presentation was reported with 90% of the expected events having occurred in the non-transplant arm. The final analysis of CALGB-9082 is not expected to be significantly different than the recent ASCO presentation. ECOG-2190 completed accrual in 1999 and the data are expected to be mature in the summer of 2002. SWOG-9623, the only US study in patients with 4 or more involved axillary nodes and the only study which incorporated a taxane in the non-transplant arm, was closed in February of 2001, due to poor accrual after the 1999 ASCO meeting. A total of 602 patients out of an intended 1000 were enrolled. The designs of each study will be reviewed, as will the results which have been published or presented to date. How these studies have been interpreted and presented will be critically discussed.

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Avoidance of cystectomy in carcinoma in situ

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CIS of the bladder is a high-grade lesion recognized as a morphologic entity. Bladder irritability is the leading symptom in patients with primary CIS. Exfoliative urinary cytology is the most important diagnostic tool. Biopsies have to be taken from suspicious areas, preselected sites in the bladder and from the prostatic urethra. While cystectomy was the initial treatment of choice, the high response rate to intravesical BCG justifies a more conservative approach to management. The complete response rate with BCG immunotherapy is $\geq$70%. Patients not responding to BCG immunotherapy without evidence of progression may be treated with alternative immunotherapies such as alpha-2b interferon, keyhole limpet hemocyanin (KLH) or bropirimine, with intravesical chemotherapy or photo dynamic therapy. If treatment is ineffective, cystectomy should not be delayed for more than 6 months. Further studies with long-term observation will be warranted to elucidate the natural history and to identify prognostic factors of CIS of the bladder.

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Biological selection for organ conservation

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Bachground: Clinical criteria helpful in determinating patients for bladder preservation include such variables as small tumor size and a possible complete transurethral resection (TUR) prior to radiochemotherapy (RCT). Tumor heterogeneity, however, is so great in bladder cancer that conventional histopathologic classification is inadequate for predicting the response to RCT for individual lesions. Molecular markers that may predict a tumor's true malignant potential as well as its response to specific cytotoxic therapies are sorely needed.

Methods: Several markers have been linked to radio- and chemosensitivity of bladder cancer cells, including p53, pRb, cyclin D1 and bcl-2 as key protein regulators of the cell-cycle and the apoptotic pathway. We and other groups have evaluated these biological markers as possible predictors for response to RT/RCT and as prognosticators for local control with preserved bladder.

Results: In an analysis of 70 patients treated uniformly within our bladder sparing protocol of TUR and RCT, we found the spontaneous apoptotic index (AI > median) and the proliferation rate (Ki-67 > median), but not the p53- and bcl-2 expression, to be significantly related to inital response and local control with preserved bladder at five years. In an exploratory multivariate analysis, which included clinicopathological and molecular factors, only AI, Ki-67 and the combined AI/Ki-67 variable retained significance for local control with preserved bladder at five years. Other groups have confirmed the predictive value of a high spontaneous AI for response to RT/RCT, however, the role of the various apoptosis-related regulators is often contradictory and their interrelationship needs to be further elucitated.

Conclusion: We anticipate that translational research will help to predict treatment response of bladder tumors and, thus, to tailor individually adjusted therapy. However, only a multi-parametric assay will allow early choice of the best treatment regimen and therefore avoid unnecessary morbidity associated with cystectomy or RCT. Then, both strategies would no longer be competitive, but complementary.

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Chemotherapy in organ preservation in muscle invasive bladder cancer

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Neo-adjuvant chemotherapy was designed in order to treat micrometastatic disease, found in up to 50% of patients at presentation. Implications of bladder preservation are less surgery, no need for a urinary diversion and a normal sexual life. Quality of life should be improved. Bladder preservation is possible in selected patients, and can be safely achieved with neo-adjuvant chemotherapy implemented by definitive local treatment such as radiotherapy (RT), partial cystectomy, or TURB.

The combination of neo-adjuvant chemotherapy and RT produces overall 5-year survival rates from 42% to 63%, with organ preservation in approximately 40% of patients. With the advent of neo-adjuvant chemotherapy the indications for partial cystectomy have been expanded to: a) attain a clinical CR or significant PR to neo-adjuvant chemotherapy; b) who have solitary lesions in favorable anatomical locations; c) no carcinoma in situ; d) with no history of previous or recurrent infiltrative bladder cancer; and e) who have a good bladder capacity.

Neo-adjuvant chemotherapy and TURB alone have also been used: In selected patients survival is similar to that attained with radical cystectomy. There is interest in molecular markers to optimize therapy and predict chemo-sensitivity. Molecular markers such as p53 Rb, p21 and EGFR have been evaluated in bladder cancer.

Bladder sparing in patients in patients selected on the basis of response to neo-adjuvant chemotherapy is a feasible though controversial approach, as radical cystectomy is regarded as the gold standard of treatment. Bladder Prognostic factors should be studied to evaluate those patients most likely to benefit from this approach.

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Altered fractionation in chemo-radiation for bladder cancer

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To improve the results obtained by cystectomy (CT) alone and to specify the place of a conservative treatment in invasive bladder cancer, we designed a prospective study using a neoadjuvant 5FU-CDDP regimen with bifractionated split course radiation therapy followed by CT or additional chemo-radiotherapy. One hundred twenty patients (pts) with operable tumor were treated from 02/88 to 11/95 (52 T2, 31T3a, 37 T3b-T4). All patients underwent an initial trans-urethral resection with complete macroscopic debulking in 63 pts and received the neoadjuvant program. The neoadjuvant dose was 24 Gy delivered in 8 fractions over 17 days, according to a modified bifractionated split course schedule. Each fraction delivered 3 Gy twice on day D1, D3, D15 and D17. The pts received concomitant CDDP (15 mg/m^2) and 5-FU (400 mg/m^2) on day D1, D2, D3 and D15, D16, D17. A control cystoscopy and resection was performed 6 weeks later. Pts with persistent tumor uuderwent a CT. Complete responders were treated by additional chemo-radiotherapy. Ninety three pts (77%) achieved a complete histological response (CR) after the neoadjuvant program. Twelve pts developed a local recurrence (including 3pTa and 3pT1). Metastatic disease was seen in 28 pts, more frequently in non responder pts (63% vs 12%; $p < 0.0001$). The five-year survival was 63%, significantly better for responders (73% vs 29%; $p < 0.0001$). Definitive results will be presented. Others schedules with altered fractionation will be compared and discussed.