Cytogenetic and Molecular Tumor Profiling for Type 1 and Type 2 Papillary Renal Cell Carcinoma

Tobias Klatte,1 Allan J. Pantuck,1 Jonathan W. Said,1,2 David B. Seligson,2 Nagesh P. Rao,2 Jeffrey C. LaRochelle,1 Brian Shuch,1 Amnon Zisman,1 Fairooz F. Kabbinavar,3 and Arie S. Belldegrun1

Abstract  Purpose: The goal of this study was to evaluate immunohistochemical and cytogenetic features and their prognostic value in papillary renal cell carcinoma (PRCC) subtypes.  Experimental Design: One hundred fifty-eight cases of PRCC were identified and reclassified by subtype. Tumoral expression of 29 molecular markers was determined by immunohistochemistry. Cytogenetic analyses were done on a prospective series of 65 patients. Associations with clinicopathologic information and disease-specific survival were assessed.  Results: Fifty-one patients (32%) had type 1 and 107 (68%) type 2 PRCC. Type 2 patients had worse Eastern Cooperative Oncology Group performance status, higher T stages, nodal and distant metastases, higher grades, and a higher frequency of necrosis, collecting system invasion and sarcomatoid features. Type 2 showed greater expression of vascular endothelial growth factor (VEGF)-R2 in the tumor epithelium, and of VEGF-R3 in both tumor epithelium and endothelium. Loss of chromosome 1p, loss of 3p, and gain of 5q were exclusively observed in type 2, whereas type 1 more frequently had trisomy 17. Type 2 PRCC was associated with worse survival than type 1, but type was not retained as an independent prognostic factor. Lower PTEN, lower EpCAM, lower gelsolin, higher CAIX, and higher VEGF-R2 and VEGF-R3 expression, loss of 1p, 3p, or 9p, and absence trisomy 17 were all associated with poorer prognosis.  Conclusions: Type 2 PRCC is associated with more aggressive clinicopathologic features and worse outcome. Molecular and chromosomal alterations can distinguish between PRCC subtypes and influence their prognosis. The effect of 3p loss on survival in PRCC is opposite to the relationship seen in clear cell RCC.
comprises 1,825 patients treated from 1985 to 2007. After approval by the Institutional Review Board, chart and slide review of all cases were done. Patients with hereditary renal tumors, those who were not surgical candidates and those with incomplete data sets were not included. PRCC was defined as RCC with papillary or tubulopapillary architecture in at least 75% of the microscopic fields (15). With this definition, 158 PRCCs were identified and rereviewed. Cases were subtyped into type 1 and 2 PRCC by a single expert genito-urinary pathologist (J.W.S) in accordance with Delahunt and Eble’s original description (9). Because nucleolar grade but not Fuhrman grade is applicable for PRCC, all tumors were reggraded according to the scheme described by Sika-Paotonu (16). Additional information included sarcomatoid features, collecting system invasion, necrosis, and multifocality. Tumor necrosis was defined as the presence of any microscopic coagulative necrosis. Multifocality was defined as separate renal cell tumors in the same kidney, diagnosed intraoperatively or by histologic examination. Radiographic, operative, and pathology reports were used to assess the tumor-node-metastasis stage (17). An Eastern Cooperative Oncology Group (ECOG) performance status was prospectively assigned at diagnosis (18).

**Tissue array construction and immunohistochemistry.** Out of the 158 tumors with type 1 or 2 PRCC, 40 specimens were randomly obtained from the Department of Pathology at the University of California at Los Angeles Medical Center. Three core tissue biopsies, 0.6 mm in diameter, were taken from morphologically representative regions of each paraffin-embedded PRCC and precisely arrayed as described previously (19).

