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# JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Impact of Surveillance Imaging Modality on Survival After Recurrence in Patients With Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group

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# ABSTRACT

The use of computed tomography (CT) for routine surveillance to detect recurrence in patients with Wilms tumor (WT) has increased in recent years. The utility of CT, despite increased risk and cost, to improve outcome for these patients is unknown. We conducted a retrospective analysis with patients enrolled in the fifth National Wilms Tumor Study (NWTS-5) to determine if surveillance with CT correlates with improved overall survival (OS) after recurrence compared with chest x-ray (CXR) and abdominal ultrasound (US).

#### Patients and Methods

Overall, 281 patients with recurrent unilateral favorable-histology WT were reviewed to assess how WT recurrence was detected: sign/symptoms (SS), surveillance imaging (SI) with CT scan, or SI with CXR/US.

#### **Results**

Purpose

The estimated 5-year OS rate after relapse was 67% (95% CI, 61% to 72%). Twenty-five percent of recurrences were detected with SS; 48.5%, with CXR/US; and 26.5%, with CT. Patients with SS had a 5-year OS rate of 59% (95% CI, 46% to 72%) compared with 70% (95% CI, 63% to 77%;  $P = 0.23$ ) for those detected by SI. Recurrences detected by CT had a shorter median time from diagnosis to recurrence (0.60 years) compared with SS (0.91 years) or CXR/US (0.86 years;  $P = .003$ ). For recurrences detected by SI, more tumor foci at relapse ( $P < .001$ ) and size of the largest focus greater than 2 cm  $(P = .02)$  were associated with inferior OS. However, there was no difference in OS after relapse when recurrence was detected by CT versus CXR/US (5-year OS rate, 65%  $v$  73%;  $P = 0.20$ ).

#### Conclusion

In patients with favorable-histology WT, elimination of CT scans from surveillance programs is unlikely to compromise survival but would result in substantial reduction in radiation exposure and health care costs.

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### **INTRODUCTION**

Modern multimodality therapy has resulted in an overall cure rate of 90% for children with Wilms tumor  $(WT)$ .<sup>1-5</sup> The survival rate for patients who experience relapse ranges from 50% to 80% and depends on the initial tumor stage and treat-ment.<sup>[6-8](#page-7-0)</sup> Scheduled interval diagnostic imaging surveillance during and after completion of therapy is standard practice, with the goal of detecting relapse before physical signs and symptoms develop. This practice is based on the presumption that a lower disease burden may improve post-relapse survival, though the validity

of this assumption, and whether the mode of detection of relapse is important, remains un-tested in most pediatric cancers.<sup>[9](#page-7-0)</sup>

With the widespread availability and high sensitivity of computed tomography (CT) scans to detect pulmonary and soft tissue nodules, the practices of surveillance imaging have shifted to frequent utilization of this modality. Although recommended imaging surveillance on the fifth National Wilms Tumor Study (NWTS-5) consisted of interval chest x-rays (CXR) and abdominal ultrasounds (US), many clinicians used CT scans. The recently closed Children's Oncology Group (COG) renal tumor studies formalized this surveillance practice with required interval

chest/abdomen/pelvic CT scans that alternated with CXR and US. We reviewed patients enrolled in NWTS-5 who experienced recurrence to assess whether the presenting features of relapse, the burden of disease at relapse, and the modality of surveillance imaging to detect relapse were associated with overall survival (OS) after relapse. We also calculated the relative cost and radiation exposure burdens of these two surveillance strategies.

### PATIENTS AND METHODS

NWTS-5 ([Clinicaltrials.gov](http://Clinicaltrials.gov) identifier: NCT00002610) enrolled 2,596 participants between 1995 and 2002 in 214 institutions in the United States, Canada, Australia, New Zealand, Switzerland, and the Netherlands. Institutional review board approval was obtained by all participating sites. Parents or guardians of the participants provided written informed consent. A retrospective review of the research records of 479 patients coded as having recurrent disease was conducted by four study authors (E.A.M., J.I.G., K.J.S., and J.S.D.). Patients were excluded for the following reasons: histologic diagnosis other than WT ( $n = 34$ ), never achieved remission ( $n = 27$ ), and incomplete or unavailable charts ( $n = 14$ ). In addition, patients with bilateral WT ( $n = 68$ ) were excluded, because it is difficult to distinguish between a metachronous tumor and a true relapse and because the kidneys of patients with bilateral WT often appear abnormal, which makes it difficult to define a precise time of recurrence. The following variables were derived from research flowsheets and imaging reports provided by treating institutions: reason for imaging, type of imaging (CT, CXR, or US), timing of relapse, site(s) of relapse, number of lesions, size of the largest lesion, and interval at relapse from the last normal imaging study. Patients were assigned to three study groups: (1) Patients were classified as presenting with signs/symptoms (SS) if the records indicated that SS precipitated an imaging study that diagnosed the relapse. (2) If the patient's relapse was detected on CXR/US that had been scheduled for routine surveillance, that was scored as a surveillance imaging (SI) CXR/US, regardless of whether the patient had SS. (3) Likewise, for any relapse detected by CT that had been scheduled as a planned surveillance scan, the patient was classified as SI CT.

