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Tumor Regression Grade of Urothelial Bladder Cancer After Neoadjuvant Chemotherapy

A Novel and Successful Strategy to Predict Survival

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Abstract: Histopathologic tumor regression grades (TRGs) after neoadjuvant chemotherapy predict survival in different cancers. In bladder cancer, corresponding studies have not been conducted. Fifty-six patients with advanced invasive urothelial bladder cancer received neoadjuvant chemotherapy before cystectomy and lymphadenectomy. TRGs were defined as follows: TRG1: complete tumor regression; TRG2: >50% tumor regression; TRG3: 50% or less tumor regression. Separate TRGs were assigned for primary tumors and corresponding lymph nodes. The prognostic impact of these 2 TRGs, the highest (dominant) TRG per patient, and competing tumor features reflecting tumor regression (ypT/ypN stage, maximum diameter of the residual tumor) were determined. Tumor characteristics in initial transurethral resection of the bladder specimens were tested for response prediction. The frequency of TRGs 1, 2, and 3 in the primary tumors were n = 16, n = 19, and n = 21; corresponding data from the lymph nodes were n = 31, n = 9, and n = 16. Interobserver agreement in determination of the TRG was strong ($\kappa = 0.8$). Univariately, all evaluated parameters were significantly ($P \leq 0.001$) related to overall survival; however, the segregation of the Kaplan-Meier curves was best for the dominant TRG. In multivariate analysis, only dominant TRG predicted overall survival independently ($P = 0.035$). In transurethral resection specimens of the chemotherapy-naive bladder cancer, the only tumor feature with significant ($P < 0.03$) predictive value for therapy response was a high proliferation rate. In conclusion, among all parameters reflecting tumor regression, the dominant TRG was the only independent risk factor. A favorable chemotherapy response is associated with a high proliferation rate in the initial chemotherapy-naive bladder cancer. This feature might help personalize neoadjuvant chemotherapy.

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In patients with muscle-invasive bladder cancer, the 5-year survival rate after cystectomy and pelvic lymphadenectomy is 50%.[1,2] To improve this result, neoadjuvant chemotherapy has been explored, which shows a survival benefit of 5% to 7% at 5 years in meta-analysis.[3] In 2011, the long-awaited mature results of the randomized Medical Research Council/European Organisation for the Treatment and Cure of Cancer trial validated that neoadjuvant chemotherapy significantly increased survival of bladder cancer patients.[4] These data should shift the paradigm toward routinely administered neoadjuvant chemotherapy before surgery in muscle-invasive bladder cancer, as stated by Bajorin and Herr.[5] Consequently, as the number of bladder cancers treated in this manner will increase significantly in the near future, the challenge will be to define prognostic and predictive features in surgical specimens of these tumors. Previous studies[6–9] have used the ypTNM stages[10] in cystectomy specimens as a parameter for tumor response to neoadjuvant chemotherapy and to predict survival. However, tumor regression grades (TRGs), which quantify the histopathologic extent of tumor response to chemotherapy, have shown stronger prognostic impact than the ypTNM stages in rectal[11,12] and esophageal[13–16] cancers. In bladder cancer, these studies are missing and features of the initial chemotherapy-naive tumors that predict regression are unknown.

The aim of the present study was to define histopathologic TRGs for urothelial bladder cancer, to determine their prognostic relevance, and to correlate histopathologic characteristics of the initial tumor in the transurethral resection of the bladder (TURB) specimens with tumor response.

MATERIALS AND METHODS

Patients and Follow-up

From January 2000 to August 2011, 621 consecutive patients with muscle-invasive urothelial cancer of the

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bladder underwent cystectomy with standardized bilateral extended pelvic lymphadenectomy as a single procedure at the Department of Urology, University of Bern. Staging after initial diagnosis included chest x-ray, bone scan, and computed tomography scan of the abdomen and pelvis in all patients. Radiologically, lymph node metastasis was presumed in the presence of pathologically enlarged lymph nodes >1 cm in diameter. Whenever enlarged lymph nodes were accessible to needle biopsy, histologic/cytologic proof was obtained. Fifty-six patients (15 women, 41 men) received neoadjuvant chemotherapy because of locally advanced primary tumors (cT4, n = 15), radiologic suspicion of lymph node metastases (n = 39; 21 confirmed by biopsies), or other reasons (n = 2). All patients underwent cystectomy with standardized bilateral extended pelvic lymphadenectomy in curative intent as a second procedure 6 weeks after termination of the chemotherapy. Follow-up was done according to a standard protocol at 3 and 6 months postoperatively, then at 6-month intervals until 5 years and yearly thereafter.

