Bladder-sparing, Combined-modality Approach for Muscle-invasive Bladder Cancer

A Multi-institutional, Long-term Experience

Sisto Perdonà, MD[1]
Riccardo Autorino, MD, PhD[2]
Rocco Damiano, MD[3]
Marco De Sio, MD, PhD[2]
Brunello Morrica, MD[4]
Luigi Gallo, MD[1]
Giustino Silvestro, MD[4]
Antonio Farella, MD[5]
Sabino De Placido, MD[6]
Giuseppe Di Lorenzo, MD, PhD[6]

[1] Comprehensive Urology Unit, National Tumor Institute, "G. Pascale" Foundation, Naples, Italy.

[2] Urology Clinic, Second University of Naples, Naples, Italy.

[3] Department of Urology, Magna Graecia University, Catanzaro, Italy.

[4] Comprehensive Radiotherapy Unit, National Tumor Institute, "G. Pascale" Foundation, Naples, Italy.

[5] Department of Diagnostic Imaging and Radiotherapy, Federico II University, Naples, Italy.

[6] Department of Oncology, Federico II University, Naples, Italy.

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The first and second authors contributed equally to this article.

Address for reprints: Riccardo Autorino, MD, PhD, Clinica Urologica, AOU Policlinico, Seconda Università degli Studi di Napoli, Piazza Miraglia 2, 80138 Naples, Italy; Fax: (011) 39-081-446664; E-mail: ricautor@tin.it

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BACKGROUND. The authors evaluated their long-term experience with combined-modality, conservative treatment in patients with muscle-invasive bladder cancer.
METHODS. In total, 121 patients with T2, T3, or T4 bladder cancer (mean age, 63 years; ratio of men to women, 3:1) underwent induction by transurethral resection (TUR) of the tumor and received 2 cycles of neoadjuvant chemotherapy followed by radiotherapy (RT) (n = 43 patients) or radiochemotherapy (RCT) (n = 78 patients). Six weeks after RT or RCT, responses were evaluated by restaging TUR. Patients who achieved a complete response (CR) were observed at regular intervals. In patients who had persistent or recurrent invasive tumor, further treatment was recommended.
RESULTS. Local response evaluation by restaging TUR was possible in 119 patients, and 102 of those patients (85.7%) achieved a CR. After a median follow-up of 66 months (range, 6–182 months), no local or distant disease recurrences were observed in 67 of 102 complete responders (65.7%), 17 of 102 complete responders (16.7%) experienced superficial local disease recurrence, and 18 of 102 complete responders (17.6%) had a muscle-invasive relapse. The 5-year tumor-specific, overall, and bladder-intact survival rates were 73.5%, 67.7%, and 51.2%, respectively. Treatment modality, tumor classification, and resection status after initial TUR had an impact on survival rates ($P = .04$, $P = .02$, and $P = .02$, respectively).
CONCLUSIONS. The current results indicated that conservative combined treatment is a reasonable alternative to radical cystectomy in selected patients with muscle-invasive bladder cancer. ***Cancer*** **2008;112:75–83.** © *2007 American Cancer Society.*

KEYWORDS: bladder cancer, chemotherapy, conservative treatment, radiotherapy, transurethral resection.

The standard of care for localized muscle-invasive bladder cancer is radical cystectomy.[1] However, although this procedure is associated with excellent local control, it is not without risk of complications and, sometimes, poor quality of life (QoL) results. Although significant improvements in continent urinary diversions have been made recently, there still is no substitute for the patient's own fully functional bladder.

In view of these problems, several clinical studies have been conducted using a bladder-sparing approach to the treatment of the disease. For example, radical transurethral resection (TUR) may be sufficient as monotherapy in some selected patients, as reported by Herr.[2] However, in patients with deep muscle penetration who are treated exclusively with TUR, poor results have been observed.

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TABLE 1
Patient and Tumor Characteristics

Characteristic	RT	RCT	Total
No. of patients	43	78	121
Sex (men/women)	30/13	60/18	90/31
Mean age, y	64.3	61.8	63
Clinical tumor classification			
T2	34	58	92
T3–T4	9	20	29
Tumor grade			
2	12	23	35
3	31	55	86
Concomitant CIS			
Yes	4	8	12
No	39	70	109
Hydronephrosis			
Yes	3	7	10
No	40	71	111
Visibly complete TURB			
Yes	33	65	98
No	10	13	23

RT indicates radiotherapy; RCT, radiochemotherapy; CIS, carcinoma in situ; TURB, transurethral resection of the bladder.

