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Editorial

Prostate Cancer—What Should be Studied?

N.D. James and J. Glaholm

THE EXPLOSION in diagnosis of prostate cancer in the United States has resulted in a doubling in the detection of new cases, to 200 000 in 1994, making it the most commonly diagnosed tumour after skin cancer. This has focused considerable attention on this previously relatively overlooked tumour. There are a number of areas of critical interest in the management of prostate cancer, some of which require urgent study to define optimal treatment policies. These include the detection and management of early disease, the optimal use and timing of hormone therapy and thereafter the treatment of hormone resistant disease, and whether there is a role for adjuvant therapy with, for example, bisphosphonates, in locally advanced or metastatic disease. Finally, the issue of how to assess treatments for systemic disease, such as chemotherapy and hormone manipulation, which may directly affect the principal tumour marker, prostate specific antigen (PSA), has a major bearing on how studies should be carried out.

As it is known that up to 80% of 80-year-old men and 32% of 60-year-old men have post mortem evidence of subclinical prostate cancer [1], the increased use of more sensitive diagnostic techniques could result in continued rises in the numbers of cases diagnosed. To date, the increased diagnosis rate in the U.S.A. has not been mirrored by increased prostate cancer mortality [2], suggesting that the cases diagnosed may be clinically insignificant. If early diagnosis is indeed worthwhile, then a coherent screening policy is needed as well as good evidence on which to base treatment policies. Studies of screening are underway in both Europe and the U.S.A. [3, 4], and should provide valuable data on the utility of screening. If widespread screening becomes a reality as a result of these studies, treatment of early cases, already contentious, will pose a major problem as the uncritical adoption of, for example, radical prostatectomy for early cases will result in a massive burden on surgical resources. Even relatively conservative surgical strategies, for example confining radical treatment to T1 and T2 disease of Gleason grade 5–7, combined with a screening programme could result in additional costs to the U.S. health services of $8.5–17.6 billion [5]. Alternatively, if it seems likely on the basis of screening studies that radical treatment of an early tumour in younger patients may result in cure, the problem of selection of patients most likely to benefit from radical treatment, sparing those who are unlikely to be helped, will become acute. There is thus an urgent need to define the optimal treatment of early disease, and trials such as the recently opened Medical Research Council PR04 study, comparing radical radiotherapy, surgery with observation and deferred treatment, will provide critical data in this area if recruitment is adequate. However, the problems of recruiting to such a study (which allows two way randomisations) are immense, given the very different natures of the treatment options. If these difficulties are overcome and the trial provides an answer to the question of the effects of different treatment policies at a population level, in particular the relative efficacies and toxicities of surgery and radiotherapy, it may not solve the individual problem of whether a given patient should or should not be offered treatment.

The answer to this question may lie at the opposite end of the scientific spectrum in the molecular make-up of the tumour. Molecular markers of prognosis have been shown to provide information distinct from that obtained with conventional staging in a number of settings, for example, breast cancer and neuroblastoma. Knowledge of the molecular abnormalities contributing to prostate cancer is limited, but genes commonly mutated in other cancers, for example, *RAS*, are mutated at low frequency in prostate cancer [6]. It is known that tumour ploidy is a prognostic marker in advanced disease [7–9]. Data on chromosomal abnormalities in prostate cancer suggest frequent losses on chromosomes 8, 10 and 1 [10, 11]. For example, data on losses on chromosome 8p suggest loss of heterozygosity (LOH) in up to 60% of cases [11, 12]. Although no one marker appears likely to be useful in isolation, pooled data from multiple loci may be able to provide useful prognostic information that could guide the choice of therapy, particularly taken in conjunction with conventional prognostic data, such as tumour stage, grade and PSA at diagnosis [9]. More data are clearly needed to help reliably distinguish clinically important from unimportant disease and avoid an epidemic of unnecessary operations and radiotherapy.

Treatment of metastatic disease constitutes a major problem in the management of prostate cancer. Androgen deprivation is the mainstay of therapy but is not curative, and new therapies for hormone resistant disease are needed. Chemotherapy has been explored and the paper by Brausi and co-workers in this issue (pp. 1622–1626) reports the efficacy of epirubicin in metastatic hormone resistant disease. Sadly, despite careful

Correspondence to N.D. James at the CRC Institute for Cancer Studies, Queen Elizabeth Hospital, Birmingham B15 2TH, U.K.
N.D. James is at the CRC Institute for Cancer Studies; and N.D. James and J. Glaholm are at the Birmingham Oncology Centre, Queen Elizabeth Hospital, Birmingham, U.K.
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patient selection, the partial response rate of 24% was relatively low and the toxicity, although reported as tolerable, was clearly not insignificant. Furthermore, at least 2 patients had pre-existing cardiac disease worsened without achieving a response. It must be concluded that the role of chemotherapy in this setting is limited to very carefully selected patients, and is not applicable to the majority of elderly, frail patients with the disease.

The study also addressed the difficult area of response assessment. PSA is a relatively sensitive and specific marker for prostate cancer, and allows tracking of responses to therapy and of disease progression. However, PSA expression is partially hormonally regulated, and thus falls in PSA with hormone therapy do not necessarily indicate disease responses. Conversely, PSA relapse often precedes clinical relapse by many months [13]. Both of these factors make assessment of disease responses with PSA unreliable, in turn making objective evaluation of new therapies problematic. The study correlated PSA levels with objective responses in patients with soft tissue metastases receiving chemotherapy. As PSA expression is partly hormonally regulated [14], responses to chemotherapy may give a better guide to the utility of PSA as a marker than responses to hormone therapy, where a fall in PSA may not be due to reduced tumour bulk but downregulation of PSA expression. It is disappointing, therefore, that although a positive trend was seen, 2 non-responding patients showed a >50% fall in PSA level.

Assessment of response in bone secondaries, the principal cause of morbidity in metastatic prostate cancer, is particularly problematic as other means of assessing response, such as isotope bone scans, do not usually normalise even in the presence of complete subjective and PSA responses. New endpoints are thus needed for assessing responses in this area. Another approach has been to focus on clinical endpoints, such as development of new symptomatic metastases, pathological fracture rates, courses of radiotherapy given and analgesic consumption rather than PSA levels [15]. Two recently opened randomised, placebo controlled British Medical Research Council studies employ such strategies. Trials PR04 and PR05 are investigating adjuvant clodronate in patients having locally advanced disease with a high risk of systemic relapse and patients with established metastases commencing or responding to first line hormone therapy. As such clinical endpoints are of more direct relevance to the patient than a blood test they should become more widely used in future studies of advanced disease.

Finally, for patients with advanced disease, at present incurable with current therapies, there is a clear need for new treatments. It seems unlikely that conventional cytotoxic chemotherapy will ever have much to offer as the response rates are generally low, toxicity high and the patient group elderly. Novel approaches based on emerging technologies, such as gene therapy, would seem to offer the best hope for the future.

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