CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Index Lesion and the Origin of Prostate Cancer

Hashim Uddin Ahmed, M.R.C.S., B.M., B.Ch.

Prostate cancer is a perplexing type of malignant disease. Its long natural history means that men who receive the diagnosis in their 50s or 60s do not necessarily require treatment. Most of these men neither die prematurely nor have a reduced quality of life if the cancer is left untreated. The problem is that there is no definitive way to identify those who will die from the disease. Efforts have thus been focused on reducing the considerable burden imposed by complications related to treatment.

The use of formal and informal screening has led to a dramatic increase in the number of clinically insignificant cancers that are being detected. Every year, prostate cancer is diagnosed in more than 250,000 men in the United States, and most undergo surgery or radiation therapy. However, these treatments cause impotence (in 50% of cases), incontinence (in 5 to 10% of cases), and rectal toxic effects such as diarrhea, bleeding, and proctitis (in 5 to 20% of cases). Randomized, controlled trials carried out in the United States and Europe have shown that screening for prostate cancer, at worst, is of no benefit in reducing mortality[1] and, at best, prevents the death of 1 man for every 48 men who are treated over a period of 10 years.[2] Over the years, numerous predictive models have been developed to classify prostate cancer as low risk or high risk for death from the disease. The fact that these models are derived from case series that used surrogate markers of progression rather than mortality makes them far from ideal.

Pertinent in this regard is a study by Liu and colleagues,[3] which suggests that a single precursor cell is responsible for generating metastatic disease. These researchers initiated the Project to Eliminate Lethal Prostate Cancer (PELICAN) in 1994, in which men with prostate cancer were asked to donate their bodies in the event of death from their disease. Liu et al. were thus able to analyze 94 samples of malignant tissue from metastatic sites in 30 men who had died of disseminated disease. Using a high-resolution genomewide survey of single-nucleotide and copy-number polymorphisms, the investigators concluded that different, anatomically distinct metastases within the same patient originated from a single precursor cell (Fig. 1). These findings have implications beyond the investigators' suggestion that researchers should now focus on changes within individual cancer foci to improve the poor signal-to-noise ratio of clinically relevant molecular changes.

Until recently, no one questioned whether the whole prostate should undergo surgical extirpation or be treated with ionizing radiation. Since prostate cancer is usually multifocal, treating the whole gland has been standard practice. Research strategies have therefore focused on refining the delivery of these radical therapies through the use of laparoscopic or robotic surgery and intensity-modulated radiation therapy; however, these approaches have met with little success in the effort to reduce toxicity. The problem is that treatments aimed at the whole gland result in damage to surrounding structures, such as the bladder neck, neurovascular bundles, external sphincter, and rectum.

Focal therapy has been suggested as a way to avoid this "collateral damage."[4] It is based on the idea that the management of localized prostate cancer can follow the organ-preservation approach taken in the treatment of almost all other solid tumors. In other words, ablation of only the malignant areas within the prostate, along with a margin of normal tissue, and preservation of normal prostate and surrounding structures will help reduce side effects. Research efforts in this area have centered on the 20 to 30% of men who have unilateral or unifocal cancer.

