ORIGINAL ARTICLE

Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice

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Background: Most Wilms tumours occur in otherwise healthy children, but a small proportion occur in children with genetic syndromes associated with increased risks of Wilms tumour. Surveillance for Wilms tumour has become widespread, despite a lack of clarity about which children are at increased risk of these tumours and limited evidence of the efficacy of screening or guidance as to how screening should be implemented.

Methods: The available literature was reviewed.

Results: The potential risks and benefits of Wilms tumour surveillance are finely balanced and there is no clear evidence that screening reduces mortality or morbidity. Prospective evidence-based data on the efficacy of Wilms tumour screening would be difficult and costly to generate and are unlikely to become available in the foreseeable future.

Conclusions: The following pragmatic recommendations have been formulated for Wilms tumour surveillance in children at risk, based on our review: (1) Surveillance should be offered to children at >5% risk of Wilms tumour. (2) Surveillance should only be offered after review by a clinical geneticist. (3) Surveillance should be carried out by renal ultrasonography every 3–4 months. (4) Surveillance should continue until 5 years of age in all conditions except Beckwith–Wiedemann syndrome, Simpson–Golabi–Behmel syndrome and some familial Wilms tumour pedigrees where it should continue until 7 years. (5) Surveillance can be undertaken at a local centre, but should be carried out by someone with experience in paediatric ultrasonography. (6) Screen-detected lesions should be managed at a specialist centre.

Wilms tumour is an embryonal tumour of the kidney that affects 1 in 10 000 children and is diagnosed in about 80 children in the UK every year. Treatment for Wilms tumour is one of the foremost successes of paediatric oncology, with long-term survival in >90% of the cases for localised disease and in >70% of the cases for metastatic disease.[1] Most tumours occur in otherwise well children, but a small number occur in children with genetic syndromes. Wilms tumour has been reported in association with >50 different syndromes, but there is conclusive evidence of an increased risk of Wilms tumour in only a minority of these conditions.[2]

Regular surveillance in children thought to be at increased risk of Wilms tumour has become widespread in the UK, US and parts of Europe. However, there is little evidence available regarding the efficacy of screening or the balance of potential risks and benefits. Moreover, little guidance as to how Wilms tumour surveillance should be implemented has been available. This has resulted in ad hoc surveillance protocols lacking in consistency of practice or equity of provision. In turn, this has led to confusion, controversy and dissatisfaction for patients and clinicians.

We formed a working group of clinical geneticists (EM, NR, LW), paediatricians (AC), paediatric oncologists (KP-J, GL) and radiologists (IK, CMO, ØEO) to formulate recommendations for Wilms tumour surveillance based on a review of the available evidence from the literature, current practice and expert opinion. This article is a synopsis of the working group's recommendations to which the reader is encouraged to refer.[3]

METHODS

To comprehensively review information regarding Wilms tumour screening and Wilms tumour-associated syndromes, we undertook extensive searches for relevant articles using the PubMed, Online Mendelian Inheritance of Man and Winter-Baraitser Dysmorphology databases. To facilitate searches we also created a database of more than 8000 references with "Wilms tumour" or "nephroblastoma" in the title or abstract, which we downloaded from PubMed. We were then able to search this database for generic terms such as "syndrome" and "screening". We also reviewed the references of identified papers for additional relevant literature. We compiled a database of all conditions reported in association with Wilms tumour. For each condition, we reviewed the evidence for an increased risk of Wilms tumour, the likely magnitude of the increased risk and any literature regarding Wilms tumour surveillance.[3]

Using the Scottish Intercollegiate Guidelines Network criteria, we considered all the existing evidence on Wilms tumour screening to be of level 2 (evidence from case–control or cohort studies with a high risk of confounding, bias or chance and a considerable risk that the relationship is not causal), level 3 (evidence from non-analytic studies) or level 4 (evidence from expert opinion); therefore the recommendations are all grade D (ie based on level 4 evidence or extrapolated from level 2, 3 or 4 evidence).[4]

Once the recommendations had been completed, they were circulated to geneticists and paediatric oncologists, and were reviewed and approved by the UK Cancer Genetics Group and UK Children's Cancer Study Group radiological committee.