Neoadjuvant Chemotherapy

In all cases, the recommendation for neoadjuvant chemotherapy was made by a multidisciplinary tumor board. The standard treatment consisted of a median of 4 (range, 1 to 6) cycles of cisplatin and gemcitabine (n = 47). In patients with cisplatin contraindications (creatinine clearance <60 mL/min, poor performance status, clinically relevant hearing loss or tinnitus, neuropathy), carboplatin was used (n = 8). One patient received 4 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC).

Surgical Technique

Pelvic lymph nodes were uniformly dissected as previously described.[17] In short, all lymphatic and connective tissues were meticulously removed bilaterally from the external iliac region up to the crossing of the ureter with the commune vessels, from the obturator fossa and the internal iliac region. The dissected tissue, fixed separately in neutral buffered formalin (4%), was submitted for pathologic evaluation. The protocol of the cystectomy procedure has been reported in detail earlier.[18]

Pathology

All tissue slides from each patient were reevaluated independently for this study by 2 investigators experienced in uropathology (A.F. and R.S.) blinded to outcome data.

TURB specimens of 40 patients with muscle-invasive urothelial carcinoma of the bladder were processed at the Institute of Pathology, University of Bern, and the others were processed at different pathology departments in Switzerland. Microscopically, the following tumor characteristics were evaluated for response prediction to neoadjuvant chemotherapy: grade, squamous or glandular differentiation,[7] nuclear anisocaryosis (maximum size >4 lymphocytes), and tumor-associated inflammation (tumors with absent or scant inflammatory reaction were considered negative, whereas tumors with moderate or intense inflammatory reaction were considered positive).[19] Purely nonurothelial carcinomas (eg, adenocarcinoma and squamous carcinomas) were excluded for analyses. Finally, to assign a mitotic activity to the tumor, the proliferative hot spot was identified, and here the number of mitotic figures was counted in a high-power field (diameter of the visual field: 0.54 mm) as done by others.[20] All cystectomy and lymphadenectomy specimens were processed and evaluated at the Institute of Pathology, University of Bern. All tissues were fixed in neutral buffered formalin (4%) for approximately 24 hours. Characteristics of bladder lesions (residual tumors, ulcers, scars) were described (location, size, relation to the bladder wall and surrounding tissues), and corresponding tissue samples were taken for histologic examination. Whenever no residual cancer was detected, the area of the tumor bed was totally embedded. Routinely, samples from the bladder neck with trigone, dome, anterior and posterior wall, and the resection margins of ureters and urethra were embedded. Microscopically, tumor grade and tumor stage were noted. Scoring of regression is described in detail in the next paragraph. The maximum diameter of the largest residual primary tumor focus was determined. The lymph node specimens of each anatomic location were examined by inspection and palpation separately, and all macroscopically detected lymph nodes were embedded completely. Whenever no lymph nodes were found, the entire tissue was embedded for histologic examination. One hematoxylin and eosin-stained section was taken per tissue block, and no immunostaining analyses were performed routinely. All tumors and lymph node metastases were staged according to the seventh International Union Against Cancer classification of 2009.[10] The use of patient material was approved by the local ethics committee.

Morphologic Determination of the TRG

The TRG was based on a histologic estimations of the size of the residual viable cancer tissue in relation to the size of the original tumor bed, indicated by zones of fibrosis in the bladder wall and in the perivesical soft tissue. The zones of regression (Figs. 1, 2) in general showed a tumor bed consisting of dense fibrosis without cancer cells. Sometimes edema was noted in these areas. Regularly accumulations of macrophages were present focally. In addition, inflammatory infiltrates with lymphocytes and rarely eosinophilic and neutrophilic granulocytes were often seen in these zones. Regressive changes in lymph node metastases (Figs. 3A–C) were comparable to changes in primary tumors; however, in addition, the macrophages could fill the entire tumor bed of resorbed metastases. Larger zones of necrotic tumor cells, indicative of chemotherapy effect, were infrequently seen probably due to the long duration between the first cycle of chemotherapy and the surgical procedure, which was performed in general 6 weeks after the last cycle. In addition, very rarely, cytoplasmic vacuolation and small groups of apoptotic cells were observed in the residual neoplastic tissue, but these minimal cytologic changes were not specific.

