The optimal treatment of men with positive lymph nodes after radical prostatectomy (RP) is an active debate in the urologic community. In addition, this topic has seemed to gain scientific attention in recent years because of the shift to offering RP to higher risk patients. However, patients with positive lymph nodes represent a paradigmatic group for which indications for and types of treatment have been based mainly on eminence-based rather than on evidence-based medicine. In the past, these patients were generally not considered suitable for radical treatment because of the assumption that cure was neither possible nor helpful. For several years, any definitive therapy attempt was denied because of undisputed dogma: Patients with lymph node metastasis are affected by a systemic disease. This assumption led to three misguided concepts in clinical practice. First, maximizing local control was considered either useless or of limited therapeutic value. Second, extending the template of pelvic lymph node dissection (PLND) was not justified because, according to opponents of such an extensive approach, these patients would progress anyway, regardless of the extent of PLND. Third, patients with positive lymph nodes needed lifelong adjuvant androgen-deprivation therapy because of the presence of disseminated disease.

Such statements can certainly be challenged today. We should still understand whether the presence of pelvic lymph node metastasis indicates systemic dissemination. The etymology of the term metastasis shows that it comes from the Greek terms meta-, meaning across, and histanai, meaning to place. Therefore, the terms indicate a tumor spread outside of the organ of origin. For this reason, strictly speaking, patients with lymph node invasion have metastatic disease. However, such statement should be balanced by several key and still unknown aspects of the metastasizing process of prostate cancer (PCa).

Cancer cells that spread to the lymph nodes have acquired certain phenotypic changes that confer to them the ability to invade lymphatic vessels and access lymph nodes; however, we still do not know what happens next. Lymph nodes can represent the door to hematogenous dissemination to other organs [1]. Tumor cells could spread from lymph nodes to distant organs via blood vessels associated with the nodes or by entering the venous system via the major lymphatic ducts and then spreading via blood vessels. In mice with metastatic lymph nodes, the expression of lymphangiogenesis signals the increased probability of metastasization to additional organs [2]. However, in some cases, these draining lymph nodes may also represent dead ends rather than temporary stopping points from which more distant metastases are launched [3]. Moreover, as demonstrated in breast cancer, these cells may have specific epigenetic modifications that predispose to selective metastasization to the lymph nodes instead of visceral organs [4]. Therefore, the routes of systemic and nodal metastasization may also be different and separated.

Cancer metastasized to the lymph nodes can also enter a quiescent state. This status is well known as tumor dormancy [5]. Tumor dormancy ensues when cancer cell proliferation is counteracted by other mechanisms such as apoptosis because of impaired vascularization or immunosurveillance, and cellular dormancy ensues when growth of the cancer cells is arrested. Several mechanisms can explain tumor dormancy, including disruption of crosstalk between
growth factor and adhesion signaling; inability of a tumor cell population to recruit blood vessels, despite active proliferation; and immunosurveillance, which can prevent residual tumor cell expansion [5]. It is possible that metastasization from primary tumor can occur early from particular cell clones that then enter into a state of tumor dormancy in the lymph nodes. Taken together, the mechanisms of nodal dissemination and systemic spread represent much more complex events than what was previously thought.

Such biological processes are paralleled by clinical retrospective observations that argue against the invariably systemic status of nodal disease. Local disease status such as positive surgical margins and/or local disease stage represent significant predictors of metastasis-free and cancer-specific survival [6]. Therefore, local disease status matters in the prognosis of node-positive patients. Consequently, there is a rationale for maximizing local control, even in the setting of node-positive disease. This is true especially in men with a low volume of nodal invasion.

As we have shown previously [6], Touijer et al. found significant differences in patient outcome according to the extent of nodal invasion, quantified as the number of positive nodes [7]. As we and others have already demonstrated [6], Touijer et al. found that a cut-off of two positive lymph nodes was better to stratify the outcomes of node-positive patients [7]. We also showed that stratification of node-positive men into two categories (those with fewer than two positive lymph nodes and those with three or more nodes) increased the accuracy of survival predictions [6]. Despite this, the current TNM classification does not take into account the extent of nodal invasion. We advocate a change in the TNM classification to stratify these patients into at least two subcategories. Compared with previous studies, the added value of the study by Touijer et al. is the lack of routine adjuvant therapy administration, which allowed the authors to study the natural course of the disease in these men. Interestingly, they found that approximately 30% of men left untreated after surgery were free from biochemical recurrence (BCR) at 10-yr follow-up [7]. This rate was even higher in men with a single lymph node metastasis. Given such high cancer control rates, it is hard to support the assumption that lymph node–positive prostate cancer equals systemic disease, at least not in all cases.

