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REVIEW

Prostatic Cancer*

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The International Conference on Prostatic Cancer brought together clinicians, pathologists, steroid chemists, and statisticians to consider the biology of the disease, data from scientific investigations in a number of fields and the influence and side-effects of various types of treatment. Participants were internationally representative and there were contributions from three multi-disciplinary research groups - The Veterans Administration Co-operative Urological Research Group (VACURG), The EORTC and the Prostate Study Group.

THE BIOLOGICAL PICTURE

Clinical

From observations in various clinical series it appeared that clinically latent cancer was present in between 10 and 20 per cent of men in their sixties and between 20 and 40 per cent of those over 70. These neoplastic changes suggested a morphological but not necessarily invasive cancer. Such cases had shown survival rates over 3 and 5 year periods comparable with cases of benign hyperplasia within the same age range. It was claimed that early disease (T 0/1/2 or Stage 1/2) therefore justified observation until symptoms or a change in the characteristics of the tumour supervened. This however required the definition of parameters which would reliably indicate the imminence or likelihood of progression. Late disease (T 3/4 or Stage 3/4) showed survival rates of 28 per cent at 3 years and 21 per cent at 5 years, death not necessarily being associated with the tumour itself. Poor survival rates were associated with early evidence of local invasion and this was more frequently associated with anaplastic morphology.

Pathological Features

Pathology of the condition confirmed a tendency to bilateral, multifocal tumour and a peripheral location in the gland. Tumour grade could be related to the tendency or otherwise to extension and metastasis, the likelihood of response to various forms of treatment and ultimately to the survival time. The frequently heterogeneous morphology complicated grading and the VACURG practice was to use primary and secondary grading numbers in each case according to the main and next predominant histological pattern present.

Lymphatic metastases were present in 70 per cent of undifferentiated tumours at first presentation but in only 30 per cent of those with well differentiated histology. There was also an association between the extent of local invasion and lymphatic metastases, at least 50 per cent of T3 tumours showing node involvement. However, between 20 and 40 per cent of early cases (T1, 2) had disease in the regional nodes and 15 per cent had para-aortic node involvement. 76 per cent with lymphatic metastases also had metastases in bone.

Hormone Profile

The plasma hormone profile offered the possibility of more specific evaluation of each case. Ongoing studies, which included the measurement of testosterone and its metabolites, oestrogen, prolactin, follicle stimulating

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hormone (FSH), luteinising hormone (LH) and growth hormone had shown no clear pattern on statistical analysis to date and it was therefore not yet possible to use these measurements in prognosis or assessment of response to treatment. Many factors apart from the disease itself could influence one or more elements of the profile.

The results so far showed predictable responses to hormone manipulation. Orchiectomy was accompanied by a fall in testosterone to 20 per cent of its original level and this had been maintained over long periods even with sub-capsular techniques. Oestrogen treatment resulted in diminution in plasma testosterone, oestradiol, LH and FSH. Prolactin was either increased or maintained at the initial levels. The effect of Diethylstilboestrol (DES) on plasma testosterone appeared to be dose related over a narrow range but when the dose exceeded 3 mg per day, the degree of suppression remained constant. In general, growth hormone tended to increase during oestrogen treatment but in those cases in whom there was a fall, there had been an earlier mortality. Synacthen stimulation of the adrenal cortex in patients receiving endocrine therapy had confirmed its responsiveness in these circumstances and its potential to contribute to plasma androgen and therefore the possibility of this influencing progress. Progestogens reduced plasma testosterone, FSH and LH but were inferior in this respect to DES. Estramustine phosphate was a potent inhibitor of plasma FSH and LH although in other respects it had a weaker oestrogenic action.

CLINICAL ASSESSMENT AND PROGNOSIS

The means of assessment should be simple and easily available, inexpensive and as non-invasive as possible.

Gland size was a significant factor in prognosis at the outset but not subsequent to hormone treatment. Digital assessment was, however, inaccurate in estimation of the size or infiltration of the prostate. Ultrasound now permitted definition of size, shape, homogeneity and the margins of the gland. Although the acceptance of this method differed between centres, it was evident that it can provide objective evidence of progression or regression of the local disease.