Similarly, neither chemotherapy (CT) nor radiation therapy (RT) alone results in significant local control.[3]

Therefore, recent strategies have combined the aforementioned interventions in an attempt to improve long-term survival and bladder preservation rates. However, despite promising results, reluctance to accept trimodality therapy as an alternative to cystectomy remains widespread because of a concern that the risk of recurrence remains and that any recurrence may increase the risk of death from cancer.

At our institutions, we offer a conservative, multimodal approach to patients who refuse radical surgery. In the current article, we present our experience in this selected population and report on factors that may predict treatment response, risk of relapse, and long-term survival.

MATERIALS AND METHODS

Study Population

Between 1994 and 2002, 121 patients (ratio of men to women, 3:1; mean age, 63 years; age range, 42–77 years) with biopsy-confirmed, muscle-invasive (tumor classification 2 [T2]-T4) bladder cancer were entered in a bladder-sparing protocol. Exclusion criteria were as follows: an Eastern Cooperative Oncology Group performance status >2, evidence of distant metastases, prior CT or RT, hemoglobin <10 mg/dL, white blood cell count <4000/mL, platelet count <100,000/mL, serum creatinine >2 mg/dL, transaminase levels >3 times the upper limit of normal, and total bilirubin >3 mg/dL. Informed written consent was obtained from all patients. All patients had refused radical cystectomy out of a desire to preserve their health-related QoL. Patient and tumor characteristics are listed in Table 1.

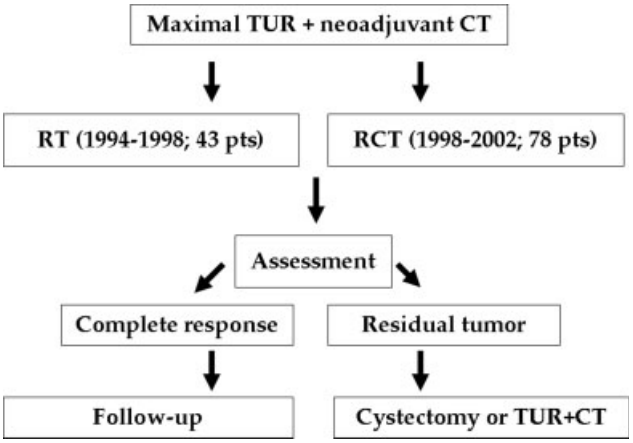

FIGURE 1. Bladder-sparing treatment protocol is depicted. TUR indicates transurethral resection; CT, chemotherapy; RT, radiotherapy; pts, patients; RCT, radiochemotherapy.

Treatment Protocol

Treatment commenced with TUR aimed at maximal (complete, if feasible) resection of the tumor mass (Fig. 1). Residual tumor was assessed at the end of the procedure by representative biopsies from all resection margins. All patients received neoadjuvant cisplatin-based CT as follows: combined methotrexate, cisplatin, and vinblastine (MCV), with methotrexate 30 mg/m^2 intravenously on Days 1 through 15 of each 21-day cycle, cisplatin 70 mg/m^2 on Day 2, and vinblastine 3 mg/m^2 on Days 2 through 15. The doses of methotrexate and vinblastine were reduced if severe leukopenia or thrombocytopenia occurred, and the methotrexate dose was reduced if the serum bilirubin level increased to >2 mg/dL. Doses of methotrexate and cisplatin were reduced if the serum creatinine level increased to >1.5 mg/dL. The doses of cisplatin and vinblastine were reduced if neuropathy, weakness, or severe paresthesias occurred. Doses of methotrexate were reduced if the patient developed stomatitis.

