

## Radiochemotherapy After Transurethral Resection for High-Risk T1 Bladder Cancer: An Alternative to Intravesical Therapy or Early Cystectomy?

Christian Weiss, Carolin Wolze, Dirk Gerhard Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, and Claus Rödel

From the Department of Radiation Therapy, Department of Urology, University of Erlangen, Erlangen; and Department of Radiation Therapy, University of Lübeck, Lübeck, Germany.

Submitted January 20, 2006; accepted March 7, 2006.

Presented in part at the 47th Annual Meeting of the American Society of Therapeutic Radiology and Oncology, October 16-20, 2005, Denver, CO.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Claus Rödel, MD, Department of Radiation Therapy, Universitätsstr 27, D-91054 Erlangen, Germany; e-mail: claus.roedel@strahlen.med.uni-erlangen.de.

© 2006 by American Society of Clinical Oncology

0732-183X/06/2415-2318/\$20.00

DOI: 10.1200/JCO.2006.05.8149

### A B S T R A C T

#### Purpose

For high-risk T1 bladder cancer, the most important issue is how to restrict radical cystectomy to selective patients with a high likelihood of tumor progression and to choose an initial bladder-sparing approach in others without affecting survival. Radiotherapy or radiochemotherapy (RT/RCT) may help to strike a balance between intravesical treatment and early cystectomy.

#### Patients and Methods

Between 1982 and 2004, 141 patients with high-risk T1 bladder cancer (84 patients with T1 grade 3 [T1G3]; others with T1G1/2 and associated carcinoma-in-situ, multifocality, tumor diameter > 5 cm, or multiple recurrences) were treated with RT (n = 28) or platinum-based RCT (n = 113) after transurethral resection of bladder tumor (TURBT). Six weeks after RT/RCT, response was evaluated by restaging TURBT. Salvage cystectomy was recommended for patients with persistent disease and for tumor progression after initial complete response (CR). Median follow-up was 62 months; 65 patients have been observed for 5 years or more.

#### Results

CR was achieved in 121 of 137 patients (88%; four patients without restaging TURBT). Tumor progression for the entire group of 141 patients was 19% and 30% at 5 and 10 years, respectively (for 121 patients with CR, 15% and 29%; for 84 patients with T1G3, 13% and 29%, respectively). Disease-specific survival rates were 82% and 73% at 5 and 10 years (CR, 89% and 79%; T1G3, 80% and 71%, respectively). More than 80% of survivors preserved their bladder; 70.4% were "delighted" or "pleased" with their urinary function.

#### Conclusion

RT/RCT after TURBT with selective bladder preservation is a reasonable alternative to intravesical treatment or early cystectomy for high-risk T1 bladder cancer.

*J Clin Oncol* 24:2318-2324. © 2006 by American Society of Clinical Oncology

### INTRODUCTION

Management of high-grade transitional cell carcinoma involving the lamina propria (stage T1) but not penetrating into the muscularis propria represents a challenge for the treating physician. With transurethral resection of the bladder tumor (TURBT) alone, the risk of recurrence for this group of patients approaches 80% and the risk of progression to muscle-invasive disease is 50% to 65%.<sup>1</sup> Adjuvant intravesical therapy with Bacille Calmette-Guérin (BCG) or chemotherapeutic agents, such as mitomycin, may decrease the overall recurrence rate by approximately 30% compared with TURBT alone. However, tumor progression still occurs in 15% to 40% within the first 5 years, and these patients are at risk of dying from urothelial cancer.<sup>2</sup>

Thus, several groups have recommended immediate cystectomy without a trial of intravesical treatment to prevent any risk of progression.<sup>3-6</sup> Five-year disease-specific survival (DSS) rates in the range of 70% to 90% have been achieved with this radical approach; however, the morbidity and mortality associated with cystectomy are still in the range of 20% and 1% to 4%, respectively, and quality of life is altered despite techniques of orthotopic bladder reconstruction. It is evident that undertreatment and overtreatment are critical and controversial issues for this group of patients.<sup>7</sup>

It is our hypothesis that radiotherapy (RT) with or without chemotherapy may be more effective in preventing tumor progression than standard intravesical treatment, and that this approach may also help to select nonresponding patients at high risk for

tumor progression for salvage cystectomy at an early time point. It has been the ongoing policy at the University of Erlangen (Erlangen, Germany) to use RT or radiochemotherapy (RT/RCT) after TURBT with selective bladder preservation for high-risk T1 bladder cancer since 1982.<sup>8-10</sup> We now present the long-term result of this approach in a group of 141 patients with a median follow-up of 62 months.

## PATIENTS AND METHODS

### Patient Characteristics

Between September 1982 and December 2004, a total of 141 patients with primary or recurrent high-risk T1 bladder cancer were treated with either RT alone (n = 28) or concomitant RCT (n = 113) after initial TURBT. Risk factors for T1 tumors were defined as high grade (grade 3), associated carcinoma in situ (Tis), multifocal lesions, tumor diameter more than 5 cm, or tumors refractory to repeated TURBT with or without intravesical therapy. Patient and tumor characteristics are listed in Table 1. Patients were informed both by the treating urologists and the radiotherapists about treatment alternatives (ie, intravesical treatment or early cystectomy), and gave informed consent to undergo RCT. This series included patients unfit for cystectomy because of advanced age or comorbidities, as well as patients refusing radical surgery.

### Treatment Protocol

Treatment was commenced by TURBT aimed at maximal, complete resection (if feasible) of the tumor mass. Residual tumor was assessed histologically by biopsies from all resection margins: R0 indicated a visibly and microscopically complete TURBT, R1 indicated microscopic residual tumor, and R2 indicated macroscopic residual tumor. Additional evaluation included

chest radiography and computed tomography of the abdomen and pelvis. RT was initiated 4 to 6 weeks after initial TURBT using 6- to 10-MV photons and a four-field box technique with individually shaped portals and daily fractions of 1.8 to 2 Gy on 5 consecutive days. A median dose of 55.8 Gy (range, 45.0 to 61.4 Gy) was applied to the bladder. Pelvic nodes were irradiated with a median dose of 50.4 Gy (range, 36.0 to 54.1 Gy). Since October 1985, chemotherapy has been given simultaneously for 5 consecutive days during the first and fifth week of RT. Forty-three patients received cisplatin 25 mg/m<sup>2</sup>/d; in 16 patients with decreased creatinine clearance (< 50 mL/min), carboplatin 65 mg/m<sup>2</sup>/d was administered. Since 1993, 54 patients were treated with a combination of cisplatin or carboplatin and fluorouracil 600 mg/m<sup>2</sup>/d. A total of eight patients also received deep regional hyperthermia within an ongoing phase II study.

