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PROSTATIC CANCER: THE CASE FOR SURVEILLANCE*

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Asymptomatic and unsuspected cancer of the prostate is found at autopsy (latent cancer) in up to 30% of men aged 70 years or more[1]. In addition cancer which is clinically localized to the prostate often progresses very slowly without treatment. In one series only 50% of patients developed evidence of metastases after 5 years of observation[2]. Metastatic cancer of the prostate carries a much worse prognosis and, irrespective of initial therapy, only 30 - 40% of patients survive 3 years[3]. In many of these patients death is due to some cause other than the cancer, as one would expect in patients of this age group[4]. For patients with symptoms from bony metastases, treatment is of course required. Despite this, there is no evidence that such patients survive any longer because of their treatment.

In this contribution it is assumed that appropriate steps have been taken to make a histological diagnosis and that obstruction has been relieved. In this situation the debate relates to the advisability or otherwise of further treatment in the absence of symptoms or of evidence of progression.

Therapy

From the basic principles of oncology it would seem logical to excise the primary tumor and to use systemic therapy to kill (or control) any metastases. Some of the common treatment options and their complications are listed in Table I.

If treatment is given the patient will suffer an impairment of his quality of life. Without it he may show progression sooner than would otherwise be the case. The possible effects of treatment must be judged against the potential hazards.

The literature on the results of therapy for different groups of patients may be briefly summarized as follows:-

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TABLE I

Treatment Options in Prostatic Cancer

Treatment options	Hazards
None	Progression
Radical surgery	Impotence Incontinence (20%)
Radiotherapy	Rectum - bleeding, stenosis Bladder - hematuria Urethra - stricture
Hormonal therapy	
— orchiectomy	Libido
— estrogens	Impotence Cardiovascular
— antiandrogens	Libido Adrenal suppression Cardiovascular
Chemotherapy	Not negligible

1. Latent Cancer

There is no evidence that active therapy is indicated for this form of prostatic cancer. There is however evidence that patients with this form of the disease nearly always die of other causes[5].

2. Tumors Localized to the Prostate

Tumors which are clinically localized to the prostate may be treated with curative intent by radical surgery or by radiotherapy. Although individual clinicians hold strong views on the merits of radical prostatectomy, external beam therapy and implantation of I^{125} seeds[6-7], the inevitable variations in case selection make it difficult for anyone to be convinced that one form of therapy is superior to another.

The Veterans Administration Cooperative Urological Research Group (VACURG) undertook two trials for patients with cancer localized to the prostate. In one, patients were randomized to receive estrogens or no additional therapy. In the second the randomization was between radical prostatectomy and placebo treatment. In the 247 patients followed in the first study and in the 111 followed in the second study, there was no significant difference in survival between any of the groups.

In addition fewer than 10% of the patients died of prostatic cancer in any of the treatment groups. This supports the concept of deferred therapy for patients with

the disease localized to the prostate. In 1981 Paulson came to a similar conclusion when he stated that for patients with non-metastatic prostatic cancer, "multimodal therapy consisting of pelvic lymphadenectomy with or without external beam radiotherapy has no benefit over surgery or no treatment"[10].

In Paulson's own trial of radical radiotherapy versus radical prostatectomy in patients in whom pelvic lymph node dissection had shown no evidence of metastases there was a suggestion, again in a small number of patients (97 in all) that the time to first progression was shorter after radiotherapy than after radical surgery. Survival data, however, are not yet available. For patients entered into his second trial in which those in whom pelvic node dissection had shown evidence of metastases, treatment was given by radiotherapy or deferred hormonal therapy. The results to date have not shown any benefit in survival for the group receiving immediate treatment[11,12].

The data on radiotherapy showed good control of local disease but has not so far conclusively demonstrated any benefit in terms of survival[13-16].

3. Tumor Extending Beyond the Prostatic Capsule, Including Asymptomatic Metastatic Disease

These patients have no symptoms once their obstruction has been relieved and the first VACURG study[3], showed no survival benefit from a policy of immediate as compared with one of deferred therapy.

In those receiving immediate treatment there was a reduction in the death rate from prostatic cancer. This was compensated by an increase in cardiovascular deaths (Table II).

TABLE II

Causes of Death in VACURG Study 1. (patients in stages 3 + 4)

	Initial Therapy (with number of patients)			
Causes of Death	Placebo (485)	Des (476)	Orch^{y} (469)	Orch^{y} + Des (473)
Prostatic cancer	148	95	127	103
Cardiovascular	137	175	138	160
Other	63	67	70	80
Total	348	337	335	343

NB The overall death rate is very similar; treatment reduces the rate of death from cancer of the prostate but increases that from cardiovascular disease by almost the same amount.

In the second VACURG study in which diethylstilbestrol (DES) was used in a dose of 1 mg (as compared with 5 mg) daily, the cardiovascular death rate was reduced. In this study, however, there was no deferred treatment arm and the benefit of DES at this dose is still open to debate.

None of the recently introduced drugs, including cyproterone acetate, estracyt and medroxyprogesterone acetate has been shown to be superior to DES and all have some side effects.

In the studies of the EORTC (European Organization for Research in the Treatment of Cancer) Urological Group, DES at a dose of 1 mg three times per day has been compared with cyproterone acetate, estracyt and medroxyprogesterone acetate. DES at a dose of 1 mg three times per day has been shown to have a significant cardiovascular hazard, but DES has also been shown to be at least equivalent to the other agents.

The literature on the lesser known compounds such as aminoglutethimide, flutamide and the LHRH analogues is as yet so limited that no firms view can be taken.

Studies of the combination of DES or orchiectomy with cytotoxic agents[17], carried out by the National Prostatic Cancer Project (NPCP) have shown no benefit for the patients receiving chemotherapy. They have, however, had a significant additional toxicity.

There has been little obvious progress in the management of prostatic cancer in the last 40 years since Huggins and Hodges introduced the concept of hormonal therapy. This treatment does relieve symptoms in 75 - 80% of the patients with bone pain and will produce objective evidence of tumor remission in approximately 30% of patients[16-17]. It is, however not without toxicity and the search continues for equally effective agents which can be given with more safety.

Conclusions

The failure of active therapy to improve survival in patients with prostatic cancer appears to justify the further consideration of deferred therapy in patients who, following diagnosis, are free of obstructive and of other symptoms. Such a policy of active surveillance would give much useful information on the time to local and distant progression and on the quality of life.

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A COMMENT

Mr. Smith: — Can I make one more comment? We had a meeting in Rotterdam last week and it was on prostatic cancer, for one and a half days. Someone came from the national prostatic cancer project and showed the results of many studies and covering 2000 patients. Someone else came from the EORTC group and showed the results of their studies on 900 or so patients. I was chairing a round table session, and there being not much time I decided to ask one question of these people who had been involved in so many trials and had been thinking in detail about prostatic cancer for really quite a lot of years. I said "If you had yourself suddenly been found to have prostatic cancer, what treatment would you want?" And one of them asked: "Well, what stage is the disease at?" And I said "Well, the disease is metastatic without symptoms, and your prostatism has been relieved" and both of them, one committed to the EORTC and the other to the NPC said: "Until can find further evidence to the contrary, I would like to receive no treatment until progression or the development of symptoms demanded it". I really thought that was quite an interesting response from two people who, as it were, made their living out of prostatic cancer.