Prognosis and Outcomes

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38.1 Introduction

Clinical outcome in Wilms' tumor (WT) has progressively improved. The credit for this certainly goes to ongoing National Wilms Tumor Study Group (NWTSG)/Children Oncology Group (COG) and International Society of Pediatric Oncology (SIOP) trials, which have identified a variety of novel factors affecting prognosis other than staging. With the incorporation of multimodality therapy, the 4-year overall survival (OS) for low-risk (LR) WT is reported at 98.4% [1]. However, despite this success, a subset of high-risk (HR) WT continues to elude the researchers and treating physicians. Whereas favorable histology (FH) has 4-year OS of 99% to 86%, OS in unfavorable histology (UH) continues in ranges from 78% to 28% depending on the stage [2]. These HR WT carry poor clinical prognosis with high recurrence rates, and therefore, survival rates are low worldwide.

Aggressive chemotherapy (ChT) and radiation therapy (XRT) in HR WT or those with relapsed tumors have their own set of complications affecting outcomes adversely. The results of these therapies are comparable to conventional ChT but with low survival. There is therefore urgent need to think beyond the multimodal approach of surgery, ChT, and XRT to improve prognosis in this subset of patients.

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38.2 Prognostic Factors

As mentioned previously, additional prognostic factors have been incorporated as a result of international trial studies. These factors aid in the risk stratification scheme, thereby providing treatment with precision. There are a lot of future potentials as further success may be achieved through novel markers to refine risk stratification.

Although both SIOP and National Wilms Tumor Study Group (NWTSG)/COG approach provide excellent overall outcomes, all prognostic factors are not adaptable in both approaches. One prognostic factor that is predictive of outcome in NWTSG/COG may not be having the same value in SIOP. This is because the approach to clinical management is distinct. COG permits immediate histological diagnosis, accurate staging, and lymph node (LN) status without alteration in staging post nephrectomy. In SIOP instead, because of preoperative ChT, fewer patients have LN involvement detection. Response to ChT may be assessed by reduction in tumor volume. Response is also assessed by histological changes following ChT. These factors, viz., staging, histology, reduction in tumor volume, and initial responsiveness to ChT, are utilized for risk stratification in SIOP [3].

As WT appears to have a spectrum with a subset of very low-risk (VLR) WT at one end and HR WT or diffuse anaplastic histology (AH) tumor at another, a special mention for the subset of VLR WT seems imperative to define a

Y. K. Sarin (ed.), *Wilms' Tumor*, https://doi.org/10.1007/978-981-19-3428-5_38

class of tumor where the prognosis is reported as excellent. These are defined as stage I, FH WT with weight less than 550 g, and age at diagnosis less than 2 years. Studies regarding the need for post-nephrectomy ChT or observation and chances of relapse in VLR WT have been conducted. AREN0532 study enrolled such 116 patients who didn't receive ChT with a median follow-up of 80 months. Tumors were analyzed for 1p and 16q loss, 1q gain, and 11p15 imprinting. Relapse was seen in 12 patients. Results showed that 11p15 methylation status was associated with relapse. Loss of heterozygosity (LOH) was 20% and loss of imprinting (LOI) was 25%. So, most of these patients can be safely managed with observation alone, but there is a need to incorporate biomarkers along with clinical features for observation strategy [4].

Recently, tumor-associated macrophages (TAMs) have been known to predict the prognosis in WT; presence of high-density M2-type macrophages was pointer to higher tumor stage and shorter OS [5].

Important prognostic factors that contribute to high recurrence and mortality include:

1. Tumor stage.
2. Tumor histology.
3. Tumor weight (COG), tumor volume (SIOP).
4. Age > 2 years.
5. Molecular and genetic markers (LOH 16q,1p and 1q gain).

38.2.1 Tumor Stage

While details of COG and SIOP staging have been mentioned elsewhere, it is well known that since the beginning, the tumor stage is considered a prognostic factor for WT. It is an established factor to have prognostic importance or to assign treatment regimens since the first NWTS study in 1969. Higher stages (III to V) are linked with poorer prognosis due to extensive disease as compared to lower stages (I and II) (Table 38.1) [6]. Ehrlich et al. advocated stratifying stage III subgroup patients into risk appropriate treatment groups after evaluating patients enrolled on NWTS-5. According to this study, among patients with local stage III disease, the LN involvement and microscopic residual disease combination were associated with 8-year event-free survival (EFS) of 71% and OS of 86%. This was lower to results with LN involvement alone (8-year EFS and OS of 82% and 91%, respectively), the microscopic residual disease only (8-year EFS and OS of 84% and 94%), and neither LN involvement nor microscopic residual disease (8-year EFS and OS, 90% and 95%, respectively) [7]. SIOP 93–01 estimated 5-year OS for stage I and IV were 97% and 82%, respectively [3, 8].

