Staging

18

Manish Pathak

18.1 Introduction

Staging for malignancy is the process of determining the extent of the tumor. The stage generally takes into account the tumor's extension or invasion into the surrounding structures, involvement of regional or distant lymph nodes (LNs), and distant metastasis. Staging for the tumor is important for risk stratification, prognostication, and facilitation of comparison between groups of patients sharing similar stage defining characteristics. As the appropriate therapy and prognosis are based on tumor stage, it is imperative to stage the tumor accurately.

Staging systems for Wilms' tumor (WT) are based exclusively on anatomical extent of the tumor. The staging is not dependent on clinical characteristics, molecular markers, histology, or biology of the tumor [1, 2]. The anatomical extent of the tumor is determined by the pathologic examination of the surgically excised tumor and sampled LNs. Thus, it is a surgico-pathologic system where both surgeons and pathologist have an important role to play.

Stage is an important criterion in the risk stratification of the WT. Advanced tumor stage at the time of diagnosis is associated with an increased risk of recurrence [3, 4]. One of the important benefits of accurate staging is that it enables the

universal comparison of treatment outcomes. Multi-center trials have shown that staging still represents a major problem. The large size of the renal tumors at the time of nephrectomy results in difficulty in the assessment of its relationship with normal renal anatomical structures such as the renal sinus and the renal capsule. Thus, it is of utmost importance that the pathologist ensures to take the blocks from all the critical sites and register the location of each block accurately [1, 5].

18.2 COG and SIOP Staging

Currently, two major surgico-pathologic staging systems are in use. Children's Oncology Group (COG) recommends upfront surgery, and staging is based on combination of operative findings at the time of immediate nephrectomy and imaging for distant metastasis [6, 7]. Operative findings determine the local stage, while the disease stage is determined by the imaging done to look for distant metastasis.

Societe Internationale D'oncologie Pediatrique (SIOP) uses the preoperative chemotherapy (ChT) approach, and staging is done after 4–6 weeks of neoadjuvant ChT as per protocol [5, 8]. Localized tumor receives 4 weeks of preoperative ChT, while metastatic WT receives 6 weeks of preoperative ChT. The staging is done again based on local operative findings and preoperative imaging to define metastatic disease.