Immunohistochemical staining was done with a panel of 29 tumor markers with a Dako Envision (Dako) or Vectastain Elite ABC (Vector) staining system (20, 21). The primary antibodies used targeted gelsolin (Sigma Co; concentration, 3.8 μg/mL), HIF-1α (Novus Biologicals; 6 μg/mL), Ki-67 (Dako; 0.5 μg/mL), vimentin (Dako; dilution, 1:1,000), CAIX (gift from Dr. Eric Stanbridge, Irvine, CA; 1:25,000 dilution), CAIXII (gift from Dr. Michael Lerman, Laboratory of Immunobiology, National Cancer Institute, Frederick, MD; 1:450 dilution), EpCAM (BD Pharmingen; 20 μg/mL), p21 (Calbiochem; dilution, 1:100), p27 (Dako; 8 μg/mL), p53 (Dako; 1:100 dilution), CXCR3 (R&D Systems; 0.1 μg/mL), pS6 (Cell Signaling; 0.125 μg/mL), pAkt (Cell Signaling; 1.5 μg/mL), PTEN (Zymed; 2 μg/mL), vascular endothelial growth factor (VEGF)-A (Santa Cruz Biotechnology; 4 μg/mL), VEGF-C (Zymed; 3 μg/mL), VEGF-D (R&D Systems; 3 μg/mL), VEGF-R1 (Santa Cruz; 1 μg/mL), VEGF-R2 (Santa Cruz; 2 μg/mL), and VEGF-R3 (gift from Dr. Kari Alitalo, Haartman Institute, University of Helsinki, Helsinki, Finland; 2 μg/mL).

Semiquantitative assessment of staining was done by a single pathologist (DBS) blinded to clinicopathologic variables and outcome. The extent of staining was recorded as percentage of the entire tumor sample that stained positive. The overall score used for subsequent statistical analysis was the pooled mean from the three spots of the same tumor.

**Cytogenetic analysis.** Tumor samples were collected immediately postoperatively in 65 consecutive patients. After short-term culture, chromosomes were banded using the GPG (G-Bands by Pancreatin using Giemsa) technique. Twenty metaphases were investigated and analyzed in accordance with the International Standing Committee on Human Cytogenetic Nomenclature by one cytogeneticist (PNR; ref. 20). Ploidy levels were classified as pseudodiploid (modal number, 46), hypodiploid (<46), hyperdiploid (47–57), and polyploid (>58). Of the 65 tumors, 57 (88%) showed an abnormal karyotype, which form the principal study cohort.

**Statistical analysis.** A P value of <0.05 was considered statistically significant and the statistical software R4 was used for all analyses. Categorical data were compared using the χ² test or Fisher’s Exact test, whereas the Kruskal-Wallis test and Student’s t test were used to assess continuous data. The end point of this study was disease-specific survival (DSS), defined from the date of nephrectomy to the date of RCC death. Cause of death was determined from the death certificate, physician correspondence, or clinical history. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test applied to compare curves. Univariate and backward stepwise multivariate Cox proportional hazards regression models were fit. For multivariate Cox proportional hazards regression models, variables were removed backward as defined by the likelihood ratio statistic (P_in = 0.05, P_out = 0.10). The rank of elimination was given when a variable was removed from the equation, and the hazard ratio, 95% confidence interval (CI), and P value for the removed variables were obtained on the step of removal. The proportional hazard assumption was tested by the Schoenfeld test. For identification of high-risk patients for disease-specific death according to immunohistochemical protein expression, we used dichotomized protein expression values (high/low), identified by univariate recursive partitioning based survival tree analysis. Recursive partitioning is a method that can be used for univariate and multivariate analysis. It constructs a decision tree that classifies patients based on dichotomized, dependent variables.

**Results**

**Clinicopathologic features and prognosis of type 1 and 2 PRCC.** Fifty-one patients (32%) had type 1 and 107 (68%) had type 2 PRCC. Type 2 was associated with worse ECOG performance status, higher T stage, lymph node and distant

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4 http://cran.r-project.org/
Metastases, greater size, higher grade, necrosis, collecting system invasion, and sarcomatoid features (Table 1).

Median follow-up was 38 months (range, 1-199). At the time of analysis, 39 patients (25%) had died from the disease. Ninety percent of the patients who died had type 2 PRCC, of which 39 patients (25%) had died from the disease. Patients with higher T stages showed lower gelsolin expression, and higher endothelial VEGF-R1 and VEGF-R3 expression. Spread to distant sites was associated with lower gelsolin, lower EpCAM, and higher cytoplasmatic p27, endothelial VEGF-A, VEGF-R1, and VEGF-R3 expression. Higher grades were observed in tumors with higher cytoplasmatic p27, epithelial VEGF-R2, epithelial VEGF-R3, and endothelial VEGF-R3 expression. Tumors with necrosis expressed epithelial VEGF2 to a greater degree than tumors without. Finally, higher epithelial VEGF-A, epithelial VEGF-R1, and endothelial VEGF-R1 and endothelial VEGF-R3 expression were all associated with collecting system invasion.