Moreover, even in this patient group, BCR does not invariably translate into clinical recurrence or cancer-specific death, as in all other patient categories with PCa. In the study by Touijer et al., although 65% of the enrolled men suffered from BCR at 5 yr after surgery, only 35% developed distant metastases and only 28% had died from PCa at 10 yr [7]. In addition, another study showed that even when clinical recurrence occurred, this was in the pelvic area rather than in distant organs in up to 50% of men with nodal metastases [8]. Therefore, the risk of local or pelvic recurrence is as high as the risk of distant failure in recurring node-positive patients. For all these reasons it is important to stress that cancer-specific mortality rather than other surrogate outcomes should be considered the main end point of any study focused on node-positive patients.

In view of these considerations as well as the heterogeneity of patients with positive lymph nodes, it is difficult to justify the use of lifelong adjuvant hormonal therapy (HT) after surgery in all node-positive patients, despite the presence of level 1 evidence supporting its use [9]. We believe that overtreatment should be avoided, even in this patient group, given the possible detrimental effects of long-term HT. Patients with low volumes of nodal invasion and undetectable prostate-specific antigen after surgery, for example, may be spared HT, given their excellent cancer control rates. Alternatively, and not too dissimilar from radiation therapy, perhaps some need HT for only a period of time, as yet undefined in the perioperative setting. This approach may have a considerable impact on the treatment of contemporary node-positive patients who generally have a low median number of positive lymph nodes, even when treated with extensive nodal dissections [10].

In conclusion, we believe that prospective randomized trials in contemporary node-positive patients should be considered to address the optimal adjuvant treatment. However, any prospective study should have one main inclusion criterion: a well-performed surgery aimed at maximizing local and pelvic disease control. This should be done by reducing the rates of positive surgical margins and performing an anatomically defined extended PLND. If a significant amount of tumor load is left in situ, any treatment benefit is highly diluted if not annulled. No adjuvant or salvage treatment would overcome the detrimental effects of a bad surgical procedure performed upfront. Only when patients are correctly treated can predictions be accurate and the treatment strategy likely successful. Until then, the debate on the optimal treatment of node-positive patients will certainly continue.

Conflicts of interest: The authors have nothing to disclose.

References

In prostate cancer, the presence of lymph node metastasis, along with high pathologic Gleason score, is the main determinant of outcome. Specifically, the long-term risk of cancer-specific death after radical prostatectomy is substantially increased in patients with lymph node metastasis. In 1987, Golimbu and colleagues reported their experience with node-positive disease in 42 patients with prostate cancer and were among the first to demonstrate a difference in prognosis between patients with low and high metastatic burden in the lymph nodes [1]. This initial observation was later confirmed on a larger scale by several other investigators from academic centers in Europe and the United States [2–5].

Our report on the long-term outcomes of a large cohort of node-positive patients is unique in that patients were treated exclusively with surgery (no adjuvant therapy) [6] and, as stated in the editorial by Briganti et al. [7], provides insight on the natural history of surgically treated prostate cancer with lymph node metastasis. Moreover, our series comes as another confirmation of the prognostic distinction between metastasis involving one or two nodes versus three or more, regardless of whether or not surgery is followed with hormonal therapy [6].

Together, this body of evidence is consistent enough to consider revising the present staging system. But most important, it defines one of the most vulnerable groups of prostate cancer patients: those at high-risk for metastasis and death and who are prime candidates for clinical trials assessing a role in this setting for the recent innovations in castrate-resistant prostate cancer.

In the discussion of our results, we raised the following questions regarding the interpretation of our findings [6]: Should we assume causality and conclude that the fact that 30% of patients with nodal metastasis remained free of disease at 10 yr is due to the surgery that completely removed the disease? Or should we hypothesize that the 30% of patients with good outcomes had cancers in the lymph nodes that were biologically immature and would have fared just as well without our surgical intervention? As in many other areas of surgical oncology, this timely debate is challenging our comfort with the Halstedian model, in which metastasis follows an orderly pattern [8], compared with novel theories derived from new findings in cancer biology. In fact, new theories of cancer metastasis may not completely negate our current understanding. The hypothesis that primary tumors first develop locally, enlarge, acquire the capacity to migrate through blood or lymphatic channels, and then lodge in distant organs is validated by the success of the sentinel lymph node concept and the positive results of screening programs in some cancers. This therapeutic philosophy invests heavily in early detection and intervention to disrupt the unidirectional spread of cancer in its infancy. However, the knowledge that circulating tumor cells sometimes become undetectable when the primary cancer is treated [9], the indolent prognosis of isolated cancer cells in the axillary nodes of women with breast cancer [10], and the fact that patients with no more than three positive sentinel nodes do well without a full axillary node dissection [11] raise a number of puzzling oncologic questions. Moreover, these scenarios give credence to biology-driven theories of cancer growth, such as the self-seeding concept of Norton and Massague [12]. These investigators have proposed, and explored through a series of experiments [13], the hypothesis that the primary tumor sheds cancer cells into circulation early on and that local growth could be a result either of a high mitotic index or of circulating tumor cells returning and implanting at the primary cancer site via chemoattractants. The encouraging research examining these novel theories is likely to change our treatment paradigms.

Conflicts of interest: The author has nothing to disclose.

References


* Department of Urology, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.

E-mail address: touijera@mskcc.org.