### Assessment of Response, Local Control, Late Toxicity, and Quality of Life

Six weeks after completion of RT/RCT, treatment response was evaluated by cystoscopy and deep TURBT of the former tumor site(s). Patients with persistent tumor were considered nonresponders. For histologically proven complete response (CR) and negative urine cytology, patients were observed at 3-month intervals for the first 2 years and every 6 months thereafter. Evaluation consisted of pertinent medical history, physical examination, CBC and blood chemistry, urine cytology, and cystoscopy and biopsies of all areas suggestive of disease. For persistent tumor after RT/RCT or tumor recurrence after CR, patients received additional treatment such as TURBT plus intravesical treatment or salvage cystectomy. Evaluation of late treatment-related toxicity was performed according to the grading system of late effects of normal tissue.<sup>11</sup> Quality of life due to urinary symptoms for patients alive and with their bladder preserved was assessed using the International Prostate Symptom Score.<sup>12</sup>

**Table 1.** Prognostic Factors for CR, Overall Failure and Progression Rates, and Disease-Specific Survival Rates

Factor	No. of Patients	CR at Restaging TURBT (%) <sup>*</sup>		Overall Failure Rate at 5 Years		Progression Rate at 5 Years		Disease-Specific Survival at 5 Years	
		%	P	%	P	%	P	%	P
All patients	141	88		49		19		82	
Age									
≥ median	71	82		54	.26	19		69	
< median	70	90	.52	46		18	.88	91	.002
Male	123	84		50		19		83	
Female	18	100	.18	47	.28	18	.38	78	.94
Primary tumor	91	89		46		18		82	
Recurrent tumor	50	80	.34	54	.46	21	.89	83	.53
Grading									
T1G1/2†	57	80		70		28		84	
T1G3	84	89	.09	35	.006	13	.42	80	.66
Associated Tis									
Yes	48	83		41		13		80	
No	93	87	.74	54	.81	22	.99	82	.95
Multifocal tumor									
Yes	73	84		54		22		80	
No	68	88	.58	43	.21	17	.52	82	.32
R status after TURBT									
R0	79	91		42		14		88	
R1	37	89		52		15		75	
R2	14	50	.001	83	.0003	51	.08	62	.07
RX	11	82		27		9		100	
RT alone	28	82		64		37		68	
RCT	113	87	.97	46	.16	14	.09	85	.03

Abbreviations: CR, complete response; TURBT, transurethral resection of bladder tumor; Tis, carcinoma in situ; RT, radiotherapy; RCT, radiochemotherapy.

<sup>\*</sup>Four patients without restaging TURBT (n = 137).

<sup>†</sup>With risk factors, such as associated Tis, multifocality, tumor diameter > 5 cm, multiple recurrences.

## Statistics

At the time of analysis, the median follow-up for all 141 patients was 62 months (range, 5.8 to 233.3); 65 patients have been observed for 5 years or more, and 31 patients have been observed for 10 years or more. The definition of overall failure of TURBT plus RT/RCT was any persistent tumor after RT/RCT and any local or distant relapse after CR. Tumor progression was considered as muscular invasion ( $\geq T2$ ) in the bladder, or any evidence of pelvic lymph node involvement or distant metastases. Actuarial rates of overall failures, tumor progression, and survival were calculated from the time of initial TURBT to the time of the respective end point, the last follow-up visit, or death using the method of Kaplan and Meier. Differences were analyzed using the log-rank test. The  $\chi^2$  test (two tailed) was used to determine statistical significance between proportions for the end point CR after RT/RCT. Level of significance was .05 (two sided) in all of the statistical testing.

## RESULTS

### Response to RT/RCT at Restaging TURBT

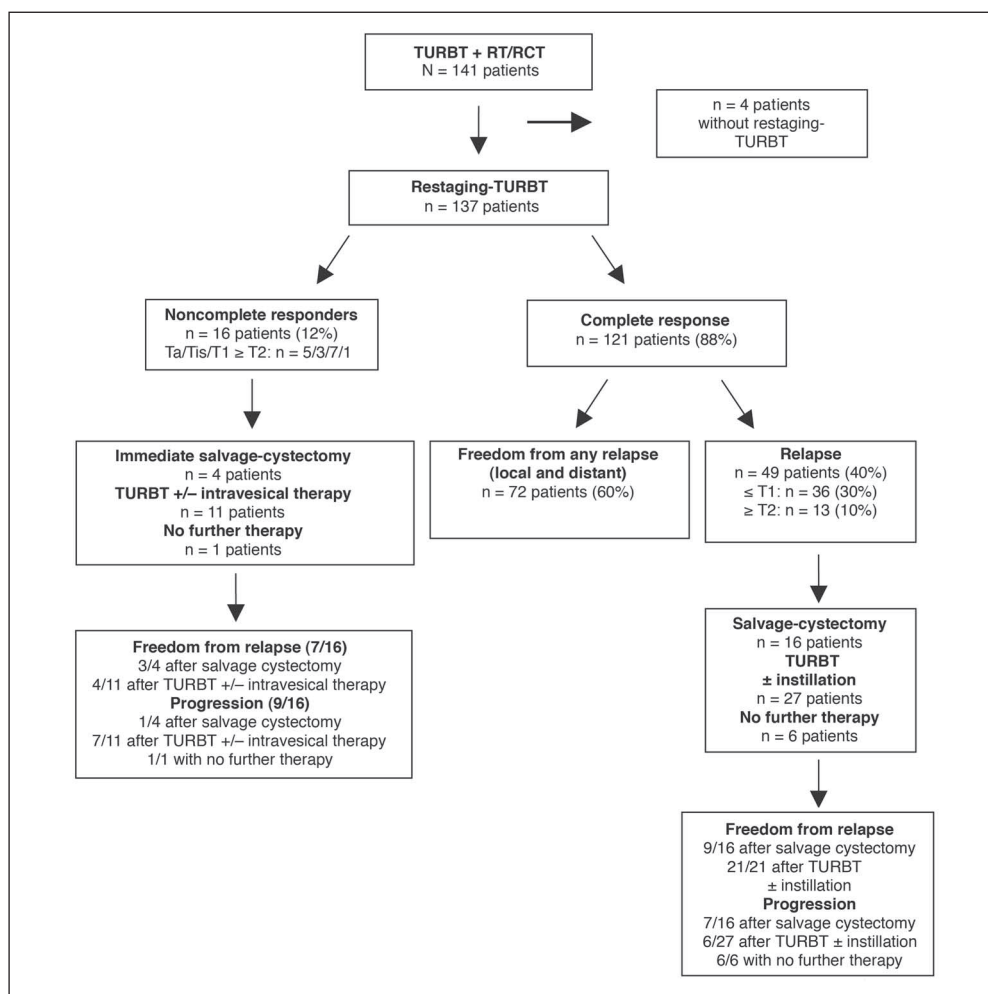
A CR at restaging TURBT was achieved in 121 of 137 patients (88%; Fig 1). Four patients did not undergo restaging TURBT due to noncompliance<sup>2</sup> or advanced age/comorbidity,<sup>2</sup> but additional follow-up for these patients was available (two were free of tumor, one experienced disease progression, one died as a result of unrelated disease). Fifteen patients had persistent tumor (Ta, five patients; Tis, three patients;