Fourteen of the 40 patients (35%) with immunohistochemical analysis died from PRCC. We first fit univariate Cox proportional hazards models with continuous marker expressions and identified lower PTEN (P = 0.027), lower gelsolin (P < 0.001), lower EpCAM (P = 0.044), higher endothelial VEGF-R2 (P = 0.001), and higher endothelial VEGF-R3 (P = 0.014) as predictors of diminished DSS for both types. Additionally, higher CAIX expression was associated with poorer prognosis in type 2 (P = 0.0370). Subsequently, we identified expression level cutoff points (low/high) with recursive partitioning based survival tree analysis. Survival curves of these dichotomized marker expressions are presented in Fig. 3. A multivariate Cox model was fitted with tumor-node-metastasis stage, grade, necrosis, and significant markers. Tumor-node-metastasis stage (hazard ratio, 4.48; 95% CI, 2.03-9.88; P < 0.001) and endothelial expression of VEGF-R2 (hazard ratio, 1.17; 95% CI 1.01-1.36; P = 0.039) were independent prognostic factors.

**Table 1.** Clinicopathologic features and DSS of type 1 and type 2 PRCC

| Feature                        | Type 1 (n = 51) | Type 2 (n = 107) | P       |
|--------------------------------|-----------------|------------------|---------|
| Age (mean ± SD)                | 62.1 ± 11.9 y   | 61.8 ± 12.7 y    | 0.889   |
| ECOG                           | 38 (75%)        | 62 (58%)         | 0.043   |
| ECOG ≥ 1                       | 13 (25%)        | 45 (42%)         |         |
| Incidental diagnosis           | 26 (51%)        | 49 (46%)         | 0.542   |
| T stage                        | 37 (50%)        | 53 (50%)         | 0.013   |
| pT1                            | 4 (8%)          | 8 (7%)           |         |
| pT2                            | 9 (18%)         | 41 (38%)         |         |
| pT3                            | 0               | 5 (5%)           |         |
| Lymph node metastases (pN1/2)  | 3 (6%)          | 23 (21%)         | 0.013   |
| Distant metastases (M1)        | 4 (8%)          | 29 (27%)         | 0.005   |
| Tumor size (mean ± SD)         | 4.9 ± 4.4 cm    | 6.6 ± 4.4 cm     | <0.001  |
| Nucleolar grade                | 14 (27%)        | 1 (1%)           |         |
| G1                             | 35 (69%)        | 48 (49%)         |         |
| G2                             | 2 (4%)          | 58 (54%)         |         |
| G3                             | 8 (16%)         | 18 (17%)         | 0.857   |
| Multifocality                  | 12 (24%)        | 58 (54%)         | <0.001  |
| Necrosis                       | 5 (10%)         | 37 (35%)         | 0.001   |
| Vascular invasion (V1/2)       | 0               | 7 (7%)           | 0.062   |
| Sarcomatoid features           | 5 (10%)         | 24 (22%)         | 0.055   |
| Collecting                     | 90 ± 5%         | 61 ± 6%          | 0.005   |

**Immunohistochemical profile.** Forty PRCC tumor samples, 13 with type 1 and 27 with type 2, were immunohistochemically evaluated. Type 2 had greater expression of VEGF-R2 in the tumor epithelium (57% versus 30%; P = 0.007), and VEGF-R3 in both tumor epithelium (19% versus 6%; P = 0.028) and endothelium of associated vessels (11% versus 0.2%; P = 0.009) than type 1. All other evaluated molecular markers were not differentially expressed between type 1 and type 2.

Associations of protein expression with clinicopathologic variables are summarized in Fig. 2. Patients with higher T stages showed lower gelsolin expression, and higher endothelial VEGF-R1 and VEGF-R3 expression. Spread to distant sites was associated with lower gelsolin, lower EpCAM, and higher cytoplasmatic p27, endothelial VEGF-A, VEGF-R1, and VEGF-R3 expression. Higher grades were observed in tumors with higher cytoplasmatic p27, epithelial VEGF-R2, epithelial VEGF-R3, and endothelial VEGF-R3 expression. Tumors with necrosis expressed epithelial VEGF2 to a greater degree than tumors without. Finally, higher epithelial VEGF-A, epithelial VEGF-R1, and endothelial VEGF-R1 and endothelial VEGF-R3 expression were all associated with collecting system invasion.

