Diagnostic Biopsy

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11.1 Introduction

The management of Wilms' tumor (WT) is regarded as one of the real success stories in pediatric oncology with an overall cure rate of over 85% [1]. This success is mainly due to the collaborative work of multiple worldwide groups in particular the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (COG) (formerly the National Wilms Tumor Study Group, NWTSG).

COG considers primary nephrectomy as the gold standard in most cases; however preoperative biopsy is recommended in a number of varied clinical scenarios. If primary nephrectomy cannot be safely performed, then a biopsy is recommended, either open or with multiple cores. The contraindications to primary nephrectomy according to the COG protocol include caval tumor thrombus extending up to the hepatic veins, large tumor where nephrectomy would result in significant morbidity/mortality, spillage, or incomplete resection or that involves contiguous structures putting them at risk of removal (e.g., spleen, pancreas, colon, or liver) and finally if the patient suffers from extensive pulmonary compromise from either lung or liver deposits [2, 3]. Bilateral disease usually does not require tissue diagnosis if the patient has classic radiology and falls within the typical age group; nevertheless if one of the lesions is regarded as indeterminate, then pathological assessment is recommended [4, 5]. In the COG protocol, bilateral disease is treated initially with chemotherapy (ChT) and reassessment at 6 weeks, and if the response (tumor shrinkage) is less than 30%, then a biopsy would be indicated to determine the histology. If anaplasia is detected, the ChT regime is changed, and if the histology revealed stromal differentiation, or rhabdomyomatous changes, then definitive surgery is recommended as no further response would be expected [6].

The SIOP protocol recommends preoperative empirical two-drug ChT for 4 weeks with for unilateral localized cases and 6 weeks three-drug ChT for metastatic tumor in children aged 6 months or older without a biopsy. Therapy is initiated purely on imaging and no tissue diagnosis in the majority of cases [7, 8].

Below the age of 6 months, the recommendation is an upfront nephrectomy, and the likely diagnoses are WT or a congenital mesoblastic nephroma (CMN). Renal cell carcinoma mean age for presentation is 14 years; radiographically it is indistinguishable from WT. RCC accounts for approximately 2–4% of childhood renal tumors; however this increases to over 50% in adolescents [9]. So, in the age group >6 months

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Y. K. Sarin (ed.), *Wilms' Tumor*, https://doi.org/10.1007/978-981-19-3428-5_11

to <7 years, biopsy is not recommended, as the likely diagnosis is WT and ChT may be started based on radiology as per the SIOP protocol. There is a caveat however to this strategy, and alternative pathology has to be ruled out by performing a battery of investigations in addition to the standard tests and staging imaging.

Atypical radiology permits a biopsy in both COG and SIOP protocols [3]. On the other hand, small infants below six months of age and cystic tumors are generally resected primarily in both protocols without biopsy globally as the majority will not require ChT, provided the tumors were considered resectable. Biopsy is generally also avoided if rupture is suspected, unstable patient or a patient with known predisposition syndromes, for example, Beckwith-Wiedemann syndrome.

In the United Kingdom, the traditional treatment was an upfront surgery followed by ChT and/or radiotherapy (XRT) depending upon stage and histology (similar to NWTSG). Nevertheless, following the UKW3 study (1991–2001), there was a shift to adopt the upfront ChT as the standard of care including the biopsy [10]. The Children's Cancer and Leukemia Group (CCLG) joined the SIOP-WT-2001 study; however, the routine biopsy at presentation continued to be the standard of care in the United Kingdom. More recently, despite of Brexit, the United Kingdom has moved closer to Europe by adopting the European-SIOP protocol and only performing a biopsy in selected cases following a stringent selection criterion [11].

In countries where the treatment of WT is non-consistent, there is a tendency to follow the COG guidelines for lower-stage disease where surgery is thought to be safe and feasible. However, when risk of intraoperative spillage deemed to be high, preoperative ChT is considered. Few centers believe in performing a biopsy before ChT is instituted [12].