Abbreviation: WAGR, Wilms tumour-aniridia-genitourinary-mental retardation

REVIEW OF LITERATURE AND CURRENT PRACTICE

The efficacy of a surveillance procedure can be evaluated in several ways, the most simple of which is crude survival.[3] For conditions such as Wilms tumour, where survival rates are very high, screening will probably not lead to a substantial decrease in mortality. An alternative, or additional, basis on which to evaluate screening could be a more favourable stage distribution among screened patients, resulting in lower treatment-related morbidity. This may be applicable to Wilms tumour, as more advanced stage tumours receive more intensive chemotherapy and radiotherapy.[1]

To date, three small retrospective evaluations of Wilms tumour surveillance have been published,[5–8] only one of which reported a marked difference in stage distribution between screened and unscreened individuals.[8] Of note, three of 15 screened children in this study had false positive scans that resulted in extensive further imaging and major surgery, suggesting that significant negative sequelae of Wilms tumour surveillance can occur. Additionally, although difficult to quantify, the anxiety and practical difficulties associated with regular surveillance can be appreciable.

Conditions with high risks of Wilms tumour are rare, and therefore an international multicentre study conducted over many years would be required to effectively evaluate screening. This would be complex and very expensive to conduct. Moreover, there are considerable uncertainties about the risk and natural history of Wilms tumour in different conditions, and even in different subtypes of conditions, and changes in treatment for Wilms tumour or staging over the course of the study could confound the results. These difficulties and uncertainties may lead to the study giving inconclusive results, even after many years. We believe that conclusive evidence to inform the implementation of screening will probably not become available in the foreseeable future.

Although there is no definitive evidence that screening results in a marked decrease in either overall mortality or tumour stage, tumours detected by surveillance should, overall, be smaller than tumours that present clinically, as they will have been detected earlier. There is preliminary evidence from Germany, where the use of routine abdominal ultrasound in children is common and 10% of Wilms tumours are diagnosed before symptoms, that asymptomatic tumours are of lower stage than tumours that present due to clinical symptoms (Graf N, personal communication 2004). As lower-stage tumours currently receive less treatment, screening could plausibly result in lower mortality or reduction in treatment-related morbidity in some children. We believe it is reasonable to offer surveillance on this premise to children at increased risk of Wilms tumours.

Recommendations

Table 1 lists the summary and grade of recommendations of Wilms tumour surveillance.

Table 1 Summary and grade of recommendations for Wilms's tumour surveillance

Recommendation	Grade
1. Surveillance should be offered to children at >5% risk of Wilms's tumour.	D
2. Surveillance should be offered only after review by a clinical geneticist.	D
3. Surveillance should be carried out by renal ultrasonography every 3–4 months.	D
4. Surveillance should continue until 5 years in all conditions except Beckwith–Wiedemann syndrome, Simpson–Golabi–Behmel syndrome and some familial Wilms's tumour pedigrees, where it should continue until 7 years.	D
5. Surveillance can be undertaken at a local centre, but should be carried out by someone with experience of paediatric ultrasonography.	D
6. Screen-detected lesions should be managed at a specialist centre.	D

Surveillance should be offered to children at >5% risk of Wilms tumour

Given the finely balanced potential positive and negative sequelae of Wilms tumour screening, only individuals with conditions that include a clearly demonstrated increased risk of Wilms tumours should be offered screening. We have arbitrarily set the threshold Wilms tumour risk for inclusion in surveillance at 5%, although most of the cited conditions are associated with risks much greater than this (table 2). The conditions eligible for surveillance are briefly reviewed later. The complex clinical and molecular heterogeneity of Wilms tumour-associated conditions precludes a more detailed exposition, but the reader is referred to a recent review of syndromes associated with Wilms tumour, which includes estimates of Wilms tumour risk, background information and original references regarding the conditions covered by these recommendations and other conditions reported in individuals with Wilms tumours.[2]

WT1-associated syndromes

A variety of overlapping phenotypes are associated with heterozygous mutations or deletions of *WT1*, including Wilms-aniridia-genitourinary-mental retardation (WAGR), Denys–Drash and Frasier syndromes (table 1).[2 9] *WT1*-associated conditions are characterised by various combinations of three cardinal features: Wilms tumour, genitourinary abnormalities and renal dysfunction.

WT1 deletions are found in individuals with WAGR syndrome and are associated with a Wilms tumour risk of at least 50%. All children with aniridia should have a constitutional karyotype and fluorescence in situ hybridisation using probes for both *PAX6* and *WT1*, whether or not any additional features of WAGR syndrome are present. If *WT1* is deleted surveillance should be offered. If *WT1* is not deleted, the Wilms tumour risk is similar to the population risk, and no screening or renal follow-up is required, either for the proband or relatives.

