Survivin as a Prognostic Marker for Urothelial Carcinoma of the Bladder: A Multicenter External Validation Study

Shahrokh F. Shariat,1 Pierre I. Karakiewicz,3 Guilherme Godoy,1 Jose A. Karam,1 Raheela Ashfaq,2 Yves Fradet,4 Hendrik Isbarn,3 Francesco Montorsi,5 Claudio Jeldres,3 Patrick J. Bastian,6 Matthew E. Nielsen,7 Stefan C. Müller,8 Arthur I. Sagalowsky,1 and Yair Lotan1

Abstract

Purpose: The aim of the current study was to externally validate the value of survivin as a prognostic marker for bladder cancer in a large multi-institutional cohort of patients treated with radical cystectomy.

Methods: The study comprised 726 patients treated with radical cystectomy and bilateral pelvic lymphadenectomy. Survivin staining and scoring were done with automated systems coupled with advanced color detection software. Specimens showing at least 10% reactivity were considered altered. Predictive accuracy was quantified using the concordance index and 200-bootstrap resamples were used to reduce overfit bias.

Results: Survivin was an independent predictor of disease recurrence and cancer-specific survival in multivariable analyses that controlled for the effects of standard clinicopathologic features (hazard ratios, ~1.6; P values ≤ 0.002). In all patients (n = 726), addition of survivin to a model including standard clinicopathologic variables did not improve its predictive accuracy (P = 0.67 for disease recurrence and P = 0.27 for cancer-specific survival). In the subgroup of patients with pT1-3N0M0 disease (n = 398), addition of survivin improved the accuracy of standard clinicopathologic features for prediction of disease recurrence and cancer-specific survival (1.3%, P < 0.001 and 1.2%, P < 0.001, respectively).

Conclusions: Survivin expression improves our accuracy for prediction of cancer recurrence and survival in pT1-3N0M0 patients by a small but statistically significant margin. Our findings support the need for further evaluation of survivin and its signaling pathways as well as survivin-targeted therapies in bladder cancer.

In the United States, urothelial carcinoma of the bladder (UCB) is expected to affect 68,810 patients in 2008, resulting in 14,100 deaths (1). Radical cystectomy is the standard treatment for patients with refractory non-muscle-invasive and muscle-invasive UCB. Despite advances in the surgical techniques and perioperative chemotherapy, overall 10-year disease-specific survival after radical cystectomy remains ~45% (2–5). Standard prognostic features, such as pathologic stage and grade, have limited ability to predict outcome of these patients. Therefore, it is important to understand the molecular events that explain the clinical heterogeneity of these lethal tumors. Molecular biomarkers predictive of outcomes could help clinicians to provide individualized prognostications and allow risk-stratified clinical decision-making regarding adjuvant therapy (6–9).

Alterations in apoptosis are important in carcinogenesis, as they allow neoplastic cells to survive longer, develop resistance to stress, and increase invasiveness, resulting in disease progression and metastasis (10). Survivin is a member of the inhibitor of apoptosis family of proteins (11). Because of its selective and substantial upregulation in UCB and its causal role in cancer progression, survivin is currently undergoing intensive investigation as a possible tumor marker and target for therapy (12, 13). Numerous small retrospective studies suggest that measurement of survivin in urine or tissue may be valuable in cancer diagnosis, prognosis, and prediction of response to intravesical or systemic therapies (14). We have previously investigated survivin expression in a single-institutional retrospective study of

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Survivin Expression and Bladder Cancer

Translational Relevance

Standard prognostic features such as pathologic stage and grade have limited ability to predict outcome of these patients. Accurate prediction of disease recurrence and survival is necessary for patient counseling, frequency and extent of monitoring, and adjuvant therapy planning. Molecular biomarkers predictive of outcomes could help clinicians provide individualized prognostications and allow risk-stratified clinical decision-making regarding adjuvant therapy. In this study, we found that the addition of survivin expression improves the predictive accuracy of competing-risk analyses for prediction of bladder cancer recurrence and survival following cystectomy for patients with pT1-3 node-negative tumors by a prognostically and clinically significant margin. Stage pT1-3N0M0 patients with normal survivin expression regardless of pathologic features have excellent survival rates and could be spared from unnecessary chemotherapy. Conversely, pT1-3N0M0 patients with altered survivin expression have a worse prognosis and may benefit from early aggressive therapy such as adjuvant chemotherapy.