11.2 Fallacies of Imaging Alone

Patients who have classic radiological evidence of WT are exempted from biopsy in European, and now United Kingdom, guidelines provided they fulfill the strict exemption criteria (Fig. 11.1); otherwise there is a small but recognized risk of missing an alternative diagnosis (Figs. 11.2 and 11.3) resulting in suboptimal or unnecessary treatment.

The typical appearance of WT on CT is a mass confined to the kidney and may show a "bear-claw" sign and irregular effacement of normal parenchyma overlying the tumor. On SIOP 93-01 study, about 5% of renal tumors treated with empirical ChT were found to be non-WT; this included 1.8% benign lesions [13].

Miniati et al. reviewed histology reports of nephrectomies and open biopsies of 92 patients

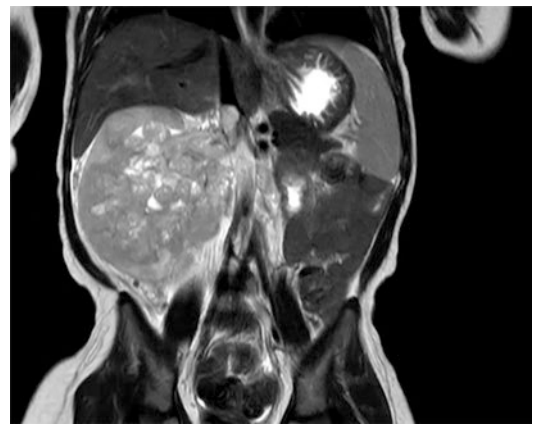

Fig. 11.1 2-year old: typical renal mass with caval extension, hence no biopsy before ChT. WT confirmed on final histology

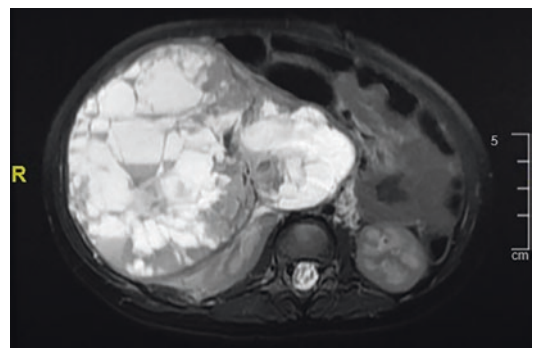

Fig. 11.2 15-month old. Cystic renal tumor. In view of age being atypical for nephroma, a US-guided biopsy by an interventional radiologist was done into the solid component of the tumor. Cytogenetic studies of the sample did not show the typical features of a CMN. Immunohistopathology showed a clear cell sarcoma of the kidney (CCSK)

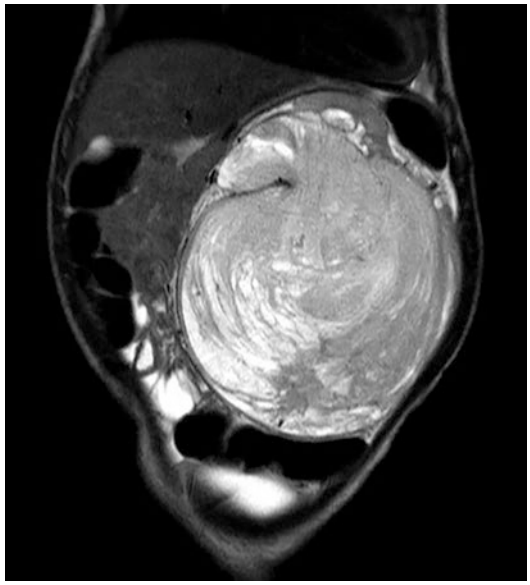

Fig. 11.3 21-month old. Although this was completely solid left renal tumor on imaging, the "swirling" seen on the MRI was not typical of WT; hence, a percutaneous biopsy was performed. This showed it to be a clear cell sarcoma of kidney

at a single institution and calculated the accuracy of the imaging in identifying specific tumors; CT reports stated potential diagnosis in 89% with a diagnostic accuracy of 82% [14].