T1, seven patients), and in one patient tumor progression (distant metastases) was detected at the time of restaging TURBT. If analysis is restricted to patients with T1 grade 3 (T1G3;  $n = 84$ ), the CR rate was 89% (Table 1). The only significant predictive factor for CR was the completeness (R status) of the initial TURBT ( $P < .001$ ; Table 1).

### Salvage Treatment for Persistent and Recurrent Disease

For nonresponders, salvage cystectomy was performed in four patients with persistent Ta (two patients) or T1 (two patients) tumor, three of whom remained tumor free for 121, 150, and 187 months, respectively, and one of whom died as a result of urothelial cancer 43 months after cystectomy (Fig 1). For the remaining 11 patients with residual tumor, TURBT with or without intravesical therapy resulted in long-term local control in four patients (Tis, three patients; T1, one patient); in seven patients (Ta, three patients; T1, four patients), disease progression occurred at further follow-up. Thus, for nonresponders, salvage treatment was successfully applied in seven of 16 patients (44%), tumor progression occurred in 56%, and eight patients died as a result of urothelial cancer (in one patient, the cause of death was unknown).

Among the 121 patients with CR at restaging TURBT, 72 (60%) have been continuously free of tumor, 36 patients (30%) experienced



**Fig 1.** Initial response, local control, and salvage treatment after transurethral resection of bladder tumor (TURBT) and radiotherapy or radiochemotherapy (RT/RCT) in 141 patients with high-risk T1 bladder cancer.

a  $\leq$  T1 tumor relapse, and 13 patients (10%) had tumor progression (Fig 1). Nine of 36 patients with a  $\leq$  T1 relapse, and seven of 13 patients with muscle-invasive relapse ( $\geq$  T2) received salvage cystectomy. Nine of these 16 patients (56%) remained free of tumor, six (37.5%) ultimately experienced disease progression and died as a result of distant metastases, and one patient died with unknown tumor status. A total of 27 patients were treated with TURBT with or without intravesical therapy; 21 patients (78%) remained tumor free at additional follow-up, and six patients (22%) showed progressive disease and died as a result of bladder cancer. Thus, for the 49 patients with tumor recurrence after CR, salvage treatment was successfully applied in 30 patients (61%), tumor progression occurred in 19 patients (39%), and 18 patients died as a result of urothelial cancer.

### Overall Failure Rates and Tumor Progression

Overall failure rates for the entire group of 141 patients (defined as any evidence of persistent tumor or tumor recurrence after CR) was 49% and 64% at 5 and 10 years, respectively (Fig 2). If the analysis was restricted to 84 patients with T1G3, the figures were 35% and 46% at 5 and 10 years, respectively. The overall failure rates for patients with CR after RT/RCT were 44% and 61% at 5 and 10 years, respectively. The completeness of initial TURBT and tumor grade were the only significant prognostic factors for overall failure rates (Table 1).

Tumor progression for the entire group of 141 patients was 19% and 30% at 5 and 10 years, respectively. In 84 patients with T1G3, the figures were 13% and 29% at 5 and 10 years, respectively. For 121 patients with CR, tumor progression occurred in 15% and 28% at 5 and 10 years, respectively (Fig 2). None of the factors analyzed significantly predicted tumor progression (Table 1).

### DSS, Overall Survival, and Bladder Preservation

Of the 59 deaths that occurred during follow-up, 27 were related to urothelial cancer and 30 were related to other causes; in two patients the cause of death was unknown (but was regarded as an event for DSS). DSS and overall survival (OS) rates for all 141 patients were 82%

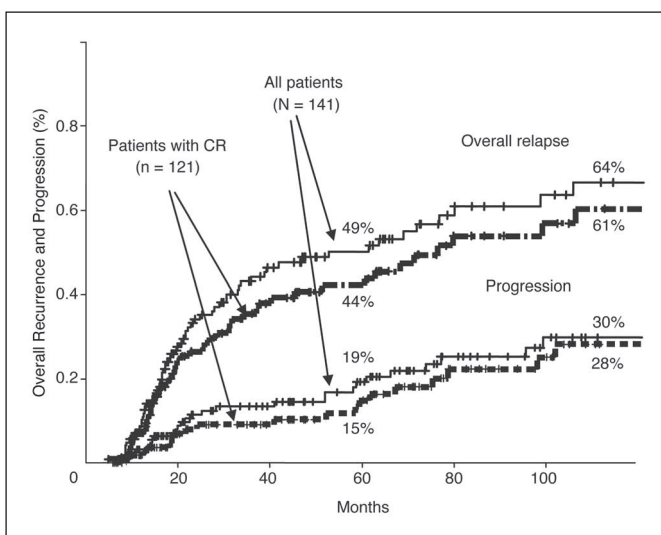
and 71% at 5 years, and 73% and 51% at 10 years, respectively (Fig 3). Of all surviving patients, more than 80% preserved their bladder. DSS and OS for patients with T1G3 cancer were 80% and 64% at 5 years, and 71% and 47% at 10 years, respectively. For patients with CR, DSS and OS figures were 89% and 75%, and 79% and 53% at 5 and 10 years, respectively.

