

These advantages must be weighed against concerns regarding increased morbidity and mortality of a combined modality approach and, in case of an ineffective induction regimen, progression of local disease in patients whose tumor could have been resected initially.

An important randomized trial of preoperative chemotherapy to include significant numbers of stage II patients was reported by Depierre et al. While no significant survival benefit was found for the induction treatment, a detailed analysis revealed an increased death rate within the treatment period for the chemotherapy arm. When correcting for this excess of death during treatment, the effect of preoperative chemotherapy turned out to be significant on survival.

Very recently, the randomized phase 3 SWOG S9900 trial, compared preoperative carboplatin and paclitaxel with surgery alone in 335 patients with stage Ib, II, and selected IIIa (non-pN2) NSCLC (abstract LBA7012). Preoperative chemotherapy was tolerated relatively well, with few toxic deaths. About 84% of patients in both the carboplatin/paclitaxel group and the surgery alone group could undergo complete resection. Preoperative chemotherapy improved median progression-free survival (PFS) compared with surgery alone (31 months vs 21 months), though this improvement did not reach statistical significance (HR = 0.80; P = 0.14). There was also a trend toward improved OS in the preoperative chemotherapy group (median OS, 47 months) compared with the surgery alone group (median OS, 40 months) (HR = 0.84; P = 0.32).

Conclusively, the use of preoperative chemotherapy followed by surgery, in patients with stage IB–IIB should be limited to patients enrolled in clinical trials.

Scientific Symposium Advances in bladder cancer

151

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Strategies for bladder preservation

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The goal of any organ preservation strategy should be to achieve equivalent cancer survival to extirpative surgery, while maintaining quality of life in the individual patient. Improvement in surgical techniques and the development of continent urinary diversions has resulted in decreased morbidity and better postoperative quality of life for patients undergoing radical cystectomy for muscle-invasive bladder cancer, leading some to suggest that bladder preservation is not necessary.

Although mortality rates with radical cystectomy have decreased by half since the 1990s, survival rates with surgery alone have remained steady, with five-year survival rates of 66% for pathologic stage T2, 35% for T3, and 27% for T4 disease. In addition, up to 15% of patients with muscle-invasive disease will have no pathologic residual disease at the time of cystectomy, indicating the potential curability of select patients with transurethral resection alone. These findings suggest that while bladder preservation can be a viable option to radical cystectomy in selected patients, surgery alone will be successful in only a small percentage of patients. The risk of clinical under staging in around 30% of patients, the limited effectiveness of surgery alone, and the advent of more effective combination chemotherapy has led to a multidisciplinary approach to treatment of bladder cancer with the possibility, in select patients, of bladder preservation.

Surgery, radiotherapy, and chemotherapy should be seen as complementary rather than competing treatment modalities. It appears that the results are not different from those obtained with radical cystectomy.

The goal of a bladder preservation strategy should be to achieve equivalent cancer survival to cystectomy, while maintaining good quality of life.

Randomized studies are needed to evaluate the feasibility of this approach.

152

INVITED

Innovations in radical cystectomy

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Although bladder-sparing treatment protocols have a growing impact radical cystectomy remains the mainstay and therapy of choice for most patients with muscle-invasive bladder cancer. The mortality of the procedure has been reduced dramatically in the last 2 decades, so that even octogenarians can be treated in this manner with similar results. Nevertheless, the morbidity of cystectomy both from postoperative complications and a reduction of quality of life as a result of loss of the bladder remains daunting, and the main impetus of innovations is directed at lowering this.

Immediate postoperative morbidity has been shown to correlate to the volume of cases, and it is lower at high experience centers. It is

further reduced by generous correction of blood loss (+10%), routinely using epidural catheters for prolonged pain control, avoiding mechanical bowel preps, and commencing early with enteral nutrition. Laparoscopic cystectomy is a most promising approach to a further reduction in morbidity, but at present the need for urinary diversion still presents as a major obstacle to procedures performed completely intracorporeally. Some laparoscopic techniques are already simplifying standard incisional surgery, such as GIA-stapling of the vesico-prostatic pedicles.

The main rehabilitation problems after cystectomy result from urinary diversion and impaired sexuality. Orthotopic continent urinary diversion has become standard in healthy, well informed patients. Adherence to surgical details such as atraumatic dissection of the urethral stump, avoiding all tubularization of the new-bladder at the anastomosis and fixation of the neobladder to the anterior abdominal wall reduces diurnal and nocturnal incontinence to ~15% and ~30% respectively. Nevertheless, a growing body of evidence shows that in elderly, higher risk patients with less pronounced body-image problems simple conduit diversion provides a better quality of life. Nerve-sparing cystectomy continues to provide mixed results only in the effort to retain erectile function but in selected younger patients unilateral nerve preservation in conjunction with supportive measures permits acceptable sexual function. Ongoing attempts of nerve preservation by sparing the prostatic apex, the seminal vesicles and prostatic capsule, and even the entire prostate give better functional results, but are marred by higher rates of local tumor recurrence.