Tumour histology and cytology offered a dynamic means of assessment both at the outset and during treatment. Well-differentiated tumours had a 50 per cent survival and intermediate and undifferentiated tumours a 30 per cent survival at 5 years. The histological pattern could be correlated with stage, a glandular pattern being associated more often with early stages of the disease and a good chance of regression with treatment, whatever the modality, whereas solid or cribriform patterns were usually associated with more advanced disease and resistance to treatment. There was less than 50 per cent chance of survival for two years with an undifferentiated tumour and this was relevant in assessing the advantages of DES treatment against its risks.

The heterogeneity of tumours introduced a complication in prognosis and the VACURG study had attempted to circumvent this by allocating primary and secondary histological assessments. By classifying histology in Grades 1-5 and clinical status in stages 1-4 categorisation was possible by summation of the dual histological grade numbers and the stage number giving a range of categories between 3 and 15. Those patients in whom the sum of grade and stage was 8 or less were found unlikely to succumb to the effects of the tumour itself.

Continuous cytological assessment was possible with Franzen-type biopsy which was virtually free of complications. This could provide information on the DNA content of cell nuclei which could be related to the tendency of the tumour to progress and have invasive tendencies.

In the assessment of bone metastases (M category), scanning provided a means of earlier detection than radiology, sometimes by as much as 18 months. There was also a strong case for bone scanning before considering lymphangiography (N category) which was more invasive. Indeed, only if the M category was negative should an assessment of N category be made.

Lymphangiography was essential for N staging but was limited in that it frequently did not outline the obturator or internal iliac glands and the accuracy of interpretation was open to question. For this reason there was an indication for pelvic node biopsy especially in the consideration of treatment modalities such as irradiation and radical surgery.

Although the estimation of serum prostatic acid phosphatase was simple its significance was questionable. Elevation was suggestive of metastatic disease and there was evidence that metastases preceded any rise. There was correlation between raised phosphatase levels and lymphatic metastases. Serum levels gave some indication of response to treatment.

Whilst serum acute-phase reactant protein profile had been of use in evaluation and prognosis in bowel cancer, it was of less help in the case of the prostate since changes could be produced both by the disease and by

various forms of treatment. Certain sub-sets of patients had been defined whose profile might influence clinical management. Sex-hormone binding globulin (SHBG) and SP2-glycoprotein were induced by oestrogen and absence of this induction had been associated with failure of depression of plasma testosterone and poorer response to this treatment. Depression of alpha-2-antithrombin by oestrogen below 0.02 grams per litre was associated with an increased risk of thrombo-embolic disease; it could therefore help in monitoring oestrogen therapy. Haptaglobulin and alpha-1-acid glycoprotein were raised with large tumours and high levels were also associated with widespread metastatic disease.

MODALITIES OF TREATMENT AND THEIR EFFECT

The potentiality of the tumour to remain latent and non-invasive for long periods emphasised the need for complete case assessment at the outset in view of the morbidity and mortality associated with some forms of treatment.

Oestrogen Therapy

Oestrogen treatment in addition to inhibiting FSH and LH and producing atrophy of the Leydig cells of the testis also possibly had a direct effect on the tumour. The oestrogen effect in general was similar to that seen with radiation treatment, consisting of nuclear degeneration and pyknosis with loss of ribosomes, degeneration of the cytoplasm, vacuole-formation and destruction of the tumour-cell membrane. There was proliferation of collagen and loss of the border between tumour and stroma. A proliferation of basal cells had been noted but there was no differentiation of these to mature cells. These changes were not uniform throughout and intact tumour cells were often found within an area of degenerated cells. These might be cells of a different clone, resistant to treatment and possibly responsible for tumour recurrence later on.