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**Fig. 1.** DSS after nephrectomy for type 1 and type 2 PRCC. HR, hazard ratio.
Table 2. Univariate and multivariate models of DSS for both type 1 and type 2 PRCC

| Covariate                      | Univariate                  | P       | Rank | Multivariate                  | P       |
|--------------------------------|-----------------------------|---------|------|------------------------------|---------|
| ECOG performance status        | 7 (3.28-14.9)               | <0.0001 | -    | 2.56 (1.06-6.21)             | 0.0369  |
| Symptomatic presentation       | 5.75 (2.41-13.8)            | <0.0001 | -    | 2.9 (1.10-8.34)              | 0.0485  |
| T stage                        | 3.55 (2.46-5.12)            | <0.0001 | -    | 2.83 (1.70-4.72)             | 0.0001  |
| Lymph node metastases          | 8.63 (4.42-16.9)            | <0.0001 | 3    | 0.83 (0.35-1.97)             | 0.6767  |
| Distant metastases             | 40 (17.7-90.7)              | <0.0001 |    n  | 16.9 (6.49-43.9)             | <0.0001 |
| Nucleolar grade                | 3.8 (2.00-7.21)             | <0.0001 | 7    | 1.37 (0.63-2.95)             | 0.4262  |
| Multifocality                  | 0.83 (0.35-1.98)            | 0.6733  |      |                              |         |
| Necrosis                       | 2.49 (1.30-4.78)            | 0.006   |      |                              |         |
| Vascular invasion              | 4.92 (2.3-10.5)             | <0.0001 | 6    | 1.26 (0.56-2.81)             | 0.5744  |
| Sarcomatoid features           | 8.91 (3.54-22.4)            | <0.0001 | 1    | 0.92 (0.29-2.98)             | 0.8938  |
| Collecting system invasion     | 5.49 (2.83-10.6)            | <0.0001 | 4    | 1.17 (0.55-2.46)             | 0.6825  |
| Papillary subtype              | 3.93 (1.39-11.1)            | 0.01    | 5    | 0.7 (0.21-2.30)              | 0.5525  |

**Cytogenetic profile.** Of the 57 tumors with an abnormal karyotype, the following complex patterns were observed: hypodiploid in 12 cases (21%), pseudo-diploid in 6 (11%), hyperdiploid in 47 (87%), and polyploid (≥58%) in 5 (9%). The most frequently observed cytogenetic abnormalities were trisomy 7 (n = 35, 61%), trisomy 10 (n = 31, 54%), trisomy 12 (n = 28, 49%), trisomy 16 (n = 22, 39%), trisomy 3 (n = 13, 23%), trisomy 20 (n = 17, 30%), monosomy 21 (n = 8, 14%), loss of 3p (n = 8, 14%), gain of 5q (n = 7, 12%), loss of 1p (n = 6, 11%), loss of 9p (n = 6, 11%), trisomy 10 (n = 6, 11%), and loss of chromosome Y in men (n = 32, 71%). Trisomy 7, trisomy 10, trisomy 12, trisomy 16, trisomy 20, monosomy 21, and loss of chromosome Y were all not linked with papillary type, pathologic variables and survival.

We sought to identify chromosomal signatures of type 1 (n = 22) and 2 (n = 35). Type 2 PRCC had a greater number of chromosomal aberrations than type 1 (median 8 versus 6, P = 0.018). Loss of 1p (17% versus 0%, P = 0.040), loss of 3p (23% versus 0%, P = 0.016), and gain of 5q (20% versus 0%, P = 0.025) were exclusively observed in type 2 tumors, whereas type 1 tumors more frequently had trisomy 17 (73% versus 43%, P = 0.028).