In 2014, Farmakis and Siegel reported a case of intrarenal neuroblastoma (IR NB) in a 14-month-old boy who presented with a palpable large abdominal mass confirmed on CT to be arising from the left kidney, and there were no calcifications; however there were multiple lung nodules. The diagnosis was secured by sampling one of the lung lesions as there was fear from rupture during a primary nephrectomy [4, 15].

The radiology has to be fairly conclusive to allow commencement of ChT without tissue diagnosis in the SIOP protocol. Reference radiology review is usually carried out for the purpose of quality control in trials in particular. Schenk et al. described reference radiological evaluation can improve the diagnostic accuracy with therapeutic relevance; however they have pointed out that differentiation between the different renal tumors is not completely possible using imaging methods. They concluded that the rate of patients with false preoperative ChT for all renal neoplasms is 5.2% and 1% for benign renal tumors [16].

11.3 Children Cancer and Leukemia Group Guidelines–UK [11]

The UKCCLG recommends consideration of biopsy in the following situations:

1. Children aged 7 years and above.
2. Signs of urinary tract infection that would be consistent with xanthogranulomatous pyelonephritis.
3. Hypercalcemia suspicious of malignant rhabdoid tumor of the kidney.
4. Raised lactate dehydrogenase (LDH) level more than four times the normal value that would be suspicious of neuroblastoma or hematological malignancies.
5. Raised urinary catecholamines—suspicious of neuroblastoma
6. Imaging suggestive of other diagnosis (e.g., psoas infiltration, tumor encasing vascular structures, numerous calcifications in the tumor-all suspicious for neuroblastoma). Renal parenchyma not visible or predominantly extrarenal process, extrahepatic, and extrapulmonary metastases and pulmonary metastasis in a patient less than 2 years of age (suspicious for malignant rhabdoid tumor of the kidney).

11.4 Limitations

The biopsy has its own limitations and cannot always differentiate between WT and nephroblastomatosis, or between the stromal subtype WT and soft tissue sarcoma. The core biopsy may frequently miss areas of diffuse anaplasia too [17].

It appears that overall concordance between biopsy and final nephrectomy remained comparable between the early 1980s at 93% and more recent data at 91.7% to 94%, for all UK data [17–19]. Nevertheless, Vujanic et al.'s study only

included cases where both the biopsy and nephrectomy were sent for central pathology review (CPR). This suggests that where biopsy is performed, CPR may help improve diagnostic accuracy, as is the case for nephrectomy specimens [20].

The biopsy was nondiagnostic in 8% (relatively small sample 36 cases historical data 1982–1986) [18] to more recent 6.5% (20) and 4% in the UKW3 study [17].

The biopsy can be nondiagnostic for a number of reasons, for example, due to necrotic tumor or sampling normal renal tissue. The specimen may be indeterminate if it reveals malignant neoplasm that is not a WT, but it is not clear which is non-WT. All these scenarios can result in delays to initiate definitive therapy with the potential of adverse consequences.

Sebire and Roebuck demonstrated in their systematic review that image-guided needle core biopsies provided adequate tissues for diagnosis in pediatric oncology in about 95% of cases and complications requiring intervention to treat occurred in 1% [21]. They highlighted that a small specimen may be adequate and demonstrate all the necessary diagnostic features, whereas a larger biopsy showing part of a fibrous or stromal area may be inadequate for the pathologist to make definitive diagnostic comment. Immunohistochemical tests, for example, CD56 and nuclear WT1 in the blastema of WT, require only small amount of tissue to diagnose [21].