#### Statistical Methods

Survival after recurrence was defined as the time from recurrence to death as a result of any cause. For patients with recurrence detected by SS, the date that the SS were noted was used to mark the recurrence. Survival after recurrence for patients not known to be dead was censored at the date the patient was last known to be alive. Kaplan-Meier curves were used to provide estimates of survival after recurrence by patient characteristics. Differences in survival after recurrence among patient subsets were assessed using the log-rank test. Differences in time from diagnosis to recurrence and from the last normal imaging to relapse were assessed using the Wilcoxon or Kruskal-Wallis test. The  $\chi^2$  test was used to assess differences in clinical features. A Cox regression multivariable analysis was conducted.

#### Radiation Exposure Estimates and Cost Model

The cost of surveillance imaging was estimated using 2018 Centers for Medicare and Medicaid reimbursement rates in the United States.<sup>[10](#page-7-0)</sup> The number and type of imaging studies required were abstracted from the NWTS-5 and COG AREN0532 and AREN0533 studies (Data Supplement) The model assumed that patients with relapse had their relapses detected at 12 months after diagnosis, consistent with the median time to recurrence demonstrated in AREN0532.<sup>2</sup> Radiation exposure estimates were calculated according to the recommended imaging schedule, which assumed 0.1 millisievert (mSV) for each two-view CXR, 3 mSV per chest CT, and 5 mSV per abdominal  $CT<sup>11,12</sup>$  $CT<sup>11,12</sup>$  $CT<sup>11,12</sup>$  No age adjustments were made.

# RESULTS

#### Patient Characteristics

A total of 336 patients were initially identified for the analysis: 281 had favorable-histology WT (FHWT), and 55 had anaplastic histology. The proportion of patients with anaplastic WT (16.4%) in this cohort was higher than in cohorts of newly diagnosed patients because of the higher relapse rate for anaplastic histology. The median duration of follow-up from the time of first relapse for all surviving patients was 10.1 years (range, 0 to 20 years). The estimated 5-year OS rate after relapse for the 336 patients was 57% (95% CI, 51% to 63%). The 5-year OS rate after relapse for patients with FHWTwas 67% (95% CI, 61% to 72%), whereas it was only 10% (95% CI, 2% to 18%) for those with anaplastic tumors ( $P < .001$ ; Data Supplement). The low survival rate after recurrence for anaplastic WT prevented identification of imaging features associated with outcome. Hence, the following analysis was restricted to the 281 patients with FHWT (CONSORT diagram, [Fig 1](#page-3-0)).

#### Detection of Relapse

Sixty-six recurrences (25%) presented with SS, 128 (48.5%) were detected with SI CXR/US, 70 (26.5%) were detected with SI CT, and 17 did not have the mode of detection recorded [\(Table 1](#page-3-0)). The most common presenting SS was pain  $(n = 20)$ , followed by palpable abdominal mass ( $n = 15$ ) and abdominal distention ( $n =$ 6). Less common SS included fever, cough, hematuria, constipation, seizures, vomiting, decreased breath sounds, respiratory distress, and fatigue. None of the patients had recurrence detected by surveillance magnetic resonance imaging (MRI).

Several differences in the clinical characteristics of these groups were observed ([Table 1\)](#page-3-0). The stage distribution at diagnosis indicated that more patients in the SI CT group had initial stage IV disease (31%) than in either the SS group (18%) or the SI CXR/US group (11%;  $P = .02$ ). More patients in the SS group (83%) had their relapses detected after completion of therapy compared with the SI CXR/US (74%) and the SI CT (54%) groups ( $P < .001$ ), which perhaps reflected an increased frequency of imaging during therapy.

Extrapulmonary lesions were more likely to manifest with SS: In the SS group, 86% of patients had recurrence outside the lung compared with 40% in the SI CXR/US group and 34% in the SI CT group ( $P < .001$ ). In the SS group, 93% of the patients had a lesion greater than 2cm compared with 60% of those in the CXR/US group and 37% of those in the CT group ( $P < .001$ ). Only eight patients (2.8%) had pelvic disease detected at relapse; four presented with SS, and four had disease detected on surveillance US. In patients with recurrence detected by imaging, a similar percentage of relapses in the abdomen/operative bed were detected by US and CT (24%  $\nu$  27%); likewise, a similar percentage were detected in the lung using CXR and CT (60%  $\nu$  66%).