The Wilms tumour risk in children with truncating *WT1* mutations or missense mutations in the zinc finger domains, including children with Denys–Drash syndrome and other *WT1*-associated phenotypes, is at least 50%. Such individuals should be offered surveillance. Most mutations occur de novo, in which case there is a potential offspring risk but other relatives will not be at risk. Mutation testing in parents and, if appropriate, other relatives can be undertaken and screening offered to mutation-positive cases. Missense mutations outside the zinc finger domains may be rare non-pathogenic polymorphisms and caution should be exercised in their interpretation, particularly if they are not de novo. There is a 5–10% risk of Wilms tumour in children with *WT1* intron 9 splicing mutations that alter the ratio of WT1 isoforms and cause Frasier syndrome. These children should also be offered surveillance.

Familial Wilms tumour

A small proportion of familial Wilms tumour pedigrees are due to the familial occurrence of syndromes covered elsewhere in these recommendations and should be managed accordingly. However, the cause is unknown in most families.[2 10] A familial Wilms tumour gene, *FWT1*, has been mapped to 17q21 and a second gene, *FWT2*, has been proposed to exist at 19q13. However, neither gene has been identified and there is evidence that further genes exist.[11] All at-risk children in families with more than one case of Wilms

Table 2 Molecular and phenotypic abnormalities with Wilms's tumour risks in excess of 5%

Gene	Phenotypes	Tests available	Who should have WT surveillance	WT risk*
WT1	WAGR syndrome Denys–Drash syndrome Frasier syndrome† Familial WT Aniridia Isolated WT	Karyotype 11p13 FISH Mutation screen	All with *WT1* deletion/pathogenic mutation	High
FWT1/ *FWT2*/ other genes	Familial WT	–	All potential carriers	High
BRCA2 (biallelic)	Fanconi anaemia D1 Some childhood cancer clusters	Mutation screen	All with biallelic *BRCA2* mutations	High
BUB1B, other genes	Mosaic variegated aneuploidy	Karyotype Mutation screen (research)	All	High
Unknown	Perlman syndrome	–	All	High
11p15 defects	Beckwith–Wiedemann syndrome Some hemihypertrophy cases	Karyotype 11p15 uniparental disomy *H19* methylation (research) KvDMR1 methylation *CDKN1C* mutation screen (research)	All with paternal uniparental disomy 11p15 All with isolated *H19* hypermethylation All with Beckwith–Wiedemann of unknown cause Not those with isolated loss of methylation of KvDMR1‡ Not those with CDKN1C mutations‡ Not those with HH of unknown cause‡	Moderate
GPC3	Simpson–Golabi–Behmel syndrome	Mutation screen	All males with *GPC3* mutation/deletion	Moderate

FISH, fluorescence in situ hybridisation; WAGR, Wilms's tumour-aniridia-genitourinary-mental retardation; WT, Wilms's tumour.
*Risk of developing WT: high>20%, moderate (5–20%).
†The risk of WT associated with *WT1* intron 9 splice site mutations/Frasier syndrome is moderate.
‡These individuals are at low risk of WT (<5%).

tumour should be offered surveillance as the risk of these tumours is estimated to be at least about 30% overall. Rare familial clusters of Wilms tumours and neuroblastoma are known, and at-risk children from such pedigrees would also be eligible for surveillance. Non-syndromic familial clusters of other childhood cancers and Wilms tumour are not associated with risks of Wilms tumour>5% and do not require surveillance.

Fanconi anaemia D1

Fanconi anaemia D1 is a chromosomal breakage disorder caused by biallelic *BRCA2* mutations.[2 12] Biallelic *BRCA2* mutation carriers have risks of Wilms tumour in excess of 20% and should be offered surveillance. Monoallelic (ie, heterozygous) *BRCA2* mutation carriers are at increased risk of breast and ovarian cancer, but not childhood cancer, and do not require Wilms tumour surveillance.

Mosaic variegated aneuploidy

Mosaic variegated aneuploidy is an autosomal recessive condition characterised by constitutional losses or gains of whole chromosomes. It is caused by biallelic *BUB1B* mutations in approximately 50% of cases, and is associated with risks for Wilms tumour >20%.[2 13] Children with either cytogenetic confirmation of the diagnosis or *BUB1B* mutations should be offered surveillance.