M. Pathak (✉)
Department of Pediatric Surgery, All India Institute of Medical Sciences, Jodhpur, India

Recently, definitions that are more detailed have been introduced to aid correct staging [9].
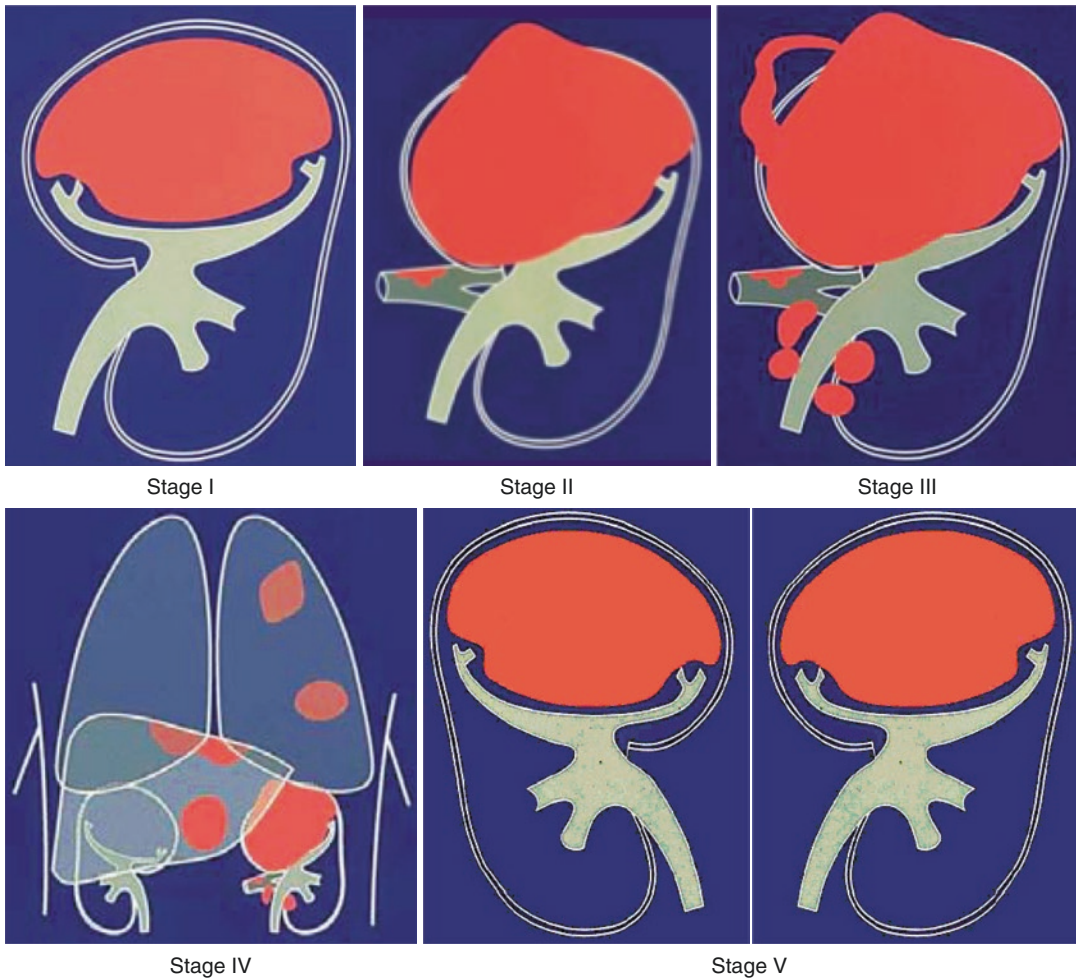
It is important to understand the concept of local stage and disease stage in WT. The local staging is based on operative findings, while the disease staging on preoperative image findings of presence or absence of distant metastasis. The need for local radiation and its dose depends on local stage, while the disease stage determines the type and duration of ChT to the patient.

Both staging systems for WT are essentially very similar, and both have been found to be useful in predicting outcome; however, stage-wise comparison of two staging systems is not possible due to the difference in the timing of ChT relative to the surgico-pathologic evaluation [10] (Fig. 18.1) (Tables 18.1 and 18.2).

Staging of WT also has changed as the data emerged during the course of multicenter trials that subgroups within stage categories have varying prognosis. The stage definitions have been modified over the years, as per the available data. It was observed that patients with "local tumor spill" have significantly high rate of local recurrence in comparison to the patients without local spill, and this led to reassignment of these patients from stage II to stage III in the recent NWTS/COG staging system [11, 12].

As the appropriate therapy and prognosis is based on tumor stage, it is imperative to stage the

Stage I   Stage II   Stage III

Stage IV   Stage V

Fig. 18.1 Tumor staging; the general concept

Table 18.1 COG staging

Stage	Criteria
I	Complete resection of the tumor that is limited to the kidney
	No preoperative or intraoperative rupture of the tumor. Tumor was not biopsied prior to removal
	There is no involvement of renal sinus or any penetration of the renal capsule
II	The tumor extends beyond the capsule of the kidney but was completely resected with no evidence of tumor at or beyond the margins of resection
	The tumor penetrates the renal capsule or there is invasion of the renal sinus vessels
III	Gross or microscopic residue postoperatively, including inoperable tumor, positive surgical margins, or tumor spill
	Preoperative or postoperative tumor rupture
	Tumor biopsy prior to removal
	Abdominal or pelvic LNs positive for tumor
	Penetration of the tumor through the peritoneal surface
	Presence of peritoneal tumor implants
	Local infiltration into vital structures making the tumor not completely resectable
	Patients receiving neoadjuvant ChT
	Tumor transection during surgery or if tumor is removed in more than one piece (e.g., tumor cells are found in a separately excised adrenal gland; transection of the tumor thrombus)
	Tumor thrombus extension into the abdominal vena cava, thoracic vena cava, or right atrium (adhered to wall) is considered stage III, rather than stage IV, even though outside the abdomen
IV	Lymphatic or hematogenous metastases outside the abdomen (e.g., lung, liver, bone, brain)
V	Bilateral renal tumor at diagnosis (each side is staged separately for local stage)