There was little to choose between the various forms of oestrogen preparation but whilst a 5 mgm dose of DES reduced the plasma testosterone more than a 1 mgm dose, the latter was less often accompanied by cardio-vascular complication. Early oestrogen treatment could reduce the size and extent of the tumour in the gland, relieve obstructive symptoms, delay the appearance or temporarily halt the progress of metastases and postpone a cancer death; at the same time, there was increased risk of cardiovascular complications and death from this cause. Contraindications to oestrogen treatment were a bed-ridden patient, previous history of cardiovascular disease, extreme weight loss or a patient more than 75 years old; positive indication included evidence of progression of the disease, pain, a primary tumour of greater than 30 sq. cms size, a VACURG grade + stage category of more than 10 and haemoglobin of less than 12 grams per cent.

The oestrogen-nitrogen mustard combination, Estramustine phosphate, was absorbed more readily than oestradiol in uptake studies and there appeared to be a selective concentration after several hours in the rat ventral prostate. Concentration in the human prostate suggested similar selectivity possibly in association with a specific receptor protein. It appeared to remain unhydrolysed in the cell and to penetrate the nucleus. Its mode of action had not been completely elucidated but it was a potent inhibitor of FSH and LH, a weak oestrogen and had been shown to inhibit 5-alpha-reductase, preventing the formation of 5-alpha-dihydrotestosterone within the gland. It therefore influenced prostatic function on at least 2 levels.

Clinical improvement with its use had occurred in 72 per cent of those with a well differentiated tumour and in 57 per cent with moderate or poorly differentiated neoplasms. Side effects of treatment had been few but had included thrombophlebitis at the site of injection, leucopaenia and thrombocytopaenia.

Progestogen Treatment

Progestogens exert a negative feed back effect on the hypothalamic receptors, leading to reduced gonadotrophin release and diminished synthesis of testicular androgen.

The progestogen medroxy-progesterone acetate (Provera) reduced plasma testosterone in this way. Experience was too limited to permit definition of its role in treatment at the moment. Although able to produce partial remission of early cancers it appeared to be inferior to DES.

Cyproterone acetate is both a progestogen and an anti-androgen. In addition to its progestogenic action it also blocks androgen receptors within the cell thereby interfering with 5-alpha-dihydrotestosterone receptor complex. It has the advantage that it may not be accompanied by cardiovascular side-effects. Results in limited series from a number of centres were favourable regarding its ability to control both progression of the disease and symptomatology.

Castration

A strong case was made for orchiectomy, either total or subcapsular. This could achieve plasma testosterone values as low as those obtained by standard doses (3 mgms daily) of DES over prolonged periods. Advantages of orchiectomy were its lack of feminising side-effects, the absence of anaemia, cardiovascular and hepatic complications and the freedom from the necessity to take regular medication.

Impotence was not invariable. It could produce remission of symptoms and regression of tumour both locally and in metastases. It was possibly less effective than DES in a 5 mgm dose but had none of the complicating features. It was particularly indicated in those with cardiovascular disease and in the unreliable or forgetful patient.

Radiotherapy

Supervoltage external irradiation could deliver a radical, tumourcidal dose to the prostate and to the lumbar and pelvic nodes without significant side-effects. Well-differentiated tumours responded better than undifferentiated. Serial biopsies from the prostate during treatment often showed primitive tumour cells surviving side-by-side with necrotic calls suggesting their relative radio-resistance. Clinical response was therefore again directly related to the degree of differentiation. In one series with well differentiated histology a 100 per cent 4 year survival had been recorded.

Comparison between radiotherapy and hormone treatment in several series showed a marginal superiority of radiotherapy. There was a clear necessity for inclusion of radiotherapy in controlled therapeutic trials in the future but this necessitated more accurate staging of the disease than had been achieved hitherto and, in particular, definition of lymph node involvement. Radiotherapy perhaps should be limited at the outset to those in whom there was no lymphatic spread despite the ability to irradiate effectively both pelvic and lumbar nodes.

Prostatectomy

Total prostatectomy is the only potential cure for a disease which is otherwise managed at the present time as though it were incurable; only radiotherapy or chemotherapy might in due course be alternatives. Operation, however, could only be justified in cases of well-differentiated tumours confined to one lobe and with no lymphatic involvement or metastases. The frequency of metastases in so many cases on first presentation further emphasised the need for more accurate means of staging the disease and it was anticipated that these would stem in due course from the results of ongoing studies of various groups.

