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Efficacy of Preoperative Chemotherapy in Patients With Nephroblastoma and Imaging Findings Suggestive of Preoperative Tumor Rupture

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ABSTRACT

Background and Aims: If Wilms tumor (WT) rupture is suspected preoperatively, it is unclear whether preoperative chemotherapy (preop-CT) can be safely given and whether such patients need to be treated according to local stage III postoperatively.

Methods: We retrospectively analyzed characteristics, treatment, and outcome of patients with preoperative rupture suspected by imaging and clinical symptoms in 119 patients from Germany, Austria, and Switzerland with unilateral WT treated within SIOP studies.

Results: There was no difference in age and gender distribution compared with the overall cohort of patients with WT. The general health condition was characterized at least severely impaired (37.8%). Eighty-nine patients 89 (74.8%) received preop-CT and 30 (25.2%) had upfront surgery. The mean tumor volume at diagnosis undergoing preop-CT was 605 mL compared with 312 mL at primary surgery. Metastases were found in 20 out of 89 (22.5%) and two out of 30 (6.7%) patients, respectively. After preop-CT, 31 patients (34.8%) had local histological stage I, 16 (18.0%) had stage II, 41 (46.1%) had stage III, and one (1.1%) had unknown. Low risk histology was diagnosed in seven (7.9%), intermediate risk in 65 (73.0%), and high risk in 17 (19.1%) patients. After preop-CT, nine patients relapsed (10.1%), compared with four (13.3%) after primary surgery. Relapses were independent of local radiotherapy. Altogether seven patients died. A total of 14 out of 31 patients (45.2%) with overall local stage I of intermediate risk after preop-CT received only 4 weeks AV without radiotherapy after surgery with 100% relapse-free survival.

Abbreviations: AV1, 4 weeks actinomycin and vincristin; GPOH, German Society of Pediatric Oncology and Hematology; preop-CT, preoperative chemotherapy; RFS, relapse-free survival; WT, Wilms tumor.

Jens-Peter Schenk and Rhoikos Furtwängler contributed equally to this work.

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Conclusions: Preop-CT can be given safely, and postoperative treatment can follow the histological staging and risk group, given that a thorough review of the specific situation is done.

1 | Introduction

A suspected rupture of a Wilms tumor (WT) at diagnosis poses unique clinical challenges, as it may increase the risk of peritoneal spread, complicate staging and treatment decisions [1–4]. Careful assessment is required to determine the feasibility of preoperative chemotherapy (preop-CT), as it must balance potential benefits such as tumor shrinkage, downstaging and histologic response with the risk of repetitive bleeding leading to circulatory instability, increased transfusion need, and exacerbating further tumor cell dissemination. Additionally, accurate classification of disease stage is crucial, as misclassification could lead to suboptimal treatment strategies and impact patient prognosis. Multidisciplinary discussions involving oncologists, radiologists, radiation oncologists, and surgeons are essential to tailor individualized treatment approaches that optimize treatment and outcome based on surgical and pathological local staging. Therefore, in the event of suspected preoperative rupture of WT, substantiated through clinical symptoms and imaging studies, two critical questions arise: first, can preop-CT be safely administered in such patients? Second, should these patients be classified and treated as local stage III?

2 | Patients and Methods

We retrospectively analyzed the characteristics, treatment, and outcomes of patients enrolled in three consecutive studies and trials conducted by the German Society of Pediatric Oncology and Hematology (GPOH): SIOP9-GPO, SIOP-93-01/GPOH, and SIOP-2001/GPOH. These studies included patients from Germany, Austria, and Switzerland who had been recruited between 1989 and 2022. Details of the recruitment and the protocols have been published previously [5, 6]. All clinical trials were reviewed and approved by the Ethics Committee of the "Ärztekammer des Saarlandes" (/LS of 23/04/1993, no. 136/01 of 20/09/2002, and 248/13 of 13/01/2014) and local Ethics Committees as appropriate. Informed consent was obtained from all patients or their legal guardians, depending on the patient's age. Pertinent information about the entire cohort is provided in Table 1.