External-beam RT with computed tomography-based images was performed with 9-megavolt (MV) or 12-MV photon beams from a linear accelerator 15 to 45 days after the completion of neoadjuvant CT. Treatment fields included the entire bladder, the tumor surface, the prostate and prostatic urethra (or proximal vagina), and pelvic (external and internal

iliac) lymph nodes. A 4-field "box technique" was used with individually shaped portals. Planning cystograms were used, and the field borders were the fifth lumbar/first sacral interspace cephalad, at least 1 cm beyond the pelvis bone laterally, and the inferior border of the obturator foramen caudally. The median total dose delivered to the pelvis was 45 grays (Gy) (range, 34–56 Gy), and a median total dose of 65 Gy (range, 34–67 Gy) was delivered to the bladder. The daily fraction was from 1.8 Gy to 2 Gy delivered in a once-daily radiation scheme on 5 consecutive days. Beginning in 1998, concomitant CT was administered during the first and fifth weeks of RT and consisted of cisplatin (25 mg/m^2 per day as a 30-minute infusion on 5 consecutive days) in 53 patients or carboplatin (65 mg/m^2 per day as a 30-minute infusion on 5 consecutive days) in 25 patients with decreased creatinine clearance (<60 mL per minute) or congestive heart disease.

Assessment

Six weeks after the completion of RT or combined radiochemotherapy (RCT), response was evaluated by cystoscopy and deep TUR of the former tumor bed. In patients who presented with initial, concomitant carcinoma in situ, random biopsies were obtained routinely. A complete response (CR) was defined as the absence of any endoscopically visible tumor, the absence of any microscopic tumor in the biopsy specimen, and negative urine cytology. Patients who achieved a CR were observed at 3-month intervals for the first 2 years and every 6 months thereafter. Evaluations consisted of a physical examination, blood counts and chemistry panels, urine cytology, cystoscopy, and biopsies of suspicious areas. Each year, thoracic and abdominopelvic computed tomography scans, bone scans, and other instrumental examinations, if indicated, were performed. In patients who had persistent or recurrent tumor, additional treatment was recommended, such as TUR followed by intravesical therapy for superficial tumors or salvage cystectomy for muscle-invasive tumors. Toxicity data were recorded using the World Health Organization toxicity scoring system. The Late Effects of Normal Tissue grading system[4] was used to evaluate late treatment-related toxicity.

Statistics

At the time of analysis, the median follow-up for the entire group was 66 months (range, 6–182 months). Survival rates were computed according to the Kaplan-Meier method. Overall and tumor-specific survival intervals were calculated from the day of the first TUR to the time of death or the last follow-up examination, and death or disease-related death was scored as an event. Bladder-intact and cystectomy-free survival intervals were calculated from the date of diagnosis to the time of death or the last follow-up examination, and any bladder intervention or cystectomy was scored as an event.

Statistical comparisons were performed using 2-tailed tests. The level of significance was set at .05 for all statistical testing. Multivariate analyses and determination of odds ratios were performed using logistic regression analysis (initial response) and the Cox proportional hazards model (censored data). The following factors were tested for their predictive and prognostic impact on initial response and survival rates: resection status after TUR, grading, tumor (T) classification, the presence of carcinoma in situ, the presence of hydronephrosis, and treatment modality (RT or RCT).

TABLE 2
Complete Response According to Prognostic Factors

Prognostic factor	No. of patients	No. of complete responders (%)	*P**
Resection status			.004
R0	98	86 (87.7)	
R1	23	16 (69.5)	
Grade			NS
2	35	28 (80)	
3	86	74 (86)	
Tumor classification			.007
T2	92	81 (88)	
T3–T4	29	21 (72.4)	
CIS			NS
Yes	12	10 (83.3)	
No	109	92 (84.4)	
Hydronephrosis			NS
Yes	10	8 (80)	
No	111	94 (84.6)	
Treatment modality			.015
RT	43	32 (74.4)	
RCT	78	70 (89.7)	

NS indicates not significant; CIS, carcinoma in situ; RT, radiotherapy; RCT, radiochemotherapy.
* *P* values were determined by using the 2-tailed Fisher exact test.