On the other hand, Jackson et al. found that the biopsy would be expected to correctly change management in only 6.7% cases [19]. However, reviewing the European data showing that with improved imaging and using selective biopsies, the chance of giving inappropriate ChT was around 1%. Hence there is a change of practice in the United Kingdom.

The authors have conducted a similar study of renal tumor biopsy of three regional centers in the United Kingdom, a total of 140 cases; average age 4 years 3 months (5 months to 15 years 5 months) and 5% of the cases had non-WT pathology including clear cell sarcoma of the kidney (CCSK), renal cell carcinoma and nephroblastomatosis. One patient bled post-procedure, but none required emergency nephrectomy.

11.5 The Technique

Someone competent with the technique, usually a pediatric surgeon or an interventional radiologist, performs the biopsy. It is preferable to liaise with the pathologist while the procedure is performed in order to ensure representative and adequate tissue is obtained for histopathology, immunohistochemistry, cytogenetics, and tissue banking if the patient is enrolled in a trial.

It is critical to review the cross-sectional images (more commonly now MR than CT) in all planes in order to locate the best site for biopsy and ascertain the depth in order to adjust the length of the biopsy needle (Figs. 11.4 and 11.5).

The percutaneous procedure is aseptically in the operating theater under general anesthesia using ultrasound guidance (Sonosite® W S-Nerve; SonoSite Inc, Bothell, WA) (Fig. 11.6). Few milli-

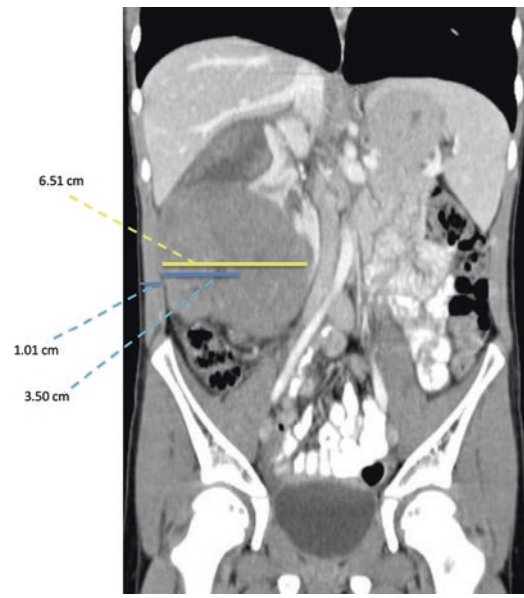

Fig. 11.4 Coronal view of an MR of a right-sided WT, with measurements, showing abdominal wall thickness (1.01 cm), the tumor depth (6.51cm), and the desired depth (3.50 cm)

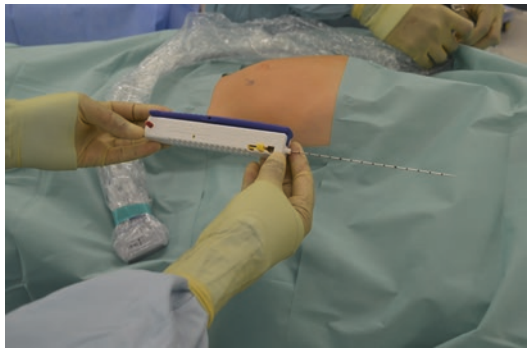

Fig. 11.5 Biopsy site cleaned and draped. The needle's depth is adjusted

Fig. 11.7 It is crucial the sample is sent fresh in a dry, sterile container

Fig. 11.6 Multiple cores are taken using ultrasound guidance

meter incision is made on the skin to avoid unnecessary biopsy of the skin! A cutting biopsy needle is used, for example, full core biopsy instrument BioPince™ Argon Medical Devices, TX, or an Adjustable Coaxial Temno™ (ACT) Biopsy Device, Merit Medical, UT. The main advantage of the latter device is its co-axial sheath which reduces the numbers of points of entry of the needle tract hence allowing multiple sampling cores from one puncture in the capsule of the tumor and reducing hemorrhage and potential tract recurrence, in addition helping minimize damage to surrounding tissue.

