

Neo-adjuvant and adjuvant chemotherapy of bladder cancer: Is there a role?

C. N. Sternberg

Medical Oncology, Vincenzo Pansadoro Foundation, Clinic Pio XI, Rome, Italy

Introduction

Radical cystectomy is the standard treatment for patients with muscle invasive bladder cancer. Cystectomy provides palliation and accurate staging and can be considered in the context of combination therapy.

Survival is dependent primarily upon pathological stage and nodal status. Five-year survival after radical cystectomy for patients with muscle invasive bladder cancer varies from 36% to 48% [1]. Nodal metastases are evident in approximately one half of patients with tumors pathologically staged as pT3b or greater. Long-term survival is the exception when bladder cancer invades the pelvic sidewall or adjacent structures. Five-year survival rates after radical cystectomy stage pT3b tumors ranges from 17% to 46% [2].

Neo-adjuvant chemotherapy

Invasive bladder cancer is considered as a systemic disease. Neo-adjuvant chemotherapy may be administered prior to cystectomy or in some instances before radiation therapy. There are two principal reasons for the use of neo-adjuvant chemotherapy: (i) to improve survival in patients with micrometastatic disease and (ii) to preserve the bladder [1, 3, 4]. This approach has been useful in the treatment of several other solid tumors.

Patients with operable stages T2 to T4a are candidates for neo-adjuvant chemotherapy. This approach was devised to treat micrometastases present at the time of diagnosis; however, it has also been useful in determining response to chemotherapy. The bladder tumor remaining after transurethral resection of the bladder (TURB) may serve as an *in vivo* marker to evaluate response. In this way treatment that is effective may be continued, and ineffective therapy may be discontinued. The toxicity associated with neo-adjuvant therapy is generally lower than the toxicity in patients with metastatic disease, since patients generally have a better performance status and localized disease.

A major disadvantage of neo-adjuvant chemotherapy has to do with the difficulties in assessing response in the primary tumor, because clinical rather than pathological criteria are used. This means that one must base any early conclusions

about the impact of neo-adjuvant therapy upon the TURB results, which may be misleading. A potentially more important disadvantage is that definitive local therapy (cystectomy or radiotherapy) is delayed during the treatment period. In addition, any chemotherapy is associated with a certain degree of toxicity. In the European Organisation for Research and Treatment of Cancer (EORTC)/Medical Research Council (MRC) international trial that used neo-adjuvant cisplatin, methotrexate and vinblastine (CMV) chemotherapy, there was a 1% mortality rate due to CMV [5].

Table 1 presents the results of randomized neo-adjuvant chemotherapy trials in the literature. There are differences between trials, due to differences in the type of chemotherapy and the eligibility criteria. Thus far, individual randomized trials have been unable to definitively demonstrate a significant improvement in survival in patients treated with neo-adjuvant chemotherapy.

Some of the trials have used single-agent cisplatin and some have used combination therapy. Although the equivalence of radiotherapy, cystectomy, or a combination of both has not been proven by a randomized trial, all of these are used as local definitive treatments for muscle-invasive bladder cancer. There is no particular reason to expect that a benefit from chemotherapy would differ greatly with different local treatments. It seems that most of these trials appear to show no difference, but they may not have enrolled sufficient numbers of patients to detect realistic differences in survival.

The International EORTC/MRC BA06 trial of CMV chemotherapy prior to cystectomy or radiotherapy versus cystectomy or radiotherapy is the largest published trial of neo-adjuvant chemotherapy [5]. The trial enrolled 976 patients from 106 institutions in 20 countries. Accrual was over 5½ years. It showed a small difference in survival, in favor of the chemotherapy group, that was not statistically significant at conventional levels of significance. It is the largest trial, representing approximately one-third of patients in all neo-adjuvant trials.