RESULTS

Response Evaluated by Restaging TUR

Initial TUR resulted in a visibly complete resection (R0) in 98 patients (81%). Local response evaluation by restaging TUR was possible in 119 patients, and 102 patients (85.7%) achieved a CR. Two patients did not undergo restaging TUR because of noncompliance 1 patient and death from intercurrent disease unrelated to treatment in the other patient. Predictive clinicopathologic and treatment-related factors that influenced CR are listed in Table 2. Complete-

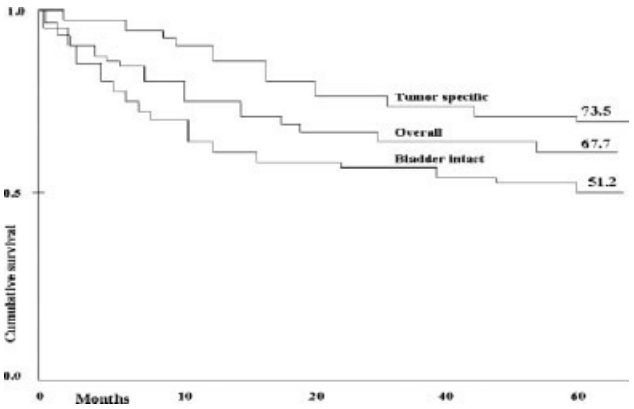

FIGURE 2. Survival curves according to the Kaplan-Meier method are shown.

ness of initial TUR, early T classification, and treatment modality had the strongest impact on initial response. Of the 17 patients who had incomplete responses, 10 patients underwent immediate salvage cystectomy, 5 patients received intravesical CT, and 2 patients received systemic CT because they developed regional or distant metastases.

Disease Recurrence

At a median follow-up of 66 months, no local or distant disease recurrence was observed in 67 of 102 complete responders (65.7%) of 102 complete responders, 17 of 102 complete responders (16.7%) experienced superficial local disease recurrence and were treated conservatively with TUR and intravesical therapy, and 18 of 102 complete responders (17.6%) had a muscle-invasive relapse. For the whole group of patients, the 5-year rate of local control without any relapse was 56.3%, and the 5-year rate of freedom from muscle-invasive disease was 70.5%.

Overall, 24 of 119 patients (20.2%) underwent salvage cystectomy for invasive residual or recurrent tumor, including 10 of 17 noncomplete responders (58.8%) and 14 of 102 patients (13.7%) with an initial CR who experienced a local relapse. The pathologic tumor (pT) classifications were as follows: pT2, 14 patients; pT3, 7 patients; and pT4, 3 patients. In 4 patients, radical surgery could not be performed because of poor general health status, advanced age, or patient refusal, all of which were not regarded as exclusion criteria for RT or RCT. The median interval between initial TUR and cystectomy was 5.8 months for nonresponders and 28 months for patients who had an invasive relapse. Patients who underwent salvage cystectomy for an invasive relapse had a 5-year disease-specific survival rate of 50% (calculated from the time of surgery). This rate decreased to 28.5% for nonresponding patients who underwent immediate cystectomy ($P = .002$).

TABLE 3
Survival Rates

Variable	% RT (n = 43)	% RCT (n = 78)	*P*	% Total (n = 121)
Overall survival	60.4	71.8	.008	67.7
Bladder-intact survival	46.5	53.8	.02	51.2
Tumor-specific survival	62.8	79.4	.003	73.5
Cystectomy-free survival	65.1	70.5	.04	68.6

RT indicates radiotherapy; RCT, radiochemotherapy.

For the 4 patients with muscle-invasive recurrent or residual tumor who were not cystectomy candidates or who declined salvage cystectomy, the median survival was 9.2 months, and no patients remained alive at 5 years. In the subgroup of patients who had superficial recurrent tumors after initial CR, salvage treatment with TUR and intravesical therapy resulted in a 5-year disease-specific survival rate of 70%. Conversely, among the 22 patients with superficial tumors after RT or RCT who underwent TUR and received instillation therapy, the 5-year disease-specific survival rate was 41%. Distant metastases were diagnosed in 34 patients, for an actuarial rate of 28% at 5 years. The metastasis-free survival rate was 77.4% for patients who achieved a CR, but this rate decreased to 52.9% among patients who had residual tumor after combined-modality treatment.

Survival and Bladder Preservation

Five-year tumor-specific, overall, and bladder-intact survival curves for all 121 patients are depicted in Figure 2. When only the 102 patients who achieved a CR were considered, these rates were 79.4%, 60.7%, and 48.0%, respectively. Table 3 shows that a statistically significant difference was observed between RT- and RCT-treated patients in terms of overall and tumor-specific survival ($P = .008$ and $P = .003$, respectively).