### Prognostic Factors for Survival After Recurrence

Patients with SS had 5-year OS rate of 59% (95% CI, 46% to 72%) compared with 70% (95% CI, 63% to 77%;  $P = .23$ ) for those detected by SI ([Fig 2](#page-4-0)). Among patients whose recurrences were detected off therapy, those with SS had a 5-year OS rate of 55% (95% CI, 41% to 69%) compared with 76% (95% CI, 69% to 84%;  $P = .02$ ) for those detected by SI (Data Supplement).

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<span id="page-3-0"></span>

Fig 1. CONSORT diagram. CT, computed tomography; CXR, chest x-ray; NWTS-5, National Wilms Tumor Study 5; US, ultrasound.

For relapses detected by SI, outcome differed according to the number of tumor foci at relapse; 5-year OS estimates were 76%, 88%, 58%, and 38% for patients with one, two to three, four to six, or more than six foci ( $P < .001$ ; [Fig 3\)](#page-4-0). A diameter of the largest recurrent lesion greater than 2 cm was associated with inferior survival ( $P = .02$ ; [Fig 4](#page-5-0)). However, patients who experienced relapse with lesions of 1 cm or smaller had survival similar to that of patients with lesions of 1 to 2 cm (Data Supplement). The adverse prognostic significance of number of relapse foci and maximum diameter of relapse persisted when the analysis was restricted to patients whose recurrences were detected off therapy (Data Supplement).



Abbreviations: CT, computed tomography; CXR, chest x-ray; US, ultrasound.

\*Statistical comparison excludes patients with unknown number of lesions or unknown size of lesions.

<span id="page-4-0"></span>

Fig 2. Survival after relapse by method of detection in favorable-histology Wilms tumor. Patients with signs/symptoms (SS) had a 5-year overall survival rate of 59% (95% CI, 46% to 72%) compared with 70% (95% CI, 63% to 77%) for those detected by surveillance imaging (SI).

A multivariable analysis indicated that four to six disease foci, greater than six disease foci, recurrence diameter greater than 2 cm, and relapse in a site other than lung or abdomen were all associated with higher hazard ratios for death after recurrence (Data Supplement).

## Imaging Modality, Frequency, and Survival After Relapse

There was no difference in OS when recurrence was detected by CXR/US versus CT (5-year OS rate, 73%  $\nu$  65%; P = .20; [Fig 5\)](#page-5-0). This held true when the analysis was restricted to patients whose relapses were detected off therapy (Data Supplement). Patients with metastatic disease at diagnosis were more likely to undergo SI with CT rather than CXR/US [\(Table 1](#page-3-0)), so survival after recurrence was stratified by stage. There was no difference in outcome for patients with stages I or II FHWT between the CXR/US and CT groups (5-year OS rate, 79%  $\nu$  85%;  $P = .53$ ). Among patients with initial stages III and IV disease, there was no difference when relapse was detected by CXR/US rather than by CT (5-year OS rate, 66%  $\nu$ 52%;  $P = .11$ ). The same was observed when the analysis was



restricted to patients with stage IV disease (5-year OS rate, 64% with CXR/US  $\nu$  48% when detected by CT;  $P = .17$ ). Because CT may have greater benefit in detection of certain locations of relapse (lung  $\nu$ ) other), a separate analysis was conducted for lung versus other sites of relapse. There was no survival benefit when recurrences were detected by CXR/US versus CT for patients with lung only relapse (5-year OS rate, 73%  $v$  73%;  $P = .91$ ). There was a survival benefit for patients with recurrence at other sites that were detected by CXR/US compared with CT (5-year OS rate, 72%  $\nu$  48%;  $P = .02$ ).

To determine whether presentation with greater disease burden was associated with less frequent imaging, we assessed the time elapsed between the last scan with no evidence of disease and the scan on which relapse was detected. There was no difference in time from the last disease-free scan to the detection of recurrence in patients who had more foci of disease or signs/symptoms at recurrence ( $P = .87$ ; Data Supplement).