Pretreatment tumor rupture in imaging was suspected if the following characteristics were detected:

- *Fluid findings*: Ascites beyond the cul-de-sac (regardless of the Hounsfield units), retroperitoneal fluid collections, and fat stranding surrounding the tumor (e.g., ascites beyond the rectouterine/rectovesical pouch and perinephric fat stranding) together with
- *Structural abnormalities*: Infiltration into adjacent organs together with bulky retroperitoneal lymph nodes

Tumor mass was defined in cross-sectional images by the solid tumor including central liquid parts but not extra tumoral fluid accumulations, retroperitoneal edema and ascites. The maximal tumor length in three dimensions was measured by radiologists using CT or MRI scans and tumor volume was calculated using the ellipsoid formula:

- Volume [mL] = height [mm] × width [mm] × depth [mm] × 0.523.

The general health status was given by local physicians and categorized into five levels according to the study protocols: 1: normal activity, 2: low health impairment, 3: moderate health impairment, 4: severe health impairment, and 5: intensive care needed. Data on Hb drop, pulse rate, and blood pressure were included in this categorization. These had not been separately documented in the database but were retrospectively retrieved from medical records and telephone notes at the data center.

Since 2017, postoperative treatment was discussed in a multidisciplinary tumor board based on clinical data, pathohistological tumor stage and type, and the surgical findings, like peritoneal deposits, adhesion to other organs, being suspicious for tumor rupture. Before 2017, postoperative treatment was a local decision.

All data were collected in standardized CRFs and anonymized before statistical analysis being in accordance with the general data protection regulation of the European Union. Computational and statistical analysis was conducted using SPSS 27 for Mac (IBM Corp. Released 2020. IBM SPSS Statistics for Mac 27.0.; 64bit; Armonk, NY, USA). Qualitative and quantitative values are presented as relative and absolute frequencies, as well as mean and standard deviation. A *t*-test for two independent samples was employed to compare means between two independent groups. Values that did not exhibit a normal distribution were compared using Mann–Whitney *U* tests for two independent groups. To compare relative frequencies between independent groups, we utilized the χ^2 and the Fisher exact test. Survival was evaluated using Kaplan–Meier analyses. Two-sided significance was defined as $p < 0.05$ for all statistical tests. Due to the exploratory nature of the investigation, we did not account for the issue of multiple statistical testing. Consequently, we report raw, two-sided *p* values.

3 | Results

3.1 | Study Cohort and Baseline Characteristics

A preoperative tumor rupture was diagnosed in 119 patients with unilateral WT through primary imaging studies and clinical symptoms. At the same time, 3086 patients with WT were diagnosed within the GPOH studies resulting in a prevalence of 3.9%. Figure 1 shows the imaging studies of a WT patient diagnosed with retroperitoneal preoperative tumor rupture by imaging studies at diagnosis and after preop-CT.

TABLE 1 | Characteristics of the patient cohort.