In this trial, a 15% reduction in the risk of death, which translated into a 3-year survival difference of 5.5% (50% in the no chemotherapy arm and 55.5% in the chemotherapy arm) was observed. Looking at the hazard ratio (HR) of 0.85 [95% confidence interval (CI) 0.71–1.02], with a two-sided

Table 1. Randomized phase III trials of neo-adjuvant chemotherapy

Study group	Neo-adjuvant arm	Standard arm	Patients	Results
Australia/UK [43]	DDP/RT	RT	255	No difference
Canada/NCI [44]	DDP /RT or preop RT+Cyst	RT or preop RT+Cyst	99	No difference
Spain (CUETO) [45]	DDP/Cyst	Cyst	121	No difference
EORTC/MRC [5]	CMV/RT or Cyst	RT or Cyst	976	No significant difference
SWOG Intergroup [7]	M-VAC/Cyst	Cyst	298	Benefit with M-VAC, 1 sided <i>P</i> value
Italy (GUONE) [13]	M-VAC/Cyst	Cyst	206	No difference
Italy (GISTV) [14]	M-VEC/Cyst	Cyst	171	No difference
Nordic 1 [15]	ADM/DDP/RT/Cyst	RT/Cyst	311	No difference, 15% benefit with ADM/DDP in T3–T4a
Nordic 2 [16]	MTX/DDP/Cyst	Cyst	317	No difference
Abol-Enein et al. [46]	CarboMV/Cyst	Cyst	194	Benefit in disease-free survival with CarboMV

ADM, doxorubicin; Carbo, carboplatin; Cyst, cystectomy; DDP or C, cisplatin; M, methotrexate; E, epirubicin; RT, radiation therapy; V, vinblastine.

P value of 0.075, this difference was not statistically significant by conventional methodology. The median length of follow-up for live patients was 4 years.

These results are being updated, and are still consistent with the possibility of either a benefit or no benefit in survival for neo-adjuvant chemotherapy. The improvement in 3-year survival may be anywhere from 0% to 11%. To reliably confirm a 5.5% advantage would have required a trial of more than 3000 patients (power 90%, type 1 error 5%) [6]. Updated results will be presented in May 2002.

The South West Oncology Group (SWOG) Intergroup trial randomized patients between three cycles of neo-adjuvant M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy prior to cystectomy versus cystectomy alone [7]. The aim of this trial was to detect an increase in survival with the use of neo-adjuvant M-VAC chemotherapy.

The investigators designed the trial with a one-sided *P* value, despite the fact that most randomized trials undertake two-sided testing [8]. One needs to observe 30% more events for two-sided testing, as compared with one-sided testing, so the design of a clinical trial is important in comparisons between trials.

A trial with adequate power for the detection of a 10% survival advantage of investigational chemotherapy over standard therapy (60% 3-year survival for patients receiving chemotherapy compared with 50% in those treated with local therapy alone) requires some 1000 patients to be randomized over a 3–4 year period with a further 1–2 years follow-up [9]. Approximately 400 deaths are required in order for the study to have a 90% chance of detecting this difference [6]. In a smaller study of 400 patients recruited over a period of 3–4 years, typically 170 deaths would be observed and based on a two-sided log rank test ($\alpha = 0.05$, 85% power), one would be able to reliably detect differences of the order of 15% (from

50% to 65%). The SWOG trial recruited 307 patients and because of the long accrual period, a total of 186 deaths were observed. Thus this trial could only realistically detect large improvements in survival of the order of 15% in absolute terms.

Accrual to the SWOG study was over an 11-year period. Standards of diagnosis, patient care and surgery have changed over this period, and patient selection factors may have been important in deciding entry into the trial. Forty per cent of patients in both arms of the trial had T2 disease, which could indicate an excellent prognosis, and may have been cured by cystectomy alone [10, 11]. In addition, of the ‘eligible’ patients in both arms of the trial only 80% of the planned cystectomies were performed.

The survival curves of the EORTC/MRC and the SWOG trials are similar. The two-sided *P* value ($P = 0.088$) for the survival curves is actually less significant than what was observed in the EORTC/MRC study ($P = 0.075$), which has thus far been interpreted as inconclusive on its own [8]. Updated results will be presented.

In addition, the difference in the medians can be misleading, because it does not represent the whole curve, just a single point on the curve. It is not correct to simply choose a point in time because the curves appear to be separated at that point [12]. The best estimate is HR which summarizes the data comparing the whole curves, over the entire period of follow-up. For the SWOG trial, the 95% CI for the HR crosses 1, the line of equivalence [HR = 0.78, 95% CI (0.58–1.04)]. In addition, given the shape of the survival curves, there is a suggestion that the curves come together in the end, which means that even given an early benefit, there is no clear evidence of long lasting benefit. The American trial did not present an ‘intention to treat analysis’ as not all randomized patients were included in the survival curves. The intergroup trial is clearly a

very important trial, but it represents only 10% of all patients randomized into trials of neo-adjuvant chemotherapy and should be considered in that context.