38.2.2 Tumor Histology

In COG protocol, histological assessment is done before the administration of chemotherapy, and tumor is categorized based on:

(a) Focal anaplasia.
(b) Diffuse anaplasia (DA).
(c) No anaplasia/Favorable histology (FH).

In SIOP, following ChT, the tumor is histologically classified as low, intermediate, and high risk based on the degree of necrosis and balance of cell types (blastemal, epithelial, and stromal). Those with DA and/or blastemal-type tumor are HR categories.

In COG, patients showing FH WT stage I or II disease without LOH experienced EFS of more than 85% and OS of more than 99% [9]. A comparison of outcome in FH WT and those with diffuse anaplasia revealed significant difference in NWTS-5. Four-year OS for stage I/II FH and III/IV FH were 98% and 92%, respectively. For those with diffuse anaplasia in stage I/II, stage III, and stage IV, it was 83%, 65%, and 35% respectively. For bilateral tumors with diffuse anaplasia, 4-year OS was adjudged as 55% [10].

38.2.2.1 Anaplastic Histology

Five to 10% of WT demonstrate AH. AH is established by the presence of atypical cells, polyploid mitotic figures, large nuclear size, and hyperchromatic nucleoli [11]. In a NWTSG

Table 38.1 Stagewise survival rates for WT children as reported in NWTS/COG (AREN0321, AREN0532, and AREN0533)

Stage	NWTS/COG study protocols	Reported survival (%)
I and II	Primary surgical resection followed by 19 weeks of VCR and AMD	*Surgery alone* [31] 5-year EFS 84%
VLR WT (age < 2 years, FH, tumor <550 g)	May be managed by resection alone [4, 31]	*Surgery, adjuvant ChT* 5-year EFS 97% 4-year EFS 90%; no deaths
Stage I and II with LOH at 1p and 16q	± DOX	4-year EFS 75% improved to 4-year EFS 84% with addition of DOX [3]
Anaplastic WT	Flank XRT	4-year EFS 33–70% depending on stage [10]
Stage III	Primary surgical resection followed by 25 weeks of VCR, AMD, DOX, and XRT based on LN involvement or peritoneal contamination	4-year EFS 66%
Stage III FH with LOH 16q and 1p	Addition of CTX and ETOP; regimen M [34]	4-year EFS 91%
Stage IV	Primary surgical resection followed by 25 weeks triple drug or intensive therapy. Regimen M in LOH evidence XRT if metastasis persisted	Resolution of lung metastasis OS 95% (6-week triple drug regimen) [35] *Without WLI* 4-year EFS 78% *With WLI*[a] 4-year EFS 85% ***C**ombined radiation with regimen M* 4-year EFS 88%
Stage V	[b]6-week triple drug regimen → NSS→postoperative ChT depends on histology and presence of tumor in LN or peritoneal cavity	*Depending on Stage II to IV* 4-year EFS 83% to 33%

VLR WT very low-risk Wilms' tumor, *DOX* doxorubicin, *VCR* vincristine, *AMD* actinomycin-D, *CTX* Cyclophosphamide, *ETOP* Etoposide, *XRT* radiotherapy, *ChT* chemotherapy, *LN* lymph node, *LOH* loss of heterozygosity; *OS* overall survival, *EFS* event free survival, *NSS* nephron-sparing surgery, *WT* wilms' tumor, *WLI* whole lung irradiation, *FH* fovarable histology

[a]A previous NWTS/COG study figure

[b]Similar in SIOP

study, a multivariate analysis of 632 patients not having metastasis at the time of diagnosis, it was concluded that anaplasia is associated with a high risk of mortality, metastases, and recurrences [11]. DA, fortunately less common, is associated with more than 60% of deaths. It is the most important predictor for shorter survival at the time of diagnosis. As in COG, in SIOP too, DA is considered the most important negative predictor of outcome. Percentage of viable cells in the tumor and the cell type in viable component after administration of neoadjuvant ChT also contribute to prognostic information in revised SIOP histological classification [12].