		Preoperative chemotherapy		Primary surgery		All		
		N	**%**	***N***	**%**	***N***	**%**	***p* value**
Study	SIOP 9/GPO	1	1.1	3	10.0	4	3.4	χ^2-test 0.001
	SIOP 93-01/GPOH	13	14.6	11	36.7	24	20.2	
	SIOP 2001/GPOH	75	84.3	16	53.3	91	76.5	
Mean age [month]		55.6 ± 31.2		78.1 ± 75.1		61.2 ± 47.0		*t*-Test 0.022
Gender	Male	43	48.3	12	40.0	55	46.2	χ^2-test 0.430
	Female	46	51.7	18	60.0	64	53.8	
Syndrome	No	86	96.6	27	90.0	113	95.0	χ^2-test 0.684
	Yes	3	3.4	3	10.0	6	5.0	
General condition at diagnosis	Normal activity	22	24.7	4	13.3	26	21.8	χ^2-test <0.001
	Low health impairment	38	42.7	4	13.3	42	35.3	
	Moderate health impairment	17	19.1	8	26.7	25	21.0	
	Severe health impairment	7	7.9	6	20.0	13	10.9	
	Intensive care needed	1	1.1	6	20.0	7	5.9	
	Unknown	4	4.5	2	6.7	6	5.0	
Side	Right	57	64.0	19	63.3	76	63.9	χ^2-test 0.944
	Left	32	36.0	11	36.7	43	36.1	
Metastasis	No	69	77.5	28	93.3	97	81.5	χ^2-test 0.054
	Yes	20	22.5	2	6.7	22	18.5	
	Lung	18	90.0	1	50.0	19	86.4	
	Liver	5	25.0	2	100	7	31.8	
	Intraabdominal	*2*	*10.0*	*1*	*50.0*	*3*	*13.6*	
	Mediastinum	1	5.0	0	0	1	4.5	
Metastatic response after preoperative CT	CR after CT	7	35.0			7	35.0	
	CR after CT + surgery	3	15.0			3	15.0	
	No CR	6	30.0			6	30.0	
	Unknown	4	20.0			4	20.0	
Tu-volume at diagnosis	<500 mL	40	44.9	20	66.7	60	50.4	

(Continues)

TABLE 1 | (Continued)

		Preoperative chemotherapy		Primary surgery		All		
		N	**%**	***N***	**%**	***N***	**%**	***p* value**
	≥500 mL	31	34.8	4	13.3	35	29.4	
	Unknown	18	20.2	6	20.0	24	20.2	
	Mean volume [mL]	605 ± 601		312 ± 329		532 ± 559		*t*-Test 0.025
Tu-volume after preoperative CT	<500 mL	43	48.3			43	48.3	
	≥500 mL	7	7.9			7	7.9	
	Unknown	39	43.8			39	43.8	
	Mean volume [mL]	228 ± 356				228 ± 356		
Histological risk group	Low risk	7	7.9	0	0	7	5.9	χ^2-test <0.001
	Intermediate risk	65	73	29	96.7	94	79.0	
	High risk	17	19.1	1	3.3	18	15.1	
	Diffuse anaplasia	*10*	*58.8*	*1*	*100*	*11*	*61.1*	
	Blastemal type	*7*	*41.2*			*7*	*38.9*	
Suspicious intraoperative findings	No	54	60.7	17	56.7	71	59.7	χ^2-test 0.630
	Yes	24	27.0	10	33.3	34	28.6	
	Unknown	11	12.3	3	10.0	14	11.8	
Pathological local stage	I	31	34.8	1	3.3	32	26.9	χ^2-test < 0.001
	II	16	18.0	2	6.7	18	15.1	
	III	41	46.1	27	90.0	68	57.1	
	Tumor rupture	*18*	*20.2*	*13*	*43.3*	*31*	*26.1*	<0.001
	Positive lymph nodes	*8*	*9.0*	*0*	*0*	*8*	*6.7*	0.089
	Incomplete resection	6	6.7	1	3.3	7	5.9	
	Unknown	9	10.1	13	48.1	22	18.5	
	Unknown stage	1	1.1	0	0	1	0.8	
Relapse	No	80	89.9	26	86.7	106	89.1	χ^2-test 0.714
	Yes	9	10.1	4	13.3	13	10.9	
	Local	5	5.6	3	10.0	8	6.7	0.467
	Metastatic	7	7.9	3	10.0	10	8.4	0.796
Death	No	83	93.3	29	96.7	112	94.1	χ^2-test 0.493
	Yes	6	6.7	1	3.3	7	5.9	
All		89	74.8	30	25.2	119	100	

Abbreviations: CR, complete remission; CT, chemotherapy.