Beckwith–Wiedemann syndrome

Beckwith–Wiedemann syndrome is an overgrowth disorder caused by a variety of genetic and epigenetic abnormalities at chromosome 11p15.[2 14] The risk of Wilms tumour differs between these genetic or epigenetic subgroups.[15] The risk of Wilms tumour is increased in children with paternal uniparental disomy 11p15 or with isolated *H19* hypermethylation, and in those who fulfil the diagnostic criteria for Beckwith–Wiedemann syndrome but in whom no underlying cause can be found. Such cases should be offered Wilms tumour surveillance. Children with isolated loss of methylation of *KvDMR1* or *CDKN1C* mutations have not been shown to have increased risks of Wilms tumour and do not require surveillance.

Simpson–Golabi–Behmel syndrome

Simpson–Golabi–Behmel syndrome is an X-linked overgrowth disorder primarily caused by mutations or deletions in *GPC3*.[2 16] Affected males with *GPC3* mutations or deletions have an approximately 10% risk of Wilms tumour and should be offered surveillance. Carrier females are not at increased risk of Wilms tumour and do not require surveillance. Individuals without *GPC3* mutations are at <5% risk of Wilms tumour and do not require surveillance.

Perlman syndrome

Perlman syndrome is an autosomal recessive overgrowth disorder, the cause of which is unknown.[2 17] Early morbidity and mortality is high, and thus most affected cases are already under close supervision. The risk of Wilms tumour is high and surveillance should be offered. Unaffected siblings and extended relatives do not require surveillance.

Hemihypertrophy with 11p15 defects

The utility of hemihypertrophy as a surrogate indicator of Wilms tumour risk is unclear and the overall risk of Wilms tumour in isolated hemihypertrophy cases is <5%.[2 14] Hemihypertrophy can occur in individuals with Beckwith–Wiedemann syndrome, and the 11p15 abnormalities that underlie this syndrome have been reported in a minority of children with isolated hemihypertrophy. However, the cause of the disorder in most children with isolated hemihypertrophy is unknown. We recommend that Wilms tumour surveillance should be offered to children with hemihypertrophy with paternal uniparental disomy 11p15 or isolated *H19* hypermethylation, but not in other individuals with asymmetric growth.

Children should be referred for screening only after review by a geneticist

For the conditions discussed earlier, diagnostic molecular tests are available that have genetic implications for cases and their families and that directly affect eligibility for surveillance. We therefore recommend that a clinical geneticist reviews all children in whom the above diagnoses are being considered. The geneticist can undertake the appropriate diagnostic tests, discuss the genetic implications for families, and the benefits and risks of surveillance, and can refer the child for screening, if appropriate.

Renal ultrasonography is the optimal screening modality

Abdominal ultrasound is the best screening modality currently available. It is readily accessible, non-invasive, has good sensitivity and specificity, and has minor resource implications.[19] Abdominal palpation has been proposed as an alternative, but cannot detect very small tumours and is therefore unlikely to provide appreciable benefit compared with no screening. Magnetic resonance imaging or computed tomography scanning may be sensitive in detecting small lesions, but these modalities are unacceptable as many children would require sedation and computed tomography carries a considerable radiation burden. Screening ultrasounds can be undertaken at the local hospital, but should be carried out by a radiologist or sonographer with experience in paediatric ultrasonography. Table 3 presents the recommendations for operational procedures.

Ultrasound scans should be performed every 3–4 months

The optimal interval between surveillance tests depends on the doubling time of the tumour, the duration of detectable preclinical disease, acceptability to the family and available resources. At scanning intervals over 4–6 months, tumours have been reported at several intervals and this is consistent with the estimated Wilms tumour doubling time.[20] Therefore, we recommend that scans should be undertaken every 3–4 months and no less frequently than three times a year. Even at this frequency, occasional tumours may present clinically between scans and families should be made aware of this. However, there is no evidence to suggest that such tumours have a worse outcome.