This is where the findings of Liu and col-

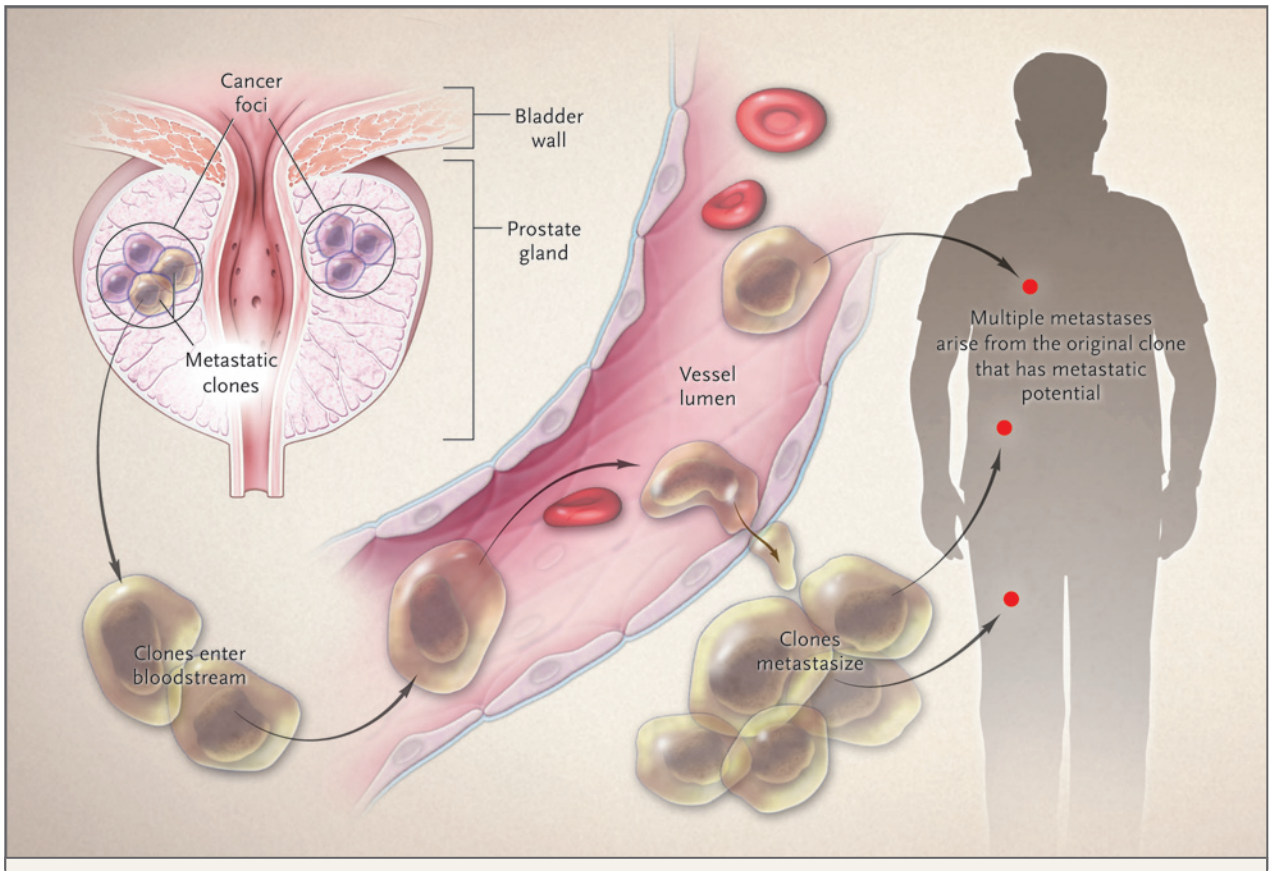

Figure 1. Monoclonal Origin of Prostate-Cancer Metastases.

A recent study by Liu and colleagues[3] has shown that metastases in prostate cancer have a common origin — that is, they originate from the same clone. If the single lesion harboring this metastatic clone could be accurately identified and then targeted, it seems likely that the side effects of treatment for prostate cancer would be reduced. The other lesions (depicted as purple cells in the prostate) would undergo surveillance.

leagues have relevance. There is increasing evidence that the largest tumor focus within the prostate (called the index lesion) drives the natural history of prostate cancer.[5] The pathological characteristics of the index lesion — namely, the grade and the presence or absence of extracapsular extension — generally indicate the prognosis. Both the index-lesion hypothesis and the monoclonal origin of metastatic prostate cancer open the way to a consideration of focal therapy in the majority of men who have multifocal, bilateral disease in which only the clinically important lesion might be ablated.

Unfortunately, Liu et al. were not able to provide a detailed histologic and genomic analysis of individual lesions within the prostate. Because the men who donated their bodies for this study had, by definition, locally advanced disease and had received androgen-deprivation therapy, they had small prostate glands with indistinct individual foci devoid of the histologic characteristics that would allow grading.

The key question thus remains: Does the index lesion harbor the single precursor cell that gives rise to progression, metastases, and death? Even if the index lesion is not the culprit, researchers must now focus on identifying the one malignant lesion that does harbor the metastatic clone. Once a means of identification can be determined, clinical trials will be warranted to investigate the effect of ablating that single lesion. A positive result would have important implications for men with prostate cancer who currently endure much treatment-related harm.

Dr. Ahmed reports that he is an investigator in clinical trials of focal ablation to treat prostate cancer. No other potential conflict of interest relevant to this article was reported.

From the Division of Surgery and Interventional Sciences, University College; and the National Institute for Health Research–Comprehensive Biomedical Research Centre, University College Hospital — both in London.

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