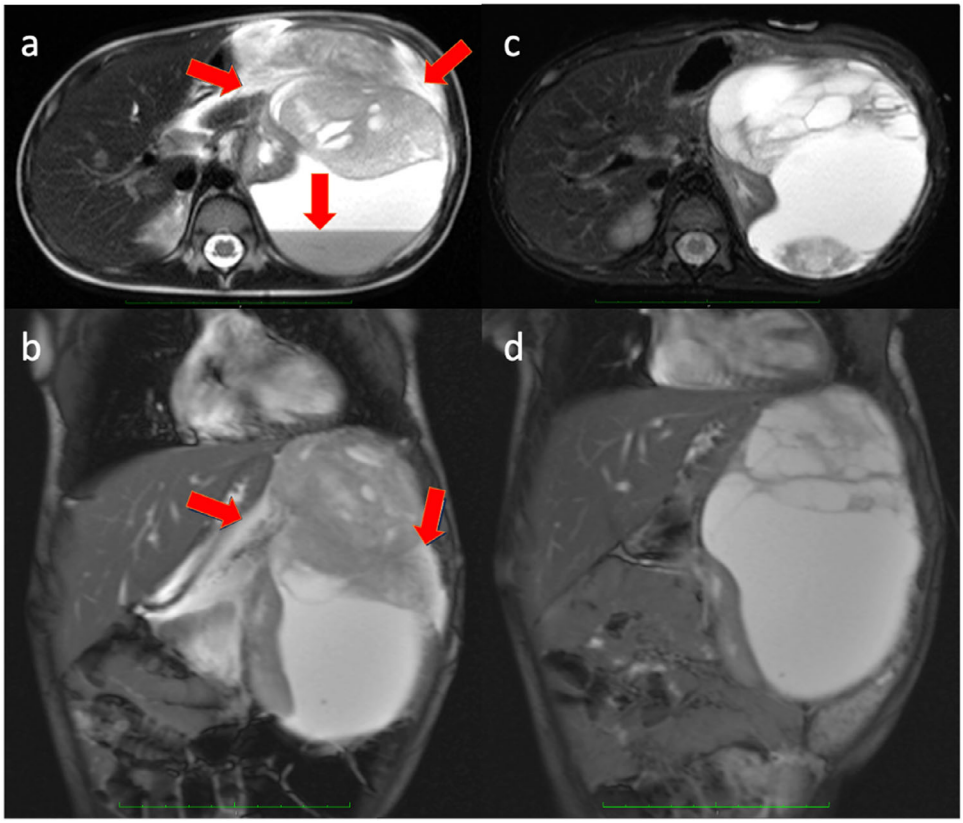

FIGURE 1 | MRI of a 2y 3m old patient with retroperitoneal tumor rupture. Desintegration of renal parenchyma and tumor parenchyma (arrow) with strong bleeding in the retroperitoneal space (fluid–fluid level, arrow), expansion of fluid into retrogastral and peripancreatic space. MRI at diagnosis (a and b) and after preoperative chemotherapy (c and d).

In this cohort of 119 patients with ruptured WTs at diagnosis, 30 patients (25.2%) underwent upfront surgery while 89 (74.8%) received preop-CT. Both groups shared a similar age and gender distribution to the overall WT cohort (Table 1). However, patients treated with preop-CT had a higher tumor burden at diagnosis (mean tumor volume: 605 ± 601 mL), and 20 of them (22.5%) presented with metastatic disease compared with 312 ± 329 mL and two (6.7%) with metastasis in the upfront surgical group (Table 1). Additionally, a general health evaluation indicated that 37.8% of the entire cohort were at least in a severely impaired clinical condition, a proportion that is markedly higher (66.7%) in those undergoing upfront surgery compared with the group with preop-CT, suggesting that the choice of initial treatment was, in part, influenced by poorer baseline health leading to emergency surgery (Table 1).