38.2.2.2 Blastemal Histology

Blastemal-type WT has been reclassified by SIOP as a HR histological subgroup in WT in 2002 [13]. This histological subtype fortunately contributed only 10% in SIOP 93–01 cohort but was responsible for one-third of events. This morphology is therefore a strong prognostic factor associated with adverse outcome, if seen in patients who received preoperative ChT. The risk of relapses also appears to be high in patients with blastemal-type histology as compared to other histological subtypes in the non-anaplastic tumor [14].

The benefit of knowledge of histological subgroup was seen in SIOP 2001 study as patients

with blastemal histology received extra ChT, which increased 5-year EFS of 67% in SIOP 93–01 to 80% in SIOP 2001 for all stages of localized disease [3]. The addition of doxorubicin (DOX) Nto vincristine (VCR) and actinomycin-D (AMD) also showed an increase in EFS in blastemal-type WT. Post-ChT histological classification also permitted reduced therapy in some subgroups. OS was comparable in patients with VCR and AMD, with or without DOX in stage II or III intermediate-risk WT [15].

38.2.3 Tumor Weight (COG) and Volume (SIOP)

As discussed above, a subgroup of patients with tumor weight below 550gm along with age below 2 years and FH have excellent prognosis in COG studies. In risk stratification scheme, this subset of patients was observed, while those in similar age group but with tumor weight equal to or above 550gm were subjected to EE4A (VCR-AMD) for 18 weeks) [3].

Tumor volume as a prognostic factor is valuable in SIOP experience. It was used as a prognostic factor in the German Society of Pediatric Oncology and Hematology (GPOH) institutions. In SIOP93–01 and 2001, a cutoff volume of 500 mL in intermediate-risk subgroup showed a distinctive difference in the outcome of the non-epithelial, non-stromal types of intermediate-risk WT. Five-year OS and EFS were 95% and 88% for smaller tumors as compared to 90% and 76%, respectively, for larger tumors [3]. This difference led to more intensification of therapy in patients with tumor greater than 500 mL.

38.2.4 Age

In COG studies, higher age was associated with higher recurrence rates and hence poorer outcome. This was possibly due to fact that anaplasia was rarely seen in below 1-year age group. Now, with improved therapeutic options, the impact of age as a prognostic factor is reduced. Impact of age as prognostic factor is well defined in VLR WT as mentioned above. Children with age less than 24 months generally have a lower relapse and better prognosis than the older children. A study showed that 20% of infants had an incidental diagnosis of WT; this subset of infants had a relatively smaller-sized nonmetastatic tumors and higher rate of malformations than infants of the matching age group having symptoms. It was also noted that oncological outcomes such as 5-year EFS rate in infants (under 1 year of age) of 96% were much better than 80% EFS rates in children aged 1–2 years ($P = 0.018$) [16]. Age is not used in SIOP trials for risk stratification.

Adult patients with WT have higher treatment-related toxicity than their younger counterparts, though the survival rates are comparable with children having the same stage and histology.

38.2.5 Molecular and Genetic Markers

38.2.5.1 Loss of Heterozygosity

One of the important goals of NWTS-5 was to prospectively estimate the prognostic importance of LOH at chromosomes 1p and 16q and 1q gain. Coexisting LOH for chromosomes 1p and 16q observed in approximately 5% of FH WT was seen to be significantly associated with an increased relative risk (RR) of relapse and death [17]. For patients with stage I/II disease, the RR of relapse and death were 2.9 ($p = 0.001$) and 4.3 ($p = 0.01$) individually. Among the cases with stage III/IV, the RR of relapse and mortality were 2.4 ($p = 0.01$) and 2.7 ($p = 0.04$), respectively.

38.2.5.2 Gene Expression Profiles

The WT1 alteration and 11p15 LOH or loss of imprinting (LOI) are thought to make distinct pathogenetic mechanisms for the growth and/or progression of WT; yet these events are not necessarily independent given the proximity of the 11p13 and 11p15 loci. In a study conducted by Perlman et al., all patients with WT1 mutations also had 11p15 LOH, yet 11p15 LOH was identified without WT1 mutations in a proportion of patients. Accordingly, 11p15 is apparently an added sensitive prognostic indicator [18].