Among both subtypes, trisomy 17 was associated with lower T stages (81% versus 19%, P = 0.003), less frequent nodal (6% versus 31%, P = 0.016) and distant metastases (10% versus 31%, P = 0.044), and longer survival (P = 0.034; Fig. 4). Aberrations leading to loss of 1p material were observed in 6 tumors (11%) and included three derivative chromosomes 1 (der(1)t(1;12)(p13;p11.2), der(1)t(1;2)(p13;11.2), der(1)t(1;6)(p32;q21)), one add(1)(p36.2), one terminal deletion del(1)(p35), and one loss of the entire chromosome 1. Patients with loss of 1p had more frequently T stages 3 to 4 (83% versus 31%, P = 0.013), lymph node metastases (67% versus 11%, P = 0.001), and grade 3 tumors (83% versus 26%, P = 0.004). DSS was worse for patients with loss of 1p compared with those without (P = 0.045; Fig. 4).

Loss of chromosome 3p material was noted in 8 cases (14%). Three tumors had numerical loss of chromosome 3, three were terminal deletions with breakpoints at 3p12, 3p14, and 3p25, one tumor showed interstitial loss of 3p12-p21 and one had unbalanced translocation der(3)t(3;10)(p11.2;q11.2). Loss of 3p was associated with higher T stage (all had T3-4, P < 0.001), lymph node involvement (63% versus 10%, P < 0.001), distant metastasis (63% versus 12%, P = 0.001), higher grades (G3: 63% versus 27%, P = 0.042), and larger tumor sizes (8.8 ± 2.8 cm versus 5.9 ± 5.5 cm, P = 0.031). In terms of outcome, patients with loss of 3p had worse survival (P < 0.001), representing a 13.4-fold increased risk of death from PRCC (95% CI 3.35-54.3; Fig. 4).

Loss of 9p occurred in six cases, of which five had type 2 PRCC. Three were terminal deletions of the short arm of chromosome 9 with the breakpoints identified at 9p13, 9p21, 9p22, two were numerical losses of the entire chromosome, and one tumor had unbalanced translocation der(7)(9;2)(p11.2;p13). Loss of 9p material was associated with higher T stage (all were T3-4; P = 0.001), lymph node involvement (50% versus 14%; P = 0.027), distant metastases (67% versus 14%; P = 0.002), and larger tumor sizes (14.5 ± 9.1 cm versus 5.3 ± 3.8 cm; P = 0.001). Loss of 9p carried a 5.1-fold increased risk of death from PRCC (95% CI, 1.27-20.7; Fig. 4).

**Discussion**

The main findings of this study are as follows: (a) type 1 and type 2 PRCC possess unique clinico-pathologic and molecular profiles; (b) type 2 PRCC is associated with worse survival; however, metastatic type 1 has poorer survival than metastatic type 2 PRCC; (c) VEGF-R2 and VEGF-R3 can assist in subdividing type 1 and type 2 PRCC because they are differently expressed; (d) PTEN, EpCAM, gelsolin, CAIX, and proteins of the VEGF family are associated with survival in PRCC; (e) trisomy 17 predicts improved survival, whereas loss of 1p, 3p, or 9p material lead to worse prognosis.

Stratification of PRCC into two subtypes was first proposed by Delahunt and Eble (9). The value of subdividing has been evaluated throughout multiple studies with the consensus that type 2 tumors are usually of higher stage and grade (9, 11, 12) and are associated with poorer prognosis (12–14). However, as in our series, type does not seem to be an independent prognostic factor on multivariate analysis (13).

Multifocality and necrosis are both pathologic landmarks of PRCC. In our series, the incidence of multifocality was ~15%, which is greater than the incidence in other RCC subtypes (21, 22). We found that multifocality is equally prevalent in type 1 and 2 and is not a prognostic factor, which confirms data.
from a recent report (22). Sengupta et al. (23) determined that necrosis leads to worse survival in clear cell and chromophobe RCC but not PRCC. In our study, the incidence of necrosis was higher in type 2 tumors and presence of tumor necrosis was retained as an independent prognostic factor of poor survival. An interesting finding was that prognosis of metastatic type 1 PRCC was poorer than for type 2. We speculate that unique genetic and molecular aberrations in type 1 and type 2 tumors lead to activation of different molecular pathways, which may account for this finding.