3.2 | Correlation Between Clinical Symptoms, Intraoperative Findings, and Local Stage III

Patients who were treated with immediate surgery exhibited a significantly higher concordance of pathological stage III, clinical severe impairment, and surgical suspicion of preoperative rupture (Figure 2). Compared with eight out of 30 (26.7%) in the immediate surgery group, only five out of 89 (5.6%) in the pretreated CT patients exhibited the above-mentioned findings, a difference that is statistically significant (Fisher exact test, $p < 0.001$).

3.3 | Local Stage and Histological Risk Group Postchemotherapy

Following preop-CT, the distribution of local stages after surgery was as follows: stage I: 31 patients (34.8%), stage II: 16 patients (18.0%), and stage III: 41 patients (46.1%), with one case (1.1%) remaining unknown. Low risk histology was diagnosed in seven (7.9%), intermediate risk in 65 (73.0%), and high risk in 17 (19.1%) patients. Compared with upfront surgery with 90% local stage III, the difference in local stage distribution was significant lower after preop-CT. But patients receiving preop-CT showed significant more high risk tumors (19.1 vs. 3.3%) (Table 1).

3.4 | Relapse, Mortality, and Treatment Details

Within the preop-CT group, nine relapses (10.1%) occurred, compared with four relapses (13.3%) among patients who underwent upfront surgery. The relapses distributed by local stage were four in stage I, two in stage II, and three in stage III in the pretreated group and four relapses only in stage III in patients with immediate surgery. Local relapses occurred in all stages in patients after preop-CT and only in stage III after primary surgery (Table 2).

Notably, neither histological risk classification nor the addition of local radiotherapy significantly impacted the relapse rate. Data

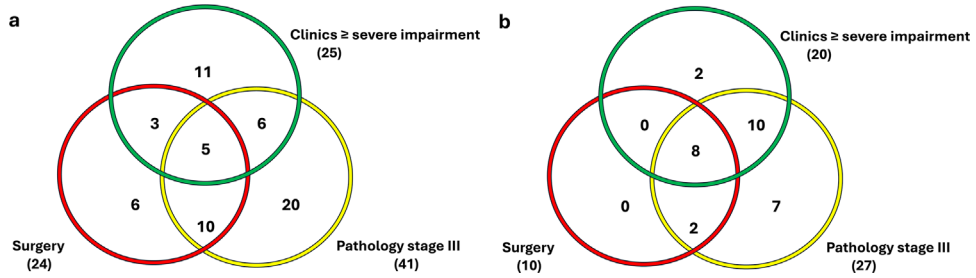

FIGURE 2 | Correlation between findings of rupture in surgery, pathology (stage III), and clinical presentation at diagnosis (≥severe impairment) for the patients with complete data across all modalities. In all these patients, imaging showed signs of rupture. (a) Patients after preop-CT, (b) patients after immediate surgery; (χ^2-test $p < 0.001$).

TABLE 2 | Number of relapses and deaths according to local stage and initial treatment.

	Preop-CT			Primary surgery		
	Relapses	**Local relapses**	**Deaths**	**Relapses**	**Local relapses**	**Deaths**
Stage I[a]	4	3	1	0	0	0
Stage II[b]	2	1	2	0	0	0
Stage III[c]	3	1	2	4	3	1
Unknown stage	0	0	1	0	0	0
All	9	5	6	4	3	1

[a]None of the patients received local irradiation.
[b]unknown local irradiation.
[c]all of these patients received local irradiation.