Table 18.2 SIOP staging

Stage	Criteria
I	The tumor is limited to the kidney or surrounded all around with a fibrous pseudocapsule. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected. The tumor may be protruding into the pelvic system and dipping into the ureter, but it is not infiltrating the walls. The intrarenal vessels may be involved but the renal sinus is not involved
II	Viable tumor in the perirenal fat without any surrounding pseudocapsule but is completely resected. Renal sinus infiltration by the viable tumor. Viable tumor infiltrating the wall of the renal pelvis or of the ureter. Viable tumor infiltrates the vena cava or adjacent organs (except the adrenal gland) but is completely resected
III	Presence of viable tumor at the resection margin. Nonviable tumor or ChT-induced changes at a resection margin are not regarded as stage III. Abdominal LN involvement (viable or nonviable). Preoperative or intraoperative tumor rupture, if confirmed by microscopic examination (viable tumor at the surface of the specimen at the area of the rupture). Transection of viable or nonviable tumor thrombus. Presence of viable or nonviable tumor at resection margin of ureter. Wedge or open tumor biopsy before preoperative ChT or surgery. Intraabdominal tumor implants (viable or nonviable). Peritoneal tumor implants (viable or nonviable)
IV	Lymphatic or hematogenous metastases outside the abdomen (e.g., lung, liver, bone, brain)
V	Bilateral renal tumor at diagnosis (each side is staged separately for local stage)

tumor accurately. Tumor stage is a critical component of risk-stratified therapy [13]. Both the surgeon and the pathologist play an important role in correctly determining the local stage of the tumor. Diagnostic imaging as per protocol and its correct interpretation by radiologist is also warranted for the adjudication of the disease stage [14]. Initial imaging study should be able to

confirm the organ of origin to be the kidney, delineate the contiguous spread of the tumor into the ureter or vena cava, status of the opposite kidney, and delineate the metastasis if present. Additionally, a computerized tomography (CT) of chest should be done in order to look for lung metastasis, as it has been found in study trials that CT-only nodules fare worse if the treatment is

administered according to the local primary stage alone [15]. An interesting study was conducted by Gow et al. to find the correlation between local staging based on CT findings and histology findings. Their study concluded that there is a poor correlation of CT scan to histological staging. Therefore, therapy based solely on radiological imaging may lead to under- or overtreatment of patients. Histological assessment of the tumor should continue to be the standard for staging WTs. The authors found it consistently difficult to identify the capsular or nodal involvement thus making them unable to correctly differentiate between stage II and stage III [16]. Failure to sample the LN is one of the most frequent errors committed by the surgeon that may lead to incorrect downstaging and undertreatment to the patient thereby leading to increased risk of local relapse [14]. The operating surgeon must be aware of the surgical factors that may upstage the tumor to avoid any such mishap. These factors include tumor spillage, transection of the tumor thrombus, removing the tumor piecemeal, etc. [16–18]. It is the duty of the operating surgeon to document the operative findings in detail.

The pathologist is expected to gross the specimen correctly and extensively. He/she must ensure to take the blocks from all the critical sites and document the site of each block correctly [9].