### Toxicity and Quality of Life Due to Urinary Symptoms

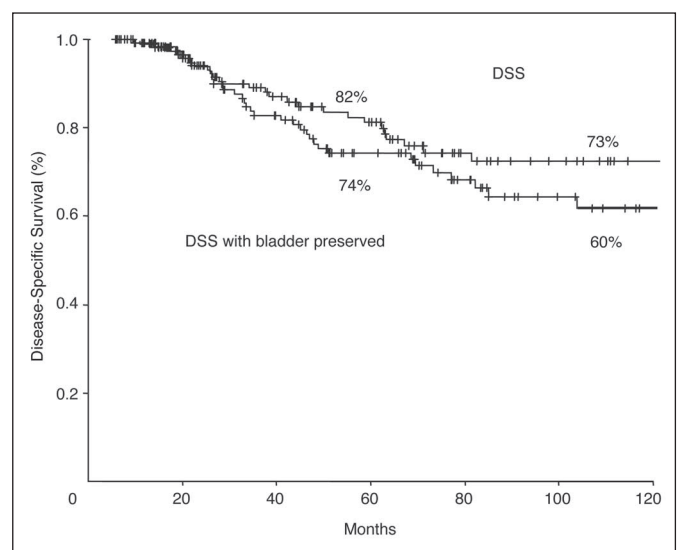
Grade 3 and 4 acute toxicity due to RT/RCT were restricted to 23% of patients with diarrhea, 4% with nausea/vomiting, and 20% with leucopenia. No treatment-related death occurred. The percentages of patients with chronic sequelae are listed in Table 2. Two patients underwent cystectomy because of a shrinking bladder and another two patients required surgical intervention due to intestinal obstruction. Seventy-one of 72 patients alive with their bladder preserved completed the quality-of-life questionnaire due to urinary symptoms of the International Prostate Symptom Score (Table 3): 50 patients (70.4%) were "delighted" or "pleased" with their urinary condition. Forty-four of these 50 patients (88%) have been free of tumor continuously. In the group of patients less content with their urinary condition ( $n = 21$ ), 12 patients (57%) had experienced a superficial tumor relapse and had received additional TURBT with ( $n = 6$ ) or without ( $n = 6$ ) intravesical BCG.

## DISCUSSION

Urothelial cancers are sensitive to radiation. The rationale to use RT/RCT as a treatment component in high-risk T1 bladder cancer arises from the proven efficacy of this approach in more advanced disease. Several groups have reported excellent results of combined-modality treatment, including TURBT, RT, and concomitant chemotherapy in muscle-invasive bladder cancer.<sup>13,14</sup> With these programs, cystectomy has been reserved for patients with incomplete response or local relapse after trimodality treatment. In patients with high-risk T1 disease, the most important issue is how to restrict radical cystectomy



**Fig 2.** Overall recurrence and progression ( $\geq$  T2; N1, M1) for all 141 patients with high-risk T1 bladder cancer, and for 121 patients with complete response (CR) after transurethral resection of bladder tumor and radiotherapy or radiochemotherapy.



**Fig 3.** Disease-specific survival (DSS) and DSS with preserved bladder for 141 patients with high-risk T1 bladder cancer after transurethral resection of bladder tumor and radiotherapy or radiochemotherapy.

**Table 2.** Late Toxicity According to LENT/SOMA

Grade	No. of Patients With Late Toxicity	Total No. of Patients	%
4			
Salvage-cystectomy due to contracted bladder	2	121	1.6
Bowel obstructions requiring surgical intervention	2	141	1.4
3			
Reduced bladder capacity (100-200 mL) with < 2-h intervals of micturition	11	121	9
2			
Frequency with urgency and nocturia	22	121	18
Dysuria, intermittent and tolerable	17	121	14
Moderate diarrhea	19	141	13
Proctitis	3	141	2

Abbreviation: LENT/SOMA, Late Effects of Normal Tissue/Subjective, Objective, Management and Analytic scales.

\*For GI toxicity, the entire cohort of 141 patients was considered; for bladder toxicity, patients with preserved bladder were evaluated (n = 121).

to selective patients with a high risk of tumor progression, and to choose an initial bladder-sparing approach in others without affecting survival. For most patients, initial management involves TURBT, and intravesical immunotherapy or chemotherapy.

The initial diagnosis of T1 disease is associated with significant understaging errors of as much as 25% to 40%.<sup>1</sup> Moreover, in approximately 5% of correctly staged pT1 lesions and in up to 36% of nonmuscle-invasive bladder cancer upstaged to  $\geq$  pT2 after radical cystectomy, pelvic lymph node metastases have been detected.<sup>15,16</sup> It is evident that tumor cell deposits in the muscle layer and in pelvic lymph nodes are not treated adequately with intravesical therapy, which may also explain the observation that intravesical BCG and mitomycin mainly reduce the risk of superficial recurrences but not the risk of tumor progression. Given that with RT/RCT, deeper cell deposits and pelvic lymph nodes are located within the treatment volume, RT should exert certain advantages over intravesical instillation therapy.

In our series of 141 high-risk T1 bladder cancer patients, tumor progression occurred in 19% at 5 years and 30% at 10 years. If this analysis was restricted to T1G3 patients, the progression rate was 13% at 5 years and 29% at 10 years, which compares favorably to most contemporary series of T1G3 patients treated with standard BCG (Table 4). The DSS rate for the entire group of 141 patients was 82% at 5 years and 70% at 10 years. These figures are in the same range as a primary cystectomy series in T1 bladder cancer (62% to 90% at 5 years).<sup>3-6</sup> However, in our series, more than 80% of the surviving patients preserved their bladder, and more than 70% were "delighted" or "pleased" with their urinary function.

