



# Phase III Trial of Neoadjuvant Chemotherapy in Patients with Invasive Bladder Cancer Treated with Selective Bladder Preservation by Combined Radiation Therapy and Chemotherapy: Initial Results of Radiation Therapy Oncology Group 89-03

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## Background

Multimodality bladder-sparing treatment regimens, consisting of limited surgery, followed by concurrent chemoradiation, is an area of intense interest. Initial phase I/II data have been collected looking at the use of neoadjuvant chemotherapy.

## Purpose

To conduct a randomized prospective trial to assess possible long-term benefit of neoadjuvant chemotherapy in patients with muscle-invading bladder cancer. Design study to evaluate effect of MCV (methotrexate, cisplatin, vinblastine) on following parameters:

1. bladder preservation rate
2. freedom from distant metastases
3. overall survival
4. survival with functional bladder.

## Methods

A total of 123 eligible patients with clinical stage T2-T4a nonmetastatic bladder cancer were randomized to either receive (arm 1 = 61 pts) or not receive (arm 2 = 62 pts) neoadjuvant chemotherapy. All patients first underwent transurethral resection of the bladder (TURB). This was followed by 2 cycles of neoadjuvant MCV chemotherapy in arm 1 only. Both arms then received concurrent chemoradiation (cisplatin x 1 + 4-field pelvic radiation) followed by a 4-week break. At that time all patients were restaged by clinical exam under anesthesia, cystoscopy with tumor-site biopsy and urine cytology. If a complete clinical remission was documented by the above three procedures, consolidation chemoradiation was given (cisplatin x 1 + boost radiation). If a complete clinical remission was not achieved, patients were recommended to undergo radical cystectomy at that time.

Patients were followed every 3 months for 2 years, then every 6 months, with median follow-up of 5 years.

## Results

The study only accrued 71% of its intended number of patients secondary to premature closure due to serious adverse effects from chemotherapy.

- Of 123 patients, 61 (50%) are alive at 5 years:  
30 (49%) in arm I and 31 (50%) in arm II
- 5-year overall survival is 49% in entire group:  
48% in arm I and 49% in arm II
- 5-year overall survival with functioning bladder is 38% overall:  
36% in arm I and 40% in arm II
- Clinical complete response rate is 59% overall:  
61% in arm I and 55% in arm II

On subgroup analysis, there were two factors that approached statistical significance:

- 5-year overall survival without hydronephrosis vs. with ( $p=0.06$ )
- 5-year bladder-intact survival with visibly complete TURB vs. incomplete ( $p=0.02$ )

## Conclusions

No survival benefit is seen with the use of neoadjuvant MCV chemotherapy in this study. However, the authors clearly admit the study is underpowered (not enough patients) to detect a survival difference. The main reason for that, in turn, is the study's premature closure secondary to an unexpectedly high rate of chemotherapy-related toxicity. In fact, only 74% of all patients were able to complete the protocol as specified or with minor changes. Thus it seems any conclusions derived from this trial are severely limited by the low number of patients who actually completed the trial as intended.

Nonetheless, it would appear that the benefit to risk ratio of using neoadjuvant MCV chemotherapy is unfavorable.

The authors encourage the study of new agents with more efficacy and less toxicity in the neoadjuvant setting of multimodality bladder-sparing therapy.

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