18.3 Salient Differences Between the SIOP and COG Staging System

Surgico-pathologic staging in COG staging system is done upfront while in SIOP this staging is done after neoadjuvant ChT. Upfront surgery in COG protocol provides the unique opportunity to do the histological examination of naïve tumor tissue. It also avoids unnecessary preoperative ChT to the benign tumor. In addition, it also avoids the inappropriate preoperative ChT to the tumors with histology other than WT. In contrast, preoperative ChT as per SIOP protocol decreases the tumor size, leads to favorable stage distribu-

tion, and reduces the chances of tumor rupture. This significant benefit reduces the need for radiotherapy to almost half of that required in upfront surgery protocol of COG. SIOP staging is often criticized for under-staging the WT patients. However, patients' stages as I or II by SIOP have the same overall and event-free survival as COG stages I and II, thus invalidating the argument of under-staging against SIOP [19]. Another criticism is that it may lead to unnecessary pre-nephrectomy ChT to the benign renal tumors. The SIOP rebuttal is that this incidence is only 1.5%, and it is well balanced by the favorable stage distribution and lower risk of tumor ruptures [19, 20].

Important points to remember:

1. The tumor extending into renal pelvis and ureter does not upgrade the tumor, if it can be removed in toto as the tumor specimen without transecting through the tumor. On the contrary, if the tumor in the ureter is transected at the time of surgery, then it upstages the tumor to stage III. If the tumor extends along the ureter through the uretero-vesical junction and is dipping into the bladder, then the surgeon should remove the cuff of bladder around the uretero-vesical junction so as to remove the tumor in a single piece avoiding the transection through the tumor. This will prevent the tumor to be upstaged to stage III based on surgical resection margin.

2. The tumor extending into renal vein or inferior vena cava makes it minimum stage II.

3. Extension of the primary tumor within the thoracic vena cava or heart that is removed piecemeal or separately from tumor is considered stage III not stage IV, even though outside the abdomen [10].

4. Any residue, even when it is microscopic, makes the tumor stage III.

5. Positive LN makes the tumor stage III, but if the positive LN is present outside the abdominal cavity, then it will be considered metastasis and stage IV.

6. FNAC of the tumor does not upstage the tumor. In COG, core needle biopsy upstages the tumor to stage III.

7. Core needle biopsy will not upstage the tumor in SIOP. However, open biopsy will upstage the tumor to stage III in both SIOP and COG staging system,

8. Even in those with stage IV disease, local stage is still a prognostic feature.

9. In case of a bilateral WT, a local stage should be provided for each tumor.

18.4 Role of Surgeon in Appropriate Staging

1. Trans-peritoneal incision for wide exposure—retroperitoneal surgery may not be able to stage the tumor correctly.

2. The peritoneum and liver should be examined to look for any tumor implant; presence of it will upstage the tumor to stage III or stage IV, respectively. Exploration of the contralateral kidney is no longer mandated before nephrectomy if the preoperative CT or Magnetic resonance imaging (MRI) demonstrates a normal kidney [21].

3. Thorough inspection should be done to look for any evidence of preoperative or intraoperative rupture. Bloody peritoneal fluid suggests rupture, and surgeon should thoroughly inspect the tumor surface. Free communication of the open neoplastic tissue surface with peritoneal cavity is also a sign of tumor rupture. Rupture of the tumor upstages it to stage III.

4. Tumor dissection should be done carefully to prevent any intra-operative spill or tumor rupture during surgery; this will upstage the tumor to stage III [16]. "Spill" refers to a break in the tumor capsule during surgery, whether accidental, unavoidable, or by design. In COG protocol, spill is considered to have occurred if a preoperative or intraoperative needle or open biopsy is performed, thus, upstaging the tumor to stage III. Any tumor spill increases the risk of local tumor recurrence [17, 18]. In SIOP protocol, fine needle or Tru-cut needle biopsy is permitted and does not upstage the disease, while the incisional biopsy upstages it to stage III. In the United

Kingdom Children's Cancer and Leukemia Group (UKCCLG) trial, preoperative percutaneous cutting needle biopsy, preferably using coaxial technique through retroperitoneal route to obtain multiple core biopsies, used to be performed routinely in all cases at diagnosis [9].

5. Ureter and renal vessels should be palpated to look for any tumor extension, if the tumor extension is present then it mandates the appropriate technique so as to avoid any transection of the tumor; this will also upstage the tumor to stage III [9].