Chromosome 1q gain is one of the most frequent cytogenetic findings in WT, seen in approximately 30% of WT cases [19]. Data gathered through the NWTS-5 clinical trial was used to evaluate the prognostic importance of 1q gain in FH WT. Among all stages, 8-year EFS and OS for patients with 1q gain were 77% and 88%, respectively. For cases without 1q gain, 8-year EFS and OS were 90% and 96%, respectively. But, no significant variation in particular histologic predominance based on presence or absence of 1q gain was observed [20].

TP53 gene mutations in WT are associated with high risk for relapse and fatal outcome [21]. Whereas FH WT practically never carries TP53 mutations, approximately 75% of AH WT does so. It shows that TP53 mutation may lead to the development of AH and provide predictive pointer toward aggressive disease [20, 22]. TP53 mutations are found in at least 90% of fatal cases of AH WT, more so in the presence of diffuse anaplasia. Importantly, even among non-anaplastic fatal tumors, 26% had TP53 changes; so, the mere presence of TP53 gene mutations cannot be taken as diagnostic of AH WT.

Some contemporary molecular profiling has demonstrated significant associations linking AH and loss of 4q and 14q [19]. Distinct candidate genes involved in WT pathogenesis at these latter loci have not been recognized yet, and the importance of these genomic alterations remains unknown.

As mentioned above in the discussion of VLR WT, 11p15 methylation analysis may be used as a biological prognostic marker in patients who do not require postoperative ChT. Patients may be divided into three categories, viz., retention of imprinting (ROI), LOI, or LOH. There was a significant relapse in LOH at 11p15 [18].

MYCN gene has frequently been reported in WT as well as other embryonal tumors, and its overexpression due to P44L mutation in WT has been recognized as an inherent prognostic feature as its connection with poorer relapse-free and overall survival is independent of histology [23]. Further details of molecular markers are mentioned elsewhere in this book.

38.3 Prognosis in Special Population

38.3.1 Children with Bilateral Wilms' Tumor

Approximately 1% of children with unilateral Wilms' tumor (uWT) develop metachronous lesions. End-stage renal disease (ESRD) in metachronous bilateral Wilms' tumors (BWT) with diffuse anaplasia is quite high. High risk of recurrence with BWT results in relatively poor prognosis as compared to uWT. The addition of renal failure also creates a difference in the quality of life.

To conserve renal function, nephron-sparing surgery (NSS) is an acceptable norm. But it may bring an extended risk of relapse, which should be controlled by other approaches such as ChT and XRT [24]. However, it continues to be a challenge, to adjust between preserving renal function and preventing recurrence, emphasizing the need for further prospective studies. These patients are at high risk of renal impairment leading to ESRD, especially if they also receive RT.

In 81 children with synchronous BWT who received radiation therapy as part of their treatment in NWTSG study, almost one-third of patients had raised serum creatinine; 18 patients had moderate renal insufficiency, and 10 had severe renal insufficiency with estimated GFR < 60 mL/min/1.73 m^2 [25].

38.3.2 Children with Lung Metastasis

In COG AREN0533, "rapid complete responders" (RCR), considered as those with complete radiological disappearance of lung metastasis after DD4A regimen or whose residual nodule is negative for tumor at 6-week reevaluation, were continued with DD4A without whole lung irradiation (WLI). This study perceived superior OS after omission of primary WLI in patients with complete response (CR) [26]. Similarly, patients who did not have complete resolution of nodules were labeled as "slow, incomplete responders" (SIR). EFS was significantly increased, with the excellent OS, in patients with

stage IV FH WT and SIR using four cycles of cyclophosphamide/etoposide in addition to DD4A drugs in this study.

In SIOP 93–01 trial, 5-year EFS and OS were 73% and 88%, respectively. Survival was better in stage IV patients with complete response to pre-nephrectomy 6-week ChT and those who underwent metastasectomy, compared to those with incomplete response who had only 48% survival [27].

38.3.3 Children with Recurrence

Recurrence occurs in about 15% of FH WT and nearly 50% of AH WT [27]. So, UH is a significant prognostic factor associated with recurrence. Apart from histology, stage and presence of certain molecular markers like LOH contribute to relapse significantly in certain patients, even with FH. The majority of recurrences are seen in the lung and within 2 years of therapy.