Stage and nodal involvement remain the only independent prognosticators of survival after cystectomy. Negative frozen sections of the distal margin of resection at the prostatic apex or the bladder neck in women are reliable indicators of a low risk of urethral recurrence and hence adequate parameters for urethra-preserving orthotopic bladder substitution. Magnetic resonance lymphangiography using ferromagnetic nanoparticles dramatically improves the reliability of preoperative lymph node staging, but extensive pelvic node dissection has been shown to significantly impact survival rates after cystectomy. Although in patients with histologically negative nodes this appears to mainly be a function of stage migration, some patients with positive nodes may actually be cured. The optimal template for pelvic node dissection is still at debate, but prospective studies clearly show that all patients need at least a bilateral, complete endopelvic node dissection; dissection limited to the obturator and hypogastric nodes frequently misses isolated positive nodes.

153

INVITED

Neo-adjuvant or adjuvant chemotherapy

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Objective: Examine the role of systemic chemotherapy before or after cystectomy for muscle-invasive cancer of the urinary bladder.

Material and Methods: Reported individual patient data meta-analyses of neoadjuvant and adjuvant randomized trials are reviewed with focus on effects on survival.

Results: The neoadjuvant analysis was based on 11 trials, 3005 patients; comprising 98% of all patients from known eligible randomised controlled trials. The platinum-based combination chemotherapy had a significant survival benefit with a overall hazard ratio for survival of 0.86 (95%CI: 0.77–0.95, p=0.003) and a 5% absolute improvement in survival at 5 years. No differences in effect by subgroup could be found.

A corresponding analysis of adjuvant chemotherapy was performed on 491 patients from six trials, representing 66% of patients from all eligible trials. The overall hazard ratio for survival was 0.75 (95%CI: 0.60–0.96, p=0.019) suggesting a 25% relative reduction in the risk of death for combination chemotherapy compared to that on control. The power of this meta-analysis was limited because of small sample size and questionable trial methodology.

Conclusions: A significant but modest survival benefit is achieved with neoadjuvant chemotherapy. Patients should be informed about this option prior to treatment decisions. Efforts to identify the patients most likely to benefit from this kind of therapy are necessary to optimize its use. The trials of adjuvant chemotherapy indicate a survival benefit but are hampered by questionable methodology.

154

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Recent advances in metastatic bladder cancer

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M-VAC (cisplatin, methotrexate, adriamycin, vinblastine) combination chemotherapy has been for long time the standard of care in fit patient with advanced urothelial tumors. Throughout the years, many phase III trials

have evaluated new combinations such as, gemcitabine/cisplatin (CG), carboplatin/paclitaxel, docetaxel/cisplatin and interferon- α /5-fluorouracil/cisplatin. Unfortunately, in all of these randomized trials, the new regimens have failed to demonstrate superiority in terms of overall survival when compared with the classical M-VAC. However, Gemcitabine/cisplatin with similar results and an improved toxicity profile has proved to be a new standard alternative. Recent results on long term follow-up data with classical and new regimens (doublets and triplets) are now mature showing us a potential improvement in long term survival with the new combinations. However, because of a lot of biases and limitations, there is still an urgent need for moving ahead. For "unfit" patients, outside of a clinical trial, M-CAVI (methotrexate, carboplatin (CBDCA), vinblastine), CBDCA-gemcitabine, CBDCA-paclitaxel, gemcitabine-taxane, or monotherapy with gemcitabine, CBDCA, or a taxane can be considered on an individual basis. New drugs like pemetrexed and vinflunine are now being studied as active for salvage therapy.

In addition to the new active drug combinations and targeted therapies, new approaches are emerging for treatment. Chemotherapy optimization using molecular markers predicting chemosensitivity like intratumoral molecular/ molecular pharmacology predictive markers (pharmacogenomics) are being applied. Paradigms developed in other oncological fields analysing RNA using archival paraffin-embedded tissue are now being used for the management of bladder cancer. Recent results suggest that DNA repair genes like ERCC1 may play an important role in the prognosis of advanced stage bladder cancer patients. Further validation of these findings with larger sample size and in prospectively randomized studies is needed. However, to individualize and improve therapy, full molecular signatures obtaining both mRNA using microarray technology and protein information using proteomic analysis (proteomics) are needed. It is conceivable that in the next future, cancer patients will be fingerprinted from their sera or cells, and the management of their disease will be individualized using molecular profiling.