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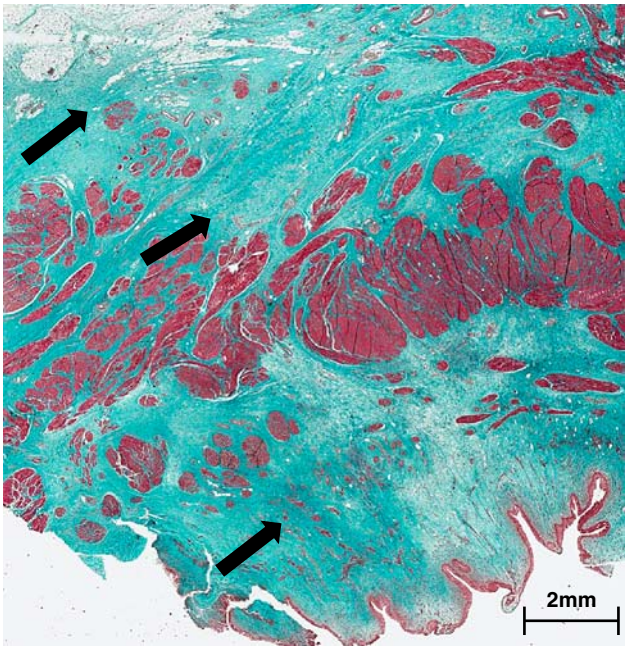

FIGURE 1. Fibrotic scar without cancer cells (TRG1) in the submucosa, muscularis propria, and perivesical tissue (arrows) representing the original primary tumor bed (Masson trichrome).

TRGs were defined in analogy to Mandard et al[16] but with condensed grades as done by others[21]:

TRG1:	Complete response: Absence of histologically identifiable residual cancer cells and extensive fibrosis of the tumor bed (Figs. 1, 2).
TRG2:	Strong response: Predominant fibrosis of the tumor bed and residual cancer cells occupying $< 50\%$ of this area (Fig. 4).
TRG3:	Week and no response: Predominant residual cancer cells outgrowing tumor bed fibrosis ($\geq 50\%$ of this area occupied by cancer cells) or absence of regressive changes (Fig. 5).

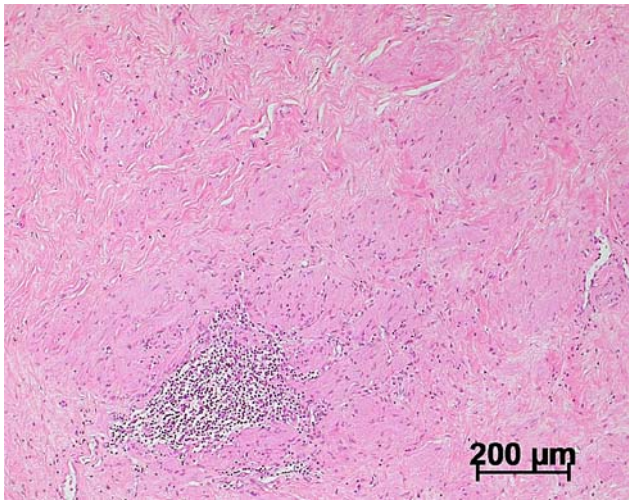

FIGURE 2. Higher magnification shows a dense fibrosis and scarce lymphocytic infiltrates (hematoxylin and eosin).