concerning radiotherapy were available of 82 out of 89 preop-CT patients. Among 38 out of 82 patients, who did not receive local irradiation, three experienced local relapse, compared with two relapses among 44 out of 82 patients who received local radiotherapy. In stage I after preop-CT, seven out of 31 (22.6%) patients received local irradiation. One of them had diffuse anaplasia, three were at least severe impaired at diagnosis. All of them were irradiated before 2017 based on clinical decision by the local center only. After 2017, none of these patients received local irradiation in stage I after implementation of an interdisciplinary tumor board meeting, taking clinical performance, surgical report, and histopathology into account. Five-year local relapse-free survival (RFS) was similar between the groups (0.95 without irradiation vs. 0.94 with irradiation). Overall RFS was 0.86 versus 0.90, and overall survival was 0.91 versus 0.95, with no statistically significant differences. In total, the study reported seven deaths (radiotherapy data available for six out of seven patients) and 13 relapses (radiotherapy data available for nine out of 13 patients) across both treatment groups (see Figure 3 and Table 1). A particularly promising observation was noted in pretreated localized stage I patients: of the 31 patients in this subgroup, 14 (45.2%) received only the AV1 regimen (4 weeks AV postoperatively) without radiotherapy and none of these patients relapsed or died. In contrast, patients with local stage I who underwent at least three-drug postoperative treatment over 28 weeks (due to factors like high-risk histology or overall stage IV disease) had significantly worse outcomes, with a notable difference observed only in RFS after 5 years (Figure 3).

4 | Discussion

In addition to evaluating the location of renal masses, cross-sectional imaging plays a crucial role in assessing tumor rupture. Radiologists rely on several imaging features to identify preoperative tumor rupture that are explained in Section 2. These criteria have been shown to aid in the detection of tumor rupture in several studies [3, 7]. Similar diagnostic performance can be achieved with CT and MRI, both with and without contrast enhancement [8].

The spread of tumor cells into the abdominal cavity, whether occurring pre- or intraoperatively, is a well-established risk factor for future abdominal disease recurrence [9, 10]. This dissemination is incorporated into the stage III criteria of the Stockholm classification for renal tumors [11, 12]. Consequently, the precise identification of tumor rupture is essential to avoid both under- and overtreatment. Even with modern radiotherapy techniques that aim to protect organs at risk and achieve dose homogeneity postrupture, late effects cannot be completely eliminated, especially when whole abdominal radiotherapy is warranted [13].

4.1 | Accurate Determination of Preoperative Rupture on Imaging is Challenging

Despite the above-mentioned criteria, imaging studies alone are limited in definitively determining the presence or absence of a preoperative WT rupture. In our pretreated patient cohort,