Another trial that is very similar to the SWOG trial is the Italian GUONE trial, in which 206 patients were accrued over a 6½ year period [13]. Patients were randomized between four cycles of M-VAC before cystectomy and cystectomy alone. The sample size was calculated to detect an improvement in 3-year overall survival of 15%, from 45 to 60%. Survival at 3 years was 62% for the M-VAC arm and 68% for the cystectomy alone arm. This is a small trial, like the SWOG trial in which no clear difference in survival was observed. Likewise, no evidence of a difference in survival was seen in another Italian trial of methotrexate, vinblastine, epirubicin and cisplatin (M-VEC) versus cystectomy, when epirubicin was substituted for doxorubicin [14].

The Nordic cystectomy I trial reported a small difference in a subgroup analysis of patients with T3–T4 disease [15], but did not confirm these results in the subsequent Nordic cystectomy II trial in 317 patients with muscle-invasive disease, with methotrexate and cisplatin instead of the Nordic I regimen containing doxorubicin, cisplatin and radiation prior to cystectomy [16].

Although data from individual trials have not reliably shown a benefit with neo-adjuvant chemotherapy, it is possible that combining the data from all of the trials will produce conclusions either in favor of or against the use of neo-adjuvant chemotherapy. Information from randomized trials in the form of an updated meta-analysis will be presented. This meta-analysis is currently being performed by the MRC.

Neo-adjuvant chemotherapy and bladder preservation

Since orthotopic bladder substitution has become available, many urologists prefer immediate cystectomy and continent urinary diversion. However, the possibility of bladder preservation should not be dismissed. This approach has been used in the treatment of other solid tumors, such as breast cancer, anal cancer, laryngeal carcinoma and osteosarcoma. Bladder preservation means less surgery, no need for a urinary diversion and a normal sexual life. These factors are clearly important in determining quality of life.

Following neo-adjuvant chemotherapy, bladder preservation may be possible in selected patients who respond to chemotherapy [17]. The pathological complete response rate in the cystectomy specimen (pT0) was 38% in M-VAC treated patients in the SWOG trial. Likewise, the pT0 rate in the EORTC/MRC trial was 33% for patients who had CMV chemotherapy and surgery, as compared with 12% for those who had TURB and cystectomy without chemotherapy.

Several investigators have shown that response to chemotherapy is an important prognostic factor [18–21]. However, this may represent patient selection factors, as it is always

possible that patients who do well have characteristics that would make them survive longer whether or not they were treated with chemotherapy.

In our Italian neo-adjuvant M-VAC series, patients with muscle-infiltrating bladder cancer were given three cycles of neo-adjuvant M-VAC. Based upon their response to chemotherapy, they were placed in one of three groups: TURB alone, partial cystectomy or radical cystectomy [18, 21]. Those who failed to respond to chemotherapy underwent cystectomy. Five-year survival was 59% for all patients, 70% for those who responded to T0 or superficial tumors, and only 22% for patients with remaining muscle invasive disease. These data compare favorably to the recently published cystectomy series.

At the University of Southern California (USC), 5-year survival in 633 patients after cystectomy was 48% (72% for pT2, 58% for pT3a, 38% for pT3b and 33% for pT4) [22]. In 284 patients at Memorial Sloan Kettering Cancer Center, 5-year survival was 36%, (59% for pT2 tumors, 25% for pT3 and 29% for pT4) [23]. In Padua 5-year survival in 258 patients with muscle-invasive disease was 44% (63% for pT2, 53% for pT3a, 32.5% for pT3b and 28% for pT4) [24]. Likewise, in series combining chemotherapy and radiation in an attempt to spare the bladder (Table 2), survival for patients with T2–T3 invasive bladder cancer is similar to that observed in contemporary cystectomy series. In chemoradiation series from the Massachusetts General Hospital and from the Radiation Therapy Oncology Group, 5-year survivals were 54% and 49%, respectively [25, 26].

There is a similarity between contemporary cystectomy series and selected bladder preservation series, although the interpretation of results may be difficult due to the differences between clinical and pathological staging. Clinical staging is more likely to understage the extent of disease. Thus if there is a favorable outcome, it is usually in favor of the pathologically staged patients.