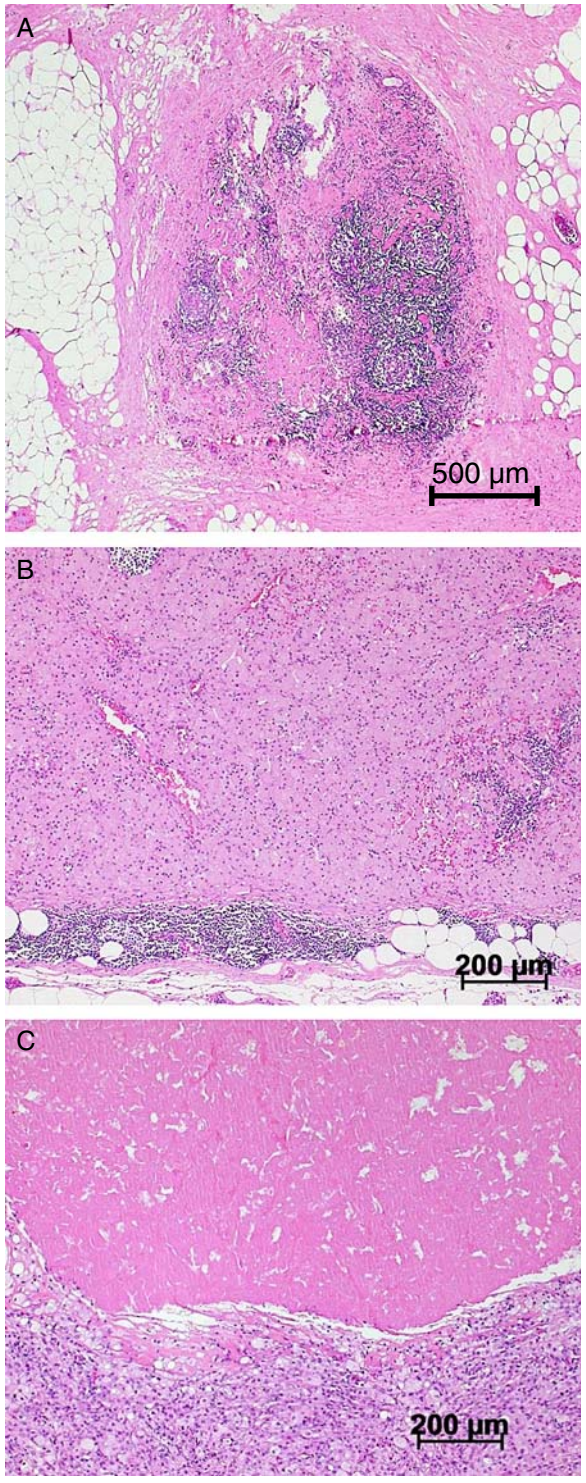

FIGURE 3. Completely regressed lymph node metastases without cancer cells indicated by a nodular fibrotic zone in A (HE), by a nodular accumulation of macrophages in B (HE), and by a nodular zone of necrosis surrounded by granulation tissue and fibrosis in C (HE). HE indicates hematoxylin and eosin.

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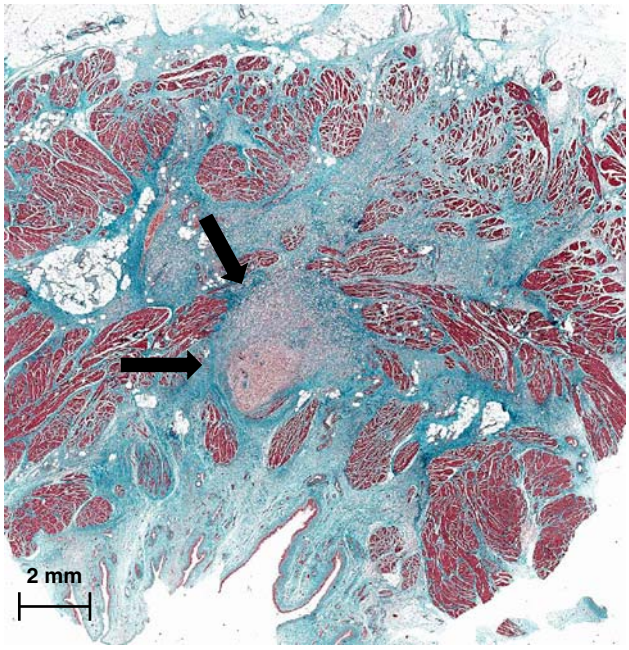

FIGURE 4. Residual cancer cells (arrows) in a predominant fibrotic tumor bed (TRG2, Masson trichrome).

This grading system was used separately for primary tumors and lymph node metastases. All of our patients showed only 1 invasive primary cancer that was assigned a TRG. Rarely, we observed, in addition, noninvasive papillary tumors or carcinomas in situ. These lesions were not considered for tumor regression. Lymphadenectomy specimens without histologic evidence for prior metastases were assigned TRG1*, those with fibrotic zones indicative of completely regressed metastases were assigned TRG1^{+}, and both constituted the nodal TRG1 group. In patients with several lymph node metastases, each could show different amounts of regression (Figs. 6A, B), and the average regression determined the TRG. Finally, for every patient the "dominant" TRG, which is the higher TRG between primary tumor and lymph nodes, was determined.

Statistical Analyses

Interobserver variability in determination of the TRG was measured by the Cohen κ. Discrepant cases were reevaluated, and a consensus was always reached. The 3 TRGs were compared with regard to histopathologic and clinical characteristics using a 2-sided Wilcoxon rank sum test (for continuous, non-normally distributed data) and the Fisher exact test (categorical data). Kaplan-Meier plots and log rank tests were used to estimate overall survival (OS) from surgery to the date of death. Patients still alive were censored at the date of last follow-up. Cox proportional hazards regression models were used to determine the effect of each variable on survival time in a multivariate setting. Hazard ratios and 95% confidence intervals were estimated. A forward selection procedure was used to investigate the effect of each variable on outcome while adjusting for the remaining potential confounding variables entered into the model. A significance level of 0.05 was used for all tests. All statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL).