The strongest impact on overall survival was noted for T classification and resection status after initial TUR (Table 4). An independent value in multivariate analysis also was confirmed for treatment mode (RT vs RCT).

Toxicity

Treatment was completed, as specified or with minor deviations, in 41 of 43 RT-treated patients (95.3%) and in 74 of 78 RCT-treated patients (94.9%). During neoadjuvant CT, 4 patients experienced cardiopulmonary events that delayed or prevented completion of the protocol. Two patients received only 1 cycle of CT because of renal dysfunction in 1 patient and

TABLE 4
Survival According to Prognostic Factors

Prognostic factor	No. of patients	% Overall survival	*P**	% Tumor-specific survival	*P**
Resection status			.02		.025
R0	98	70.4		78.5	
R1	23	56.5		52.1	
Grade			NS		NS
2	35	65.7		74.8	
3	86	68.6		73.2	
Tumor classification			.02		.015
T2	92	71.7		78.2	
T3–T4	29	55.1		58.6s	
CIS			NS		NS
Yes	12	66.6		75	
No	109	67.8		73.4	
Hydronephrosis			NS		NS
Yes	10	60		70	
No	111	68.4		73.8	
Treatment modality			.04		.02
RT	43	60.4		62.8	
RCT	78	71.8		79.4	

NS indicates not significant; CIS, carcinoma in situ; RT, radiotherapy; RCT, radiochemotherapy.
* *P* values were determined by using the 2-tailed Fisher exact test.

TABLE 5
Treatment-related Acute Toxicity*

	No. of patients (%)			
Toxicity	RT, n = 43	RCT, n = 78	Total, n = 121	*P*
Bone marrow	6 (13.9)	13 (16.6)	19 (15.7)	NS
Bladder	5 (11.6)	9 (11.5)	14 (11.5)	NS
Intestinal	4 (9.3)	11 (14.1)	15 (12.4)	NS
Other†	5 (11.6)	7 (8.9)	12 (9.9)	NS

RT indicates radiotherapy; RCT, radiochemotherapy; NS, not significant.
* Grade 3 and 4 toxicity according to the World Health Organization Scoring System.
† Fatigue, pain, neuropathy.

TABLE 6
Late Toxicity According to the Late Effects of Normal Tissue Grading System

Toxicity	No. of patients
Grade 4	
Salvage cystectomy for contracted bladder	1
Bowel obstruction	2
Grade 3	
Reduced bladder capacity	4*
Grade 2	
Frequency, urgency, and nocturia	11*
Dysuria	18*
Moderate diarrhea	16
Proctitis	28

* For bladder toxicity, only patients with preserved bladder and without local relapse were evaluated.

fatigue in other patient. Table 5 shows that thrombocytopenia and leukopenia were the most frequent toxicities, followed by urocystitis and enteritis, and were managed easily with symptomatic treatment.

The proportions of patients with chronic sequelae reported during the follow-up period are shown in Table 6. One patient underwent cystectomy because of a shrinking bladder, and 2 patients experienced late gastrointestinal toxicity (grade 4) and required surgical intervention. Four patients developed reduced bladder capacity, with less-than-voiding intervals <2 hours. Mild dysuria, diarrhea, and urgency with nocturia occurred in 9% to 24% of assessable patients.

DISCUSSION

Over the last 15 years, the concept of organ preservation in muscle-invasive bladder cancer has been investigated in several prospective series (Table 7). Each strategy began with complete TUR of the tumor, followed by induction CT with external-beam RT, and a concurrent radiosensitizer. Complete responders to induction therapy were candidates for bladder preservation. The objective of concomitant RCT was to increase tumor radiosensitivity in the hope that better local control and survival would be achieved without a reduction in QoL.[5]

Although we advocate radical surgery as first-line treatment for nonmetastatic, muscle-invasive bladder cancer, and we offer this bladder-sparing protocol only to patients who are seeking bladder preservation, our findings support the safety and effectiveness of multimodality treatment. We observed that the rates of CR (85.7%), bladder-intact survival (51.2%), and overall survival (67.7%) were similar to those determined in previously published series. Our study's obvious selection bias may have affected the results. Patients were selected according to strict criteria (relatively young age, good performance status, mostly T2 tumors with no hydronephrosis, no significant comorbidities). In highly selected patients like these, radical surgery can produce the best results with low morbidity.