Immunohistochemical differences in PRCC subtypes have been previously reported. Ki-67, AgNOR, and topoisomerase IIα are more highly expressed in type 2 (10, 24), whereas type 1 expresses CK7 and MUC1 to a greater degree (14, 24). In our study, we compared the immunohistochemical expression of tumor markers that are involved in the hypoxia induced pathway, the mammalian target of rapamycin pathway, the cell cycle, cell adhesion, proliferation, and angiogenesis. We found that only VEGF-R2 and VEGF-R3 are differential diagnostic markers between both subtypes. However several VEGF

![Graph showing protein expression for type 1 and type 2 PRCC and association with clinical and pathologic variables.](https://www.aacrjournals.org/clin-cancer-res/article-pdf/15/4/1166/3639546/1166.pdf)
receptors are highly expressed in both subtypes of PRCC, particularly in the tumor epithelium. This finding supports the application of VEGF-tyrosine kinase-inhibitors in PRCC. In fact, responses in PRCC were recently shown (25).

A wide variety of proteins seemed to influence DSS in PRCC including endothelial VEGF-R2 and VEGF-R3, EpCAM, gelsolin, and PTEN expression. EpCAM is an adhesion molecule that has been previously identified as a favorable prognostic factor in clear cell RCC (26). We observed higher expression of EpCAM in PRCC than in clear cell RCC and noted significantly better survival in patients with higher EpCAM expression. Higher expression of gelsolin, a member of the actin-binding protein family, is associated with worse cancer-specific survival in clear cell RCC (27). In contrast, PRCC with higher gelsolin exhibited better prognosis.

PRCC is characterized by a cytogenetic pattern distinct from other types of renal cancer. Trisomies of chromosomes 7, 12, 16, 17, and 20 are the most frequently noted karyotype aberrations (1, 11, 15, 28). Additionally, loss of chromosome Y and loss of 9p material have been reported (11, 28, 29). It has been further shown that gains of chromosome 7 and 17 are associated with type 1 cancers (11, 28). Hierarchical cluster analysis, however, has not shown distinct cytogenetic profiles for the two subtypes (11). We examined the chromosomal patterns of type 1 and 2 PRCC and their prognostic relevance. Trisomy of chromosome 17 was more frequent in type 1, whereas aberrations of chromosome 1p, 3p, 5q, and monosomy 21 are restricted to type 2. These observed cytogenetic aberrations are in accordance with previous studies (11, 28–30). Our data does not support that gains of chromosome 7p are more frequent in type 1 PRCC as suggested by Jiang and colleagues (28).

Previous studies showed that loss of 9p material correlates with of higher stages grades (11, 29). Our analyses yield similar findings in addition to poorer survival with loss of 9p material. We further showed that occurrence of trisomy 17 favors better prognosis. Indeed, the majority of grade 1 tumors exhibit trisomy 17 (30), whereas type 2 tumors have a lower incidence of trisomy 17 (11, 28). Loss of chromosome 3p in PRCC implied a more aggressive phenotype and was associated with worse survival. This is the opposite of what is seen in clear cell RCC, where loss of the VHL gene on chromosome 3p has been linked with a more favorable outcome (31). It is possible that other tumor-suppressor genes on the short arm of chromosome 3p may be more important in PRCC tumorigenesis.

A new strategy for treatment of PRCC is to target the c-Met receptor or its ligand, hepatocyte growth factor. Mutation of the MET proto-oncogene has been frequently observed in hereditary PRCC and in a subset of sporadic PRCC (32–34). Additionally, trisomy of chromosome 7, which contains the MET and HGF genes, is a frequent aberration in sporadic PRCC. Hepatocyte growth factor and MET protein expression are frequently observed in clear cell RCC and may be associated with improved survival (35, 36). In our analysis, however, trisomy 7 was not correlated with survival in PRCC.

Our results have some limitations that must be addressed including the retrospective nature. The cytogenetic analysis, however, was prospectively collected at time of nephrectomy. Further prospective studies on a larger cohort should be undertaken to confirm our findings.

Conclusions

Unique clinicopathologic and molecular profiles of PRCC were identified. Type 2 PRCC is associated with poorer
ECOG performance status, higher stage and grade, and necrosis, leading to worse prognosis compared with type 1 PRCC. VEGFR-2 and VEGFR-3 are differentially expressed between PRCC subtypes and PTEN, EpCAM, gelsolin, CAIX, and proteins of the VEGF family are further important prognostic factors. Trisomy 17 predicts improved survival, whereas loss of 1p, 3p, or 9p material leads to worse prognosis.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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