The biopsy has to be taken through a retroperitoneal approach for the obvious reason. The two common gauges used are 18 and 16. Several cores are taken to ensure sufficient sample to make the diagnosis, at least three, as WT can be often extensively necrotic. The surgeon needs to appreciate that a short narrow core will have less cells for the pathologist to assess, compared to a wider, longer core.

The surgeon, with experience, tends to get a hunch if the sample is of poor quality and will not hesitate to take more cores. Cores containing tumor tend to be whitish and hold together, whereas necrotic cores tend to look darker and often break up into multiple fragments.

The biopsy is taken promptly to the pathology laboratory fresh and unfixed (Fig. 11.7). To reduce the risk of the sample drying, it can be put into the cut finger of a glove which is then put into a sterile specimen pot that has a small saline damped swab placed at the bottom of it. It then should be transferred rapidly in a closed container, as there is risk of drying artifact during transit of fresh samples to the laboratory. The pathology request form has to be accurately completed and the specimen properly labeled.

The authors prefer to take the specimen themselves to the laboratory and review with the pathologist an imprint smear that only takes few minutes to prepare by the pathologist. Imprint is a simple touch preparation in which tissue is touched on the slide and it leaves behind its imprint in the form of cells on the glass slide; studies are prepared after staining. This technique allows confirmation of the adequacy of the sample usually for no extra time as meanwhile usually a senior trainee inserts a central venous catheter for ChT during the same general anesthetic. If the sample deemed inadequate, the author tends to take extra samples during the same anesthetic in order to avoid further trips to the operating theater. The specimen is then subjected to detailed examination including immu-

nohistochemistry and cytogenetics in addition to any necessary ancillary investigation.

A local anesthetic is infiltrated at either the beginning or end. Usually, the wound doesn't require any suturing, and a postoperative dressing is applied. The patient is usually observed for few hours, and if vital signs remain normal, clear fluids are allowed then built to diet and allowed home in about 4–6 h.

Open wedge biopsy is not recommended, and the disease would certainly be upstaged to stage III. Open biopsy is regarded as a breach or rupture of the capsule.

11.6 Complications

11.6.1 Tract Recurrence

Aslam et al. reported needle tract recurrence in a 2-year-old girl randomized for biopsy and preoperative ChT during the UKW3 study [22]. Rupture and tract recurrence was reported from North America [23]. Nevertheless, in a systematic review, there was no reported similar complication [21]. However, in 2015, a retrospective analysis of the entire UKW3 trial database was performed to evaluate potential risk factors associated with local recurrence of WT, with emphasis on biopsy as a potential risk factor. After a median follow-up of 10.1 years, 5.5% experienced local, 2.4% combined (local and distant), and 9.4% distant relapse. Biopsy, anaplasia, and tumor size were associated with local relapse in univariate analysis; furthermore in multivariate analysis, anaplasia and tumor size remained significant for local relapse, whereas the elevated risk of biopsy was marginal. The investigators concluded that biopsy should not automatically lead to upstaging of WT; nevertheless they felt further assessment of this controversial area is required [24].

11.6.2 Others

Other reported biopsy-associated morbidities include the local pain within the first day, readily controlled with oral analgesics; bleeding, rarely necessitating blood transfusion or emergency nephrectomy; infection and certainly inadequate sample or nonrepresentative sample with the need to repeat the biopsy; and damage to nearby organs which is reduced with the use of image guidance. Finally rupture and tract recurrence may complicate the procedure [17, 18, 23]. In the UKW3 study, the incidences of pain, infection, and bleeding are 19%, 7%, and 5% respectively [17].

11.7 The Future

The biopsy is only one step in the management of WT. The essence is to secure a firm diagnosis, stage, stratify risk, and deliver appropriate therapy in order to achieve cure at the lowest cost and minimum morbidity.