In a pioneering study by Housset and coworkers,[6] the efficacy of trimodality therapy in terms of bladder preservation was demonstrated. Some years later, Sauer et al.[7] reported on 184 patients who underwent TUR and received from 45 Gy to 54 Gy of RT with concurrent cisplatin or carboplatin. Like in our protocol, no consolidation therapy was given to any of the patients in that series. The 5-year overall survival rate was 56%, and the 5-year rate of survival

TABLE 7
Multimodality Treatment for Muscle-invasive Bladder Cancer: Data From the Literature

Study	No. of patients	Treatment schedule: TUR plus	% CR	Consolidation therapy for responders	% 5-Year overall survival	% 5-Year bladder-intact survival
Housset, 1993[6]	120	RCT (24 Gy plus cisplatin/5FU)	77	RCT (24 Gy plus cisplatin/5FU)	63	—
Sauer, 1998[7]	184	RCT (45–54 Gy plus cisplatin/carboplatin)	80	—	56	41
Rodel, 2002[8]	415	RCT (50.4–59 Gy plus carboplatin/cisplatin)	72	—	50	42
Tester, 1993[10]	49	RCT (40 Gy plus cisplatin)	66	RCT (24 Gy plus cisplatin)	60	42
Shipley, 1998[12]	61	MCV (2 cycles) plus RCT (39.6 Gy plus cisplatin)	61	RCT (25.2 Gy plus cisplatin)	48	36
Shipley, 1998[12]	62	RCT (39.6 Gy plus cisplatin)	55	RCT (25.2 Gy plus cisplatin)	49	40
Kachnic, 1997[16]	106	TUR plus MCV (2 cycles) plus RCT (40 Gy plus cisplatin)	66	RCT (24.8 Gy plus cisplatin)	52	43
Arias, 2000[18]	50	MVAC (2 cycles) plus RCT (45 Gy plus cisplatin)	68	RT (20 Gy)	48	—
Danesi, 2004[19]	77	MCV (2 cycles) plus RCT (69 Gy plus cisplatin/5FU)	90.3	—	58.5	46.6
George, 2004[20]	60	MVAC/MCV (2 cycles) plus RCT (65 Gy plus cisplatin/carboplatin/5FU	75	—	36	56
Cobo et al., 2006[21]	29	MCV/GC (2 cycles) plus RCT (45 Gy plus cisplatin)	86	RT (64.8Gy)	72	48

TUR indicates transurethral resection; CR, complete response; RCT, radiochemotherapy; Gy, grays; 5FU, 5-fluorouracil; RT, radiotherapy; MCV, combined methotrexate, cisplatin, and vinblastine; MVAC, combined methotrexate, vinblastine, doxorubicin, and cisplatin; GC gemcitabine.

with bladder intact was 41%. More recently, the same investigators, reporting on 415 patients aged >18 years who were at their institution, pointed out that any component of the trimodality therapy contributed considerably to overall success.[8] It should be noted that certain cytotoxic agents have the potential to sensitize tumor cells to radiation, increasing cure rates. Rodel et al.[8] observed that the addition of concurrent CT in their series was associated with a significantly improved overall survival rate, which also was our finding, as shown in Table 3. In addition, this finding is in line with what is, to our knowledge, the only prospective randomized comparison of RT alone and RCT in bladder cancer.[9]

In the last decade, results from Phase I, II, and III trials have been reported by the Radiation Therapy Oncology Group (RTOG).[10–15] In the RTOG Phase III trial, 123 patients were randomized to receive induction therapy; and 61 of those patients were administered 2 cycles of neoadjuvant MCV before they received RT and concurrent cisplatin.[12] Consolidation was performed with 24 Gy of RT and cisplatin. Adding neoadjuvant MCV did not result in a statistically significant improvement in these rates.