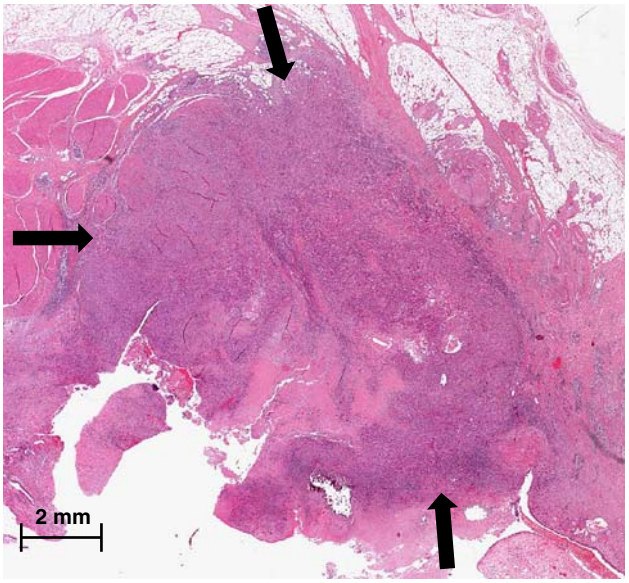

FIGURE 5. Abundant residual cancer cells infiltrating the bladder wall (arrows, hematoxylin and eosin). No relevant tumor regression present (TRG3).

RESULTS

The Cohort

Clinical and histopathologic baseline data of the cohort are given in Table 1. At the time of cystectomy, 16 patients had no residual primary tumor (ypT0) and 31 patients no lymph node metastases (ypN0) upon histologic examination. Median OS for the entire cohort was 3.7 years; 5-year OS was 49%. Median follow-up was 3.7 years.

For every patient, the corresponding TRG in the primary tumors and in the lymph nodes are given in Table 2. Half of the patients had concordant TRGs in their primary tumors and lymph nodes (n = 28). Discordant TRGs (n = 28) mostly showed a trend for stronger regression in the metastases than in the primary tumors. The highest (dominant) TRG was TRG1 in 15 patients (27%), TRG2 in 16 patients (29%), and TRG3 in 25 patients (44%). Interobserver agreement in determination of the TRGs was strong (κ = 0.8).

Analyses of TRG With Histopathologic and Clinical Characteristics

The TRGs in the primary tumor were positively correlated with the ypT stages and maximum diameter of the residual primary tumor, the lymph node TRGs with the ypN stages, and the dominant TRGs with all these tumor features ($P < 0.001$ each). Indication for neoadjuvant chemotherapy, pretherapeutic clinical tumor,

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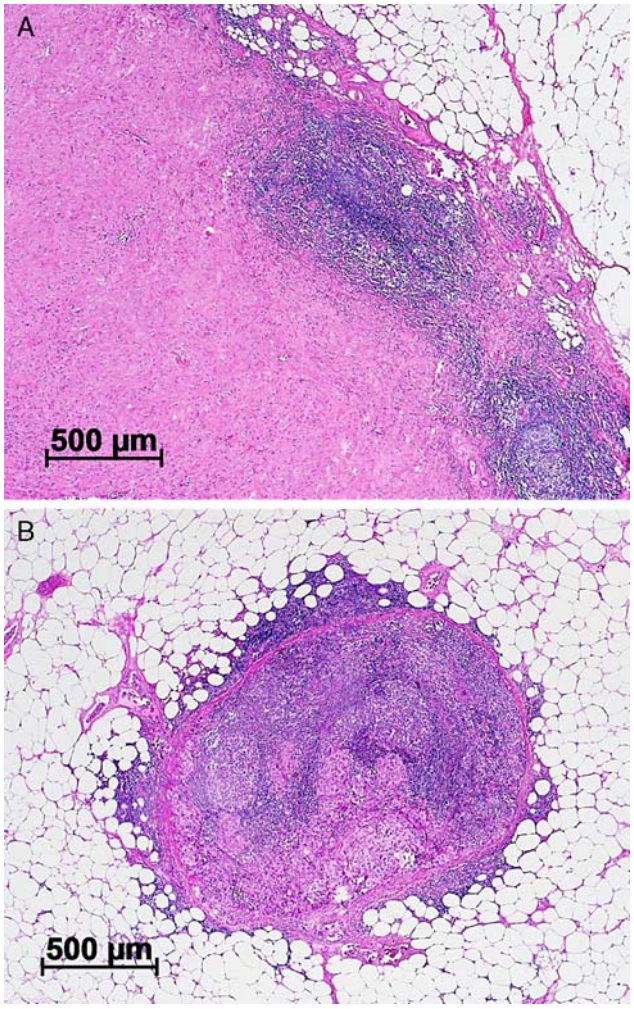

FIGURE 6. Patients may have completely regressed lymph node metastasis (A) next to ones (B) without regression (hematoxylin and eosin).

and lymph node stages were not different when compared between dominant TRGs ($P > 0.5$).