A total of 18 patients (13%) died as a result of distant metastases in our series (and an additional nine patients [6%] died as a result of

urothelial cancer, but the exact tumor location was not documented). These figures are in the same range as those reported in primary cystectomy series for superficial bladder cancer. Madersbacher et al<sup>26</sup> reported that 27% of patients with histopathologically confirmed pTa/pTis/pT1 bladder cancer developed distant metastases in their series of radical cystectomy within a median follow-up time of 31 months. The largest cystectomy series, studied by Stein et al,<sup>27</sup> comprising 1,054 patients included 208 patients with stage pT1 tumors. The recurrence-free survival rates at 5 and 10 years were 80% and 75%, respectively.

Although the progression rate was low in our series, it also became evident that about half of all patients either did not achieve a CR (12%) or experienced recurrence during follow-up. This was true well beyond 5 years. In a series studied by Herr,<sup>28</sup> tumor progression in patients with T1G3 bladder cancer treated with or without BSG occurred in 35% within the first 5 years, in 16% after 5 to 10 years, and in 12% of those observed for 10 to 15 years. Thus, close and lifelong surveillance and adequate treatment for these patients is of utmost importance. For patients with residual tumor at restaging TURBT, we generally recommend immediate salvage cystectomy regardless of (residual) tumor stage. Given that restaging is scheduled 6 weeks after completion of RT/RCT, patients with persistent, nonresponding cancer may thus be selected for radical surgery at an early point of time. This approach was successful in three of four patients. If, for different reasons (such as patient age, comorbidity, or refusal), salvage cystectomy was not performed, progression and death from urothelial cancer occurred in eight of 12 patients (67%), reflecting the aggressive nature of these RT/RCT-refractory tumors.

For patients with a  $\leq$  T1 tumor relapse after CR, treatment options may include TURBT and intravesical treatment or salvage cystectomy. Zietman et al<sup>29</sup> reported on a series of 199 patients with

**Table 3.** Quality of Life Due to Urinary Symptoms

Delighted	Pleased	Mostly Satisfied	About Equally Satisfied and Dissatisfied	Mostly Dissatisfied	Unhappy	Terrible
16.9%	53.5%	15.5%	12.7%	0%	1.4%	0%

NOTE. Seventy-one of 72 patients alive with their native bladder completed the question: "If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?"



**Table 4.** Results of Contemporary Series of TURBT Plus Intravesical Treatment for T1 Grade 3 Bladder Cancer

Reference	Treatment	No. of Patients	Follow-Up (months)		Recurrence* (%)	Progression* (%)
			Mean	Median		
Kulkarni (2002) <sup>17</sup>	TURBT + BCG	69		45	46	12
Pansadoro (2002) <sup>18</sup>	TURBT + BCG	81		76	33	15
Brake (2000) <sup>19</sup>	TURBT + BCG	44	43	28	27	16
Bogdanovic (2002) <sup>20</sup>	TURBT + BCG	43	52.5		28	16
Soloway (2002) <sup>1</sup>	TURBT + BCG	61	46	37	85	21
Patard (2001) <sup>21</sup>	TURBT + BCG	50	60		52	22
Günlüsoy (2005) <sup>22</sup>	TURBT + BCG	46		61	39	22
Peyromaure (2004) <sup>23</sup>	TURBT + BCG	57		53	42	23
Cheng (2004) <sup>24</sup>	TURBT + BCG/CT	36		45.5	44	25
Shahin (2003) <sup>25</sup>	TURBT + BCG	92		64	70	33
Present study: T1G3	TURBT + RT/RCT	84	63	50	31	16

Abbreviations: TURBT, transurethral resection of bladder tumor; BCG, Bacille Calmette-Guérin; CT, chemotherapy; RT, radiotherapy; RCT, radiochemotherapy.

\*For overall recurrence and progression, crude incidence figures during the respective follow-up times are given in the references. To compare our results with those given in the literature, we also provide crude incidence figures.

muscle-invasive bladder cancer treated with a trimodality approach. Thirty-two of these patients developed Ta/Tis/T1 recurrences and 27 were managed conservatively with TURBT and intravesical therapy. Treatment was generally well tolerated and effective; however, cystectomy finally became necessary in 10 patients (seven for additional superficial recurrences and three for progression). In our analysis, tumor progression occurred in six of 27 patients (22%) after TURBT with or without intravesical therapy. It is clear that salvage cystectomy should be applied as early as possible for any additional superficial relapse and for muscle-invasive disease.

To date, no randomized studies have been published addressing our hypothesis that RT with or without chemotherapy may be as effective as or even superior to standard BCG for high-risk T1 bladder cancer. Our long-term results in this large group of patients suggest that TURBT plus RT/RCT with selective bladder preservation may help to strike a balance between intravesical treatment and immediate cystectomy. A randomized trial comparing the efficacy of BCG versus RCT in preventing tumor recurrence and progression in this group of patients with high-risk T1 bladder cancer would be a major step forward.