There are other differences between cystectomy series and studies that seek to conserve the bladder, complicating comparisons between the two. Cystectomy series do not report by intention-to-treat and exclude those patients in whom cystectomy is inappropriate [27]. Many patients in cystectomy series do not have pre-operative proof of muscle invasion. Some 25–40% of patients in cystectomy series have less than pT2 disease, and thus a better prognosis.

Patients who elect to preserve the bladder must accept frequent follow-up, multiple invasive procedures, the possibility that cystectomy may eventually become necessary and the uncertainty of tumor relapse. Patients who respond to chemotherapy are good candidates for bladder preservation protocols, and bladder preservation is a good alternative for patients who are not candidates for radical cystectomy. Bladder sparing in selected patients on the basis of response to neo-adjuvant chemotherapy is a feasible approach which has not as yet been confirmed in prospective randomized trials.

Table 2. Trials of combined chemotherapy and radiotherapy

Series	Year	<i>n</i>	Chemo	5-year survival (%)	5-year survival with intact bladder (%)
Radiation Therapy Oncology Group study 85-121 [25]	1993	42	DDP	52	42
Radiation Therapy Oncology Group study 88-02 [47]	1996	91	MCV + RT and DDP	62 ^a	44
Radiation Therapy Oncology Group study 89-03 [48]	1998	123	MCV + RT and DDP	48	36
Massachusetts General [26]	1997	107	MCV	52	43
University of Erlangen [49, 50]	2001	199	DDP or Carbo	52	41
University of Paris [51, 52]	2001	120	DDP/5-FU	63	–

^aFour year survival data.

Carbo, carboplatin; DDP or C, cisplatin; 5-FU, 5-fluorouracil; M, methotrexate; RT, radiation therapy; V, vinblastine.

Table 3. Trials of adjuvant chemotherapy following cystectomy

Investigator	Year	Chemo	Chemo	No chemo	Randomized	Results
Logothetis et al. [53]	1988	CISCA	62	71	No	Benefit but not randomized
Skinner et al. [30]	1991	CAP	47	44	Yes	Benefit, but too few patients received therapy
Stockle et al. [31]	1992	M-VAC/ M-VEC	23	26	Yes	Benefit, small patient numbers, premature closure, no treatment at relapse
Studer et al. [54]	1994	DDP	40	37	Yes	No benefit, single-agent therapy probably inadequate
Bono et al. [55]	1995	CM	48	35	Yes	No benefit for N0M0
Freiha et al. [56]	1996	CMV	25	25	Yes	Benefit in relapse-free survival
Otto et al. [33]	2001	M-VEC	55	53	Yes	No benefit

From Sternberg and Calabrò [1] with modifications.

A, doxorubicin; DDP or C, cisplatin; E, epirubicin; M, methotrexate; V, vinblastine; CISCA, cytoxan, adriamycin and cisplatin.

Adjuvant chemotherapy

For high risk patients with pT3–pT4 and/or pN+ M0 bladder cancer, 5-year survival after radical cystectomy is only 25–35% [1, 22, 23, 28]. Failure is usually due to occult systemic disease. Nodal metastases carry a poor prognosis despite pelvic lymphadenectomy and radical cystectomy. Yet some node positive cases with otherwise localized bladder cancer and very few lymph nodes may benefit from surgery alone [29].

Adjuvant chemotherapy is used after cystectomy in an effort to delay recurrence and prolong survival [1, 4]. This technique of giving chemotherapy after local treatment has led to increases in survival in patients with several solid tumors.

The rationale for giving adjuvant as opposed to neo-adjuvant chemotherapy is that local definitive treatment is performed immediately. There is no delay in surgery and no time is wasted, especially for those patients who do not respond to chemotherapy. Treatment decisions are based on pathological criteria, after careful examination of the cystectomy specimen. Micrometastases are treated after the bladder tumor has been removed. Orthotopic bladder substitutions and the decreased morbidity of cystectomy are reasons to perform cystectomy and adjuvant chemotherapy.