In order to achieve all these goals, the authors believe in the future there will be more utilization of central review of pathology and radiology by experts in the field. Complex cases will be discussed at national level, for example, the National Renal Advisory Panel (NRAP) recently established in the United Kingdom.

MR diffusion-weighted (DW) imaging may allow for differentiation of benign from malignant tumors, histological tumor subtypes, and grade. Using mathematical models of apparent diffusion coefficient (ADC) values from DW MRI may help to identify histological subtypes of WT. This may in the future help stratify risk and guide biopsies to the most malignant part of the tumor [25].

There are ongoing efforts to develop "liquid biopsy" assays as minimally invasive tool to diagnose and monitor childhood solid malignancies including WT. The liquid biopsy utilizes these circulating tumor cells, DNA, RNA, and proteins in order to advance our understanding of tumor biology and its evolution during therapy, and this may open new avenues for personalized therapy [26]. All these advances may allow securing the diagnosis without the need for invasive biopsies in the future.

References

1. 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.
2. National Cancer Institute. Wilms Tumor and other childhood kidney tumors treatment (PDQ®)–Health professional version Wilms tumor: diagnostic and staging evaluation for Wilms tumor. Available from https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq. Accessed 28 April 2020.
3. 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.
4. Servaes S, Khanna G, Naranjo A, Geller JI, Ehrlich PF, Gow KW, et al. Comparison of diagnostic performance of CT and MRI for abdominal staging of pediatric renal tumors: a report from the Children's Oncology Group. Pediatr Radiol. 2015;45:166–72. https://doi.org/10.1007/s00247-014-3138-2.
5. 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(4):1519–21. https://doi.org/10.1097/01.ju.0000179536.97629.c5.
6. Ehrlich P, Chi YY, Chintagumpala MM, Hoffer FA, Perlman EJ, Kalapurakal JA, et al. Results of the first prospective multi-institutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group. Ann Surg. 2017;266:470–8. https://doi.org/10.1097/SLA.0000000000002356.
7. Powis M, Messahel B, Hobson R, Gornall P, Walker J, Pritchard-Jones K. Surgical complications after immediate nephrectomy versus preoperative chemotherapy in non-metastatic Wilms' tumour: findings from the 1991-2001 United Kingdom Children's Cancer Study Group UKW3 trial. J Pediatr Surg. 2013;48:2181–6. https://doi.org/10.1016/j.jpedsurg.2013.07.001.
8. Pritchard-Jones K, Bergeron C, de Camargo B, van den Heuvel-Eibrink MM, Acha T, Godzinski J, et al. Omission of doxorubicin from the treatment of stage II-III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial. Lancet. 2015;386(9999):1156–64. https://doi.org/10.1016/S0140-6736(14)62395-3.
9. Cajaiba MM, Dyer LM, Geller JI, Jennings LJ, George D, Kirschmann D, et al. The classification of pediatric and young adult renal cell carcinomas registered on the children's oncology group (COG) protocol AREN03B2 after focused genetic testing. Cancer. 2018;124:3381–9. https://doi.org/10.1002/cncr.31578.
10. Mitchell C, Pritchard-Jones K, Shannon R, Hutton C, Stevens S, Machin D, et al. Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. Eur J Cancer. 2006;42:2554–62. https://doi.org/10.1016/j.ejca.2006.05.026.
11. Children's Cancer and Leukaemia Group. Treatment guidelines – renal tumours. Available from https://www.cclg.org.uk/. Accessed 28 April 2020.
12. Wang J, Li M, Tang D, Gu W, Mao J, Shu Q. Current treatment for Wilms tumor: COG and SIOP standards. World J Pediatr Surg. 2019;2:e000038. https://doi.org/10.1136/wjps-2019-000038.
13. de Kraker J, Graf N, van Tinteren H, Pein F, Sandstedt B, Godzinski J, et al. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. Lancet. 2004;364(9441):1229–35. https://doi.org/10.1016/S0140-6736(04)17139-0.
14. Miniati D, Gay AN, Parks KV, Naik-Mathuria BJ, Hicks J, Nuchtern JG, et al. Imaging accuracy and incidence of Wilms' and non-Wilms' renal tumors in children. J Pediatr Surg. 2008;43:1301–7. https://doi.org/10.1016/j.jpedsurg.2008.02.077.
15. Farmakis SG, Siegel MJ. Intrarenal neuroblastoma with pulmonary metastases mimicking a Wilms tumor. J Pediatr Surg. 2014;49:1864–6. https://doi.org/10.1016/j.jpedsurg.2014.10.043.
16. Schenk JP, Schrader C, Zieger B, Furtwangler R, Leuschner I, Ley S, et al. Reference radiology in nephroblastoma: accuracy and relevance for preoperative chemotherapy. Röfo. 2006;178:38–45. https://doi.org/10.1055/s-2005-858836.
17. Vujanic GM, Kelsey A, Mitchell C, Shannon RS, Gornall P. The role of biopsy in the diagnosis of renal tumors of childhood: results of the UKCCSG Wilms tumor study 3. Med Pediatr Oncol. 2003;40:18–22. https://doi.org/10.1002/mpo.10216.
18. Dykes EH, Marwaha RK, Dicks-Mireaux C, Sams V, Risdon RA, Duffy PG, et al. Risks and benefits of percutaneous biopsy and primary chemotherapy in advanced Wilms' tumour. J Pediatr Surg. 1991;26:610–2. https://doi.org/10.1016/0022-3468(91)90719-a.
19. Jackson TJ, Williams RD, Brok J, Chowdhury T, Ronghe M, Powis M, et al. The diagnostic accuracy and clinical utility of pediatric renal tumor biopsy: report of the UK experience in the SIOP UK WT 2001 trial. Pediatr Blood Cancer. 2019;66:e27627. https://doi.org/10.1002/pbc.27627.
20. Vujanic GM, Sandstedt B, Kelsey A, Sebire NJ. Central pathology review in multicenter trials and studies: lessons from the nephroblastoma trials. Cancer. 2009;115:1977–83. https://doi.org/10.1002/cncr.2421.
21. Sebire NJ, Roebuck DJ. Pathological diagnosis of paediatric tumours from image-guided needle core biopsies: a systematic review. Pediatr Radiol. 2006;36:426–31. https://doi.org/10.1007/s00247-006-0123-4.