6. LN sampling: Failure to sample the LNs is the most frequent error committed by the surgeon [22]. This will falsely under-stage the disease leading to undertreatment and high risk of local recurrence. Pathologic assessment of hilar and regional LNs is critical to accurately stage a child with WT. Determination of the involvement of the tumor by simply looking at the LN is highly inaccurate. There is no formal recommendation on the number of lymph nodes that need to be sampled. In a retrospective study of COG, sampling of seven LNs increased the rate of detection of metastasis [23]. Another important point is that the LN even when it contains only necrotic tumor then also it is labelled as stage III in SIOP protocol [9].

7. Proper documentation of intraoperative findings is also one of the primary goals of the surgeon.

References

1. Vujanić GM, Sandstedt B, Harms D, Kelsey A, Leuschner I, de Kraker J, et al. SIOP Nephroblastoma scientific committee revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. Med Pediatr Oncol. 2002;38:79–82. https://doi.org/10.1002/mpo.1276.

2. D'Angio GJ. Pre- or post-operative treatment for Wilms tumor? Who, what, when, where, how, why--and which. Med Pediatr Oncol. 2003;41:545–9. https://doi.org/10.1002/mpo.10395.

3. Pritchard-Jones K, Kelsey A, Vujanic G, Imeson J, Hutton C, Mitchell C, United Kingdom Children's Cancer Study Group; Wilm's Tumor Working Group.

Older age is an adverse prognostic factor in stage I, favorable histology Wilms' tumor treated with vincristine monochemotherapy: a study by the United Kingdom Children's Cancer Study Group, Wilm's Tumor Working Group. J Clin Oncol. 2003;21:3269–75. https://doi.org/10.1200/JCO.2003.01.062.

4. Breslow N, Sharples K, Beckwith JB, Takashima J, Kelalis PP, Green DM, et al. Prognostic factors in non-metastatic, favorable histology Wilms' tumor. Results of the third National Wilms' tumor study. Cancer. 1991;68:2345–53. https://doi.org/10.1002/1097-0142(19911201)68:11<2345::aid-cncr2820681103>3.0.co;2-t.

5. Kaste SC, Dome JS, Babyn PS, Graf NM, Grundy P, Godzinski J, et al. Wilms tumour: prognostic factors, staging, therapy and late effects. Pediatr Radiol. 2008;38:2–17. https://doi.org/10.1007/s00247-007-0687-7.

6. Green DM, Cotton CA, Malogolowkin M, Breslow NE, Perlman E, Miser J, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine and actinomycin D: a report from the National Wilms Tumor Study Group. Pediatr Blood Cancer. 2007;48:493–9. https://doi.org/10.1002/pbc.20822.

7. Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey ML, et al.; National Wilms Tumor Study Group. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2005;23:7312–21. https://doi.org/10.1200/JCO.2005.01.2799.

8. Dome JS, Graf N, Geller JI, Fernandez CV, Mullen EA, Spreafico F, et al. Advances in Wilms tumor treatment and biology: progress through international collaboration. J Clin Oncol. 2015;33:2999–3007. https://doi.org/10.1200/JCO.2015.62.1888.

9. Vujanić GM, Gessler M, Ooms AHAG, Collini P, Coulomb-l'Hermine A, D'Hooghe E, et al.; International Society of Paediatric Oncology–Renal Tumour Study Group (SIOP–RTSG). The UMBRELLA SIOP-RTSG 2016 Wilms tumour pathology and molecular biology protocol. Nat Rev Urol. 2018;15:693–701. https://doi.org/10.1038/s41585-018-0100-3.

10. Fernandez CV, Mullen EA, Chi YY, Ehrlich PF, Perlman EJ, Kalapurakal JA, et al. Outcome and prognostic factors in Stage III favorable-histology Wilms tumor: a report from the Children's Oncology Group Study AREN0532. J Clin Oncol. 2018;36:254–61. https://doi.org/10.1200/JCO.2017.73.7999. Epub 2017 Dec 6. Erratum in: J Clin Oncol. 2019;37:2710.

