When Does Lymphadenectomy Improve Survival of Patients With Genitourinary Malignancies?

Lymph node metastases are the middle ground between local and distant disease and, thus, the best treatment is unclear. Basic oncology principles suggest that tumors localized to the primary organ are best treated with local therapy (surgery or radiation) to destroy the tumor and eliminate precursor cells that can form new cancers. Distant metastases are best treated with systemic therapy because metastases are caused by disseminated cells that would not be eliminated by resection or treatment of individual metastatic deposits. Numerous questions surround the treatment of lymph node metastasis. Do lymph node metastases always herald the presence of distant metastases? Is radiation as effective as surgery in the management of lymph node metastasis? Is lymphadenectomy of prognostic significance only or can it cure some patients? Do any of these statements depend on the tumor type?

Three articles in this issue of The Journal highlight the concepts that proper staging allows administration of optimal treatment, that surgery can cure some patients with lymph node metastases and that the importance of lymph node dissection in urological literature is diffusing into general practice without a randomized clinical trial. Roscigno et al (page 2482) reported that lymph node dissection was not beneficial for patients with nonmuscle invasive upper tract urothelial cancer, but that it did prolong life for those with muscle invasive disease. This finding could suggest that lymphadenectomy is curative in patients with muscle invasive cancer and unnecessary for nonmuscle invasive disease, but it may show that lymphadenectomy only better stages the cancer and has no impact on survival. The authors demonstrated that node dissection was therapeutic by subdividing the cases of muscle invasive disease into groups of node negative (pN0), node dissection not done (pNx) and node positive (pN+), evaluating survival based on these categories. Patients with pN0 disease fared better than those with pN+ (94% vs 51% cause specific survival at 5 years) and those with pNx status had a better survival than pN+ (88% vs 51% cause specific survival at 5 years). However, patients with pN0 and pNx disease had a similar survival (94% vs 88%). If node dissection was therapeutic then patients with pNx status (some with unsuspected nodal metastases) should have a worse cancer specific survival than those with pN0. Therefore, it is unclear in upper tract urothelial cancer if lymph node dissection improves survival, but it does provide better staging and the ability to administer chemotherapy.

Can we extrapolate these data on upper tract urothelial cancer to bladder cancer? Hellenthal et al (page 2490) reported that the concept of extended lymph node dissection in patients with bladder cancer is diffusing into the urological community. They reported that from 1988 to 2004 the number of patients undergoing radical cystectomy who were also treated with node dissection increased from 63% to 84%, and that the number of nodes removed increased during this time as well. Are there data supporting a therapeutic benefit of lymph node dissection in patients with bladder cancer? Node density (percentage of positive nodes removed) is a predictor of cancer specific survival. The patients all had node positive disease but improved survival was found in those with more nodes removed, thus decreasing the node positive density. Since all the patients had node positive disease the survival advantage with a lower node positive density could not be due to better staging but suggests that node dissection in patients with bladder cancer may be therapeutic. However, these studies were not randomized trials and a recent article on the role of lymphadenectomy in gastric cancer did not show a survival advantage in the extended node dissection group despite previous data reporting such an advantage in a nonrandomized group of patients. Therefore, some observations from a nonrandomized series are not confirmed when tested in a controlled clinical trial. Should data from a nonrandomized trial be promulgated as a standard of care to the urological community? The argument against a randomized clinical trial evaluating node dissection in bladder cancer is that the number of patients needed for a clinical trial is prohibitive and the currently available non-
randomized data make such a study unethical. As seen in gastric cancer the results are not always what you expect and they support the concept of a randomized trial evaluating lymphadenectomy in patients with bladder cancer.

Finally Beck et al (page 2526) reported that resection of nodal disease after neoadjuvant chemotherapy for testis cancer can be curative, especially if only teratoma is present. Are there other data supporting the role of surgery in resecting residual masses? The original neoadjuvant chemotherapy trials in bladder cancer suggested that some patients with residual metastatic disease after methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy can be cured with surgical resection, particularly those with nodal disease only. It may be that chemotherapy can eliminate the circulating tumor cells but is unable to destroy well established metastatic deposits. Surgical resection of these residual masses may provide long-lasting cures in select patients.

So when does lymphadenectomy improve survival in genitourinary cancers? In patients with testis cancer if there is teratoma, a residual mass after chemotherapy, and in untreated patients with small volume lymph node metastases, lymphadenectomy can be curative. The jury is still out on urothelial cancer, although the data supporting extended node dissection in bladder cancer are strong but lack a randomized trial. For upper tract tumors node dissection provides better staging but data on cure are lacking. Lymphadenectomy in renal cancer is similar to that in upper tract urothelial cancer in that better staging is provided but curative ability is in question. Lastly inguinal node dissection for penile cancer is curative in select patients with small volume disease.

An analysis of common factors in urological tumors demonstrates that node dissection provides better staging at the very least and in some cases is therapeutic. Therefore, unless otherwise dictated by poor patient health, anatomical issues or low stage disease with a minimal risk of lymph node metastasis, complete node dissection using appropriate boundaries should be performed in patients with urological cancers.

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REFERENCES
4. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ et al: M-VAC (methotrexate, vinblastin, doxorubicin and cisplatin) chemotherapy can be cured with surgical resection, particularly those with nodal disease only. It may be that chemotherapy can eliminate the circulating tumor cells but is unable to destroy well established metastatic deposits. Surgical resection of these residual masses may provide long-lasting cures in select patients.