In recurrence, prognostic factors that are associated with better response to salvage therapy and therefore better outcome include:

1. Late recurrence more than 12 months after initial diagnosis.
2. Initial FH.
3. Lower stage at initial diagnosis.
4. Complete resection with no gross residual disease.
5. No XRT.
6. Initial treatment with VCR and AMD (Table 38.2).

Table 38.2 Showing post-relapse comparative survival after initial regimen [36, 37]

Treatment regimen	Post-relapse survival
Initial therapy VA *Salvage therapy* (CTX, DOX, and XRT)	OS 82%, 4-year EFS 71%
Initial therapy VAD, XRT *Salvage therapy* (CTX, CARB along with surgery, and XRT)	OS 48%, 4-year EFS 42%

VA vincristine-actinomycin-D, *VAD* vincristine-actinomycin-D-doxorubicin, *CTX* cyclophosphamide, *CARB* carboplatin, *XRT* radiotherapy, *OS* overall survival, *EFS* event free survival

As believed earlier, regarding increased risk of local recurrence in patients with stage III disease, a study had shown that initial needle biopsy was not clearly associated with increased risk of local recurrence in abdominal cavity [28].

After initial diagnosis of WT, around 1% of children develop metachronous lesion, and 90% of them show relapse in initial 2 years. Presence of persistent metanephric cell foci (nephrogenic rests) contributes to recurrence in the contralateral kidney.

Children who develop recurrence have post-relapse 4-year survival of 50–80%. Among them, the OS and 4-year EFS are lower in children who had initially received more intensive regimen (Table 38.3).

38.3.4 Children with Syndromic WT

Although syndromic WT is mentioned in detail elsewhere, it is imperative to mention here that these subsets of children behave differently in terms of increased mortality due to a variety of reasons. In around 10% of cases, WT occurs as a component of multiple malformation syndromes like WAGR, Beckwith-Wiedemann syndrome (BWS), or Denys-Drash syndrome (DDS). In a case series of 64 patients with WAGR syndrome and FH, 7% had bilateral disease and 50% developed chronic kidney disease after 20-year follow-up. Four patients in this study developed ESRD, requiring a transplant [29]. These patients, therefore, require aggressive renal surveillance with ultrasound. Diffuse mesangial sclerosis in DDS also gradually proceeds to nephrotic syndrome and renal failure. Higher mortality was reported in BWS earlier. But it improved progressively due to better tumor recognition and treatment. Prognosis is now favorable after childhood [30].

38.4 Survival Outcomes

OS has progressively increased from 20% in the 1960s to 90% in both SIOP and COG groups. Five-year OS rate approaches approximately 98% in children with VLRWT [31].

Table 38.3 Showing brief outcome in high- (HIC), upper middle-income (UMIC), lower middle-income (LMIC), and low-income (LIC) countries reported in different studies [33]

Author	Country	Period	*N*	M:F	Mean age at diagnosis (year)	Stage at diagnosis	Survival		Limiting factors for care
							EFS	OS	
Offer et al. [33]	England HIC	1968–2012	178	0.8–1	3	I–II—43% II–IV—34% V 7%	–	1 year 88% 5 years 76% 10 years 76%	Delayed asymptomatic diagnosis
Verma and Kumar [38]	India LMIC	2005–2014	108	4:1	2.5	I—21% II—30% III—35% IV—10% V—4%	5 years 73%	5 years 74%	Malnutrition Drug shortage Poor supportive care Lack of surgical expertise
Guruprasad et al. [39]	India LMIC	2003–2010	61	0.9:1	3.3	I—28% II—16% III—38% IV—15% V—3%	5 years 83%	5 years 85%	Loss of follow-up Late presentation
Seyed-Ahadi et al. [40]	Iran UMIC	1992–2002	55	1.2:1	3.8	I—33% II—16% III—38% IV—9% V—2%	4 years 71%	4 years 86%	Late presentation, associated anomalies
Visser et al. [41]	South Africa UMIC	1983–2007	98	0.8:1	3.8	I—37% II—18% III—24% IV—21%	–	76.5%	Malnutrition
Sangkhathat et al. [42]	Thailand UMIC	1996–2007	34	1.3:1	2.1	I—38% II—12% III—38% IV—6%	4 years 53%	4 years 65%	Late presentation Poor treatment compliance Finances
Abudidris et al. [43]	Sudan LMIC	1999–2007	37	0.9:1	4.1	I—3% II—19% III—68% IV—11%	–	11%	Finances Loss to follow-up Late presentation Lack of education
Libes et al. [44]	Kenya LIC	2008–2011	136	–	–	–	–	2 years 36%	Drug shortage Lack of education