The protocol RTOG 97-06 incorporated accelerated RT delivered at a reduced dose per fraction.[14] Consequently, the CR rate (74%) was comparable to that achieved with the other accelerated schedules,[6,13] and significant reductions in bowel and hematologic toxicities were reported. The recently closed RTOG 99-06 trial included 2 additional innovative changes: the inclusion of adjuvant cisplatin/gemcitabine and the inclusion of paclitaxel as a radiation-sensitizing agent during induction and consolidation.[15]

Investigators from the Massachusetts General Hospital initially reported on 106 patients with T2, T3, and T4 bladder tumors who were treated with a multimodality approach. In that series, the CR rate for induction therapy was 66%, the overall survival rate at 5 years was 52% and the bladder-intact survival rate was 43%.[16] The Massachusetts General Hospital experience has been updated.[17] From 1986 to 1997, 190 patients with T2, T3, and T4 bladder cancer were entered on successive prospective protocols: They all received concurrent cisplatin and RT, and 53% underwent a visibly complete TUR before induction therapy. The 10-year disease-specific survival rate in that series was 59% for all patients, and the 10-year intact-bladder survival rate was 45%.

Despite the discouraging results of the RTOG Phase III trial regarding the role of neoadjuvant CT,[12] several investigators from different institutions have reported on protocols that incorporated neoadjuvant CT into a multimodality treatment.[19–21] Danesi et al.[19]

evaluated a schedule of concurrent cisplatin and 5-fluorouracil delivered by protracted intravenous infusion during hyperfractionated RT. In that series, 42 of 77 patients also received neoadjuvant CT. A CR rate of 90.3%, the highest ever reported, was achieved, and the 5-year bladder-intact survival rate was within the range reported by others. George et al.[20] described the outcome of 60 patients who were treated with TUR plus RCT, including 22 patients who also received neoadjuvant CT. When those patients were stratified according to stage and grade, patients with T2 and T3 tumors had a statistically significant better chance of remaining relapse-free. This finding accords with our findings that T classification, together with resection status after TUR, had the strongest impact on overall survival. More recently, Cobo et al.[21] reported on 29 patients who underwent TUR and received neoadjuvant CT and RCT followed by consolidation RT when a CR was achieved. Again, those investigators reported that early-stage disease and initial complete resection were predictive of the best outcome.

The optimal regimen and combination of RT and CT remain to be established. The introduction of new drugs may improve disease control after TUR and RCT. One such drug may be gemcitabine, because it is active in bladder cancer, has a synergistic effect with cisplatin, and acts as a radiosensitizer.[22]

Salvage treatment plays an important role in any bladder-preserving treatment approach. In our series, we evaluated response 6 weeks after the completion of RCT by restaging TUR. In other studies, response was assessed much earlier, after approximately 40 Gy of induction therapy. Both strategies have theoretic advantages.

The intention of the early response evaluation is to select nonresponders as early as possible. The underlying assumption is that the curative potential of cystectomy may decrease in nonresponders if cystectomy is delayed for weeks. The effect of delaying cystectomy in patients with chemoresistant or radioresistant disease and the extent to which local recurrence affects overall survival are unknown. However, for individual patients, the obvious immediate benefit that bladder preservation offers needs to be weighed against the risk of uncontrolled pelvic disease or recurrence. In this scenario, it is not possible to quantify the impact on the outcome of surgical wait times for patients undergoing salvage cystectomy. Of course, several reports have supported the idea that delays are associated with a worse outcome, suggesting that there is a window of opportunity <12 weeks after the diagnosis of invasive disease to radical cystectomy.[23]

The late response evaluation may increase the chance of bladder preservation, because some slow responders whose tumors have not yet regressed completely after 40 Gy of radiation may retain their bladders if the response evaluation is delayed. We also chose this latter approach, because the patients in our study were not undergoing surgery based on personal choice.

Of all patients who undergo multimodality treatment, approximately 15% to 30% present with residual tumor at restaging TUR, and an additional 20% to 30% of complete responders will develop de novo or recurrent tumor in the preserved bladder. Approximately 50% of these persistent or recurrent tumors are superficial and can be managed successfully by conservative surgery in combination with intravesical therapy.[24]

Persistent or recurrent, muscle-invasive tumors require salvage cystectomy. In the Erlangen series, 83 of 415 patients (20%) underwent salvage cystectomy—37% of noncomplete responders and 15% of patients with an initial CR who experienced a local relapse. Disease-specific survival rates at 5 years and 10 years for patients who underwent salvage cystectomy were 51% and 45%, respectively.[8] Overall, 20.2% of our patients underwent salvage cystectomy, and the disease-specific survival rate at 5 years for patients who underwent salvage cystectomy for an invasive relapse was 50%. This rate decreased to 28.5% for nonresponding patients who underwent immediate cystectomy ($P = .002$). Thus, close follow-up of patients after organ-preserving treatment clearly is indicated to allow for a second curative approach.