Univariate and Multivariate Survival Analyses

In univariate analyses, all tested tumor parameters from the bladder and the lymph nodes related to tumor regression stratified survival significantly ($P \leq 0.001$, Figs. 7A–E). Importantly, the segregation of the curves was best for the dominant TRG, which factors in the higher TRG from a primary tumor and the corresponding lymph nodes (Fig. 7F). Number of identified lymph nodes ($P = 0.3$), indication for neoadjuvant chemotherapy ($P = 0.8$), pretherapeutic clinical tumor ($P = 0.8$), and lymph node ($P = 0.4$) stages failed to stratify survival.

The dominant TRG was the only independent risk factor in multivariate analyses ($P = 0.035$; Table 3) and was the only parameter that was significant in forward stepwise calculation ($P = 0.001$, hazard ratio 3.5, confidence interval 1.9-6.6). All other evaluated parameters related to tumor regression failed to add independent prognostic information.

TABLE 1. Clinicopathologic Data of the 56 Patients

Age (median [range]) at surgery (y)	63 (35-78)
Follow-up (median) (y)	3.7
Median OS (y)	3.7
Indication for neoadjuvant chemotherapy (n)	
Clinically positive lymph nodes (biopsy proven)	39 (21)
Advanced primary tumor stage cT3/4	15
Other	2
Cystectomy and lymphadenectomy data	
Tumor stage (n)	
ypT0	16
ypT1/2	17
ypT3	13
ypT4	10
Diameter of residual tumor per patient (median [range]) (n)	0.5 (0-6)
Evaluated nodes per patient (median [range]) (n)	31 (8-85)
Positive nodes per patient (median [range]) (n)	0 (0-37)
Lymph node stage (n)	
ypN0	31
ypN1	8
ypN2/3	17

Histopathologic Features in TURB Specimens and Response to Chemotherapy

Finally, we evaluated various histopathologic tumor features in chemotherapy-naive TURB specimens of complete responders (dominant TRG1) and partial/nonresponders (dominant TRG2/TRG3). Complete responders had a significantly higher number of mitotic figures per high-power field (median: 4, range: 1 to 7, $P < 0.03$; Fig. 8) compared with partial/nonresponders (median: 2, range: 1 to 6). The prevalence of all other evaluated parameters in the tumors including squamous and glandular differentiation was similar in these subgroups.

DISCUSSION

The rationale for neoadjuvant chemotherapy before surgery is to treat micrometastatic disease early, under

TABLE 2. TRGs of All Primary Tumors and Lymph Node Metastases

	Primary Tumors		
	TRG1	**TRG2**	**TRG3**
Lymph Node Metastases			
TRG1*	15 (7*)	12 (6*)	4 (1*)
TRG2	1	2	6
TRG3	0	5	11

*Number of cases with clear-cut evidence for complete cancer regression in the nodes in the form of larger foci of compact fibrosis with inflammatory infiltrates. The other cases always had smaller zones of fibrosis in their lymph nodes, what is normal in the pelvic nodes of elderly patients, and could not be assessed conclusively for regressed micrometastatic disease.