## REFERENCES

- Soloway MS, Sofer M, Vaidya A: Contemporary management of stage T1 transitional cell carcinoma of the bladder. *J Urol* 167:1573-1583, 2002
- Smith JA Jr, Labasky RF, Cockett AT, et al: Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and Tis): The American Urological Association. *J Urol* 162:1697-1701, 1999
- Amling CL, Thrasher JB, Frazier HA, et al: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. *J Urol* 151:31-36, 1994
- Freeman JA, Esrig D, Stein JP, et al: Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. *Cancer* 76:833-839, 1995
- Malkowicz SB, Nichols P, Lieskovsky G, et al: The role of radical cystectomy in the management of high grade superficial bladder cancer (PA, P1, PIS and P2). *J Urol* 144:641-645, 1990
- May M, Helke C, Nitzke T, et al: Survival rates after radical cystectomy according to tumor stage of bladder carcinoma at first presentation. *Urol Int* 72:103-111, 2004
- Manoharan M, Soloway MS: Optimal management of the T1G3 bladder cancer. *Urol Clin North Am* 32:133-145, 2005
- Rödel C, Dunst J, Grabenbauer GG, et al: Radiotherapy is an effective treatment for high-risk T1-bladder cancer. *Strahlenther Onkol* 177:82-89, 2001
- Akçetin Z, Todorov J, Tuzel E, et al: Radiochemotherapy after transurethral resection is an effective treatment method in T1G3 bladder cancer. *Anticancer Res* 25:1623-1628, 2005
- Rödel C, Grabenbauer GG, Kuhn R, et al: Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. *J Clin Oncol* 20:3061-3071, 2002
- Rubin P, Constine LS, Fajardo LF, et al: RTOG Late Effects Working Group: Overview—Late Effects of Normal Tissues (LENT) scoring system. *Int J Radiat Oncol Biol Phys* 31:1041-1042, 1995
- Barry MJ, Fowler FJ Jr, O'Leary MP, et al: The American Urological Association symptom index for benign prostatic hyperplasia: The Measurement Committee of the American Urological Association. *J Urol* 148:1549-1557, 1992
- Shipley WU, Kaufman DS, Tester WJ, et al: Overview of bladder cancer trials in the Radiation Therapy Oncology Group. *Cancer* 97:2115-2119, 2003
- Rödel C, Weiss C, Sauer R: Organ preservation by combined modality treatment in bladder cancer: The European perspective. *Semin Radiat Oncol* 15:28-35, 2005
- Ficarra V, Dalpiaz O, Alrabi N, et al: Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma. *BJU Int* 95:786-790, 2005
- Wiesner C, Pfizenmaier J, Faldum A, et al: Lymph node metastases in non-muscle invasive bladder cancer are correlated with the number of transurethral resections and tumour upstaging at radical cystectomy. *BJU Int* 95:301-305, 2005
- Kulkarni JN, Gupta R: Recurrence and progression in stage T1G3 bladder tumour with intravesical bacille Calmette-Guérin (Danish 1331 strain). *BJU Int* 90:554-557, 2002
- Pansadoro V, Emiliozzi P, de Paula F, et al: Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guérin: 18-year experience. *Urology* 59:227-231, 2002
- Brake M, Loertzer H, Horsch R, et al: Long-term results of intravesical bacillus Calmette-Guérin therapy for stage T1 superficial bladder cancer. *Urology* 55:673-678, 2000
- Bogdanovic J, Marusic G, Djovic J, et al: The management of T1G3 bladder cancer. *Urol Int* 69:263-265, 2002
- Patard J, Moudouni S, Saint F, et al: Tumor progression and survival in patients with T1G3 bladder tumors: Multicentric retrospective study comparing 94 patients treated during 17 years. *Urology* 58:551-556, 2001
- Günlüsoy B, Degirmenci T, Arslan M, et al: Recurrence and progression of T1G3 transitional cell carcinoma of the bladder treated with intravesical Bacillus Calmette-Guérin. *Urol Int* 75:107-113, 2005
- Peyromaure M, Zerbib M: T1G3 transitional cell carcinoma of the bladder: Recurrence, progression and survival. *BJU Int* 93:60-63, 2004
- Cheng CW, Chan SF, Chan LW, et al: 15-year experience on intravesical therapy of T1G3 urinary

bladder cancer: A conservative approach. *Jpn J Clin Oncol* 34:202-205, 2004

25. Shahin O, Thalmann GN, Rentsch C, et al: A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: Recurrence, progression and survival. *J Urol* 169:96-100, 2003

26. Madersbacher S, Hochreiter W, Burkhard F, et al: Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 21:690-696, 2003

27. Stein JP, Lieskovsky G, Cote R, et al: Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. *J Clin Oncol* 19:666-675, 2001

28. Herr HW: Tumour progression and survival in patients with T1G3 bladder tumours: 15-year outcome. *Br J Urol* 80:762-765, 1997

29. Zietman AL, Grocela J, Zehr E, et al: Selective bladder conservation using transurethral resection, chemotherapy, and radiation: Management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology* 58:380-385, 2001

## Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

## Author Contributions

**Conception and design:** Karl-Michael Schrott, Rolf Sauer, Claus Rödel

**Administrative support:** Karl-Michael Schrott, Rolf Sauer

**Provision of study materials or patients:** Christian Weiss, Carolin Wolze, Dirk Gerhard Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, Claus Rödel

**Collection and assembly of data:** Christian Weiss, Carolin Wolze, Dirk G. Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, Claus Rödel

**Data analysis and interpretation:** Christian Weiss, Carolin Wolze, Dirk Gerhard Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, Claus Rödel

**Manuscript writing:** Christian Weiss, Carolin Wolze, Dirk Gerhard Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, Claus Rödel

**Final approval of manuscript:** Christian Weiss, Carolin Wolze, Dirk G. Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, Claus Rödel

# JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Vol 24, No 15

C O N T E N T S

May 20, 2006

## Editorials

### **Irinogenetics: What Is the Right Star?**

Federico Innocenti, Everett E. Vokes, and Mark J. Ratain ([see article on page 2237](#)) ..... 2221

### **Is There a Role for the Irreversible Epidermal Growth Factor Receptor Inhibitor EKB-569 in the Treatment of Cancer? A Mutation-Driven Question**

Jose Baselga ([see article on page 2252](#)) ..... 2225

### **A "Bone" Fide Predictor of Metastasis? Predicting Breast Cancer Metastasis to Bone**

Scott L. Kominsky and Nancy E. Davidson ([see article on page 2261](#)) ..... 2227

### **Is Tumor Immunity the Same Thing As Autoimmunity? Implications for Cancer Immunotherapy**

Howard L. Kaufman and Jedd D. Wolchok ([see article on page 2283](#)) ..... 2230

### **Epoetin Alfa and Darbepoetin Alfa Go Head to Head**

David P. Steensma and Charles L. Loprinzi ([see article on page 2290](#)) ..... 2233

## Original Reports

### LUNG CANCER

### **Comprehensive Analysis of *UGT1A* Polymorphisms Predictive for Pharmacokinetics and Treatment Outcome in Patients With Non-Small-Cell Lung Cancer Treated With Irinotecan and Cisplatin**

Ji-Youn Han, Hyeong-Seok Lim, Eun Soon Shin, Yeon-Kyeong Yoo, Yong Hoon Park, Jong-Eun Lee, In-Jin Jang, Dae Ho Lee, and Jin Soo Lee ([see editorial on page 2221](#)) ..... 2237

### **Never-Smokers With Lung Cancer: Epidemiologic Evidence of a Distinct Disease Entity**

Chee-Keong Toh, Fei Gao, Wan-Teck Lim, Swan-Swan Leong, Kam-Weng Fong, Swee-Peng Yap, Anne A.L. Hsu, Philip Eng, Heng-Nung Koong, Agasthian Thirugnanam, and Eng-Huat Tan ..... 2245

### PHASE I AND CLINICAL PHARMACOLOGY

### **Phase I Study of EKB-569, an Irreversible Inhibitor of the Epidermal Growth Factor Receptor, in Patients With Advanced Solid Tumors**

Charles Erlichman, Manuel Hidalgo, Joseph P. Boni, Patricia Martins, Susan E. Quinn, Charles Zacharchuk, Peter Amorosi, Alex A. Adjei, and Eric K. Rowinsky ([see editorial on page 2225](#)) ..... 2252

(continued on following page)

*Journal of Clinical Oncology* (ISSN 0732-183X) is published 36 times a year, three times monthly, by American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Periodicals postage is paid at Alexandria, VA, and at additional mailing offices. Publication Mail Agreement Number 863289.