HIC high income country, *LMIC* low-middle income country, *LIC* low income country

Table 38.4 Outcomes of WT according to the histology, stage, and the income status of the country

		LMIC		HIC					
		5 years	5 years	4 years		8 years [49]		10 years [50]	
Histology	Stage	EFS %	OS %	EFS %	OS %	EFS %	OS %	EFS %	OS %
FH	I	92.3 [45]	92.6 [48]	85.4 [47]	96.87 [47]	92	97	91.2	100
	II	83.3 [45]	92.0 [48]	90.23 [47]	100 [47]	83	94	91.4	97.1
	III	94.4 [45]	69.2 [48]	84.34 [47]	97.96 [47]	88	93	82.8	88.6
	IV	80 [45]	47.1 [48]	76.5 [47]	94.1 [47]	76	82	65.6	77.9
	V	50 [45]	50.0 [48]	83.18 [47]	97.7 [47]	74	89	71.8	80.8
UH	I	87.8 [46]	100 [46]	68.4 [10]	78.9 [10]	88	88	75.0[a]	72.9[a]
	II	40 [46]	100 [46]	82.6 [10]	81.5 [10]	52	58		
	III	57.1 [46]	71.4 [46]	64.7 [10]	66.7 [10]	47	52		
	IV	80[b] 60[c]	–	33.3 [10]	33.3 [10]	36	36		
	V	–	–	25.1 [10]	41.6 [10]	40	45		

HIC high income country, *LMIC* low-middle income country, *FH* favorable histology, *UH* unfavorable histology, *EFS* event free survival, *OS* overall survival

[a]Anaplastic histology EFS, OS

[b](I–IV) Focal anaplasia [45]

[c](II–IV) Diffuse anaplasia [45]

The outcome of uWT in SIOP 2001 treated according to histological subtypes showed that while OS was above 90% in low to intermediate risk, it was only 75% in high-risk tumors after 5 years. The dismal outcome was seen in high-risk metastatic WT with 2-year OS of 33% [3].

From 1969 to 1995, 6185 patients were enrolled in a COG study, and OS was 84% through 2002 [32]. Major cause of deaths among these children included tumor related in 86%, therapy related in 9%, unrelated to disease in 5%, and unknown in 1% [32]. Ninety-one percent of deaths occurred in the first 5 years of diagnosis and were due to primary tumor. Late deaths were attributed almost equally to therapy and tumor related [32].

Survival after diagnosis and treatment is better in most high-income countries (HIC). Low- and middle-income countries (LMIC) prevail to struggle with WT detection and treatment. Overall survival varied from 70% to 97% in HIC, 61% to 94% in upper middle-income countries, 0% to 85% in lower middle-income countries, and 25% to 53% in low-income countries [33]. Delay in diagnosis, shortage of available treatment, and poor follow-up contributed to the large variations in outcomes. In comparison with HIC, in studies from LMIC, data regarding stagewise 5-year EFS and OS along with histology as parameter are relatively deficient (Tables 38.3 and 38.4).

38.5 Summary and Conclusions

Tumor stage, tumor histology, molecular and genetic markers like LOH at chromosome 16q and 1p, and presence of TP53 are therefore important prognostic factors in the management that contribute to overall outcome in WT. Poorer prognosis is associated with anaplastic histology in stage II to IV tumors, which are the most important predictors of outcome in children. Diffuse anaplasia is worse than focal. The blastemal subtype is associated with adverse outcomes. Other poor prognostic factors affecting outcome include higher stage of the tumor at the time of diagnosis, age older than 2 years, higher positive lymph node density, and large tumor size. Identification of these poor prognostic factors at the beginning of treatment is imperative for physicians to aid in utilizing available therapeutic options and also for evidence-based counseling about overall survival. Future studies in group trials shall possibly reveal more markers for unresponsive tumors.

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