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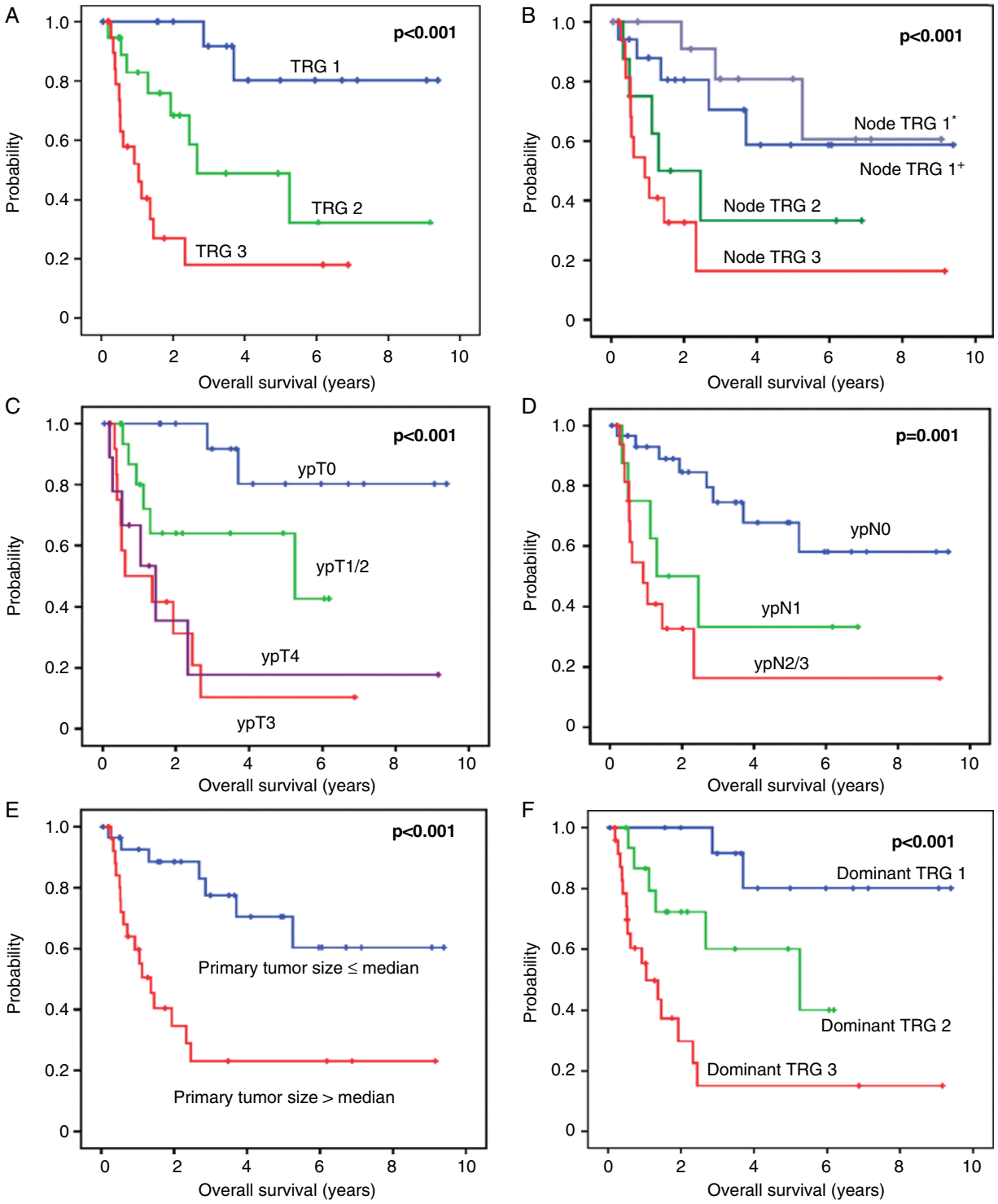

FIGURE 7. A, OS stratified according to the TRG of the primary tumors, (B) the TRG of the lymph nodes (TRG1*: lymph nodes without evidence of prior metastases; TRG1^{+}: lymph nodes with complete regression of prior metastases), (C) ypT stage, and (D) ypN stage shows better outcome in patients with lower stages. E, OS according to the largest diameter of residual primary tumor shows better outcome in patients with smaller tumors. F, Best segregation is achieved when using the dominant TRG, which is defined as the higher of both TRG assigned to the primary tumor and the corresponding lymph nodes, respectively.

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TABLE 3. Multivariate Analysis: Dominant TRG Was the Only Independent Risk Factor for Overall Survival (OS)

	OS		
	HR	**95% CI**	***P***
TRG	4.0	1.1-14.9	0.035
ypN-stage	0.3	0.8-2.4	1.4
ypT-stage	0.9	0.4-1.8	0.7
Diameter of residual tumor*	0.8	0.2-3.7	0.7

*Dichotomized according to median (> median vs. ≤ median).
CI indicates confidence intervals; HR, hazard ratio.

relatively good performance status, and to downsize the primary tumor for better operability.[22] Such multimodality treatment is a standard procedure in cancers of the rectum[23] and esophagus[24] to improve survival. For these primary tumors elaborated histopathologic TRGs with prognostic relevance exist.[11,12,14–16] However, such a concept has never been explored in bladder cancer. Therefore, we defined TRGs in analogy to the method used in esophageal cancer[16] and expanded the assessment of tumor regression on the lymph node compartment. The prognostic ability of the TRGs was tested in a uniformly treated cohort of 56 patients with advanced bladder cancer. All patients underwent platin-based neoadjuvant chemotherapy, followed by cystectomy with standardized bilateral extended pelvic lymphadenectomy at a single-center institution.

The TRG was based on estimations of the size of the residual viable cancer tissue in relation to the size of the original tumor bed. This system with 3 grades is simple, highly reproducible, and allows the comparison of regression grades between primary tumors and lymph nodes. In 50% of the patients, the TRG determined in the primary tumor and in the lymph nodes was identical. Interestingly, the remaining patients showed discordant TRG with more frequently lower TRG in the lymph nodes than in the primary tumors. Therefore, response of the primary tumor does not necessarily mirror the effects in the metastases. This information is important because early assessment of tumor response by TURB after first cycles of neoadjuvant chemotherapy to identify non-responders[25,26] might be misleading.