The most obvious reason for the establishment of bladder-preservation strategies is to avoid surgical removal of the bladder and the associated reduction in QoL, notwithstanding the finding that improvements in surgical technique and, mainly, the introduction of the orthotopic neobladder into clinical routine have weakened this argument. After multimodality treatment, approximately 40% of patients will survive with the bladder intact. However, many urologists believe that an irradiated bladder is worthless functionally, because it is prone to bleeding and contracture. In reported series, cystectomy for bladder contracture has been rare: 2% of patients in the Erlangen series[8] and none in the Massachusetts General Hospital series.[17] The majority of patients in our series have retained good bladder function and QoL, as also reported by Zietman et al.,[25] who performed functional urodynamic studies in and administered a validated QoL questionnaire to 49 long-term survivors of their trimodality protocols. Still, we believe that the assumption that leaving the native bladder

intact improves patient QoL has not been verified sufficiently.

A substantial proportion of (usually older) patients with bladder cancer patients experience significant side effects of systemic CT. Shipley et al.[12] reported a mortality rate of 4% associated with induction therapy. The RTOG Phase III trial closed prematurely because of the intolerable side effects of systemic CT.[16] Conversely, the mortality rate in contemporary radical cystectomy series has ranged between 1% and 3%.[1] During neoadjuvant CT in our series, 4 patients experienced cardiopulmonary events that delayed or prevented completion of the protocol. Two patients received only 1 cycle of CT because of renal dysfunction or fatigue. Thrombocytopenia and leukopenia were the most frequent toxicities. There were no CT-related deaths. This discrepancy with previously mentioned reports probably is because of the different study populations and CT regimens.

The primary objective of the bladder-sparing approach remains optimal patient survival. Thus, the outcome of the organ-sparing approach needs to be compared with the surgical standard. Unfortunately, primary cystectomy has not been tested against combined-modality treatment in randomized trials. Given et al.[26] suggested that cystectomy may result in better survival. They reported results in 94 patients who were treated with a bladder-sparing approach using combined TUR, 2 to 3 cycles of CT, and 64.8 Gy of RT. The 5-year survival rate in that series was significantly higher in patients who underwent radical cystectomy at some point during follow-up than in patients who had their bladder preserved (65% vs 40%).

In summary, according to currently available data, the question of whether an attempt at bladder preservation may be associated with long-term survival is difficult to answer. First, bladder-preservation strategies are based on a multitude of treatment protocols that continually are modified. Although the data shown in Table 7 indicate that bladder-preserving strategies may be as effective as initial radical surgical approaches in terms of long-term survival, several points need to be addressed. First, only if both treatment options are compared directly can it be determined whether the favorable clinical outcome reported with a multimodality bladder-preserving approach in earlier investigations is because of selection a bias that leads to the inclusion of patients with a less favorable clinical prognosis in cystectomy series.

Second, clinical criteria for selecting patients to undergo bladder preservation include variables like early tumor stage and complete initial TUR. Because of its overwhelming predictive and prognostic impact, a TUR that is as thorough as is safely possible always should be attempted. However, tumor heterogeneity is so great in bladder cancer that conventional histopathologic parameters are inadequate for predicting response. In this setting, translational research to identify markers of tumor response is sorely needed.[2]

Finally, multimodality bladder-preserving strategies are complex, requiring, apart from high patient compliance, close cooperation among several clinical specialties. In most European countries, often, this cooperation is not easy to coordinate.[27] Moreover, it has been postulated that a bladder-preservation strategy is significantly more expensive.[28]

In conclusion, it has been demonstrated that bladder preservation is feasible, even if it necessitates an extremely cautious approach. It is clear that, as more experience with organ-sparing treatment is acquired, clinical and basic research will focus on 2 main topics: optimization of the treatment modality, including the incorporation of new cytotoxic agents; and the selection of patients who are most likely to benefit from the treatment options. Even if radical cystectomy remains the standard of care for muscle-invasive bladder cancer, a combined-modality treatment can be offered as a reasonable option to carefully selected patients.

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