The major disadvantage to adjuvant chemotherapy is the delay in giving systemic therapy for occult metastases while treating the primary tumor. Response cannot be easily evaluated, and the only clinical endpoint that can be assessed is time to recurrence. An additional disadvantage may relate to the difficulty in administering chemotherapy after cystectomy. There have been very few well-performed randomized trials evaluating adjuvant chemotherapy. Most have included limited numbers of patients (Table 3).

Two studies in the literature have received considerable attention. The most referenced is a study by Skinner et al. [30]. This was the first phase III prospective trial that showed a significant increase in time to progression and survival in patients who were randomized to receive chemotherapy following cystectomy. This has been interpreted as a positive study. Median survival time for patients in the chemotherapy group was 4.3 years compared with 2.4 years in the observation group. The number of involved lymph nodes was the single most important variable.

This study has been criticized due to its retrospective use of subgroup analyses and its statistical methodology. The survival curves crossed over with longer follow-up. While chemo-

therapy appeared to prolong the median time to recurrence by 14 months, there was really no residual advantage at 2 years. In addition, patients randomized to chemotherapy either didn't receive chemotherapy at all or received a variety of different chemotherapeutic regimens.

In Mainz, patients were randomized after cystectomy to observation or chemotherapy with either M-VAC or M-VEC [31, 32]. The population had poor risk factors. Sixty per cent had positive nodes and most were stage T4. The study was prematurely closed, after an interim analysis revealed a benefit for patients randomized to chemotherapy, with only 27% progression in the treated versus 82% progression in the control arm. Survival was markedly different between the two arms, as the authors did not treat patients who relapsed in the observation arm. In an intention-to-treat analysis, 5-year progression-free survival was 59% after the recommendation to receive chemotherapy versus 13% after a recommendation of cystectomy alone [32]. However, in another even more contemporary German series, comparing M-VEC to observation after cystectomy, no difference in survival was found [33].

Due to the difficulty in interpretation of these adjuvant chemotherapy trials, a systematic review of published randomized trials of adjuvant cisplatin-containing combination chemotherapy in locally advanced bladder cancer was undertaken [34]. Although these trials appear to show a significant difference in favor of adjuvant chemotherapy, serious methodological flaws were found. Major deficiencies were found in the sample size, early stopping of patient entry, statistical analyses, reporting of results and drawing conclusions.

These trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice due to small sample sizes, confusing analyses and terminology and the reporting of questionable conclusions. Analyses of the duration of survival were either not done or were inconclusive, and quality of life was not considered. The MRC is also attempting to provide a meta-analysis of the randomized adjuvant trials.

Based on the desire to only treat patients who are really at high risk, the EORTC together with many other international groups throughout the world have now begun a large trial that will enlist 1344 patients worldwide, in the adjuvant setting after cystectomy. This is a study evaluating four cycles of immediate chemotherapy versus therapy at the time of relapse in high-risk patients with pT3–pT4 or node positive disease. Three different chemotherapy regimens are permitted: M-VAC, high-dose M-VAC (HD-M-VAC) and gemcitabine/cisplatin (GC) [35–37].

Optimal chemotherapy

The EORTC has compared HD-M-VAC plus granulocyte colony-stimulating factor (G-CSF) with M-VAC in a phase III randomized trial in patients with metastatic bladder cancer. This trial suggested an improvement in 2-year survival with

HD-M-VAC, but more importantly, less toxicity and the ability to administer chemotherapy in half the time. HD-M-VAC was better in terms of progression-free survival ($P = 0.037$; HR = 0.75; 95% CI 0.58–0.98), although not in overall survival as planned by the study ($P = 0.122$; HR = 0.80; 95% CI 0.60–1.06). Patients who received HD-M-VAC had a higher response rate ($P = 0.06$) and CR rate ($P = 0.009$) and a 25% less chance to recur or die than patients on M-VAC (HR = 0.75; 95% CI 0.58–0.98) [36].

Another large randomized trial in patients with metastatic disease revealed that the combination of gemcitabine and cisplatin was less toxic than M-VAC, with similar survival outcomes ($P = 0.75$; HR = 1.04; 95% CI 0.82–1.32) [37].

For these reasons, M-VAC, HD-M-VAC and gemcitabine–cisplatin are all considered to be acceptable alternatives for the treatment of bladder cancer. Physicians appear to be selecting the one with which they feel the most comfortable.