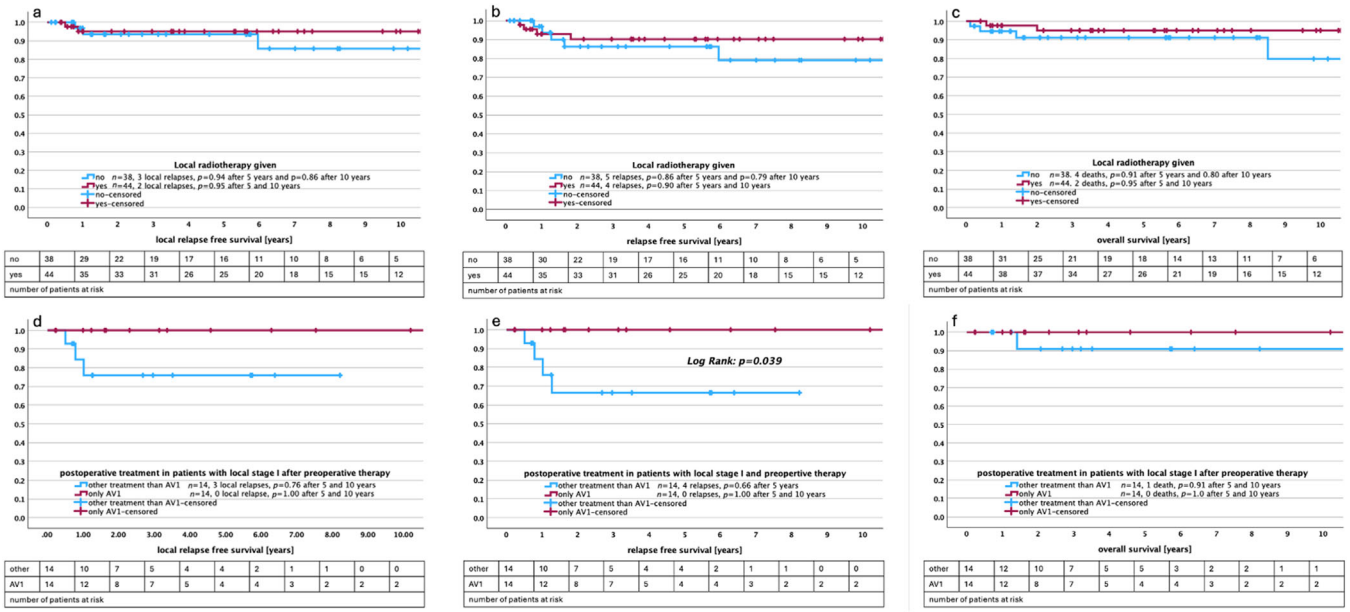

FIGURE 3 | Life tables according to Kaplan–Meier. (a–c) Patients after preoperative chemotherapy and known data about radiotherapy; (d–f) patients with local stage I and preoperative therapy depending on postoperative chemotherapy. The patients receiving non-AV1 were those with metastasis, higher local stages, and/or high risk tumors demonstrating that stage I postoperative treatment is sufficient in these cohort of patients.

radiological suspected diagnosis did poorly correlate with clinical and intraoperative findings or with local stage III pathology. In contrast, primarily operated patients with worse clinical condition at diagnosis exhibited significantly higher concordance between these parameters, emphasizing the importance of including them in treatment stratification for patients with the suspicion of preoperative tumor rupture. In one retrospective study of 57 patients with clinical and/or radiologic signs of preoperative tumor rupture in a series of 250 patients enrolled in Wilms SIOP protocols, Brisse et al. [2] concluded that CT imaging can reliably diagnose intraperitoneal rupture in WT patients and that those with intraperitoneal rupture face a significantly increased risk of peritoneal relapse. In contrast, patients exhibiting only retroperitoneal rupture should not be automatically upstaged to local stage III; their treatment should instead be directed by the findings from pathological staging [2].

In a COG study, radiological criteria, including a poorly circumscribed mass, perinephric fat stranding, obscured peritumoral fat planes, retroperitoneal fluid (differentiated as subcapsular versus extracapsular), ascites beyond the cul-de-sac, peritoneal implants, ipsilateral pleural effusion, and intratumoral hemorrhage, were compared between patients with rupture confirmed by surgery and/or pathology and those without rupture among primarily operated patients [3]. That study reported a sensitivity of only 54% and a specificity of 88% for detecting WT rupture by imaging at the time of diagnosis.

Further challenges in accurate detection were observed in the context of preop-CT. In SIOP studies, the concordance between clinical and radiological signs of suspected WT rupture was low, with only four out of 24 patients confirmed to have rupture on histological examination [4]. Similarly, in the UK IMPORT study, imaging-based diagnosis of tumor rupture could not be confirmed during subsequent surgery or pathology in 38 out of 80 patients, yielding a false positive rate of 48% [1]. Our own analysis aligns with these findings, with only 46% of radiologically suspected WT rupture cases were subsequently classified as local stage III and only 20% with tumor rupture histologically (Table 1).

These discrepancies underscore the inherent limitations of conventional CT and MRI for accurately diagnosing WT rupture preoperatively until now. Also, in adult oncology, for example, colorectal cancer, CT detection of peritoneal carcinomatosis or tumor deposits is poor [14]. In addition, interobserver differences in radiological diagnosis are statistically significant as, for example, shown by delineation variation for highly conformal flank target volume in children with renal tumors [15].