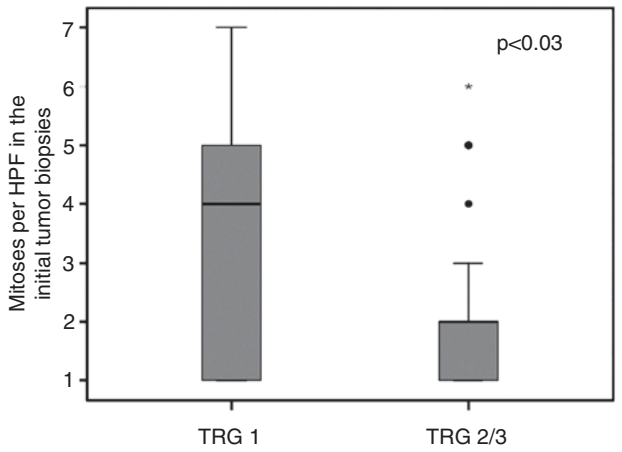

FIGURE 8. Boxplots show a significantly higher mitotic rate in the initial tumor biopsies from complete responders (dominant TRG1) compared with partial/nonresponders (dominant TRG2/TRG3).

The TRGs were outstanding prognostic factors. The survival curves according to the TRG of the primary tumors segregated better than those obtained from the ypT stages; the nodal TRG could stratify outcome of the pN0 group for patients with and those without evidence of prior metastases. Importantly, survival stratification further improved when the higher (dominant) TRG from both components, the primary tumors and the lymph nodes, was taken into account: 80% of the complete responders (dominant TRG1) showed long-term survival, whereas only 15% of the weak/nonresponders (dominant TRG3) survived 5 years postoperatively. The survival curve of strong but incomplete responders (dominant TRG2) was perfectly situated intermediately between these 2 extremes. In multivariate analyses, the dominant TRGs were better prognosticators than the pT and pN stages, which failed to add independent prognostic information.

Administration of neoadjuvant chemotherapy in bladder cancer has slowly risen over the last decade[27]; however, its application in 3.1%[28] to 9%[27] of bladder cancer patients is still low. Importantly, the long-term results of the Medical Research Council/European Organisation for the Treatment and Cure of Cancer study might accelerate the shift to multimodal therapy: patients receiving neoadjuvant chemotherapy before cystectomy had a significant survival benefit of 26% compared with patients undergoing cystectomy alone.[4] The future central issue will be to select patients who will respond to neoadjuvant chemotherapy. Separation of patients who benefit from those who do not will improve its acceptance and avoid overtreatment. Therefore, we correlated histomorphologic characteristics of the chemotherapy-naive tumors received as TURB specimens with the TRGs. The only parameter with predictive value for treatment response was the proliferation rate. High proliferation rate of the tumor was associated with complete tumor response to chemotherapy. This is in line with data from the North American Southwest Oncology Group bladder cancer trial published by Grossman et al,[29] which showed better outcome in patients with high compared with low tumor proliferation when treated by neoadjuvant chemotherapy and cystectomy. The underlying rationale might be the well-known cytotoxicity of cisplatin and analogous primarily in proliferating cells.[30] In contrast to the North American Southwest Oncology Group trial,[7] squamous or glandular differentiation was not associated with response to neoadjuvant chemotherapy in our study.

There are limitations in our study that are due to its retrospective character, with only patients having advanced, mostly metastasized tumors being included in the study. This restricts conclusions to the high end of the spectrum of invasive urothelial bladder cancers. Before

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using the TRGs routinely, as well as in populations with earlier cancers, particularly in cT2 tumors, their prognostic relevance has to be validated prospectively. In these tumors, the differentiation of a tumor bed depleted from neoplastic cells after neoadjuvant chemotherapy, and post-TURB scarring might be more problematic than in our cohort of advanced T3 and T4 bladder cancers, which cannot be completely resected and in which the effect of this surgical procedure should be equally distributed over all groups of TRG. Finally, the limited scale of our cohort might have obscured a potential impact of squamous and glandular differentiation on tumor response, as reported by Scosyrev et al.[7]

In conclusion, the method suggested for TRG determination in neoadjuvantly treated bladder cancer predicts survival independently and better than the ypT and ypN stages. A high mitotic rate in the chemotherapy-naive bladder cancer is significantly associated with favorable chemotherapy response. This parameter might help predict tumor response and personalize neoadjuvant chemotherapy.

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