Table 3 Suggested procedure for renal sonography in children at risk of Wilms's tumour

Equipment	High-resolution probes and paediatric settings. Linear (7–10 MHz) in infants, curvilinear (6–8 MHz) probe in toddlers
Preparation	Fasting and bladder preparation are not required
Target organ	Kidney only
Technique	Appropriate focal point and time gain settings. The whole renal parenchyma should be imaged longitudinally and transaxially with the child both supine and prone
Normal variants	Dromedary hump, column of Bertin, duplex or bifid collecting systems
Suspicious lesions	Solitary or multiple cystic or solid parenchymal lesions with or without sonographic signs of expansile growth. A solid lesion with internal vascular flow is more likely to represent malignancy than a simple cystic anechoic lesion

Screening should start at syndrome diagnosis and continue until 5–7 years of age

The duration of screening is dependent on the age range of Wilms tumour presentation in the predisposition condition. We recommend that surveillance should cover the age range of at least 90–95% of tumours. For all conditions, screening should begin at syndrome diagnosis. For the *WT1*-associated syndromes, mosaic-variegated aneuploidy, Fanconi anaemia D1 and Perlman syndrome, virtually all tumours occur before 5 years and thus surveillance is not recommended beyond this age. For Beckwith–Wiedemann syndrome screening until 7, 8, 9 years or beyond has been advocated.[6 8 21 22] In the past 30 years, in the UK, only one Beckwith–Wiedemann case registered with the UK Children's Cancer Study Group presented with Wilms tumour after 7 years of age. Therefore, we believe it is reasonable to stop ultrasound surveillance at 7 years for children with 11p15 defects. For Simpson–Golabi–Behmel syndrome, there is minimal data available on the age of diagnosis of Wilms tumour, but at least one presented at 7 years. Therefore, we recommend that surveillance should continue until 7 years for children with *GPC3* mutations. Familial Wilms tumour has the broadest age distribution. Cases linked to *FWT1* have an older age of onset, with a mean age of presentation of 6 years.[23] However, families with very young ages at diagnosis are also known, and overall, familial Wilms tumour has a younger mean age at diagnosis than sporadic Wilms tumour.[10] Therefore, we recommend that surveillance should continue until 5 years in most families, unless an affected child from the family has presented above this age, in which case it would be reasonable to continue until 7 years.

Management of a screen-detected lesion should take place at a specialist centre

If a suspicious lesion is detected on screening, the child should have a repeat ultrasound scan at a specialist centre. This should be arranged by the referring geneticist or the child's paediatrician. If the repeat ultrasound scan confirms the suspicious lesion, specialist radiological and paediatric oncology colleagues should be consulted and further imaging with magnetic resonance imaging or computed tomography should be carried out. Depending on the size and nature of the lesion, it may be decided to repeat imaging at a later date or to proceed with surgery. No treatment should be given until a histologically proved diagnosis of Wilms tumour has been made.

IMPLEMENTATION AND CONCLUSIONS

It is known that many children currently having Wilms tumour surveillance do not fulfil the inclusion criteria set out in these recommendations. It would not be appropriate to stop surveillance in such children without discussion with the family. We recommend that children currently in screening should be referred to a geneticist to discuss the recommendations and to decide whether to continue with screening. Some families may wish to continue with screening even if they do not meet the eligibility criteria, and may experience anxiety should surveillance be withdrawn. It may therefore be appropriate to continue screening until 5 years in some children who do not fulfil the eligibility criteria. However, prospectively, we recommend that only children with the conditions described should be offered surveillance. It is hoped that the recommendations will cover the most of the children. NR would be happy to discuss any case, the suitability of which for surveillance is uncertain.

These recommendations are broadly supported by clinical geneticists, paediatric oncologists and paediatric radiologists in the UK. Implementation should result in clarity for patients and clinicians and consistency of practice across the UK. Centralisation of screening through clinical genetics services

What is already known on this topic

- Most cases of Wilms tumour occur in otherwise well children.
- A small number of tumours occur because of a predisposing genetic syndrome.
- Screening of children considered to be at increased risk of Wilms tumour has become widespread.
- Lack of guidance about the implementation of surveillance of Wilms tumour has resulted in inconsistent, ad hoc practice.

What this study adds

- A review of the literature, current practice and expert opinion on surveillance of Wilms tumour, which shows that the potential risks and benefits are finely balanced
- Pragmatic recommendations for surveillance of Wilms tumour in children at increased risk based on the review

will allow accrual of data on the numbers and outcomes of individuals in screening, which may inform future recommendations. Future recommendations will also be influenced by clarification of the phenotypic groups and subgroups predisposed to Wilms tumour and the underlying molecular mechanisms. We have active research programmes in this area, including specific studies on familial Wilms tumours, Fanconi anaemia D1, mosaic-variegated aneuploidy and hemihypertrophy or asymmetric growth, and would be pleased to be contacted regarding such cases, inclusion of which in research studies will greatly facilitate future progress in this area.[7 12 13 24]

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