Molecular markers

Recently there has been significant interest in molecular markers such as *p53*, retinoblastoma gene and *p21* to help optimize therapy and predict chemosensitivity. Retrospective studies show that tumors with overexpression of mutant *p53* are at increasing risk of metastatic disease and decreased long-term survival [38, 39].

In a study comparing Italian and American patients with invasive bladder cancer, significant differences in the expression of the *p53*, *p21* and *Rb* genes were found between the two [40]. Italian patients with *p53*⁺/*p21*⁺ tumors had significantly lower recurrence rates after TURB and chemotherapy than those having *p53*⁺/*p21*[−] tumors. Absence of *p21* immunopositivity in the Italian tumors may have identified alterations in the *p53* pathway that predict poor outcome.

A multicenter American and international adjuvant trial is attempting to evaluate patients with low stage T1–T2 tumors, who are randomized after surgery to M-VAC versus observation based on their *p53* status. Following radical cystectomy, eligible patients are those with pT1–T2 disease, or those who have had T1–T2 on the TURB and are pT0 at the cystectomy. These patients are then evaluated for *p53* status. Patients with wild-type *p53* are entered on the study and observed, and with mutant *p53* are randomized between three cycles of M-VAC and observation.

This study is based upon the USC experience that tumors expressing alterations in *pRb* and *p53* had significantly increased rates of recurrence ($P < 0.0001$) and decreased survival ($P < 0.0001$) compared with patients without alterations in *pRb* and *p53* [39, 41]. They have also found that patients with altered *p53* are more likely to benefit from chemotherapy. Although some have questioned the USC results [40, 42], this is an important study in that it seeks to use molecular markers to determine outcome of patients with locally advanced bladder cancer.

At the present time, the use of molecular markers to direct either adjuvant or neoadjuvant chemotherapy remains investigational.

Conclusions

Muscle-invasive bladder cancer is a chemosensitive disease and should be dealt with in a multimodality approach with collaboration between the urologist, medical oncologist and radiotherapist. Thus far, no individual trial has definitively proven that neo-adjuvant chemotherapy improves survival, although it is useful in programs of bladder preservation. The results of the MRC meta-analysis of neo-adjuvant chemotherapy are awaited. Response to M-VAC neo-adjuvant chemotherapy is an important prognostic factor, but this too may represent patient selection factors. It is not known if it is better to administer chemotherapy in the neo-adjuvant or in the adjuvant setting. The international adjuvant chemotherapy trial coordinated by the EORTC will hopefully clarify some of the unanswered questions concerning whether or not adjuvant chemotherapy immediately following cystectomy is necessary in high risk patients.