22. Aslam A, Foot AB, Spicer RD. Needle track recurrence after biopsy of non-metastatic Wilms tumour. Pediatr Surg Int. 1996;11:416–7. https://doi.org/10.1007/BF00497834.
23. Lee IS, Nguyen S, Shanberg AM. Needle tract seeding after percutaneous biopsy of Wilms tumor. J Urol. 1995;153:1074–6.
24. Irtan S, Jitlal M, Bate J, Powis M, Vujanic G, Kelsey A, et al. Risk factors for local recurrence in Wilms tumour and the potential influence of biopsy - the United Kingdom experience. Eur J Cancer. 2015;51:225–32. https://doi.org/10.1016/j.ejca.2014.10.026.
25. Hales PW, Olsen OE, Sebire NJ, Pritchard-Jones K, Clark CA. A multi-Gaussian model for apparent diffusion coefficient histogram analysis of Wilms' tumour subtype and response to chemotherapy. NMR Biomed. 2015;28:948–57. https://doi.org/10.1002/nbm.3337.
26. Weiser DA, West-Szymanski DC, Fraint E, Weiner S, Rivas MA, Zhao CWT, et al. Progress toward liquid biopsies in pediatric solid tumors. Cancer Metastasis Rev. 2019;38:553–71. https://doi.org/10.1007/s10555-019-09825-1.