Re: Intravesical Bacillus Calmette-Guérin versus Mitomycin C for Ta and T1 Bladder Cancer
Shelley MD, Court JB, Kynaston H, Wilt TJ, Coles B, Mason M


Expert's summary:
The Cochrane Collaboration is the result of an international commitment to identify, retrieve, and summarise the evidence from the literature regarding several interventions in medicine, based primarily on randomised clinical trials (RCTs). It is one among the major sources of evidence-based medicine. After examining the available RCTs in the literature, the authors conclude that bacillus Calmette-Guérin (BCG) is more efficacious than mitomycin C (MMC) in the prevention of recurrences for high-risk patients and no differences were found in progression of disease or survival.

Expert's comments:
Accessibility of trials: A total of six papers and one abstract were retrieved from the literature searching for RCTs (or quasi-randomised), comparing MMC and BCG, for a total of 1527 evaluable patients, published from 1991 to 2001. About 50,000 new cases of bladder cancer with 9500 deaths were reported in the United States in the 1990s [1], and 61,420 new cases with 13,660 deaths are expected in the current year [2]. These figures show that over the last 15 yr the number of trials has been low, and the disproportion between patients with the disease and patients who had access to clinical trials has been dramatic.

Long-term data: In the meta-analysis, Ta, grade 1 patients are included in some trials along with patients with carcinoma in situ. In acknowledging this limitation, the authors performed a sensitivity analysis restricted to high-risk cases, and a 31% reduction of recurrences per time unit was observed in favour of BCG; nevertheless, there were no differences in disease progression and survival. Attention should be drawn, however, to the fact that the follow-up was 5 yr or longer in only two studies.

Heterogeneity of treatments: Several dosages and schedules of administration were used for MMC, ranging from 30 mg once a week for 1 mo and monthly for 6 months (total, 300 mg), to 20–40 mg weekly for 1 mo and monthly for 24 mo (total, 1120 mg), and also for BCG, ranging from 27 to 50 mg to 120 mg, with different strains combined in different schedules, although the issue of maintenance therapy was not addressed by the authors of this meta-analysis. Such wide variation, though, raises some concerns about the actual comparability of these studies.

Treatment alternatives: Overall, local and systemic toxicities were observed in 30% and 12%, respectively, for MMC and 44% and 19%, respectively, for BCG. In addition, some worrisome complications, such as ulcerative cystitis in one patient (requiring cystectomy) and pneumonitis in two patients, were associated with BCG; therefore, it seems wise to explore further alternatives to potentiate the effect of MMC [3–5].

References

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Re: The Concept of Lymph Node Density in Bladder Cancer: Is it Ready for Clinical Practice? Evaluation of the Relevance of Lymph Node Density in a Contemporary Series of Patients Undergoing Radical Cystectomy
Kassouf W, Leibovici D, Munsell MF, Dinney CP, Grossman HB, Kamat AM


Expert's summary:
Primary tumour stage, lymphovascular invasion, and surgical factors affect survival of patients with bladder cancer after cystectomy, but the most powerful prognostic feature is the presence of lymph node metastasis. Radical cystectomy coupled with an appropriate pelvic lymph node dissection may cure up to a third of patients with positive nodes; however, most survivors have only one or two microscopically involved nodes rather than grossly positive or multiple nodes involved. Thus, both node status and node burden determine outcomes after cystectomy. The authors of the paper from the M. D. Anderson Cancer Center evaluated lymph node density (LND) as a predictor of bladder cancer survival after radical cystectomy.

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LND (the number of positive nodes/total number of nodes examined) is a measure of nodal burden and a proxy measure of the quality of surgery. The authors found a 38% 5-yr survival rate among those with positive nodes with a nodal ratio <25% compared to only 11% with a >25% ratio ($p = 0.02$). LND performed better as a predictor of survival than number of positive nodes, including patients who received adjuvant chemotherapy ($p = 0.04$).

**Expert’s comment:**
This paper is the fifth in a series of papers [1–4], now totalling 979 patients, showing that LND correlates with recurrence-free survival after cystectomy. Enthusiasm should be tempered with a few caveats. All five studies are retrospective and vary widely in sample size and tumour stage. It is not known whether systematic examination of LND across all patient subsets would yield consistent results. In addition, because the utility of LND was not the intended focus of these studies, information regarding the comparison between LND and absolute numbers of positive nodes is not always presented. Node ratio cut-off points were arbitrarily determined to best discriminate survival and they have not been validated in alternative data sets. It is not known whether LND predicts survival any better than N categories (based on number and size of positive nodes) in the current TNM system. It is also not known whether LND will be a valid marker for survival after neoadjuvant chemotherapy, considered by many to be standard treatment for invasive bladder cancer that may favorably alter nodal burden.

Other factors such as examining the percent tumour within a single node or nodes, nodal size, capsular perforation, and even circulating tumour cells, may prove to be more important prognostic indicators of survival than a simple ratio of nodal involvement. Ideal templates for pelvic node dissections are not standardised and limited dissections are common. The current interest identifying sentinel nodes portends more limited dissections removing fewer nodes. Fewer nodes examined means that the mathematical ratio possibilities are fewer, suggesting than LND may be a less sensitive discriminator of outcome after limited dissections. Conversely, in cases where the denominator is large, such as institutions where dissections of ≥20 nodes are common, LND may be less relevant. Lastly, it is still unclear how a simple ratio expressed as LND depending on the total number of nodes harvested will have more prognostic validity than the absolute number of nodes. Surgical and pathologic bias may affect the number of nodes retrieved or identified at pelvic dissection.

Should the concept of LND be introduced into routine clinical practice? Given the paucity of existing data, the uncertainties and caveats still to be addressed in cystectomy patients, probably not! However, it offers an attractive proxy measure of quality of care, and the preliminary data are sufficiently persuasive to warrant systematic node ratio analysis from multi-institutional patient data sets as well as prospective validation of LND, preferably within the context of a chemotherapy trial.

**References**


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