References

1. Sternberg CN, Calabrò F. Chemotherapy and management of bladder tumors. *Br J Urol* 2000; 85: 599–610.
2. Lerner SP, Skinner E, Skinner DG. Radical cystectomy in regionally advanced bladder cancer. *Urol Clin North Am* 1992; 19: 713–723.
3. Sternberg CN, Calabrò F. Neo-adjuvant chemotherapy in invasive bladder cancer. *World J Urol* 2001; 19: 94–98.
4. Sternberg CN, Raghavan D, Ohi Y. Neo-adjuvant and adjuvant chemotherapy in locally advanced disease: what are the effects on survival and prognosis? *Int J Urol* 1995; 2: 76–88.
5. International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. *Lancet* 1999; 354: 533–540.
6. Machin D, Campbell MJ, Fayers PM, Pinol APY. *Sample Size Tables for Clinical Studies*. London: Blackwell 1997.
7. Natale RB, Grossman HB, Blumenstein B et al. SWOG 8710 (INT-0080): Randomized phase III trial of neoadjuvant M-VAC and cystectomy versus cystectomy alone in patients with locally advanced bladder cancer. *Proc Am Soc Clin Oncol* 2001; 20: 2a (Abstr 3).
8. Sternberg CN, Parmar MK. Neo-adjuvant chemotherapy is not (yet) standard treatment for muscle invasive bladder cancer. *J Clin Oncol* 2001; 19 (Suppl 1): 21S–26S.
9. Parmar MK. Neoadjuvant chemotherapy in invasive bladder cancer. *Trial Design Prog Clin Biol Res* 1990; 353: 115–118.
10. Solsona E, Iborra I, Ricos JV et al. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term follow-up of a prospective study. *J Urol* 1998; 159: 95–99.
11. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. *J Clin Oncol* 2001; 19: 89–93.
12. Parmar MKB, Machin D. *Survival Analysis: A Practical Approach*. Chichester, UK: Wiley 1995.
13. Bassi P, Pagano F, Pappagallo G et al. Neo-adjuvant M-VAC of invasive bladder cancer: The GUONE multicenter phase III trial. *Eur Urol* 1998; 33 (Suppl 1): 142 (Abstr).
14. GISTV (Italian Bladder Cancer Study Group). Neoadjuvant treatment for locally advanced bladder cancer: a randomized prospective clinical trial. *J Chemother* 1996; 8 (Suppl. 4): 345–346.
15. Malmstrom PU, Rintala E, Wahlqvist R et al. Five-year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy. *J Urol* 1996; 155: 1903–1906.
16. Malmstrom PU, Rintala E, Wahlqvist R et al. and members of the Nordic Urothelial Cancer Group. Neoadjuvant cisplatin-methotrexate chemotherapy of invasive bladder cancer. *Nordic Cystectomy Trial 2*. *Eur Urol* 1999; 35 (Suppl. 2): 60 (Abstr 238).
17. Sternberg CN, Pansadoro V. Transitional cell carcinoma of the urinary tract: bladder preserving treatments: chemotherapy and conservative surgery. In Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS. *Comprehensive Textbook of Genitourinary Oncology*, 2nd edition. Philadelphia, PA: Lippincott Williams & Wilkins 2000; 496–505.
18. Sternberg CN, Pansadoro V, Calabrò F et al. Neo-adjuvant chemotherapy and bladder preservation in locally advanced transitional cell carcinoma of the bladder. *Ann Oncol* 1999; 10: 1301–1305.
19. Hall RR, Roberts JT, Marsh MM. Radical TUR and chemotherapy aiming at bladder preservation. *Prog Clin Biol Res* 1990; 353: 163–168.
20. Splinter TAW, Pavone-Macaluso M, Jacqmin D et al. European Organization for Research and Treatment of Cancer Genitourinary Group phase 2 study of chemotherapy in stage T3-4N0-XM0 transitional cell cancer of the bladder: evaluation of clinical response. *J Urol* 1992; 148: 1793–1796.
21. Sternberg CN, Pansadoro V, Calabrò F et al. Can we select patients for bladder preservation based upon response to chemotherapy? *J Urol* 2000; 163; 216 (Abstr).
22. Stein JP, Lieskovsky G, Cote R et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. *J Clin Oncol* 2001; 19: 666–675.
23. Dalbagni G, Genega E, Hashibe M et al. Cystectomy for bladder cancer: a contemporary series. *J Urol* 2001; 165: 1111–1116.
24. Chang SS, Alberts G, Cookson MS, Smith JA Jr. Radical cystectomy is safe in elderly patients at high risk. *J Urol* 2001; 166: 938–941.
25. Tester W, Porter A, Asbell S. Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG Protocol 85-12. *Int J Radiat Oncol Biol Phys* 1993; 25: 783–790.
26. Kachnic LA, Kaufman DS, Heney NM. Bladder preservation by combined modality therapy for invasive bladder cancer. *J Clin Oncol* 1997; 15: 1022–1029.
27. Hussain MH, Glass TR, Forman J et al. Combination cisplatin, 5-fluorouracil and radiation therapy for locally advanced unresectable or medically unfit bladder cancer cases: a Southwest Oncology Group Study. *J Urol* 2001; 165: 56–60.
28. Bassi P, Ferrante GD, Piazza N et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999; 161: 1494–1497.
29. Vieweg J, Gschwend JE, Herr HW, Fair WR. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. *J Urol* 1999; 161: 449–454.
30. Skinner DG, Daniels JR, Russell CA et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991; 145: 459–467.