Materials and Methods

Patient population. All studies were done after approval by a local human investigations committee and in accord with an assurance filed with and approved by the Department of Health and Human Services, where appropriate. Informed consent was obtained from each subject. The study cohort was composed of 786 patients who underwent radical cystectomy and survival analysis for invasive UCB. In all models, proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual-based test (26). Because a proportion of patients treated with radical cystectomy for invasive UCB died of other causes, competing-risk regression was used to test the significance of all the above variables in competing-risk regression models that predicted UCB-specific mortality after accounting for other-cause mortality (27). The change in predictive accuracy resulting from the addition of survivin to standard predictor variables was quantified with Harrell’s concordance index (28, 29).

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Univariable recurrence and survival probabilities after cystectomy were estimated using the Kaplan-Meier method. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific survival. In all models, proportional hazards assumptions were verified using the Grambsch-Therneau residual-based test (26). Because a proportion of patients treated with radical cystectomy for invasive UCB died of other causes, competing-risk regression was used to test the significance of all the above variables in competing-risk regression models that predicted UCB-specific mortality after accounting for other-cause mortality (27). The change in predictive accuracy resulting from the addition of survivin to standard predictor variables was quantified with Harrell’s concordance index (28, 29).

Statistical analyses. Outcomes were measured by time to disease recurrence or to cancer-specific survival. The cause of death was determined by the treating physicians, based on chart review corroborated by death certificates, or by death certificates alone. To reduce bias in attribution of cause of death, only subjects who had UCB listed in part I of the death certificate were considered to have died of UCB for this study. Perioperative mortality (any death within 30 days of surgery or before discharge) was censored at time of death for cancer-specific survival analyses.

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The area under the curve was quantified using 200-bootstrap resamples (28, 29). Predictive accuracy estimates were expressed as proportions and compared with the Mantel-Haenszel test. All reported P values are two-sided and statistical significance was set at 0.05. All statistical tests were done with S-Plus Professional (MathSoft).

Results

Descriptive characteristics. Survivin expression was heterogeneous with predominant expression localized to the cell

patients treated with radical cystectomy and found it to be independently associated with UCB progression and mortality (15).

Despite the increasing number of published studies that have added to the general knowledge about molecular markers in UCB, none of these markers are used for individualized treatment recommendations. This is largely due to the lack of external validation in large, multicenter studies. Therefore, the aims of the current study were to externally validate the value of survivin as a prognostic marker for UCB in a large multi-institutional cohort of patients treated with radical cystectomy for UCB. In addition, we tested whether survivin could improve the accuracy of predictive models that include standard histopathologic features for prediction of disease recurrence and cancer-specific survival in patients with UCB.
cytoplasm. Nuclear reactivity was also observed. Survivin was expressed in 359 of the 726 patients (49.4%). Clinopathologic characteristics of 726 patients (full study cohort) and 398 patients with pT1-3N0M0 (limited cohort) and their association with survivin expression are shown in Table 1. Survivin expression was associated with a higher probability of recurrence-free and cancer-specific survival, respectively. Figure 1C and D depict the overall probability estimates for recurrence-free and cancer-specific survival, respectively. Figure 1A and B depict the overall probability estimates for recurrence-free and cancer-specific survival, respectively. Association of survivin expression with cancer recurrence and cancer-specific survival in the full cohort (n = 726). Median follow-up was 53.3 months (range, 0.1-235.6 months). Disease recurred in 292 patients (40.2%), and 388 (53.4%) patients were dead at the time of analysis. Of these 164 patients, 79 patients (48.2%) died of metastatic UCB and 85 patients (51.8%) died of other causes without evidence of disease progression. Figure 1A and B depict the probability estimates for recurrence-free and cancer-specific survival, respectively. Figure 1C and D depict the probability estimates for recurrence-free and cancer-specific survival, stratified by survivin expression, respectively. Survivin expression was associated with a higher probability of cancer recurrence [hazard ratio (HR), 1.8; log-rank \( P = 0.001 \)] and cancer-specific mortality [HR, 1.63; log-rank \( P = 0.001 \)]. Five-year cancer-specific survival was 70.4% [95% confidence interval (95% CI), 64.9-79.3%] versus 51.8% (95% CI, 46.4-58.0%) for patients with normal versus altered survivin expression, respectively.