### Radiation Exposure and Imaging Costs

The number of imaging studies to detect each recurrence for patients with stage III disease according to NWTS-5 and AREN0532 surveillance guidelines (Data Supplement) were 232 and 328, respectively, which translated to total costs to detect each recurrence of \$20,517 and \$45,404. Likewise, the number of imaging studies to detect each recurrence for patients with stage IV disease according to NWTS-5 and AREN0532 surveillance guidelines were 158 and 190, respectively, which translated to total costs to detect each recurrence of \$14,967 and \$32,986 ([Table 2](#page-6-0)). For stage III disease, the estimated effective radiation exposure for the complete surveillance imaging series recommended in NWTS-5 and AREN0532 were 9.4 mSV and 68.3 mSV, respectively. For stage IV disease, the estimated effective radiation exposure for the complete surveillance imaging series recommended in NTWS-5 and AREN0533 were 12.3 mSV and 83.7 mSV, respectively [\(Table 2](#page-6-0)).

# **DISCUSSION**

Among patients with relapsed FHWT, we found no survival advantage if the relapse was detected by CT compared with CXR/US, irrespective of stage at diagnosis. A higher number of foci of

Fig 3. Survival after relapse in patients with favorable-histology Wilms tumor detected with surveillance imaging, according to the number of tumor foci at relapse.

<span id="page-5-0"></span>

Fig 4. Survival after relapse in patients with favorable-histology Wilms tumor detected with surveillance imaging, according to maximum diameter of the recurrent disease.

recurrence and maximal diameter of the recurrent tumor greater than 2 cm correlated with inferior survival. Higher tumor burden was associated with inferior outcomes, so one may hypothesize that earlier detection of recurrence, achieved by utilizing more sensitive imaging techniques, would be beneficial. Although detection of recurrence with CT scans was associated with smaller tumor size compared with other modalities of detection, detection with CT scans was not associated with improved survival.

Several factors may explain the lack of benefit of CT scans. Although burden of disease correlated with outcome, there was no difference in survival of patients with maximum tumor diameter at recurrence of less than 1 cm versus 1 to 2 cm; it was only when the maximum tumor diameter exceeded 2 cm that the prognosis worsened. The threshold size associated with adverse prognosis was within the range of detectability by CXR or US, which may explain why CT scans did not confer an advantage. Moreover, patients with more foci of disease and signs/symptoms of recurrence surrogates of higher disease burden—did not have a longer length of time from the last normal surveillance scan. This indicates that greater disease burden at recurrence was not due to less frequent imaging. Rather, it is likely that the biology of the relapsed cancer, reflected by the rapidity of growth and metastatic potential, had the major impact on survival. Lack of any surveillance imaging may have a negative impact on survival after recurrence, but our data indicate that CXR/US has sufficient sensitivity to detect recurrence before the threshold tumor burden associated with adverse outcome is reached. Conversely, it is possible that more frequent imaging would result in detection of more relapses before SS develop, though it is unclear whether this would translate to improved survival.

Other studies have demonstrated lack of effect of intensified radiologic surveillance on OS. Studies in Hodgkin and non-Hodgkin lymphoma found that routine surveillance with CT and positron emission tomography after therapy does not result in improved OS for those patients. $13-19$  Similarly, neuroimaging surveillance of patients with medulloblastoma has no beneficial effect on OS, although the caveat in a comparison of this tumor with WT is the poor salvage rate expected with medulloblastoma relapse.[20-23](#page-7-0) A study of surveillance practices in neuroblastoma demonstrated that most relapses are identified with SS or with non-CT surveillance (eg, meta-iodobenzylguanidine [MIBG] and urine catecholamines). $24$  This study confirmed that pelvic recurrence in WT is rare  $(3%)$  and that it presents with SS.<sup>25,[26](#page-7-0)</sup> Thus, omission of the pelvis from surveillance imaging is unlikely to compromise survival.



Fig 5. Survival after relapse in patients with favorable-histology Wilms tumor detected with surveillance imaging, according to imaging modality used. CT, computed tomography; CXR/US, chest x-ray or abdominal ultrasound.

<span id="page-6-0"></span>

Abbreviations: COG, Children's Oncology Group; CT, computed tomography; FH, favorable histology; mSV, millisievert; NWTS, National Wilms Tumor Study; US, ultrasound; USD, US dollar.

NOTE. The model assumes that patients underwent primary nephrectomy and did not receive preoperative chemotherapy, which affected the number of imaging studies performed.

\*COG AREN0532 study: median time to recurrence.

†The model assumes that patients without recurrence receive all scheduled imaging studies, whereas patients with recurrence (12% for stage III and 17% for stage IV) will have recurrence detected at a median of 12 months after diagnosis, which would result in the inclusion of only a portion of the surveillance costs and radiation exposure. For example, for 100 patients with stage III disease enrolled in NWTS-5, 88 patients without recurrence would each have 30 studies (2,640 studies per 100 patients), and 12 patients with recurrence would have a median of 12 studies each (144 studies per 100 patients). The total number of positive studies would be 12/2,784 = 0.43%, with the assumption that each patient with recurrence has one positive study.