31. Stockle M, Meyenburg W, Wellek S et al. Advanced bladder cancer (stages PT3b, PT4a, PN1 and PN2): improved survival after radical cystectomy and three adjuvant cycles of chemotherapy results of a controlled prospective study. *J Urol* 1992; 148: 302–307.
32. Stockle M, Meyenburg W, Wellek S. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. *J Urol* 1995; 153: 47–52.
33. Otto T, Börgemann C, Krege S et al. Adjuvant chemotherapy in locally advanced bladder cancer (PT3/PN1–2.M0): a phase III study. *Eur Urol* 2001; 39 (Suppl. 5): 147 (Abstr).
34. Sylvester R, Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. *Ann Oncol* 2000; 11: 851–856.
35. Sternberg CN, Yagoda A, Scher HI et al. M-VAC for advanced transitional cell carcinoma of the urothelium: efficacy and patterns of response and relapse. *Cancer* 1989; 64: 2448–2458.
36. Sternberg CN, de Mulder PHM, Schornagel JH et al. for the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized phase III trial of high dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer. Protocol No. 30924. *J Clin Oncol* 2001; 19: 2638–2646.
37. von der Maase H, Hansen SW, Roberts JT et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; 18: 3068–3077.
38. Esrig D, Elmajian D, Groshen S et al. Accumulation of nuclear p53 and tumor progression in bladder. *N Engl J Med* 1994; 331: 1259–1264.
39. Cote RJ, Dunn MD, Chatterjee SJ et al. Elevated and absent pRb expression is associated with bladder cancer progression and has cooperative effects with p53. *Cancer Res* 1998; 58: 1090–1094.
40. Williams SG, Gandour-Edwards R, Deitch AD et al. Differences in gene expression in muscle-invasive bladder cancer: a comparison of Italian and American patients. *Eur Urol* 2001; 39: 430–437.
41. Cote RJ, Esrig D, Groshen S et al. p53 and treatment of bladder cancer. *Nature* 1997; 385: 123–125.
42. McShane LM, Aamodt R, Cordon-Cardo C et al. Reproducibility of p53 immunohistochemistry in bladder tumors. National Cancer Institute, Bladder Tumor Marker Network. *Clin Cancer Res* 2000; 6: 1854–1864.
43. Wallace DM, Raghavan D, Kelly KA et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. *Br J Urol* 1991; 67: 608–615.
44. Coppin CM, Gospodarowicz MK, James K et al. Improved local control of invasive bladder cancer by concurrent cisplatin and pre-operative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1996; 14: 2901–2907.
45. Martinez Pineiro JA, Gonzalez Martin M, Arocena F. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: prospective randomized phase III study. *J Urol* 1995; 153: 964–973.
46. Abol-Enein H, El Makresh M, El Baz M, Ghoneim M. Neo-adjuvant chemotherapy in treatment of invasive transitional bladder cancer: a controlled, prospective randomised study. *Br J Urol* 1997; 80 (Suppl. 2): 49.
47. Tester W, Caplan R, Heaney J. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of radiation therapy oncology group phase II trial 8802. *J Clin Oncol* 1996; 14: 119–126.
48. Shipley WU, Winter KA, Kaufman DS et al. Phase III trial of neo-adjuvant 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. *J Clin Oncol* 1998; 16: 3576–3583.
49. Sauer R, Birkenhake S, Kühn R et al. Muscle-invasive bladder cancer: transurethral resection and radiochemotherapy as an organ-sparing treatment option. Petrovich Z, Baert L, Brady LW (eds): *Carcinoma of the Bladder*. Springer 1998; 205–214.
50. Sauer R, Rodel C. Biological selection for organ conservation. *Eur J Cancer* 2001; 37 (Suppl. 6): S286 (Abstr).
51. Housset M, Dufour B, Maulard-Durdux C et al. Concomitant fluorouracil (5-FU)-cisplatin (CDDP) and bifractionated split course radiation therapy (BSCRT) for invasive bladder cancer. *Proc Am Soc Clin Oncol* 1997; 16: 319a (Abstr).
52. Durdux C, Housset M, Dufour B. Altered fractionation in chemoradiation for bladder cancer. *Eur J Cancer* 2001; 37 (Suppl. 6): S286 (Abstr).
53. Logothetis CJ, Johnson DE, Chong C et al. Adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy for bladder cancer: an update. *J Clin Oncol* 1988; 6: 1590–1596.
54. Studer UE, Bacchi M, Biedermann C. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol* 1994; 152: 81–84.
55. Bono AV, Benvenuti C, Reali L et al. Adjuvant chemotherapy in advanced bladder cancer. Italian Uro-Oncologic Cooperative Group. *Prog Clin Biol Res* 1989; 303: 533–540.
56. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996; 155: 495–499.