Editorial correspondence should be addressed to Daniel G. Haller, MD, *Journal of Clinical Oncology*, 330 John Carlyle St, Suite 300, Alexandria, VA 22314. Telephone: (703) 797-1900; Fax: (703) 684-8720. E-mail: [jco@asco.org](mailto:jco@asco.org). Internet: [www.jco.org](http://www.jco.org).

**POSTMASTER:** ASCO members send change of address to American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314. Nonmembers send change of address to *Journal of Clinical Oncology* Customer Service, 330 John Carlyle St, Suite 300, Alexandria, VA 22314.

2006 annual subscription rates, effective September 1, 2005: United States and possessions: individual, \$435; single issue, \$35. International: individual, \$605; single issue, \$45. Institutions: Tier 1: \$615 US, \$870 Int'l; Tier 2: \$715 US, \$970 Int'l; Tier 3: \$1,035 US, \$1,290 Int'l; Tier 4: \$1,140 US, \$1,395 Int'l; Tier 5: contact JCO for a quote. See <http://www.jco.org/subscriptions/tieredpricing.shtml> for descriptions of each tier. Student and resident: United States and possessions: \$215; all other countries, \$300. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Current prices are in effect for back volumes and back issues. Back issues sold in conjunction with a subscription rate are on a prorated basis. Subscriptions are accepted on a 12-month basis. Prices are subject to change without notice. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. JCO Legacy Archive (electronic back issues from January 1983 through December 1998) is also available; please inquire.



## BREAST CANCER

### 📄 ⓘ Genes Associated With Breast Cancer Metastatic to Bone

Marcel Smid, Yixin Wang, Jan G.M. Klijn, Anieta M. Sieuwerts, Yi Zhang, David Atkins, John W.M. Martens, and John A. Foekens (see editorial on page 2227) ..... 2261

### 📄 Study of Failure Pattern Among High-Risk Breast Cancer Patients With or Without Postmastectomy Radiotherapy in Addition to Adjuvant Systemic Therapy: Long-Term Results From the Danish Breast Cancer Cooperative Group DBCG 82 b and c Randomized Studies

Hanne M. Nielsen, Marie Overgaard, Cai Grau, Anni R. Jensen, and Jens Overgaard ..... 2268

### Indium-111–Labeled Trastuzumab Scintigraphy in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer

Patrick J. Perik, Marjolijn N. Lub-De Hooge, Jourik A. Gietema, Winette T.A. van der Graaf, M. Alexander de Korte, Sharon Jonkman, Jos G.W. Kosterink, Dirk J. van Veldhuisen, Dirk T. Sleijfer, Pieter L. Jager, and Elisabeth G.E. de Vries ..... 2276

## TREATMENT-RELATED COMPLICATIONS

### Enterocolitis in Patients With Cancer After Antibody Blockade of Cytotoxic T-Lymphocyte–Associated Antigen 4

Kimberly E. Beck, Joseph A. Blansfield, Khoi Q. Tran, Andrew L. Feldman, Marybeth S. Hughes, Richard E. Royal, Udai S. Kammula, Suzanne L. Topalian, Richard M. Sherry, David Kleiner, Martha Quezado, Israel Lowy, Michael Yellin, Steven A. Rosenberg, and James C. Yang (see editorial on page 2230) ..... 2283

## SUPPORTIVE CARE AND QUALITY OF LIFE

### Randomized Comparison of Every-2-Week Darbepoetin Alfa and Weekly Epoetin Alfa for the Treatment of Chemotherapy-Induced Anemia: The 20030125 Study Group Trial

John Glaspy, Saroj Vadhan-Raj, Ravi Patel, Linda Bosserman, Eddie Hu, Richard E. Lloyd, Ralph V. Boccia, Dianne Tomita, and Greg Rossi (see editorial on page 2233) ..... 2290

### Geriatric Syndromes in Elderly Patients Admitted to an Oncology–Acute Care for Elders Unit

Kellie L. Flood, Maria B. Carroll, Cyndi V. Le, Linda Ball, Debbie A. Esker, and David B. Carr ..... 2298

### ⓘ Comorbidity, Disability, and Geriatric Syndromes in Elderly Cancer Patients Receiving Home Health Care

Siran M. Koroukian, Patrick Murray, and Elizabeth Madigan ..... 2304

### Physical and Emotional Health Effects and Social Consequences After Participation in a Low-Fat, High-Carbohydrate Dietary Trial for More Than 5 Years

T. Gregory Hislop, Chris D. Bajdik, Lynda G. Balneaves, Andrea Holmes, Selina Chan, Evelyn Wu, Zenaida U. Abanto, and Andrea L. Butler ..... 2311

## GENITOURINARY CANCER

### Radiochemotherapy After Transurethral Resection for High-Risk T1 Bladder Cancer: An Alternative to Intravesical Therapy or Early Cystectomy?