Table 1. Descriptive characteristics of the full cohort (726 patients treated with radical cystectomy and bilateral lymphadenectomy) and the 398 patients with pT1-3N0M0 disease who did not receive adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Full cohort</th>
<th>Survivin altered cohort</th>
<th>Survivin normal cohort</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>726 (100)</td>
<td>359 (49.4)</td>
<td>367 (50.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>Age (mean, median)</td>
<td>67.3 (68)</td>
<td>67.3 (68)</td>
<td>67.4 (67)</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>126 (17.4)</td>
<td>63 (17.5)</td>
<td>63 (17.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Pathologic stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>pT1</td>
<td>90 (12.4)</td>
<td>44 (12.3)</td>
<td>46 (12.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>pT2</td>
<td>208 (28.7)</td>
<td>81 (22.6)</td>
<td>127 (34.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>pT3</td>
<td>309 (42.6)</td>
<td>162 (45.1)</td>
<td>147 (40.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>pT4</td>
<td>119 (16.4)</td>
<td>72 (20.1)</td>
<td>47 (12.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Pathologic grade, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Low</td>
<td>618 (85.1)</td>
<td>300 (83.6)</td>
<td>318 (86.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymph node status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphovascular invasion, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carcinoma in situ, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
</tbody>
</table>

Multivariable Cox proportional hazards regression analyses (Tables 2 and 3) showed that survivin was an independent predictor of cancer recurrence (HR, 1.64; \( P = 0.002 \)) and cancer-specific mortality (HR, 1.63; \( P < 0.001 \)). However, the addition of survivin to a model including standard clinopathologic variables did not improve the predictive accuracy of these models for either disease recurrence or cancer-specific survival (changes in predictive accuracies: 0.2%, \( P = 0.67 \) and 0.7%, \( P = 0.27 \), respectively).

Association of survivin expression with cancer recurrence and cancer-specific survival in pT1-3N0M0 patients who did not receive adjuvant chemotherapy (n = 398). Median follow-up was 57.0 months (range, 0.1-195.6 months). Disease recurred in 92 patients (23.1%), and 164 patients (41.2%) died at the time of analysis. Of these 164 patients, 79 patients (48.2%) died of metastatic UCB and 85 patients (51.8%) died of other causes without evidence of disease progression. Figure 2A and B depict the overall probability estimates for recurrence-free and cancer-specific survival, respectively. Figure 2C and D depict the probability estimates for recurrence-free and cancer-specific survival, stratified by survivin expression, respectively. Altered survivin expression was associated with an increased probability of cancer recurrence (HR, 2.2; log-rank \( P < 0.001 \)) and cancer-specific mortality (HR, 2.2; log-rank \( P < 0.001 \)). Five-year cancer-specific survival was 86.2% (95% CI, 79.8-90.7%) versus 72.9% (95% CI, 64.9-79.3%) for patients with normal versus altered survivin expression, respectively.
Multivariable Cox proportional hazards regression analyses (Tables 4 and 5) revealed that survivin was an independent predictor of both cancer recurrence (HR, 1.88; \( P = 0.004 \)) and cancer-specific mortality (HR, 1.83; \( P = 0.01 \)). The addition of survivin to a model including standard clinicopathologic variables showed a statistically significant yet small improvement in predictive accuracies of these models (changes in predictive accuracies: 1.3%, \( P < 0.001 \) and 1.2%, \( P < 0.001 \), respectively).

**Discussion**

Survivin is a multifunctional protein that inhibits apoptosis, regulates cell division, and promotes angiogenesis. A unique property of survivin is its sharp cell cycle–dependent expression at mitosis (11, 12, 25, 30). Survivin expression has been associated with inhibition of cell death initiated via both extrinsic and intrinsic apoptotic pathways (12) partly through upstream regulation of mitochondrial-dependent apoptosis (31, 32). Its expression correlates with clinical phenotypes typically associated with apoptosis resistance, including low apoptotic index, resistance to therapy, and accelerated relapses (12). Various studies have shown that targeting survivin via antisense, ribozymes, small interfering RNA sequences, or dominant-negative mutants results in caspase-dependent cell death with suppression of tumor-associated angiogenesis and anticancer activity (12, 13). In this context, survivin inhibition has also been shown to produce defects in chromosome segregation, cytokinesis, and cell division (33, 34) as well as suppression of angiogenesis (31, 35, 36).

Various small retrospective studies suggest that measurement of urinary or tissue levels of survivin may be valuable in UCB diagnosis, prognosis, and prediction of response to intravesical or systemic therapies (14). We have shown previously that survivin expression is independently associated with cancer progression and mortality in a single-institutional retrospective study of 222 patients treated with radical cystectomy (15). Although encouraging, single-institutional marker studies are not adequate for definitive evaluation of the predictive ability of any single marker. Independent, large multi-institutional studies are needed to fully evaluate prognostic markers and decrease the chance of overestimation of the predictive power of a marker (37–39).