The operative procedure required an open perineal biopsy and assumed pelvic lymphadenectomy; the perineal or retropubic route could be used but with the latter the glands could be removed concomitantly. The apex of the gland was removed in all cases.

There was insufficient hard data at the present time to define the place of this operation in relationship to either an expectant policy or other forms of treatment in the early case.

Non-hormonal chemotherapy

The experience of the Conference in the use of non-hormonal chemotherapy was limited but suggested that this could provide alternative treatment in cases which had escaped control by other means. Objective regression had been observed in approximately 20 per cent of those treated with cyclophosphamide, 5-fluoruracil, and adriamycin, either singly or in combination. There was no evidence of the superiority of combination over single-agent therapy although this had been suggested by the experience of others. Newer agents such as Bleomycin, Mytomycin C, Methotrexate, Procarbazine, DTIC and Nitrose ureas were available but would require evaluation. Preliminary results with Hexamethylmelamine had been encouraging but confirmation would be required with a larger number of cases.

Overall the results of this form of treatment had been equivocal. Both this and the potential toxicity of the various agents to kidney and bone-marrow in a disease in which the function of both might already be compromised further complicated the decision to use them.

Hypophysectomy

The place of hypophysectomy, either by Yttrium implant or surgery, was confined to the advanced case which had relapsed from other forms of treatment. Symptomatic relief was obtained in about two-thirds of these cases and occurred within a few hours of operation. This relief was of varying duration and was accompanied by a drop in plasma testosterone to levels lower than could be achieved either with DES or Aminoglutethamide.

RESEARCH - THE WAY AHEAD

In any consideration of future progress there is a need to define the epidemiology of the condition and establish aetiological factors so that preventive measures can be applied. There is a possibility in this respect of viral implications and from this the necessity to consider sexual factors in aetiology. Occupational hazard might also exist in connection with industrial contact with cadmium.
The Conference made it clear that advances in knowledge of the biology of the disease and its effective management depended on the type of basic observation and research currently being carried out by the VACURG, EORTC and Prostate Study Groups. In respect of prospective trials of various treatment modalities, a minimum number of 25 in any particular study was suggested. It is important to randomise a trial at the outset because of ethical difficulty in continuing the protocol after a more favourable effect of one preparation had been defined. Ideally, previously untreated cases should be used in the trial of a new preparation.

On the laboratory side, the finding and development of a satisfactory animal model is essential, particularly for the screening of potentially useful drugs. The study of effects of hormones and other agents on cell growth and metabolism, carcinogenesis and the definition of stromal/epithelial interaction require in vitro techniques using both organ and cell culture. Carcinogenesis had been produced in vitro using rodent tissue but this has been unsuccessful so far with human tissue. In the embryo, the stroma appears to control epithelial differentiation and growth and therefore might be responsible for the activation of carcinogens. There are limitations in existing tissue culture technology and anticipated developments in this field would significantly advance research.

Valuable information may be obtained from investigation of steroid receptors in the human prostate. Since cancer arises most often in the true or functional prostate it is essential that the distribution of steroid hormone receptors be defined in this tissue as distinct from hyperplastic tissue. The role of these receptors is possibly multiple and includes transport of steroid into the target cell, hormone preservation and storage, intracellular hormone transport and even the facilitation of the interaction of the hormone with nuclear chromatin. The necessity of the cell membrane for steroid action on the cell has been stressed since it has been shown that steroids introduced directly into the cell had no effect. The methodology of receptor work is an open field for progress before more meaningful results are likely.

Research into the role of zinc in prostate metabolism has demonstrated an inverse relationship between the level of dihydrotestosterone and the zinc concentration in benign hyperplastic tissue. There is a diminished zinc content in neoplastic tissue and this appears to precede any change in the testosterone/dihydrotestosterone ratio. It remains to be shown whether the action of zinc is confined to the enzymes responsible for the reduction of testosterone or is also associated with an androgen dependant metal-binding protein.

Summarising the Conference, it is evident that although some progress has been made as a result of the various observations and research there are numerous deficiencies in knowledge, both in the clinical and scientific fields and there is an obvious necessity for controlled trials of various forms of treatment including radiotherapy.

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