Christian Weiss, Carolin Wolze, Dirk Gerhard Engehausen, Oliver J. Ott, Frens S. Krause, Karl-Michael Schrott, Jürgen Dunst, Rolf Sauer, and Claus Rödel ..... 2318

## SARCOMAS

### Surgical Management of Advanced Gastrointestinal Stromal Tumors After Treatment With Targeted Systemic Therapy Using Kinase Inhibitors

Chandrajit P. Raut, Matthew Posner, Jayesh Desai, Jeffrey A. Morgan, Suzanne George, David Zahrieh, Christopher D.M. Fletcher, George D. Demetri, and Monica M. Bertagnoli ..... 2325

(continued on following page)

## HEMATOLOGIC MALIGNANCIES

### **Prognostic Significance of Blasts in the Cerebrospinal Fluid Without Pleiocytosis or a Traumatic Lumbar Puncture in Children With Acute Lymphoblastic Leukemia: Experience of the Dutch Childhood Oncology Group**

D. Maroeska W.M. te Loo, Willem A. Kamps, Anna van der Does-van den Berg, Elisabeth R. van Wering, and Siebold S.N. de Graaf ..... 2332

### **Alemtuzumab As Consolidation After a Response to Fludarabine Is Effective in Purging Residual Disease in Patients With Chronic Lymphocytic Leukemia**

Marco Montillo, Alessandra Tedeschi, Sara Miqueleiz, Silvio Veronese, Roberto Cairoli, Liliana Intropido, Francesca Ricci, Anna Colosimo, Barbara Scarpati, Michela Montagna, Michele Nichelatti, Mario Regazzi, and Enrica Morra ..... 2337

### **Clinical Outcomes and Prognostic Factors in Patients With Richter's Syndrome Treated With Chemotherapy or Chemoimmunotherapy With or Without Stem-Cell Transplantation**

Apostolia-Maria Tsimberidou, Susan O'Brien, Issa Khouri, Francis J. Giles, Hagop M. Kantarjian, Richard Champlin, Sijin Wen, Kim-Anh Do, Susan C. Smith, Susan Lerner, Emil J. Freireich, and Michael J. Keating ..... 2343

## PEDIATRIC ONCOLOGY

### **Treatment of Anaplastic Histology Wilms' Tumor: Results From the Fifth National Wilms' Tumor Study**

Jeffrey S. Dome, Cecilia A. Cotton, Elizabeth J. Perlman, Norman E. Breslow, John A. Kalapurakal, Michael L. Ritchey, Paul E. Grundy, Marcio Malogolowkin, J. Bruce Beckwith, Robert C. Shamberger, Gerald M. Haase, Max J. Coppes, Peter Coccia, Morris Kletzel, Robert M. Weetman, Milton Donaldson, Roger M. Macklis, and Daniel M. Green ..... 2352

## GASTROINTESTINAL CANCER

### **Immunohistochemical Test for MLH1 and MSH2 Expression Predicts Clinical Outcome in Stage II and III Colorectal Cancer Patients**

Giovanni Lanza, Roberta Gafà, Alessandra Santini, Iva Maestri, Laura Guerzoni, and Luigi Cavazzini ..... 2359

### **Duration of Adjuvant Chemotherapy for Colon Cancer and Survival Among the Elderly**

Alfred I. Neugut, Matthew Matasar, Xiaoyan Wang, Russell McBride, Judith S. Jacobson, Wei-Yann Tsai, Victor R. Grann, and Dawn L. Hershman ..... 2368

## GYNECOLOGIC CANCER

### **HER-2 Is an Independent Prognostic Factor in Endometrial Cancer: Association With Outcome in a Large Cohort of Surgically Staged Patients**

Carl Morrison, Vanna Zanagnolo, Nilsa Ramirez, David E. Cohn, Nicole Kelbick, Larry Copeland, Larry G. Maxwell, and Jeffrey M. Fowler ..... 2376

## Diagnosis in Oncology

### **Metachronous Intracranial Germinoma in a Patient With a Previous Primary Mediastinal Seminoma**

Pablo M. Bedano, Jose Bonnin, and Lawrence H. Einhorn ..... 2386

### **Intravascular Hemolysis As a Complication of Clostridium Perfringens Sepsis**

Heather L. McArthur, Bakul I. Dalal, and Christian Kollmannsberger ..... 2387

### **Paraneoplastic Erythropoietin-Induced Polycythemia Associated With Small Lymphocytic Lymphoma**

Abdulwahab J. Al-Tourah, Peter W.K. Tsang, Brian F. Skinnider, and Paul J. Hoskins ..... 2388

### **Tumor Lysis Syndrome After Treatment With Docetaxel for Non-Small-Cell Lung Cancer**

Daniel Ajzensztejn, Vinayak S. Hegde, and Siow Ming Lee ..... 2389

(continued on following page)

## Correspondence

### **Effect of Tamoxifen After Chemotherapy in Hormone Receptor–Positive, Node–Negative Breast Cancer**

Lawrence C. Panasci ..... 2392

#### **In Reply**

Laura F. Hutchins and Stephanie J. Green ..... 2392

### **Myeloid Toxicity in Breast Cancer Patients Receiving Adjuvant Chemotherapy With Pegfilgrastim Support**

Antonio C. Wolff, Richard J. Jones, Nancy E. Davidson, Stacie C. Jeter, and Vered Stearns ..... 2392

#### **In Reply**

Harold J. Burstein ..... 2394

### **Aggressive Surgery and Ovarian Cancer**

Dennis S. Chi and Richard R. Barakat ..... 2395

#### **In Reply**

Simon C. Crawford, Jim Paul, Stan B. Kaye, Paul A. Vasey, Jo A. Davis, and Andrea Hay ..... 2396

### **Importance of Surgical Aggressiveness in Advanced Ovarian Cancer**

Giovanni D. Aletti and William A. Cliby ..... 2397

#### **In Reply**

Simon C. Crawford, Jim Paul, Stan B. Kaye, Paul A. Vasey, Jo A. Davis, and Andrea Hay ..... 2398

### **Acute Chemotherapy-Induced Cardiovascular Changes in Patients With Testicular Cancer: Are There Implications for Blood Pressure Management in Patients Receiving Chemotherapy?**

Sadhna Kohli and Manish Kohli ..... 2399

#### **In Reply**

Esther C. de Haas, Janine Nuver, Andries J. Smit, Dirk Th. Sleijfer, and Jourik A. Gietema ..... 2399

**Erratum** ..... 2401

**Expressions of Concern** ..... 2404

## Also in This Issue

**Announcements**

**Information for Contributors**

**Current Abstracts**

**Calendar of Oncology Events**



Online supplementary information available at [www.jco.org](http://www.jco.org)



Article was published online ahead of print at [www.jco.org](http://www.jco.org)

[www.jco.org](http://www.jco.org)

[www.asco.org](http://www.asco.org)