Therefore, we sought to externally validate our previous findings in a large multi-institutional cohort of patients treated with radical cystectomy. We confirmed that survivin is an independent predictor of disease recurrence and cancer-specific survival in patients treated with radical cystectomy and bilateral lymphadenectomy for UCB (14, 15). Patients with altered survivin expression had a 1.6-fold increased risk of both cancer recurrence and mortality.
We found that addition of survivin expression improved the predictive accuracy of competing-risk analyses for prediction of both cancer recurrence and survival in pT1–3N0M0 patients by a small but statistically significant margin. This increment in predictive accuracy seems too small to support giving patients with altered survivin adjuvant chemotherapy. Based on our data, we cannot explain why survivin improved the predictive accuracy only for the pT1–3N0M0 subgroup and not for the whole cohort. We speculate that most patients with more advanced disease (T4 and nodal/systemic metastasis) may already have survivin overexpressed due to a later stage in the molecular pathogenesis process potentially expressing other molecular characteristics related with progression and metastasis. The effect of these patients with more advanced molecular profile would have caused the lost of significance in the whole cohort.

There are many molecular crossroads that can increase the likelihood of cancer spread such as molecules involved in cell cycle progression (6), cellular proliferation (46), and apoptosis (23). It is unlikely that a single marker can be relied on to...
provide a complete prognostic picture. Although single markers may serve in select cases, there is growing consensus that multiple (e.g., three to five) markers used either individually or as part of integrated panels will be required for most applications. UCB is a multistep genetic process wherein individual alterations of molecular determinants may have only a restricted role (7, 23, 47–49). Whereas our study supports a limited value for survivin alone, combination with other biomarkers may enhance prognostication and prediction of treatment response in UCB. Promising candidate biomarkers that could potentially compose the prediction integrated panel would include those involved in cell cycle regulation (such as p53, pRb, p21, and p27) and cell

Fig. 2. Kaplan-Meier plots of 398 patients with pT1-3N0M0 disease treated with radical cystectomy and bilateral lymphadenectomy, showing the probability of (A) overall recurrence-free survival and (B) overall cancer-specific survival and the probability of (C) recurrence-free survival and (D) cancer-specific survival stratified by survivin status.

Table 4. Univariable and multivariable competing-risk analyses predicting the probability of disease recurrence in 398 patients with pT1-3N0 disease

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariable analyses</th>
<th></th>
<th>Multivariable analyses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>Predictive accuracy (%)</td>
<td>Model without survivin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Gender</td>
<td>0.88 (0.58-1.33)</td>
<td>0.53</td>
<td>50.8</td>
<td>0.76 (0.49-1.16)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99-1.02)</td>
<td>0.32</td>
<td>59.8</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2 vs pT1</td>
<td>1.68 (0.86-3.27)</td>
<td>0.128</td>
<td>65.5</td>
<td>1.44 (0.73-2.86)</td>
</tr>
<tr>
<td>pT3 vs pT1</td>
<td>4.99 (2.67-9.32)</td>
<td>&lt;0.001</td>
<td>65.5</td>
<td>2.94 (1.49-5.79)</td>
</tr>
<tr>
<td>Pathologic grade</td>
<td>0.70 (0.48-1.04)</td>
<td>0.08</td>
<td>50.1</td>
<td>0.46 (0.31-0.69)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>5.13 (3.70-7.12)</td>
<td>&lt;0.001</td>
<td>68.4</td>
<td>4.25 (2.96-6.09)</td>
</tr>
<tr>
<td>Concomitant carcinoma in situ</td>
<td>0.77 (0.54-1.08)</td>
<td>0.13</td>
<td>56.2</td>
<td>1.01 (0.69-1.45)</td>
</tr>
<tr>
<td>Survivin</td>
<td>2.14 (1.54-2.99)</td>
<td>&lt;0.001</td>
<td>60.9</td>
<td>1.62 (1.15-2.29)</td>
</tr>
<tr>
<td>Predictive accuracy (%)</td>
<td></td>
<td></td>
<td></td>
<td>74.0</td>
</tr>
</tbody>
</table>
palliation (Ki-67) in addition to survivin. We and others have shown that structural and functional defects of these candidate biomarkers are common in human UCB and are associated with poor oncologic outcomes (6, 23–48).