While these imaging modalities remain indispensable for overall tumor assessment, their accuracy for rupture detection is suboptimal. Reference radiological evaluation improving the diagnostic accuracy of nephroblastoma [16] may also help to better distinguish between intra- and retroperitoneal rupture by describing imaging findings [17]. Advances in imaging modalities, such as diffusion-weighted MRI, as described in Ref. [18], together with clinical data may enhance the detection of preoperative ruptures. In patients receiving preop-CT, the initial findings of a possible rupture like ascites, and even peritoneal deposits, may be no longer visible. The assumption of a tumor rupture in a rare disease like WT is dependent on different experiences in local therapy centers and different weighting of rupture signs in general. In both therapy optimizing study groups, the SIOP-RTSG association and the COG, currently no clear rules exist to define radiological tumor rupture. On the other hand, tumor rupture is an important feature for upgrading to stage III and decision making for primary treatment. A clear definition in the future is necessary with weighting of rupture signs by the SIOP-RTSG recommending preop-CT. In case of ascites, cytology may also be helpful to diagnose rupture at diagnosis, if tumor cells are found.

4.2 | Histological Downstaging by Preoperative CT in Patients With Preoperative Rupture

In our patient cohort, 43.3% of those undergoing primary surgery showed pathological signs of tumor rupture, compared with only 20.2% among patients who received preop-CT. This discrepancy reflects inherent differences between the groups selected for immediate nephrectomy versus those receiving preop-CT. Patients undergoing immediate surgery were more likely to present with true ruptures, likely due to selection bias favoring urgent intervention. Our data cannot definitively determine the extent to which preoperative CT reduces pathological indicators of rupture or prevents upstaging to local stage III. However, the presence of tumor capsules containing siderophages—remnants of prior hemorrhage—may suggest a mitigating effect of chemotherapy. The benefit of preoperative CT in tumor downstaging is well known and further supported by an approximate 50% reduction in positive lymph nodes among patients treated with preop-CT compared with those undergoing upfront surgery [19].

Importantly, our findings confirm that not all patients with the initial diagnosis of a rupture need to be treated as stage III postoperatively. The clinical outcomes are comparable between patients' receiving radiotherapy or not. Even those managed as stage I with the AV1-only regimen had an excellent outcome without compromising survival or increasing relapse risk if the individual aspects of imaging, surgery, pathology, and clinical symptoms are taken into consideration and discussed in an interdisciplinary tumor bord.

Le Rouzic et al. [4] reported similar findings in a cohort of 28 patients with suspected tumor rupture. In the subgroup of 13 patients (46.4%) who did not receive radiotherapy, 11 remained in first complete remission (CR1), one achieved second complete remission (CR2) after a pulmonary relapse, and one patient died. Based on these outcomes, the authors emphasized the need for clear treatment recommendations following surgery for patients who show discrepancies between radiological and histological signs of rupture at diagnosis and after preop-CT [4].

In a separate retrospective study of 57 patients, Brisse et al. [2] observed that 48 patients had a retroperitoneal rupture. Of these, only 23 received radiotherapy and none experienced local relapse, whereas intraperitoneal rupture was associated with a high rate of local relapses [2]. Unfortunately, our dataset did not allow us to distinguish between intraperitoneal and retroperitoneal rupture.

Future research should focus on refining imaging protocols and incorporating multimodal diagnostic strategies. The integration of advanced imaging techniques alongside with clinical, surgical, and pathological findings may ultimately lead to more personalized treatment plans, minimizing unnecessary interventions and improving overall patient outcomes.

Our analysis has several limitations, including the retrospective nature of the study, the lack of an international consensus on criteria for rupture on imaging, the missing information about intra- or retroperitoneal rupture and the field of local irradiation, and the small number of patients with incomplete radiotherapy data. To address these limitations, we will prospectively validate our results within the ongoing UMBRELLA protocol using a larger patient cohort.

5 | Conclusions

This analysis shows that preop-CT can be given safely in a majority of patients with suspected preoperative tumor rupture by imaging studies and clinical symptoms in WT. Postoperative treatment can follow histological staging and risk group without jeopardizing survival, given that a thorough review in an interdisciplinary tumor board including imaging, surgical, pathological, and clinical findings is done.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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