11. Kalapurakal JA, Li SM, Breslow NE, Beckwith JB, Ritchey ML, Shamberger RC, et al. Intraoperative spillage of favorable histology Wilms tumor cells: influence of irradiation and chemotherapy regimens on abdominal recurrence. A report from the National Wilms Tumor Study Group. Int J Radiat Oncol Biol Phys. 2010;76:201–6. https://doi.org/10.1016/j.ijrobp.2009.01.046.

12. Green DM, Breslow NE, D'Angio GJ, Malogolowkin MH, Ritchey ML, Evans AE, et al. Outcome of patients with stage II/favorable histology Wilms tumor with and without local tumor spill: a report from the National Wilms Tumor Study Group. Pediatr Blood Cancer. 2014;61:134–9. https://doi.org/10.1002/pbc.24658.

13. Dome JS, Perlman EJ, Graf N. Risk stratification for Wilms tumor: current approach and future directions. Am Soc Clin Oncol Educ Book. 2014;215–23. https://doi.org/10.14694/EdBook_AM.2014.34.215.

14. Irtan S, Ehrlich PF, Pritchard-Jones K. Wilms tumor: "state-of-the-art" update, 2016. Semin Pediatr Surg. 2016;25:250–6. https://doi.org/10.1053/j.sempedsurg.2016.09.003.

15. Smets AM, van Tinteren H, Bergeron C, De Camargo B, Graf N, Pritchard-Jones K, et al. The contribution of chest CT-scan at diagnosis in children with unilateral Wilms' tumour. Results of the SIOP 2001 study. Eur J Cancer. 2012;48:1060–5. https://doi.org/10.1016/j.ejca.2011.05.025.

16. Gow KW, Roberts IF, Jamieson DH, Bray H, Magee JF, Murphy JJ. Local staging of Wilms' tumor—computerized tomography correlation with histological findings. J Pediatr Surg. 2000;35:677–9. https://doi.org/10.1053/jpsu.2000.5941.

17. Ehrlich PF, Anderson JR, Ritchey ML, Dome JS, Green DM, Grundy PE, et al. Clinicopathologic findings predictive of relapse in children with stage III favorable-histology Wilms tumor. J Clin Oncol. 2013;31:1196–201. https://doi.org/10.1200/JCO.2011.41.1165.

18. Shamberger RC, Guthrie KA, Ritchey ML, Haase GM, Takashima J, Beckwith JB, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg. 1999;229:292–7. https://doi.org/10.1097/00000658-199902000-00019.

19. Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am. 2000;27:443–54. https://doi.org/10.1016/s0094-0143(05)70092-6.

20. Tournade MF, Com-Nougué C, Voûte PA, Lemerle J, de Kraker J, Delemarre JF, et al. Results of the sixth International Society of Pediatric Oncology Wilms' tumor trial and study: a risk-adapted therapeutic approach in Wilms' tumor. J Clin Oncol. 1993;11:1014–23. https://doi.org/10.1200/JCO.1993.11.6.1014.

21. Ritchey ML, Shamberger RC, Hamilton T, Haase G, Argani P, Peterson S. Fate of bilateral renal lesions missed on preoperative imaging: a report from

the National Wilms Tumor Study Group. J Urol. 2005;174:1519–21. https://doi.org/10.1097/01.ju.0000179536.97629.c5.

22. Saltzman AF, Carrasco A Jr, Amini A, Aldrink JH, Dasgupta R, Gow KW, et al. Patterns of lymph node sampling and the impact of lymph node density in favorable histology Wilms tumor: an analysis of the national cancer database. J Pediatr Urol. 2018;14:161. e1–8. https://doi.org/10.1016/j.jpurol.2017.09.025.

23. Kieran K, Anderson JR, Dome JS, Ehrlich PF, Ritchey ML, Shamberger RC, et al. Lymph node involvement in Wilms tumor: results from National Wilms Tumor Studies 4 and 5. J Pediatr Surg. 2012;47:700–6. https://doi.org/10.1016/j.jpedsurg.2011.08.017.