fields of both diagnosis and treatment.

While no novel genes directly predisposing to prostate cancer have yet been isolated, a number of promising loci have been identified on human chromosome 1 for familial prostate cancer and most notably in chromosomes 8, 10 and 16 for sporadic prostate cancers. Genetic analysis of single tumour foci from individual patients using polymorphic microsatellite probes indicates that prostate cancer is as complex genetically as it appears clinically in terms of responses to therapy.

The significance of these gene loci will be discussed and their potential for application in new and more effective treatments, including the development of gene therapy directed into the prostate will also be described.

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### Screening programmes for prostate cancer. Is it worthwhile?

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Where the application of early diagnosis and screening seems to be driven by 'common sense', there are unfortunately only a few situations in which there are more advantages than drawbacks. Therefore, a number of conditions have to be met in order to decide the implementation of this approach for a specific disease. At this moment there seems not to be an indication that for the case of prostate cancer these premises are met.

Prostate cancer is mainly a problem in the elderly and as such rather to be described as a frequent cause of death than as a major health problem. In Western Europe, men dying from prostate cancer have a better life expectancy than the mean new-born. More men seem to die with prostate cancer than as a result of it. Unfortunately, at the moment of (early) diagnosis it is not possible to make a clear distinction between aggressive and non-aggressive malignant tumours. Even on the assumption that this major problem would not exist and that the targeted illnesses would be all histologically proven malignancies, an other problem arises. The existing methods for early diagnosis of prostate cancer (digital examination, PS and trans rectal ultrasonography), lack the validity required for implementation in general populations. Application of Bayes' theorem indicates that the predictive values of the different tests are disappointing when applied in the (low prevalence) general population. Moreover, in the asymptomatic population stage distribution is centred to the early stages which are more difficult to detect leading to a decrease of the overall sensitivity.

Although it is clear that the implementation of prostate cancer screening might elucidate on the natural history of disease and some of the aggressive tumours might be detected, the negative effects are unacceptable. Over diagnosis and over treatment will be a major problem. Moreover it is still not very clear at this moment whether the treatment of prostate cancer is beneficial in the first place. It seems therefore that for the time being screening for prostate cancer should be discouraged.

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### Adjuvant hormonal therapy in locally advanced prostate cancer treated by external irradiation

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Regional disease is represented by stages T2c-T3-4 N0 M0, or T1c-4 N1-3 M0, and is usually treated by external irradiation and/or hormone therapy. The long term results of external irradiation as regards survival and progression free survival are progressively decreasing and the higher the clinical stage, the poorer the prognosis. Prostate cancer is an hormone dependant cancer: we can assume that hormone therapy may act inside and outside the planning target volume by helping to inhibit repopulation during irradiation and destroying hormone dependent micro-metastases. By combining hormone therapy - LHRH analogue  $\pm$  antiandrogen - with external irradiation before and during, or during and after irradiation, it is now possible to improve survival.

The Radiation Therapy Oncology Group has previously reported two randomized studies which have addressed the role of a short term hormone therapy delivered before and during external irradiation (protocol 86-10) and the role of a long term hormone therapy given after external irradiation (protocol 85-31). In protocol 86-10 including patients with large T2, T3, T4 tumors, hormone therapy was initiated 2 months prior starting radiotherapy and terminated at the completion of radiotherapy, and resulted in a significant improvement of prostatic local control (P < 0.001), incidence of distant metastases (P < 0.001), progression free survival (P < 0.001). As to protocol 85-31, adjuvant hormone therapy with goserelin started at the end of radiotherapy and continued indefinitely, obtained the same results: decrease of local failure (P < 0.001), distant metastases (P < 0.001) and progression-free survival (P < 0.001). In EORTC protocol 22863 immediate hormone therapy (Goserelin, Zoladex, 3.6 mg s.c. every 4 weeks) was compared to deferred hormone therapy. Hormone therapy started on the first day of irradiation and continued for 3 years., resulted with a median follow-up of 45 months., in an increase of 5-year local control from 77 to 97% (P < 0.001), clinical disease-free survival from 36 to 74% (P < 0.001), and overall survival from 62% to 79% (P < 0.001).

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### Conformal radiotherapy of prostate cancer

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Since conventional radiotherapeutic treatment of prostate cancer is associated with a relatively high frequency of local relapses, three-dimensional conformal radiotherapy (3D-CRT) is being developed to optimize local control. The principle of 3D-CRT is that by conforming the treated volume to the target volume, the amount of irradiated normal tissue can be reduced, such that dose-escalation may be allowed without increasing the risk on normal tissue complications. Since 3D-CRT involves tight margins around the Clinical Target Volume (CTV), geometrical accuracy is a prerequisite for 3D-CRT.

The positional uncertainty of the CTV during treatment is determined by organ motion within the patient and patient setup deviations. Prostate motion has been quantified by performing repeat CT scans during treatment and could be described by rotations around the left-right axis with the apex of the prostate as centre of rotation. The random component due to daily differences in rectal filling was equal to 4 degrees (1 SD). The systematic component was caused by more rectal filling during the planning CT scan compared with the average degree of rectal filling during treatment. This component was reduced by repeating the planning CT scan in case of large rectal filling. Translational and rotational patient setup deviations have been measured by portal imaging. The random components due to daily setup deviations were equal to 1.8 mm (1 SD) and 0.7 degree (1 SD). The number of mean 3-D deviations larger than 4 mm could be reduced from 37% to 5% by applying a setup verification and correction procedure.

Using 3D-CRT with tight treatment margins, a dose escalation study has been performed, indicating that a total dose up to 78 Gy is feasible without increasing rectum and bladder complications.