‡Estimates are based on 2018 Medicare reimbursement rates of \$30.95 for chest x-ray, \$125.25 for abdominal US, \$156.28 for CT of chest without contrast, and \$314.92 for CT of abdomen with contrast.

The recognition of the potential adverse health effects from medical imaging has prompted a re-evaluation of surveillance imaging strategies.<sup>[9,27](#page-7-0)</sup> Multiple studies have discussed the risk of development of cancers related to medical ionizing radia-tion.<sup>[28](#page-7-0)-[30](#page-8-0)</sup> On the basis of the linear no-threshold hypothesis of radiation exposure, the likely cumulative nature of exposure to ionizing radiation, and the long life expectancy of children, there is increasing concern about the potential long-term effects of repeated imaging. The change in surveillance guidelines from NWTS-5 to the first generation of COG studies resulted in an estimated six- to seven-fold increase in radiation exposure. Despite progressive reduction in CT radiation doses through technologic improvements, minimization of radiation exposure is prudent. Pediatric cancer survivors have had a markedly higher rate of diagnostic imaging over time compared with matched controls, even beyond the time period of recommended routine surveillance.<sup>[15](#page-7-0)</sup> Other risks of routine surveillance with CT or MRI for young children include complications of procedural sedation and heightened concern of an association of repeated use of anesthesia with learning disability in young children.<sup>[31-34](#page-8-0)</sup> In addition, overly sensitive imaging studies produce falsely positive results that must be resolved with evaluations that pose unnecessary risks.

The economic costs of surveillance imaging should also be considered. Surveillance imaging regimens that include only CXR and US cost approximately 50% less than regimens that include CT scans. These savings are likely conservative estimates, given the

typically higher third-party insurance reimbursement rates and the reduction in investigative costs for false positives found with more sensitive imaging modalities.

Another opportunity to reduce cost and radiation exposure associated with surveillance imaging is to limit the duration of surveillance. Patients with stage III FHWT enrolled in the AREN0532 study had a median time to recurrence of 11.9 months from study entry (range,  $0.5$  to  $65.4$  months).<sup>[2](#page-7-0)</sup> Patients with stage IV FHWT with complete lung nodule response had a median time to recurrence of 9.7 months (range, 4.6 to 37 months), whereas patients with incomplete lung nodule response had a median time to recurrence of 10.6 months (range, 8.4 to 18 months). $3$  Because the vast majority of recurrences occur within the first 2 years of therapy, consideration may be given to discontinuation or curtailment of surveillance imaging after that time.

This study complements the recent report from the 2001 Renal Tumor Study Group–International Society of Pediatric Oncology study, which also assessed the timing and modality of relapse detection for patients with recurrent WT.<sup>[35](#page-8-0)</sup> Planned surveillance imaging identified 70% of the relapses with the following distribution of modalities: US (32%), CXR (31%), CT (33%), and MRI (4%)—remarkably similar to the distribution we observed. The study found that the number of scans needed to detect one asymptomatic relapse was 112 in the first 2 years after nephrectomy and 500 in years 2 through 5; these data question the need for imaging beyond the 2-year mark. The International Society of <span id="page-7-0"></span>Pediatric Oncology study did not evaluate whether CT versus CXR/ US detection of recurrence correlated with post-relapse survival.

The primary strengths of this study are the size of the cohort, the treatment with protocol-specified therapy at the time of diagnosis, and the availability of robust outcome data. Other strengths include the central pathology review to confirm favorable histology and the availability of detailed research records that allowed determination of the indication for the scan that detected recurrence. Limitations include the retrospective nature of the review and, thus, sometimes-incomplete data collection related to certain prognostic factors (number of nodules, greatest nodule diameter). Because the data were collected from imaging reports rather than central review of imaging, the technical quality of the imaging studies could not be assessed. Also, bias may have determined which patients underwent CT scan surveillance rather than CXR/US. There may be circumstances when cross-sectional imaging provides value in follow-up surveillance.

In conclusion, elimination of CT scans from surveillance programs for unilateral FHWT is unlikely to compromise survival but would result in substantial reduction in radiation exposure and health care costs. The risk-benefit ratio associated with surveillance imaging modalities should be carefully weighed and formally studied for all pediatric cancers.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org.](http://jco.org)

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Impact of Surveillance Imaging Modality on Survival After Recurrence in Patients With Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group

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