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Node-positive prostate cancer without distant metastases (T any, N+, M0) currently is encountered rarely,[1-4] primarily because of the shift to diagnosis at earlier stages, a result of widespread prostate-specific antigen (PSA) testing. Because of this and the long follow-up required to reach clinically meaningful endpoints, many of the case series and almost all of the clinical trials providing level 1 evidence were initiated 10 to 25 years ago (or longer). Interpreting the results of these studies is confounded to some degree by advances in treatments (both in surgery and radiation therapy); imaging/staging; biopsy techniques; histologic interpretation; and, perhaps most importantly, by the prevention and management of comorbid conditions. Moreover, during this time, a much wider appreciation of, and sophistication in assessing, disease- and treatment-related morbidities and lethal effects has occurred, which was not recognized or was significantly underestimated when earlier studies (those with the most mature and meaningful results) were conceived and conducted. With these caveats, I offer the following comments to the well-written and very valuable review by Mitin and colleagues.[5]

(1) As with many malignancies, the volume of disease that therapies face is a critical factor that is often overlooked in current (and prior) staging systems. It follows directly that local treatments would be expected to have some benefit in managing limited metastatic disease (N+, M0, however defined) and that the more thorough the local/regional “sterilization” is, the greater the chance for systemic therapies to have long-lasting benefit. It also means that the distinction between cN0/pN+ and cN+ disease probably has real clinical significance and can help account for some of the different results in simultaneously performed randomized trials and case series employing surgery and radiation.

(2) That said, the overwhelming majority of men with N+ (even pN1) disease have systemic prostate cancer, as evidenced by the 10% to 40% long-term biochemical-free survival in the deferred treatment arm of Eastern Cooperative Oncology Group (ECOG) study 3886 (radical prostatectomy [RP] + pelvic lymphadenectomy [PLD] + immediate vs deferred androgen deprivation therapy [ADT]) and case series.[6,7] Thus, eventually most men with N+ disease will require systemic treatment.

(3) Castrative therapies appear to have greater efficacy when administered before there are signs on conventional imaging (eg, nuclear bone scan) of osseous metastases. While some of this may simply reflect lead time bias, there are compelling experimental data to support the clinical impression that, once established in the bone milieu, paracrine production of cytokines and other factors by prostate cancer cells, local stromal cells, and infiltrating inflammatory and endothelial cells facilitates cancer growth and refractoriness to standard therapies.[8,9] Furthermore, as demonstrated in the control arm of EORTC protocol 30846, untreated pN+/cN0, cM0 disease becomes lethal moderately rapidly (6.2 years median survival when ADT was withheld until there were bone metastases or major local/regional progression).[10] Thus, administering ADT relatively early in the course of N+, M0 disease, before it becomes M1, makes sense.

(4) While not stated by Mitin et al,[5] the majority of local cancers in even pN1/cN0, cM0 disease extend beyond the confines of the prostate gland. In ECOG 3886, over 60% to 65% of participants had T3b and/or surgical margin (SM)-positive disease.[6] While surgical techniques have improved over the last 20+ years, this may explain why better local therapy (eg, RP + PLND + adjuvant RT) in pT3-4 or SM-positive disease seems justified (as shown in Figure 3 of the current article by Mitin et al).[5] However, it could be debated whether adjuvant RT should be added to the treatment of patients with pN1 disease after RP, if the local tumor is pT2 or focal pT3a with negative SMs and if postoperative PSAs (before ADT) are undetectable.

(5) The role of improved imaging with ferromagnetic MRI (which currently is unavailable in the United States)[11-13] or with 18F-fluoroethylcholine or 11C-choline PET/CT scans,[14-17] in this setting...
remains relatively investigational, and these techniques are not supported by all insurance providers. Their utility in identifying suspicious nodes in areas normally not removed in standard PLDs or in the retroperitoneum, or as guides to biopsy in patients who are planning to undergo primary RT, seems reasonable—though yet untested. (6) Similarly, molecular staging in surgical specimens in pN0 patients, using immunohistochemistry (IHC) for PSA or detection of their mRNA has been described but has not reached standard practice. [18-20] However, retrospective reports demonstrating far worse biochemical outcomes for men who were pN0 standard/pN+ by molecular staging compared with pN0 standard/pN0 by molecular staging might lead one to treat such individuals as if they were pN+. [18,20] This, however, has not been tested prospectively, and technical and other issues should be validated before these tests become part of standard care. Similarly, circulating tumor cells in the blood or bone marrow evaluated via a variety of assays are likely to be positive in N+ disease, but it is unknown whether this information can guide therapy (in terms of initial or adjuvant therapy) or be used to monitor treatment. [21] (7) Perhaps most concerning, given the guarded prognosis of men with N+, M0 disease, are the effects of eliminating or reducing PSA screening. While the merits of PSA screening have been debated widely, there is little doubt that fewer PSA screenings are being performed since the US Preventive Services Task Force’s grade D recommendation. [22,23] It has been modeled that the incidence of M+ disease at diagnosis would rise by more than three-fold with elimination of screening from standard care, [24] a ratio also reported in the European Randomized Study of Screening for Prostate Cancer (ERSPC). [25] It is likely that totally forgoing screening will also raise the number of N+, M0 cases. This is particularly true in the elderly, who already bear a disproportionately high mortality burden from this disease. [24,26] The challenge will be to properly select the roughly 33% of men 75 to 80 years old (or older) who have over 12 to 15 years of remaining life. [27] to receive the multimodal treatments described by Mitin et al. [5] and withhold them from many others.

**Financial Disclosure:** The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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**REFERENCES**


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