The clinical utility of a diagnostic tumor marker can be greatly enhanced if the marker is also a therapeutic target. One of the most significant features of survivin is its differential distribution in UCB compared with normal tissues (12, 15, 19, 50, 51). Similar to oncogenic antigens, survivin is strongly expressed in embryonic and fetal organs but is undetectable in most terminally differentiated normal tissues (12, 17, 25, 30, 52). This selective expression of survivin in malignant versus normal tissues, together with its unique role in apoptosis, control of cell division, and modulation of angiogenesis, poises it as an excellent therapeutic target in UCB. Not surprisingly, inhibition of survivin expression and/or function by dominant-negative mutants, antisense cDNA, antisense oligodeoxynucleotides, or small interfering RNA constructs have been shown to inhibit tumor cell proliferation and markedly induce apoptosis (12, 13, 24, 53, 54).

This study has several potential limitations. First and foremost are limitations inherent to any retrospective data collection. The sample size and variations in follow-up may have limited our ability to detect small differences. However, several large series have shown that UCB recurrence and associated mortality is most likely to occur within the first 3 years of surgery (2–5, 55). Another potential limitation is the reliability of immunohistochemical techniques. Immunohistochemistry suffers from many limitations. It is a semiquantitative tool that is highly dependent on a range of variables. Indeed, the quality of laboratory results is highly dependent on proper specimen collection handling procedures. As the specimens came from different institutions, we could not control for tissue processing, fixation, and storage. However, all specimens were obtained as fixed paraffin blocks that were stored at room temperature. We constructed tissue microarrays controlling for inherent variables of this procedure. We further standardized specimen handling, staining technique, choice of antibody, antibody concentration, as well as interpretation and stratification criteria as they were performed by the same team in the same laboratory conditions and location. In addition, one dedicated genitourinary pathologist reviewed all slides to confirm histopathologic features. Furthermore, to reduce the number of variables related to the immunohistochemical analysis and to allow reproducibility, we constructed tissue microarrays and used an automated autostainer and an automated scoring system based on bright-field microscopy imaging coupled with advanced color detection software. These techniques have been shown to result in experimental standardization and greater reproducibility (56–59). As quantitative immunohistochemistry using automated image analysis is becoming more prevalent in academic medical centers and large reference laboratories, these methods should be reproducible in these settings.

Finally, we did not differentiate between nuclear and cytoplasmic staining of survivin. It exists in different nuclear and cytoplasmic pools and the subcellular localization may reflect the relative amount of and/or regulatory effect of survivin and its splice variants (60). The antibody used in the present study recognizes all currently known survivin variants as well as in full-length survivin product due to the existence of an identical amino-terminal peptide (73 amino acids; ref. 22). It has been proposed that the nuclear pool of survivin is involved in promoting cell proliferation, whereas cytoplasmic pool of survivin may participate in controlling cell survival but not cell proliferation (22, 60). However, further molecular characterization of the functional mechanism and subcellular localization of survivin and its variants is needed to clarify their differential role in cancer cell survival and proliferation.

Table 5. Univariable and multivariable analyses predicting the probability of cancer-specific mortality in 398 patients with pT1–3N0 disease

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariable analyses</th>
<th>Multivariable analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Gender</td>
<td>0.84 (0.54-1.32)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99-1.03)</td>
<td>0.21</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2 vs pT1</td>
<td>1.87 (0.90-3.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pT3 vs pT1</td>
<td>5.17 (2.59-10.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathologic grade</td>
<td>0.72 (0.47-1.09)</td>
<td>0.12</td>
</tr>
<tr>
<td>Lymphovascular invasion in situ</td>
<td>6.20 (3.43-8.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concomitant carcinoma in situ</td>
<td>0.69 (0.47-1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Survivin</td>
<td>2.19 (1.53-3.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predictive accuracy (%)</td>
<td></td>
<td></td>
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</table>

Disclosure of Potential Conflicts of Interest

S. Shariat is a co-inventor of Methods to determine progress after therapy for bladder cancer. U.S. Patent Application Serial Number: Docket #675.003US1. Filed June 1, 2001. The other authors disclosed no potential conflicts of interest.

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Survivin Expression and Bladder Cancer
Correction: Survivin as a Prognostic Marker for Urothelial Carcinoma of the Bladder: A Multicenter External Validation Study

In this article (Clin Cancer Res 2009;15:7012–9), which was published in the November 15, 2009, issue of *Clinical Cancer Research* (1), the study support was incorrectly listed as "NIH T32 training grant T32CA082088." The article did not receive NIH support. The correct support listing should read as follows: "Departmental support from the University of Texas Southwestern Medical Center." The authors regret this error.

Reference

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